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September 5, 1980

Dr. Charles R. MacKay, Deputy Director
 Office for Protection from Research Risks
 Office of the Director
 Department of Health and Human Services
 3A18 Westwood Building
 5333 Westbard Avenue
 Bethesda, Maryland 20205

Dear Dr. MacKay:

This is in response to your letter of June 17, 1980, to Dr. C. C. Lushbaugh, Oak Ridge Associated Universities (ORAU), and our subsequent telephone conversation requesting an investigation and report concerning involvement of individuals as subjects of research at the Oak Ridge National Laboratory (ORNL).

Before discussing the results of our investigation, it may be helpful to clarify the role of the two institutions referred in your letter. The Oak Ridge National Laboratory is a Federally owned facility operated for the Department of Energy (DOE) by the Union Carbide Corporation, Nuclear Division. Research at ORNL for other government agencies is conducted under the DOE contract with Union Carbide Corporation. Oak Ridge Associated Universities is also a prime operating contractor of DOE. Since there are two DOE research centers in Oak Ridge, both of whom have work funded by NIH, a bi-institutional General Assurance was sought and granted by NIH with both institutions sharing the General Assurance (G01716). The ORAU/ORNL Committee on Human Studies is chaired by Dr. Robert Lange of the University of Tennessee Memorial Research Center in Knoxville, Tennessee. For continuity, Dr. Lushbaugh has agreed to have all matters relating to the Committee be addressed to him. The fact that Dr. Lushbaugh is listed as the Institutional Officer to whom correspondence concerning Board affairs should be addressed does not change the bi-institutional nature of the Committee as shown in Enclosure 1. For ORNL, Dr. John Storer is the Institutional Representative. This block diagram was included as Annex 6

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In the letter of January 17, 1977, from Dr. C. C. Lushbaugh to Dr. Roy Kinard. In view of the somewhat complex bi-institutional involvement, we determined that the best method to obtain the information you requested was for DOE to undertake this investigation and report the results directly to you.

I will address your questions in the order in which they appear in your letter of June 17, 1980.

1. "confirmation from the institution of the reported incidents, including whether or not IRB review of the activities took place and, if so, minutes of the review":

In the Spring of 1979, Dr. Thomas Slaga, a member of the Senior Staff at the Oak Ridge National Laboratory, did apply 12-O-tetradecanoyl phorbol 13-acetate (TPA) to a small area of his skin as did four other members of Dr. Slaga's research group. The application occurred only once, away from the Laboratory and during off-duty hours.

Prior to this exposure, no IRB review had occurred. Unfortunately, a formal investigation and report were not made at the time ORNL first learned of the exposure. We have already informed ORNL of our position that such an investigation should have been made immediately and the results reported to us promptly. Subsequently, Dr. Slaga did submit an application to the ORAU/ORNL Committee on Human Studies and the application was disapproved. Dr. Slaga's application and the Minutes of the Committee's review and related correspondence is contained in Enclosure 2.

2. "in the event that there had been no prior IRB approval, a report of any follow-up or corrective action taken by the institution including measures to prevent the recurrence of similar incidents":

Following a determination by the Director of the ORNL Biology Division that exposure to TPA had occurred without

1081049

prior IRB or Laboratory approval, Dr. Slaga was informed in the strongest possible terms that this was an unacceptable practice and its occurrence away from the Laboratory did not relieve Dr. Slaga of his professional responsibility. Dr. Slaga was again informed of ORNL policies with regard to human use experimental procedures which require that any proposed research involving human subjects be approved in advance by the ORAU/ORNL Committee on Human Studies. As indicated previously, Dr. Slaga did subsequently submit an application which was not approved.

As a result of this incident, all ORNL policies and procedures regarding human use experiments have been reviewed to insure that they could be reasonably expected to prevent any such future occurrence. Following this review, it has been emphasized to all ORNL Senior Research staff the importance of these procedures and their individual responsibility to see that all investigators and staff under their supervision are fully aware of the policies and adhere to them. Further, an additional administrative check has been introduced into the ORNL procedures.

3. "a statement of the institutional policy regarding IRB review of such activities and what is being done administratively to insure understanding of, and compliance with, the policy on the part of researchers":

As indicated above, the Oak Ridge National Laboratory is a Federally owned facility of the Department of Energy and must observe all regulations of the DOE and the other Federal agencies where they apply. The DOE regulations for "Protection of Human Subjects" (10 CFR, Part 745) conform to the Department of Health and Human Services' regulations and clearly require the Institutional Review Board review and approval of any activity involving human subjects. These regulations are covered at ORNL and ORAU by the "Implementing Guidelines for Research on Human Subjects", Enclosure 3. These guidelines are being updated to reflect the change from DHEW to HHS and from ERDA to DOE. Some other minor changes may also be made subject to review and approval of the Committee on Human Studies. When approved by the Committee, the revised guidelines will be promptly forwarded to you for your review.

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We have emphasized to ORNL Senior Management the importance of these regulations and their responsibility to see that they are fully complied with. Subsequently, one additional administrative check has been added to the ORNL procedures. All proposed research which has been reviewed and approved by the IRB must still be approved by the ORNL Institutional Representative before any such research activity can actually be initiated. We believe this additional decision point is administratively very useful in a Laboratory as large as ORNL.

- 4. "how the current institutional policies regarding use and handling of know carcinogenic and other hazardous materials adequately cover research involving human subject":

Prior to obtaining permission to work with any known carcinogenic or other hazardous materials, a research protocol must be submitted to the ORNL Biohazards Review Committee. This Committee functions similar to the Institutional Review Board and must review and approve the research proposed, determine that the Laboratory in which the material will be used meets all applicable safety standards and that the protocol clearly contains all procedures for handling, storage and disposal of the materials. Review and approval of the proposal for scientific merit must precede submission to the Biohazards Review Committee. The Minutes of the Biohazards Review Committee are reviewed by a professional member of the DOE staff. The DOE-Oak Ridge staff also conducts periodic occupational safety audits of the facilities used for such research to insure full compliance with all Federal regulations and standards.

If the Biohazards Review Committee approves the proposed research, it would then be submitted to the ORAU/ORNL Committee on Human Studies if human subjects were to be involved.

We have devoted considerable effort to providing the fullest possible answers to your letter request. I regret that it has taken so long and appreciate your patience. If you have suggestions or comments to improve these procedures, we would be most glad to receive them or to provide other information you might require.

Sincerely,
 Original Signed by
 William R. Bibb
 William R. Bibb, Director
 Research Division

ER-13:WRB

Enclosures:

- 1. Committee Block Diagram
- 2. Application/Minutes
- 3. Guidelines

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OAK RIDGE NATIONAL LABORATORY

OPERATED BY
UNION CARBIDE CORPORATION
NUCLEAR DIVISION



POST OFFICE BOX X
OAK RIDGE, TENNESSEE 37830

OFFICE OF THE DIRECTOR

September 2, 1980

Department of Energy, Oak Ridge Operations
Attention: Mr. J. A. Lenhard, Assistant Manager
for Energy Research and Development
Post Office Box E
Oak Ridge, Tennessee 37830

Gentlemen:

ORNL HUMAN USE EXPERIMENTAL PROCEDURES

Your letter of July 21, 1980, expressed concern with regard to the exposure of several ORNL employees to 12-O-tetradecanoyl phorbol 13-acetate (TPA). We fully share your concern with regard to this matter and would like to apprise you of the steps we have taken since the exposure.

When this matter first came to our attention in the Spring of 1979, the Director of the Biology Division informally met with Dr. Slaga to establish the facts. It was determined that exposure to TPA had occurred after hours and away from the Laboratory and without prior Laboratory approval. Dr. Slaga was informed in the strongest possible terms that this was an unacceptable practice and that its occurrence away from the Laboratory did not relieve him of his professional responsibility. Dr. Slaga was also informed again of ORNL policies with regard to human use experimental procedures which require that any proposed research involving human subjects must be approved in advance by the Human Use Committee.

We subsequently reviewed all our policies and procedures regarding human use experiments to insure that they could be expected to reasonably prevent any such future occurrence. Following this review, we emphasized to our senior research staff the importance of these procedures and their individual responsibility to see that all investigators and staff under their supervision were fully aware of the policy.

Since receiving your letter, we have again reviewed the ORNL policies and procedures to see if they are adequate and have made some changes to broaden the policy. A copy of the latest ORNL policy is enclosed. As a result of this detailed review, we are convinced that the ORNL practices and procedures

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[Handwritten signature and date]
Z. 8/21/80

Mr. J. A. Lenhard

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September 2, 1980

concerning research involving human subjects can reasonably be expected to prevent such occurrences in the future.

We trust this information is fully responsive to your request and that it will be adequate for the Office for Protection from Research Risks, NIH.

Sincerely,

Herman Postma

Herman Postma
Director

HP:jnw

Enclosure

cc: A. S. Garrett
R. A. Griesemer
R. F. Hibbs
C. C. Hopkins
C. R. Richmond
File - RC

1081053

ORAU/ORNL Committee on Human Studies

IMPLEMENTING GUIDELINES FOR RESEARCH ON HUMAN SUBJECTS

(In Compliance with DHEW and ERDA Regulations on Protection of Human Subjects)

(March 1977)

A. Basic Principles (See Definitions, Annex 1.)

The Committee on Human Studies for Oak Ridge Associated Universities and Oak Ridge National Laboratory has officially adopted the code of ethics adopted by the World Medical Association, known as the Declaration of Helsinki. It accepts as amplification of this document the statement of the British Medical Research Council. The guiding principles of operation of this Committee are, however, those set forth in detail by DHEW in Federal Register, March 13, 1975, Vol. 40, No. 50, Part II, Protection of Human Subjects, Technical Amendments, pp. 11854-11858, and by ERDA in an August 17, 1976 document titled "Protection of Human Subjects Proposed Regulations" (10 CFR Part 705) as amended in 10 CFR, Part 745 (FR 41, November 30, 1976, pp. 52434-52438). (See Annex Items 2 and 3.) Wherever these guidelines appear to differ substantively from those in the Federal Register, those in the Federal Register should be understood to be dominant and to be followed.

B. Committee Membership and Structure

The Committee shall consist of persons of either sex and any race with varying backgrounds, training, vocation and community interests who, while cognizant of the research goals and programs of the two sponsoring institutions (ORNL and ORAU), are sufficiently qualified to safeguard the rights and welfare of human subjects and review the relative merit of human studies in respect to any risks involved. The Committee will be composed of at least two lay persons, two research scientists and two clinicians. Two of the medical professionals, however, must be from institutions other than ORNL or ORAU, the institutions from which will emanate applications for permission to conduct a particular human study. Because of the dual sponsorship of this Committee, the Medical Director of the Health Division, ORNL; Director of Biology Division, ORNL; and the Chairman of the Medical and Health Sciences Division of ORAU shall be members of the Committee. The Directors of the two sponsoring institutions (ORAU and ORNL) shall designate to these divisional directors the responsibility for seeing that their respective staffs comply with HEW and ERDA regulations for the protection of human subjects. The Chairman and Secretary of the Committee shall be elected at one (January) of two annual meetings of the Committee. A person nominated for Committee membership by a member of the Committee or a sponsoring institution shall be made a member only with the concurrence of the other Committee members. Because of the complexity of modern laws and regulations protecting human rights, governing contractual obligations and guiding the use of government funds and facilities for research, at least one member will be a lawyer cognizant of the Federal Regulations. A lawyer consultant will be

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agreed upon and will be readily available to counsel the Committee if the Committee membership does not include a lawyer member. Similarly, if the membership does not contain a minister or a psychologist (or psychiatrist), some person with a related vocation who is interested in protecting persons from emotional and psychologic trauma must be available to the Committee for consultation on individual projects whether or not psychologic stress or risk is obviously involved. (See Annex 4, 5, and 6.)

C. Procedures for Carrying out Initial and Continuing Review of Applications and Projects

1. Initial Review

All applications for support of research, training, demonstration or general research support projects, including those of fellows and trainees, which involve the use of human subjects, must be presented to and approved by the Committee on Human Studies, prior to submission for funding, and with the identical experimental design used for grant submission or ERDA "189" proposals. Regardless of the nature or degree of risk anticipated, the application must be presented in writing on the proper form (Annex 7). The application should not contain extraneous material; that is, the investigator should not submit a copy of an IND or ERDA-189 as a substitute for the form specified. The applicant must be prepared to discuss in person before the Committee detailed information on the following points:

- a. The possible risk to the rights and welfare of human subjects, including the rights of privacy, freedom from harassment and confidentiality of data. A description of the provisions made to minimize these risks must also be presented.
- b. Methods used to acquire informed consent. The form on which it is obtained and the risk described. Special emphasis shall be placed on the appropriateness of a consent form to the particular situation inherent in the study plan in question (Annex 8).
- c. The relative risks of the project as compared to the probable benefits to the subjects and to society. For each application, the Committee will document whether or not physical or psychological risks are likely to ensue as a result of the proposed research study, and further, that such potential risks have been evaluated in respect to the subject and his rights, needs and benefits. In addition, informed consent documents must be submitted to and approved by the Committee for each study so that members can be ensured that each human subject will receive candid explanations of specific procedures and their purposes, of attendant specific discomforts and risks, and possible benefits, if any. In addition, the Committee must be satisfied in

each study evaluation that the subjects will be instructed that they are free to withdraw their consent to participate and to discontinue their participation in the proposed project at any time without prejudice to them. No informed consent form will be considered acceptable if it contains any exculpatory clauses or attempts in any way to absolve the Principal Investigator's responsibility for the health (physical or mental) and welfare of the human subjects to be involved.

Specific deficiencies in a proposal will be identified by the Committee in writing for the proposer and also directed to the attention of that Committee member (the Director of the Health or Biology Division, ORNL, or Chairman of the Medical and Health Sciences Division, ORAU) who also has the responsibility designated to him by the Director of his sponsoring institution (either ORNL or ORAU) to obtain staff compliance with DHEW and ERDA Regulations and Guidelines for Protection of Human Subjects. Such a statement of deficiency by the Committee will be understood to require (1) delay in submission of the proposed grant or contract application to HEW or ERDA, and (2) resubmission for Committee approval before the project proposals are allowed to go forward in the funding process. A statement of approval by the Committee will be accompanied by HEW-596 (Annex 9) for the institutional director's signature for simultaneous submission with an NIH, NSF or ERDA grant proposal.

A member of the Committee who is from the institution (ORNL or ORAU), from which the research proposal is being submitted, will be expected to attend the Committee only for his information, and will have no persuasive or voting powers concerning the acceptability of that proposal and its level of compliance with HEW and ERDA guidelines.

Approval of a proposal for a study involving human subjects shall be formalized only after a majority of the qualified (see paragraph above) Committee members have had a chance to review the written proposal, discuss it with the other members of the Committee, obtain adequate answers from the author to their questions, and reach complete agreement of acceptability. No proposal will be approved to which any Committee member objects on the basis of consideration of the physical or mental welfare of any human subject. In special cases where a Committee member cannot attend, his comment and vote can be obtained by mail.

The Committee's findings will be transmitted in writing to the appropriate officer of the laboratory proposing the research and to the applicant. Release of funds shall be controlled by the guidelines to HEW-596 (Annex 9). The applicant's administrative superior shall maintain continuing review of the project activities. If a responsible investigator plans a change in study protocol, he must submit the proposed changes to the Committee for approval before putting them into practice.

D. Procedures of the Committee to Provide Advice and Counsel to Investigators

On request, senior investigators will appear before the Committee at its called meetings to answer any questions concerning a proposal. The question and replies will form part of the official minutes of the Committee and will be distributed to the concerned staff members, together with recorded actions of the Committee on a Review and Action Form (Annex 10).

Committee Meetings

The Committee will meet at least twice a year. The first meeting of the year will be early in January, if possible, to meet the following administrative needs:

1. Election of Chairperson and Secretary,
2. Reelection of members and replacement of those members no longer able to serve,
3. Report of the Secretary on the previous year's Committee activities and on the number of approved studies that are still active and therefore require critical review in the new year. Establishment of the calendar for scheduled review of continuing projects, documented by an annual status report that reports any emergent problems and indicates the need for changes in research protocols or forms for obtaining informed consent.

The second biannual meeting will address any problems in these administrative areas that have risen since the first meeting.

Other meetings will be called to meet the scheduled annual critical reviews, and as needed, to consider a specific new proposal(s) involving humans as subjects where HEW, ERDA, NSF or other governmental funding agencies have fixed deadlines which the research applicant is trying to meet. In special cases where time is short, and particularly where the defined risk to the human subject is a commonly accepted one (i.e., a physical examination by a licensed physician) and does not require discussion with the project proposer, the appropriate members of the Committee (Annex 6) may be polled by phone by the Secretary under the Chairman's direction after the members have had a chance to review the proposal sent to them by mail.

E. Requirements for Reporting any Emergent Problems or Proposed Precedural Changes to the Committee

All senior investigators with proposed or active projects will receive notice of Committee meetings and will appear before the Committee in person. At this time they shall present in writing any proposed changes in procedures and shall describe any new risks and benefits, and any methods for safeguarding patients' rights and procedures for informed consent in advance of instituting these changes.

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All investigators with active research programs involving human subjects that have been approved by the Committee must be kept aware of the need for an immediate report to the Committee secretary, Chairperson, or institutional representatives of emergent problems bearing on the health and welfare of human subjects and of needs for protocol modifications, restrictions or termination.

F. Procedures to Maintain an Active and Effective Committee

1. The chairman will ensure an active Committee by calling, in addition to the regular Annual Meeting, at least one additional meeting each year.
2. The members will be enjoined to assess every ongoing project as well as new proposals.
3. Extramural Committee members will be paid a consultant's fee, providing they are able to accept it, and travel expenses.
4. Full Committee Minutes will be distributed promptly to all members in draft form for corrections and review, so that the opinions and actions can be recorded accurately.
5. On a regular basis, at least annually, at some full Divisional professional staff meeting, the respective institutional representative will explain this program for protection of human subjects to his staff and reinforce the importance to his division of his staff following the HEW and ERDA Regulations and Guidelines on the use of human subjects in research.

G. Location of Records

The records of this Committee will be kept in the office of the Executive Secretary and will be available to the Committee, staff, and government auditors on demand.

OAK RIDGE NATIONAL LABORATORY

OPERATED BY
UNION CARBIDE CORPORATION
NUCLEAR DIVISION



POST OFFICE BOX X
OAK RIDGE, TENNESSEE 37830

OFFICE OF THE DIRECTOR

August 27, 1980

Department of Energy, Oak Ridge Operations
Attention: Mr. J. A. Lenhard, Assistant Manager
for Energy Research and Development
Post Office Box E
Oak Ridge, Tennessee 37830

Gentlemen:

ORNL HUMAN USE EXPERIMENTAL PROCEDURES

On page one of your letter (July 21, 1980) you state that the ORNL response (Dr. T. J. Slaga's letter to Dr. T. Domanski at NCI) indicated that the "in vitro studies using TPA are not associated with my NIH grant or my NIH contract but rather with Department of Energy funding." You continue that this statement implies that DOE would condone such activities but point out that the Department of Energy would not do so. We believe there must be some misunderstanding. The experiments carried out in vitro with TPA have nothing to do with humans and are part of the long established research program into the mechanisms of carcinogenesis carried out on experimental animal tissues and cells in accordance with accepted practices.

In response to the request for information on page two, items one and two, we can provide the following:

The fact that Dr. T. J. Slaga and some of his colleagues had applied 12-O-tetradecanoylphorbol-13-acetate (TPA) to a small area of their forearms and had a subsequent biopsy performed by a dermatologist, who was not associated with nor had any reporting responsibilities to ORNL, off site and out of working hours came to our attention in the spring of 1979. Despite the fact that these activities were extramural, Dr. J. B. Storer, Director, Biology Division, and Dr. R. J. M. Fry, Section Head, Cancer and Toxicology, met with Dr. Slaga to establish the facts. Dr. Slaga was told of the need and importance of complying with the Laboratory regulations for the protection of human subjects and that the fact that the investigation only involved research workers personally interested in the action of TPA did not obviate the need for formal permission from the

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Committee on Human Studies. Furthermore, Dr. Slaga was told that on no account was any further work on TPA involving any human subjects to be considered until an application was made to the Committee on Human Studies. Those instructions have been observed by Dr. Slaga.

Members of the staff know of the regulations concerning the protection of human subjects, and no formal research program which entailed the use of human subjects could be started without the Division administration's knowledge.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Herman Postma". The signature is written in a cursive, slightly slanted style.

Herman Postma
Director

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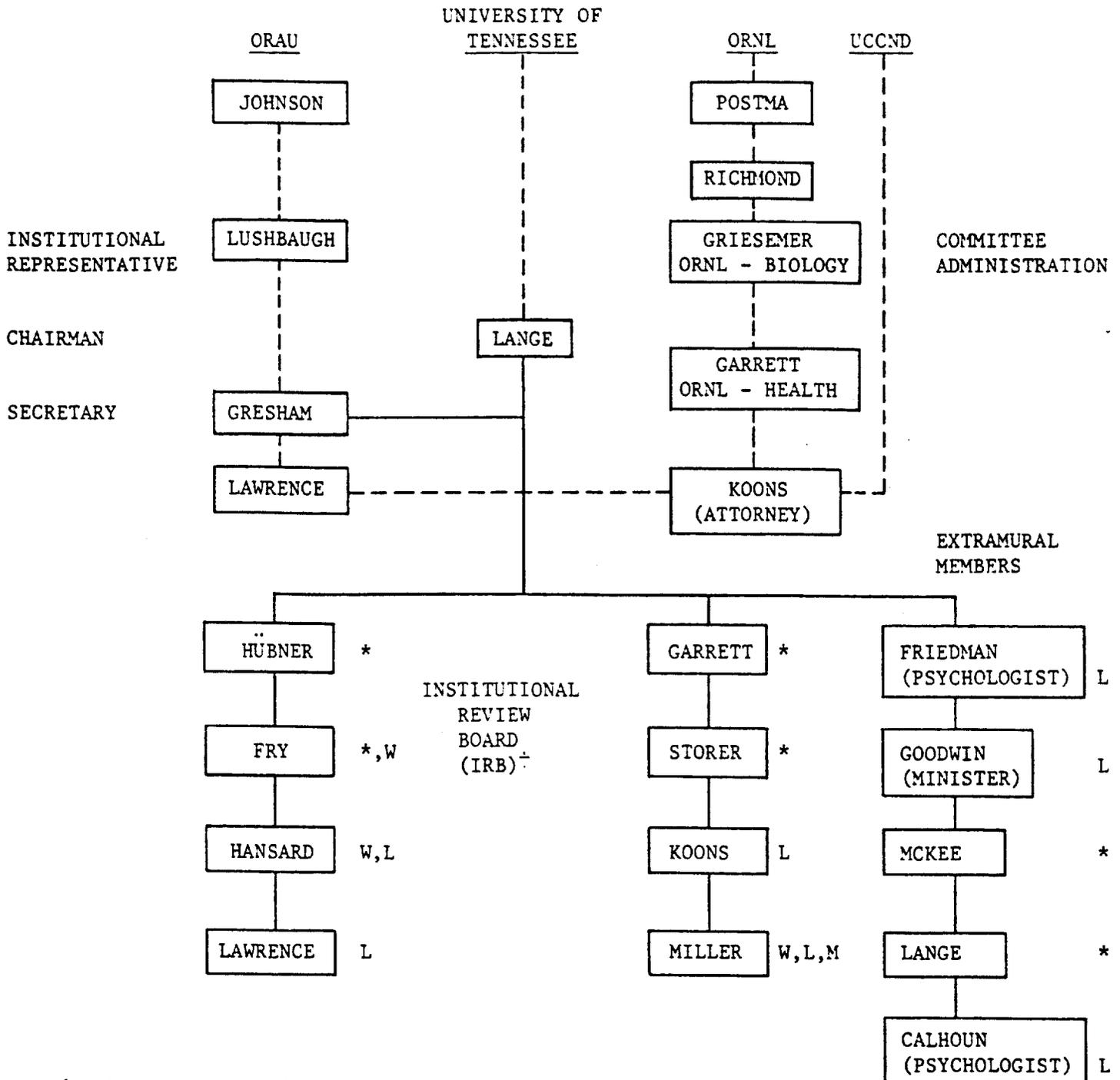
cc: A. S. Garrett
R. A. Griesemer
R. F. Hibbs
C. C. Hopkins
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Block diagram of the bi-institutional Committee structure, administration, lines of authority and present membership and functional identities.

BLOCK DIAGRAM OF ADMINISTRATIVE AND MEMBERSHIP STRUCTURE OF
ORAU/ORNL COMMITTEE ON HUMAN STUDIES

INSTITUTIONAL DIRECTORS



* = M.D. L = Layperson
W = Woman M = Minority

† ON ORNL PROPOSALS, ORNL AFFILIATES DO NOT VOTE;
ON ORAU PROPOSALS, ORAU AFFILIATES DO NOT VOTE;
EXTRAMURAL MEMBERS VOTE ON ALL PROPOSALS.

† VOTING MEMBERS

MINUTES OF THE ORAU/ORNL COMMITTEE ON HUMAN STUDIES

July 27, 1979

Present: Calhoun, Friedman, Garrett, Goodwin, Hansard, Hübner, Koons, Lange, Lawrence, Lushbaugh, McKee, and Storer. Not Present: Miller.

Proposal #56 ("In Vivo Effects of TPA on Adult Human Skin"; principal investigator, Dr. Thomas J. Slaga) was discussed at length by the Committee. Several areas of question mentioned by Committee members regarding the proposal were (1) its scientific merit, (2) its use in normal human volunteers, (3) problems stemming from possible skin irritation from TPA, (4) possibility of infection from TPA on biopsies to be performed, (5) problem regarding workman's compensation (if infection occurs and employee misses work), and (6) problems from malpractice suits if indeed infection occurs in a serious manner.

Drs. Lushbaugh and Hübner pointed out that TPA is an ingredient of croton oil. Years ago croton oil was used as a purgative, and its use has been discontinued except for veterinary purposes because of its toxicity in man. The known toxicity of the oil on human skin already presents possibilities for irritation and infection, and subsequent biopsies on the volunteers lends to additional chances of infection.

The five volunteers to be used in the study are from Dr. Slaga's laboratory. Dr. Lushbaugh pointed out that HEW Guidelines frown on the use of normal human subjects when the experimental procedure involves undue risk. Using volunteers from the laboratory where the study is to be performed presents a problem of ethics as well.

The end point of the study was unclear to the Committee, and Dr. Slaga was asked to answer questions for the Committee. Dr. Slaga stated that his research is done in hopes of aiding human medicine; if not in actual treatment, then in understanding the mechanism of cancer growth or inhibition. Dr. Lushbaugh expressed concern over the use of TPA in normal human subjects when it is not known whether it is a tumor promoting agent on human skin. Dr. Slaga noted that participants would not need to be involved more than once in this study, and the risk was minimal. Dr. Lushbaugh asked about future plans, and Dr. Slaga replied that his future projections (next 5-10 years) included the use of foreskin in culture and probably normal human skin from plastic surgery in his studies. Dr. Lange noted that the consent form would have to be expanded.

Dr. Lushbaugh asked Mr. Koons if ORNL's Blue Cross/Blue Shield policy or Workman's Compensation would cover the medical bills and any loss of time on the job if complications resulted. Mr. Koons replied that it would not. Dr. Storer expressed concern that the Medical Department of ORNL would not have the capability of treating participants with severe complications should they occur (such as reconstructive surgery).

The Committee voted not to approve Proposal #56 due to the risks involved. the selection of subjects, and the inadequate consent form and requested that Dr. Slaga redesign the proposal and resubmit it to the Committee at a later date if he so desired.

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At this point the Committee voted to modify the format of all proposals changing the section "Divisional Review" to read as follows:

The application described above has been reviewed and approved for submission to the ORAU/ORNL Committee on Human Studies.

It was noted to the Committee that Proposal #48a, "Use of ^{68}Ga -EDTA Aerosol for Quantitative Ventilation Studies by Positron Emission Computed Tomography (ECT)," had been approved by mail vote.

Drs. Uziel (Proposal ORNL-4) and Regan (Proposal #53) submitted reports on the progress of their projects; the Committee voted to approve the proposals for continued study based on these reports.

Dr. Lushbaugh reported that the revisions requested in the consent form of Proposal #52 at the March 20, 1979, meeting of the Committee would be made, and the consent form resubmitted at the next meeting of the Committee.

Dr. Lange told the Committee that Steve Lawrence had reported on 4/24/79 that ORAU is responsible for the liability coverage for all individuals outside the employment of ORAU that are involved with ORAU programs. Mr. Koons stated that individuals involved in ORNL and ORAU programs (proposals) should be listed as co-investigators on proposals to have liability coverage. (Example, Dr. Tiervo Rist, dermatologist in Dr. Slaga's proposal, should be listed as a co-investigator had the proposal been approved).

Comparison of FDA checklist and guidelines and the reporting form for investigators will be completed and submitted at a later date to the Committee.

Mr. Koons submitted two statements to the Committee regarding (1) alternative treatment and subject's right to privacy and (2) compensation and medical treatment (if any) for physical injuries resulting from research. The first statement dealing with the privacy act was changed to read as follows:

I understand further that only information obtained during this procedure from the study becomes the property of ORAU and ORNL, and only this information may be made available for review to the U. S. Food and Drug Administration. Further, that such information may be published in the scientific literature, as long as I am not identified, at the discretion of the ORAU and ORNL staffs.

The version printed above is to be reviewed by the Legal Department of UCC-ND and resubmitted at a later date to the Committee for approval and inclusion on consent forms. An additional form "Privacy Act Statement Consent Form" will also be given to the Legal Department for review and be resubmitted to the Committee with the statement cited above. The second statement explaining medical treatment for physical injuries and compensation was approved by the Committee and is to be included as part of the consent form for all new proposals and to be added to all ongoing proposals. Pat Fourney of ORNL and Steve Lawrence of ORAU will be requested by Dr. Lange to serve as information officers of their respective places of employment for consultation on compensation or treatment by research participants. All principal investigators of new proposals will be given a copy of the statement for inclusion in the consent form.

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The meeting was adjourned.

Dianne Gresham

Dianne Gresham

Dated: 1/17/80

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MINUTES OF THE ORAU/ORNL COMMITTEE ON HUMAN STUDIES

APRIL 18, 1980

The ORAU/ORNL Committee on Human Studies met at the Medical and Health Sciences Division of Oak Ridge Associated Universities on April 18, 1980. Members present were Calhoun, Friedman, Garrett, Goodwin, Hansard, Hubner, Koons, Lange, Lushbaugh, McKee, and Miller. Not present were Lawrence and Storer.

Dr. Lushbaugh circulated a copy of Chemical Week (February 13, 1980) for the members' information. It contained an article regarding Dr. Thomas J. Slaga's research practices at ORNL, which are being investigated by NIH. The Committee had rejected Dr. Slaga's proposal for the studies in question (12-O-tetradecanoylphorbol-13-acetate; Proposal #56) at their July 27, 1979, meeting. Dr. Lushbaugh stated that this incidence emphasized the importance of the Committee's functions. (See copy of article attached to minutes.)

Dr. Lange proceeded with the agenda at this point; he reported to the Committee the approval of Proposals #39a (Clinical Use of DL-tryptophan[Side Chain-3-C-11] (C-11-DL-Tryptophan) for Brain Imaging; Hubner) and #45a (Clinical Use of DL-Valine-1-C-11 for Brain Visualization; Hubner); both are amendments to the original proposals and were approved in mail votes by the Committee. Mr. Koons asked if his comment on the voting form for both proposals regarding surgical procedures was incorporated into the amendments; the addendum added to this proposal by the principal investigator, Dr. Hubner, was read to Mr. Koons. Mr. Koons acknowledged and approved the addendum.

The next items of business were three forms (new and revised) circulated among the members. The design of the "Progress Report Form" had been requested by the Committee at a previous meeting. Dr. Lushbaugh asked that the name of the institution of the principal investigator be added to the report form. The Committee secretary explained that these forms would be kept on file each year with the proposal being reported on the form, and only a summary of the yearly progress reports would be distributed to the Committee as requested at the March 20, 1979, meeting. The form met with Committee approval, and Dr. Lushbaugh's request will be incorporated.

The "Revised Voting Form" (differing from the old form by the removal of the acknowledgement of the submitter/principal investigator) was presented to the Committee. This form along with the new separate form "Acknowledgement of Principal Investigator" was approved by the Committee. These forms have been divided for accurate record keeping purposes.

The Status of Ongoing Proposals was read to the Committee by Dr. Lange. Each proposal (Nos. 38, 39, 43, 45, 46, 48 and 48a, 51, 52, 53, 54, 55, and

1081065

ORNL-4) was approved for continued research with comments and questions on the following proposals. (See attached list for complete names of proposals.)

Proposal 39. Dr. Hubner noted in his report that more scans are projected especially if a recently submitted proposal to the National Pancreatic Cancer Project is funded. Dr. Lushbaugh asked Dr. Hubner when he would know about the funding; Dr. Hubner reported news of funding should be known between June and July.

Proposal 43. Mr. Koons questioned the funding of Dr. Swartzendruber's proposal. Dr. Lushbaugh explained this was a "catch-up" proposal. Dr. Swartzendruber is using samples (fixed material) obtained long ago and is seeking approval for continued studies of this material.

Proposal 45 will be active as a part of the comparative study proposed in the grant request to the National Pancreatic Cancer Project of April 1, 1980. Referring to the grant request, Dr. Lushbaugh stressed the importance of the Committee's review of ongoing research projects and the approval of worthy ones. He stated that NIH would not consider a project unless it was approved by the Committee. Dr. Lange noted the need for accurate documentation of such approval. Dr. Hubner reported he had already been contacted by the National Pancreatic Cancer Project regarding a prior funding request; the NCPG wanted assurance that the research project had been approved by the Committee on Human Studies. Dr. Hubner explained to the NCPG that he was in the process of developing the radiopharmaceutical; and if the development came through, then it would be submitted to the Committee for approval before use in patients. Dr. Lange noted that FDA can make their requirements far reaching. At UT they asked to see the animals housed at another facility but used for research purposes at UT.

Proposal 46. Dr. Hubner noted that five separate WR-2721 projects are to be funded by NCI; no research for these projects is being carried out at ORAU. He feels that ORAU should have active studies as well because the radiopharmaceutical was developed by them. Collaborative studies are being planned now with Dr. Stroup at Vanderbilt. Dr. McKee (also of Vanderbilt) stated to Dr. Hubner that Dr. Stroup has plenty of patients for the studies if a collaborative project can be formed. Dr. Lange asked about the collaborative project previously planned between UT (Dr. Comas) and ORAU. Dr. Lushbaugh stated Dr. Comas withdrew because of possible nausea side effects in the use of WR-2721 to patients. Dr. Hubner reported that in the New Mexico studies only one case of nausea was reported.

Proposal 48 and 48a. Dr. McKee questioned Dr. Hubner about collaborative work in these studies. Dr. Hubner replied that Dr. Partain at Vanderbilt and Dr. Robertson at UT Medical Units were involved with collaborative studies. Dr. Lange suggested Dr. Hubner contact Drs. Killeffer and Reid at UT as possible collaborative contacts since they're becoming quite active in this area of research. Dr. Hubner discussed Dr. Robertson's work at UT Memphis with modified diets and his attempt to "starve" the tumor. He noted that the survival curves for patients with "modified diets" were very promising.

1081066

Proposal 51. Dr. Lushbaugh reported that DOE had awarded ORAU \$125,000 to do the updated software changes on the ECAT which will increase the activity of this proposal. Dr. Garrett asked about changes to be made in the present ECAT, and Dr. Hubner stated the ECAT II works essentially as the ECAT I with the main difference in the coincidence window which is shortened from 25 nanoseconds to 9 in the ECAT II. The ECAT II also gives better statistical data and has an automatic random subtraction technique; the ECAT II has three times the computer capacity and reconstructs as it collects data. Dr. Garrett inquired about the length of time necessary for patient scanning; Dr. Hubner estimated the average scan time per patient to be 45 minutes. He said movements by patients do not seem to be a problem.

Proposal 52. Dr. Lange noted that a new consent form for Proposal 52 was listed on the agenda. Mr. Koons asked about the symptoms for metal fume poisoning which Dr. Lushbaugh had reported. Dr. Lushbaugh explained that generally it is similar to flu with a "metal taste" in the mouth. The metal fume poisoning symptoms do not appear to be present when Zn-DTPA is given by IV rather than administered by aerosol (inhalation).

Proposal ORNL-4. The Committee approved continuation of Dr. Uziel's proposal as submitted. However, an addendum to this proposal and a new consent form must be submitted to the Committee for approval before Dr. Eversole can collect human tissue from normal surgical procedures for studies by Dr. Uziel as mentioned in the progress report under "changes." Dr. Lange stressed that the consent form must include a statement explaining to the surgical patient that the tissue will be utilized for scientific purposes at ORNL. Mr. Koons and Dr. Garrett expressed the importance of the Committee's responsibility to ensure the patient understands the purpose of the study, the use of his tissue for surgical procedures in research, and the protection of his rights as a research participant. The Committee will be held responsible by FDA and other government agencies for ensuring these practices.

Dr. Lange presented next the new proposals submitted for the Committee's review. All had been received by the Committee members two weeks prior to the Committee meeting. The first proposal discussed was ORNL-5 (Dark Epithelial Cells as Indicators of Atypia in Preneoplastic Lesions); the principal investigator is Dr. Klein-Szanto who was available for questions if the Committee needed to discuss the proposal with him. ORNL-5 was approved by the Committee in a mail vote. Three members (Drs. Garrett, Hubner, and Lushbaugh) had submitted comments. Dr. Lange read the comments to the members. Dr. Lushbaugh emphasized that Dr. Klein-Szanto was requesting to do feasibility studies on tissue embedded in paraffin received from pathologists, and the tissues would be identified by a histopathology number only. The patient donating the tissue would not be known. Dr. Lange stressed that the autopsy and biopsy material would have been received long ago. Based on this understanding the Committee stated a consent form would not be necessary. The proposal was approved for studies of electron microscopy with old tissue. Dr. Calhoun requested that Dr. Klein-Szanto be informed that the Committee would have to approve an addendum to the proposal or a new proposal if Dr. Klein-Szanto should decide to pursue the studies further and trace the tissues back to the patient for further findings. The Committee concurred, and Dr. Klein-Szanto was notified.

1081067

Proposal ORNL-6 (Repopulation of Normal Human Epithelial Cells in Tracheal Transplants) was also submitted by Dr. Klein-Szanto. There were several technical questions asked by members, and satisfactory answers were provided by other Committee members familiar with the materials through their own occupations. Dr. Calhoun requested the definition of nude mice and nude trachea. Dr. McKee explained the nude mouse has a different immune system from the other mouse populations, and the nude trachea had the epithelial cells removed. The basis for the techniques of the study was to subject human tissue transplanted into nude mice tracheas to experimental treatment without the risks of treating humans. The human tissues will be obtained from various pathology departments from Southeastern United States hospitals. Dr. Klein-Szanto submitted an example of a consent form used by pathology departments. Dr. McKee noted that the form submitted is typical of that used in all hospitals, and Dr. Lange pointed out that hospitals have their own Committees to approve consent forms. Dr. Calhoun asked if the Committee should see all the consent forms from the various hospitals before approving the proposal. The Committee acknowledged their responsibility for ensuring that the consent form used is adequate. Approval for the proposal was granted, and Dr. Klein-Szanto has been informed of the approval with the following stipulations. He is (1) to make certain that the hospital pathology departments have a consent form noting that tissues can and will be used for "other scientific purposes," (2) that the consent form submitted to the Committee with Proposal ORNL-6 is to be used as a model, and (3) that a proper consent form from the hospital pathology departments be filed with the proposal using the same words as given in Section 2 of the submitted "model" consent form.

Proposal 52 consisted of consent forms submitted by Dr. Lushbaugh. Dr. Lange read the request of the Committee from the March 20, 1979, minutes, which instructed Dr. Lushbaugh to create separate consent forms for Zn and Ca-DTPA. Several Committee members still found the forms hard to understand and felt they were too technical and too long. Dr. Hubner explained there was a reason for beginning treatment with Ca and switching to Zn depending on the amount of contamination. Mr. Koons questioned the use of the words "repeated" and "several" as not being specific enough. Dr. Garrett and Dr. Lushbaugh noted that the dose schedules related directly to the amount of contamination which was not known immediately at the initiation of the first dose. For this reason, Dr. Garrett stated the dose schedule could not be stipulated in the consent form. Dr. Lushbaugh explained that after the first dose, the amount of contamination can be calculated by urinalysis, etc., and then the schedule of treatment, if necessary, is determined at that time. Mr. Koons inquired about the possible delayed effects. Dr. Lushbaugh stated they are unknown. Dr. Calhoun found the forms confusing (technical detail) for the lay person and requested several technical terms be deleted from both forms. Ms. Miller requested a revision in both forms omitting sexist terms such as "man," and their replacement by the word "humans." With these changes, Mr. Koons felt lay persons would better understand the form and stated the physician administering the treatment could go into as much detail as he deemed necessary at that time. Dr. Calhoun expressed concern for pregnant females who might need the drug. Dr. Lushbaugh stated he would advise a female patient to take the drug because of the effects to the fetus from internal contaminants now contained within the female patient.

1081068

Dr. Lushbaugh said no women had been administered Ca-DTPA at this time. Proposal 52 was approved by the Committee with the changes noted previously and with the addition of the following statement to be added to the calcium consent form:

Dr. _____ has explained to me the possible effects to fetus that may occur from prolonged treatment with Ca-DTPA.

Dr. Hubner told the Committee that the ORAU Radionuclide Committee had approved the dosage for Proposal 57 (Ytterbium-169 Citrate for the Detection of Inflammatory Lesions); Dr. Hubner is principal investigator. Dr. Hubner reported that the studies have to be done in association with other hospitals because the patients involved are critically ill. Emphasis on clinical studies will be collaborated with Dr. Rollo at Vanderbilt, and Dr. Wagner's staff at Johns Hopkins have expressed an interest. It is doubtful that many patients will be seen at the Medical and Health Sciences Division; the compound will be made at the Medical and Health Sciences Division and shipped to Vanderbilt for use. If Dr. Rollo desires to do so, he may become a co-investigator. Dr. Hubner stated an IND will be sent to FDA if the Committee approves the proposal. Dr. Lushbaugh asked where the "previous scans" were made if there was no IND at this time. Dr. Hubner explained that scans were made in Japan and in DTPA form only in Kentucky; the citrate form has not been used in the United States. Dr. Garrett inquired about the dosage used by the Japanese, and Dr. Hubner reported they used twice as much per patient as Proposal 57 specifies. Mr. Koons asked for the time period involved for patients. Dr. Hubner said patients receiving the dose at ORAU will be detained four hours and will then return 20 hours later for Ga-67. The studies at Vanderbilt will be easier because of the computer subtraction techniques that are available to them. Mr. Koons also asked for information about the procedures, discomfort, and pain, if any, to patients. Dr. Hubner explained that part of the procedure (Ga-67) is done routinely in hospitals for diagnostic purposes, and the use of Ytterbium involves only one more injection and scan. Dr. Calhoun asked the advantages of administering the Ytterbium compound first. Dr. Hubner stated it was better to give the low energy compound first and then the higher energy compound, or Ytterbium could be filtered out by the gallium.

The consent form for Ytterbium was discussed. Mr. Koons felt the consent form did not reflect the rigorous schedule, and Dr. Calhoun expressed concern that there was not a withdrawal clause for patients involved in the study. Dr. Calhoun wanted to know how subjects for the study were engaged. Dr. Hubner stated that physicians requesting studies for patients with Ga-67 would be asked if their patient would also volunteer for scans using Ytterbium. Dr. Calhoun expressed the opinion that he could see no reason for a patient to want to volunteer and was very concerned that they would feel pressured by their physician to have these studies completed. Dr. Hubner explained that the Ga-67 study in the hospitals are quite expensive; by volunteering for studies at ORAU, the patients are not charged. Dr. Calhoun stated he felt very strongly that the consent form should contain statements saying the patient recognizes he is participating in a study with new procedures, that he is doing so of his own free will, and that he is free to withdraw at any time and will still receive necessary treatment for his health. Dr. Calhoun suggested that a subcommittee be formed to review consent forms and create a list of guidelines

1081069

with model statements for the use of principal investigators in writing consent forms for their proposals. The Committee approved the proposal, and Dr. Hubner was instructed to revise the consent form sending it to Mr. Koons for review and approval. Dr. Lange requested Dianne Gresham to obtain samples of the statements described by Dr. Calhoun from his secretary Nancy Parker at UT Hospital.

Proposal 58 (Whole Blood Procurement, Consent for Research Waiver Form and Payment Authorization), a research waiver form for cytogenetics studies, was approved by the Committee. This form is appropriate for routine cytogenetics reporting only. Dr. Lange and Dr. McKee both emphasized that another consent form must be received and approved by the Committee if any other use of the blood is planned other than reporting routine cytogenetics findings.

Dr. Lange asked Mr. Koons to reply to the statements to be incorporated into the consent forms as the next item on the agenda. These statements included (1) the Privacy Act Statement, (2) Consent to Release Information, and (3) the Compensation Statement. Mr. Koons told the Committee that DOE is in the process of compiling large amounts of material for publication in the Federal Register and would not review the statements at this time. As soon as the Federal Register material is published, DOE will review the statements; and at that time Mr. Koons will mail the forms to the Committee with revisions or changes noted by DOE. At present Mr. Koons felt the Committee should continue using the statements in consent forms until such time as DOE instructs the Committee of appropriate changes in these statement or revisions of them.

According to the Committee Guidelines, Dr. Lange instructed the Committee representatives from ORNL and ORAU to review the General Assurance with their respective staffs. Dr. Lange also asked the Committee to review the summary of the Comparison of Guidelines and FDA Checklist which was prepared by Dr. Karl Hubner and Dianne Gresham. Dr. Hubner reported that the Committee's Guidelines are in agreement with the FDA Checklist.

Dr. Lange announced to the Committee that Mr. Steve Lawrence, ORAU, and Mr. Pat Forney, ORNL, have agreed to serve as Information Officers for consultation on compensation on treatment by research participants for their respective institutions. The Committee asked that an article compiled by the University of Washington entitled "Adverse Effects Insurance for Human Subjects" be sent to both Mr. Lawrence and Mr. Fournery. This article was distributed to the Committee for their information at this meeting.

New officers were elected for the coming year. Dr. Lange was unanimously elected to the position of Chairman, and Dianne Gresham was appointed secretary. Both were commended by the Committee for their efforts in organizing and planning the functions and responsibilities of the Committee during the past year. The Chairman and the Committee expressed their appreciation to Ms. Gresham for her outstanding performance as secretary to the Committee.

Dr. Lushaugh requested that Dr. Roy Kinard, Office of Protection from Research Risks, HEW, NIH, be notified by the Committee secretary that the Committee has confirmed its membership, its responsibilities, and its functions. He also asked that Dr. Kinard be informed of the review and comparison of the

1081070

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Medical and
Health Sciences
Division

January 17, 1977

Roy Kinard, D.V.M.
Office for Protection from Research
Risks
Office of the Director
Department of Health, Education, and Welfare
Public Health Service
National Institutes of Health
Bethesda, Maryland 20014

Dear Dr. Kinard:

It was most helpful to talk with you today and have you resolve my remaining problems concerning our need to get our General Assurance (G1716) into complete compliance with HEW guidelines. I particularly appreciate your willingness to take a look at a draft just completed of the reorganized guidelines for this Committee on Human Studies. Accordingly, I am including with this letter a copy of this tentative revision for your criticism. I am simultaneously sending our Committee members a copy for their information and comments. I am hoping that with this informal approach we can obtain formal acceptance of our General Assurance by 1 February.

I appreciate your help in my meeting this goal.

Sincerely



C. C. Lushbaugh, M.D.
Chairman, Medical and
Health Sciences Division

CCL:fb

Enc.

cc: Dr. P. L. Johnson, Executive Director, ORAU
Dr. C. R. Richmond, ORNL
Committee Members

1081072

Annex Items

- Annex 1 Definitions
- Annex 2 FR 40
- Annex 3 FR 41
- Annex 4 CVs of present Committee members
- Annex 5 Summarized Committee assignments
- Annex 6 Block diagram of the bi-institutional Committee structure, administration, lines of authority and present membership and functional identities
- Annex 7 Application for approval
- Annex 8 Example of a typical informed consent form for a specific project
- Annex 9 HEW Form 596
- Annex 10 Review and Action Form

ORAU/ORNL Committee on Human Studies

IMPLEMENTING GUIDELINES FOR RESEARCH ON HUMAN SUBJECTS

(In Compliance with DHEW and ERDA Regulations on Protection of Human Subjects)

(March 1977)

A. Basic Principles (See Definitions, Annex 1.)

The Committee on Human Studies for Oak Ridge Associated Universities and Oak Ridge National Laboratory has officially adopted the code of ethics adopted by the World Medical Association, known as the Declaration of Helsinki. It accepts as amplification of this document the statement of the British Medical Research Council. The guiding principles of operation of this Committee are, however, those set forth in detail by DHEW in Federal Register, March 13, 1975, Vol. 40, No. 50, Part II, Protection of Human Subjects, Technical Amendments, pp. 11854-11859, and by ERDA in an August 17, 1976 document titled "Protection of Human Subjects Proposed Regulations" (10 CFR Part 705) as amended in 10 CFR, Part 745 (FR 41, November 30, 1976, pp. 52434-52438). (See Annex Items 2 and 3.) Wherever these guidelines appear to differ substantively from those in the Federal Register, those in the Federal Register should be understood to be dominant and to be followed.

B. Committee Membership and Structure

The Committee shall consist of persons of either sex and any race with varying backgrounds, training, vocation and community interests who, while cognizant of the research goals and programs of the two sponsoring institutions (ORNL and ORAU), are sufficiently qualified to safeguard the rights and welfare of human subjects and review the relative merit of human studies in respect to any risks involved. The Committee will be composed of at least two lay persons, two research scientists and two clinicians. Two of the medical professionals, however, must be from institutions other than ORNL or ORAU, the institutions from which will emanate applications for permission to conduct a particular human study. Because of the dual sponsorship of this Committee, the Medical Director of the Health Division, ORNL; Director of Biology Division, ORNL; and the Chairman of the Medical and Health Sciences Division of ORAU shall be members of the Committee. The Directors of the two sponsoring institutions (ORAU and ORNL) shall designate to these divisional directors the responsibility for seeing that their respective staffs comply with HEW and ERDA regulations for the protection of human subjects. The Chairman and Secretary of the Committee shall be elected at one (January) of two annual meetings of the Committee. A person nominated for Committee membership by a member of the Committee or a sponsoring institution shall be made a member only with the concurrence of the other Committee members. Because of the complexity of modern laws and regulations protecting human rights, governing contractual obligations and guiding the use of government funds and facilities for research, at least one member will be a lawyer cognizant of the Federal Regulations. A lawyer consultant will be

1081074

agreed upon and will be readily available to counsel the Committee if the Committee membership does not include a lawyer member. Similarly, if the membership does not contain a minister or a psychologist (or psychiatrist), some person with a related vocation who is interested in protecting persons from emotional and psychologic trauma must be available to the Committee for consultation on individual projects whether or not psychologic stress or risk is obviously involved. (See Annex 4, 5, and 6.)

C. Procedures for Carrying out Initial and Continuing Review of Applications and Projects

1. Initial Review

All applications for support of research, training, demonstration or general research support projects, including those of fellows and trainees, which involve the use of human subjects, must be presented to and approved by the Committee on Human Studies, prior to submission for funding, and with the identical experimental design used for grant submission or ERDA "189" proposals. Regardless of the nature or degree of risk anticipated, the application must be presented in writing on the proper form (Annex 7). The application should not contain extraneous material; that is, the investigator should not submit a copy of an IND or ERDA-189 as a substitute for the form specified. The applicant must be prepared to discuss in person before the Committee detailed information on the following points:

- a. The possible risk to the rights and welfare of human subjects, including the rights of privacy, freedom from harassment and confidentiality of data. A description of the provisions made to minimize these risks must also be presented.
- b. Methods used to acquire informed consent. The form on which it is obtained and the risk described. Special emphasis shall be placed on the appropriateness of a consent form to the particular situation inherent in the study plan in question (Annex 8).
- c. The relative risks of the project as compared to the probable benefits to the subjects and to society. For each application, the Committee will document whether or not physical or psychological risks are likely to ensue as a result of the proposed research study, and further, that such potential risks have been evaluated in respect to the subject and his rights, needs and benefits. In addition, informed consent documents must be submitted to and approved by the Committee for each study so that members can be ensured that each human subject will receive candid explanations of specific procedures and their purposes, of attendant specific discomforts and risks, and possible benefits, if any. In addition, the Committee must be satisfied in

each study evaluation that the subjects will be instructed that they are free to withdraw their consent to participate and to discontinue their participation in the proposed project at any time without prejudice to them. No informed consent form will be considered acceptable if it contains any exculpatory clauses or attempts in any way to absolve the Principal Investigator's responsibility for the health (physical or mental) and welfare of the human subjects to be involved.

Specific deficiencies in a proposal will be identified by the Committee in writing for the proposer and also directed to the attention of that Committee member (the Director of the Health or Biology Division, ORNL, or Chairman of the Medical and Health Sciences Division, ORAU) who also has the responsibility designated to him by the Director of his sponsoring institution (either ORNL or ORAU) to obtain staff compliance with DHEW and ERDA Regulations and Guidelines for Protection of Human Subjects. Such a statement of deficiency by the Committee will be understood to require (1) delay in submission of the proposed grant or contract application to HEW or ERDA, and (2) resubmission for Committee approval before the project proposals are allowed to go forward in the funding process. A statement of approval by the Committee will be accompanied by HEW-596 (Annex 9) for the institutional director's signature for simultaneous submission with an NIH, NSF or ERDA grant proposal.

A member of the Committee who is from the institution (ORNL or ORAU), from which the research proposal is being submitted, will be expected to attend the Committee only for his information, and will have no persuasive or voting powers concerning the acceptability of that proposal and its level of compliance with HEW and ERDA guidelines.

Approval of a proposal for a study involving human subjects shall be formalized only after a majority of the qualified (see paragraph above) Committee members have had a chance to review the written proposal, discuss it with the other members of the Committee, obtain adequate answers from the author to their questions, and reach complete agreement of acceptability. No proposal will be approved to which any Committee member objects on the basis of consideration of the physical or mental welfare of any human subject. In special cases where a Committee member cannot attend, his comment and vote can be obtained by mail.

The Committee's findings will be transmitted in writing to the appropriate officer of the laboratory proposing the research and to the applicant. Release of funds shall be controlled by the guidelines to HEW-596 (Annex 9). The applicant's administrative superior shall maintain continuing review of the project activities. If a responsible investigator plans a change in study protocol, he must submit the proposed changes to the Committee for approval before putting them into practice.

D. Procedures of the Committee to Provide Advice and Counsel to Investigators

On request, senior investigators will appear before the Committee at its called meetings to answer any questions concerning a proposal. The question and replies will form part of the official minutes of the Committee and will be distributed to the concerned staff members, together with recorded actions of the Committee on a Review and Action Form (Annex 10).

Committee Meetings

The Committee will meet at least twice a year. The first meeting of the year will be early in January, if possible, to meet the following administrative needs:

1. Election of Chairperson and Secretary,
2. Re-election of members and replacement of those members no longer able to serve,
3. Report of the Secretary on the previous year's Committee activities and on the number of approved studies that are still active and therefore require critical review in the new year. Establishment of the calendar for scheduled review of continuing projects, documented by an annual status report that reports any emergent problems and indicates the need for changes in research protocols or forms for obtaining informed consent.

The second biannual meeting will address any problems in these administrative areas that have risen since the first meeting.

Other meetings will be called to meet the scheduled annual critical reviews, and as needed, to consider a specific new proposal(s) involving humans as subjects where HEW, ERDA, NSF or other governmental funding agencies have fixed deadlines which the research applicant is trying to meet. In special cases where time is short, and particularly where the defined risk to the human subject is a commonly accepted one (i.e., a physical examination by a licensed physician) and does not require discussion with the project proposer, the appropriate members of the Committee (Annex 6) may be polled by phone by the Secretary under the Chairman's direction after the members have had a chance to review the proposal sent to them by mail.

E. Requirements for Reporting any Emergent Problems or Proposed Precedural Changes to the Committee

All senior investigators with proposed or active projects will receive notice of Committee meetings and will appear before the Committee in person. At this time they shall present in writing any proposed changes in procedures and shall describe any new risks and benefits, and any methods for safeguarding patients' rights and procedures for informed consent in advance of instituting these changes.

1081077

All investigators with active research programs involving human subjects that have been approved by the Committee must be kept aware of the need for an immediate report to the Committee secretary, Chairperson, or institutional representatives of emergent problems bearing on the health and welfare of human subjects and of needs for protocol modifications, restrictions or termination.

F. Procedures to Maintain an Active and Effective Committee

1. The chairman will ensure an active Committee by calling, in addition to the regular Annual Meeting, at least one additional meeting each year.
2. The members will be enjoined to assess every ongoing project as well as new proposals.
3. Extramural Committee members will be paid a consultant's fee, providing they are able to accept it, and travel expenses.
4. Full Committee Minutes will be distributed promptly to all members in draft form for corrections and review, so that the opinions and actions can be recorded accurately.
5. On a regular basis, at least annually, at some full Divisional professional staff meeting, the respective institutional representative will explain this program for protection of human subjects to his staff and reinforce the importance to his division of his staff following the HEW and ERDA Regulations and Guidelines on the use of human subjects in research.

G. Location of Records

The records of this Committee will be kept in the office of the Executive Secretary and will be available to the Committee, staff, and government auditors on demand.

DEFINITIONS

(a) "Institution" means any public or private institution or agency (including Federal, State, and local government agencies).

(b) "Subject at risk" means any individual who may be exposed to the possibility of injury, including physical, psychological, or social injury, as a consequence of participation as a subject in any research, development, or related activity which departs from the application of those established and accepted methods necessary to meet his needs, or which increases the ordinary risks of daily life, including the recognized risks inherent in a chosen occupation or field of service.

(c) "Informed consent" means the knowing consent of an individual or his legally authorized representative, so situated as to be able to exercise free power of choice without undue inducement or any element of force, fraud, deceit, duress, or other form of constraint or coercion. The basic elements of information necessary to such consent include:

(1) A fair explanation of the procedures to be followed, and their purposes, including identification of any procedures which are experimental;

(2) a description of any attendant discomforts and risks reasonably to be expected;

(3) a description of any benefits reasonably to be expected;

(4) a disclosure of any appropriate alternative procedures that might be advantageous for the subject;

(5) an offer to answer any inquiries concerning the procedures; and

(6) an instruction that the person is free to withdraw his consent and to discontinue participation in the project or activity at any time without prejudice to the subject.

(d) "Secretary" means the Secretary of Health, Education, and Welfare or any other officer or employee of the Department of Health, Education, and Welfare to whom authority has been delegated.

(e) "DHEW" means the Department of Health, Education, and Welfare.

() "ERDA" means the Energy Research and Development Administration.

(f) "Approved assurance" means a document that fulfills the requirements of this part and is approved by the Secretary.

(g) "Certification" means the official institutional notification to DHEW in accordance with the requirements of this part that a project or activity involving human subjects at risk has been reviewed and approved by the institution in accordance with the "approved assurance" on file at DHEW.

(h) "Legally authorized representative" means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to such subject's participation in the particular activity or procedure.

THURSDAY, MARCH 13, 1975

WASHINGTON, D.C.

Volume 40 □ Number 50

PART II



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DEPARTMENT OF
HEALTH,
EDUCATION, AND
WELFARE

Office of the Secretary



PROTECTION
OF
HUMAN SUBJECTS

Technical Amendments

Title 45—Public Welfare

SUBTITLE A—DEPARTMENT OF HEALTH,
EDUCATION, AND WELFARE, GENERAL
ADMINISTRATIONPART 46—PROTECTION OF HUMAN
SUBJECTS

Technical Amendments

On May 30, 1974, final regulations were published in the *Federal Register* (39 FR 17914) relating to protection of human subjects in research, development, and related activities supported by Department of Health, Education, and Welfare grants and contracts. Shortly thereafter, on July 12, 1974, the National Research Act, Public Law 93-348, was enacted. Although the Conference Report on the bill (H.R. 7724) which later became Pub. L. 93-348 expressed satisfaction with the regulations (H. Rep. No. 93-1148, at p. 26), section 212(a) of said Law added a new section 474(a) to the Public Health Service Act, which provides as follows:

The Secretary shall by regulation require that each entity which applies for a grant or contract under this Act for any project or program which involves the conduct of biomedical or behavioral research involving human subjects submit in or with its application for such grant or contract assurances satisfactory to the Secretary that it has established (in accordance with regulations which the Secretary shall prescribe) a board (to be known as an "Institutional Review Board") to review biomedical and behavioral research involving human subjects conducted at or sponsored by such entity in order to protect the rights of human subjects of such research.

Section 212(b) of Pub. L. 93-348 further stated that the regulations required to carry out section 474(a) shall apply with respect to applications for grants and contracts under the Public Health Service Act submitted after promulgation of such regulations.

The regulations published on May 30, 1974, codified at 45 CFR Part 46, would with minor, technical changes fully implement section 474(a). This would be accomplished by: (1) amending the citation of AUTHORITY to refer to section 474(a), (2) substituting references to "institutions" and "Institutional Review Boards" for existing references to "organizations" and "committees" and making related changes, and (3) revising 45 CFR 46.7, 46.11(a), and 46.12 to take account of the requirement in section 474(a) that an assurance concerning establishment of a Board must in all cases be submitted in or with the application. Since Part 46 was published initially as a notice of proposed rulemaking (38 FR 27822), and since the aforesaid changes would be minor and technical in nature, it is unnecessary to publish such changes as a notice of proposed rulemaking. The Department therefore finds that good cause exists for dispensing with this step.

Accordingly, the regulations published in the *Federal Register* on May 30, 1974 and codified at 45 CFR Part 46, as so amended, are hereby adopted as final regulations implementing section 474(a)

of the Public Health Service Act, effective March 13, 1975.

Dated: February 14, 1975.

THEODORE COOPER,
Acting Assistant
Secretary for Health

Approved: March 7, 1975.

CASPAR W. WEINBERGER,
Secretary.

Therefore, Subtitle A of Title 45 of the Code of Federal Regulations is amended by revising Part 46 to read as follows:

Sec.	
46.1	Applicability.
46.2	Policy.
46.3	Definitions.
46.4	Submission of assurances.
46.5	Types of assurances.
46.6	Minimum requirements for general assurances.
46.7	Minimum requirements for special assurances.
46.8	Evaluation and disposition of assurances.
46.9	Obligation to obtain informed consent; prohibition of exculpatory clauses.
46.10	Documentation of informed consent.
46.11	Submission and certification of applications and proposals, general assurances.
46.12	Submission and certification of applications and proposals, special assurances.
46.13	Applications and proposals lacking definite plans for involvement of human subjects.
46.14	Applications and proposals submitted with the intent of not involving human subjects.
46.15	Evaluation and disposition of applications and proposals.
46.16	Cooperative activities.
46.17	Investigational new drug 30-day delay requirement.
46.18	Institution's executive responsibility.
46.19	Institution's records; confidentiality.
46.20	Reports.
46.21	Early termination of awards; evaluation of subsequent applications and proposals.
46.22	Conditions.

AUTHORITY: 5 U.S.C. 301; sec. 474(a), 23 Stat. 352 (42 U.S.C. 2801-3(a)).

§ 46.1 Applicability.

(a) The regulations in this part are applicable to all Department of Health, Education, and Welfare grants and contracts supporting research, development, and related activities in which human subjects are involved.

(b) The Secretary may, from time to time, determine in advance whether specific programs, methods, or procedures to which this part is applicable place subjects at risk, as defined in § 46.3(b). Such determinations will be published as notices in the *Federal Register* and will be included in an appendix to this part.

§ 46.2 Policy.

(a) Safeguarding the rights and welfare of subjects at risk in activities supported under grants and contracts from DHEW is primarily the responsibility of the institution which receives or is accountable to DHEW for the funds

awarded for the support of the activity. In order to provide for the adequate discharge of this institutional responsibility, it is the policy of DHEW that no activity involving human subjects to be supported by DHEW grants or contracts shall be undertaken unless an Institutional Review Board has reviewed and approved such activity, and the institution has submitted to DHEW a certification of such review and approval, in accordance with the requirements of this part.

(b) This review shall determine whether these subjects will be placed at risk, and, if risk is involved, whether:

(1) The risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant a decision to allow the subject to accept these risks;

(2) the rights and welfare of any such subjects will be adequately protected;

(3) legally effective informed consent will be obtained by adequate and appropriate methods in accordance with the provisions of this part; and

(4) the conduct of the activity will be reviewed at timely intervals.

(c) No grant or contract involving human subjects at risk shall be made to an individual unless he is affiliated with or sponsored by an institution which can and does assume responsibility for the subjects involved.

§ 46.3 Definitions.

(a) "Institution" means any public or private institution or agency (including Federal, State, and local government agencies).

(b) "Subject at risk" means any individual who may be exposed to the possibility of injury, including physical, psychological, or social injury, as a consequence of participation as a subject in any research, development, or related activity which departs from the application of those established and accepted methods necessary to meet his needs, or which increases the ordinary risks of daily life, including the recognized risks inherent in a chosen occupation or field of service.

(c) "Informed consent" means the knowing consent of an individual or his legally authorized representative, so situated as to be able to exercise free power of choice without undue inducement or any element of force, fraud, deceit, duress, or other form of constraint or coercion. The basic elements of information necessary to such consent include:

(1) A fair explanation of the procedures to be followed, and their purposes, including identification of any procedures which are experimental;

(2) a description of any attendant discomforts and risks reasonably to be expected;

(3) a description of any benefits reasonably to be expected;

(4) a disclosure of any appropriate alternative procedures that might be advantageous for the subject;

(5) an offer to answer any inquiries concerning the procedures; and

free to withdraw his consent and to discontinue participation in the project or activity at any time without prejudice to the subject.

(d) "Secretary" means the Secretary of Health, Education, and Welfare or any other officer or employee of the Department of Health, Education, and Welfare to whom authority is delegated.

(e) "DHEW" means the Department of Health, Education, and Welfare.

(f) "Approved assurance" means a document that fulfills the requirements of this part and is approved by the Secretary.

(g) "Certification" means the official institutional notification to DHEW in accordance with the requirements of this part that a project or activity involving human subjects at risk has been reviewed and approved by the institution in accordance with the "approved assurance" on file at DHEW.

(h) "Legally authorized representative" means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to such subject's participation in the particular activity or procedure.

§ 46.4 Submission of assurances.

(a) Recipients or prospective recipients of DHEW support under a grant or contract involving subjects at risk shall provide written assurance acceptable to DHEW that they will comply with DHEW policy as set forth in this part. Each assurance shall embody a statement of compliance with DHEW requirements for initial and continuing Institutional Review Board review of the supported activities; a set of implementing guidelines, including identification of the Board and a description of its review procedures; or, in the case of special assurances concerned with single activities or projects, a report of initial findings of the Board and of its proposed continuing review procedures.

(b) Such assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by this part, and shall be filed in such form and manner as the Secretary may require.

§ 46.5 Types of assurances.

(a) General assurances. A general assurance describes the review and implementation procedures applicable to all DHEW-supported activities conducted by an institution regardless of the number, location, or types of its components or field activities. General assurances will be required from institutions having a significant number of concurrent DHEW-supported projects or activities involving human subjects.

(b) Special assurances. A special assurance will, as a rule, describe those review and implementation procedures applicable to a single activity or project. A special assurance will not be solicited or accepted from an institution which has on file with DHEW an approved general assurance.

and assurances.

General assurances shall be obtained in such form and manner as the Secretary may require. The institution must include, as part of its general assurance, implementing guidelines that specifically provide for:

(1) A statement of policies which will govern the institution in the discharge of its obligations for protecting the rights and welfare of subjects. This may include appropriate training codes or deliberations, or statement formulated by the institution itself. It is to be understood that no such principles supersede DHEW policy or applicable law.

(2) An Institutional Review Board or Board structure which will conduct initial and continuing reviews in accordance with the policy outlined in § 46.2. Such Board structure or Board shall meet the following requirements:

(1) The Board must be composed of not less than five persons with varying backgrounds to assure complete and adequate review of activities commonly conducted by the institution. The Board must be sufficiently qualified through the maturity, experience, and expertise of its members and diversity of its membership to insure respect for its advice and counsel for safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific activities, the Board must be able to ascertain the acceptability of applications and proposals in terms of institutional commitments and regulations, applicable law, standards of professional conduct and practice, and community attitudes. The Board must therefore include persons whose concerns are in these areas.

(2) The Board members shall be identified to DHEW by name; earned degrees, if any; position or occupation; representative capacity; and by other pertinent indications of experience such as board certification, licenses, etc., sufficient to describe each member's chief anticipated contributions to Board deliberations. Any employment or other relationship between each member and the institution shall be identified, i.e., full-time employee, part-time employee, member of governing panel or board, paid consultant, unpaid consultant. Changes in Board membership shall be reported to DHEW in such form and at such times as the Secretary may require.

(3) No member of a Board shall be involved in either the initial or continuing review of an activity in which he has a conflicting interest, except to provide information requested by the Board.

(4) No Board shall consist entirely of persons who are officers, employees, or agents, of, or are otherwise associated with the institution, apart from their membership on the Board.

(5) No Board shall consist entirely of members of a single professional group.

(6) The quorum of the Board shall be defined, but may in no event be less than a majority of the total membership duly convened to carry out the Board's re-

sponsibilities under the terms of the assurance.

(c) Procedures which the institution will follow in its initial and continuing review of applications, proposals, and activities.

(d) Procedures which the Board will follow: (1) to provide advice and counsel to acting directors and investigators with regard to the Board's actions; (2) to insure prompt reporting to the Board of proposed changes in an activity and anticipated problems involving risks to subjects or others, and (3) to insure that any such problems, including adverse actions to biologicals, drugs, radioisotope labeled drugs, or to medical devices, are promptly reported to DHEW.

(e) Procedures which the institution will follow to maintain an active and effective Board and to implement its recommendations.

§ 46.7 Minimum requirements for special assurances.

Special assurances shall be submitted in such form and manner as the Secretary may require. An acceptable special assurance shall:

(a) Identify the specific grant or contract involved by its full title; and b the name of the activity or project director, principal investigator, fellow, or other person immediately responsible for the conduct of the activity.

(b) Include a statement, executed by an appropriate institutional official, indicating that the institution has established an Institutional Review Board satisfying the requirements of § 46.6.

(c) Describe the makeup of the Board and the training, experience, and background of its members, as required by § 46.6(b)(2).

(d) Describe in general terms the risks to subjects that the Board recognizes as inherent in the activity, and justify its decision that these risks are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant the Board's decision to permit the subject to accept these risks.

(e) Describe the informed consent procedures to be used and attach documentation as required by § 46.10.

(f) Describe procedures which the Board will follow to insure prompt reporting to the Board of proposed changes in the activity and of any unanticipated problems, involving risks to subjects or others and to insure that any such problems, including adverse reactions to biologicals, drugs, radioisotope labeled drugs, or to medical devices are promptly reported to DHEW.

(g) Indicate at what time intervals the Board will meet to provide for continuing review. Such review must occur no less than annually.

(h) Be signed by the individual members of the Board and be endorsed by an appropriate institutional official.

§ 46.8 Evaluation and disposition of assurances.

(a) All assurances submitted in accordance with §§ 46.6 and 46.7 shall be

... by the Secretary... such officials and employees of DHEW and other officials or consultants engaged for this purpose as he determines to be appropriate. The Secretary's evaluation shall take into consideration... the proposed Institutional Review Board in the light of the institution's... and the types of subject populations likely to be involved, the appropriateness of the proposed initial and continuing review procedures in the light of the probable risks, and the size and complexity of the institution.

(b) On the basis of his evaluation of an assurance pursuant to paragraph (a) of this section, the Secretary shall (1) approve, (2) enter into negotiations to develop a more satisfactory assurance, or (3) disapprove. With respect to approved assurances, the Secretary may determine the period during which any particular assurance or class of assurances shall remain effective or otherwise condition or restrict his approval. With respect to negotiations, the Secretary may, pending completion of negotiations for a general assurance, require an institution otherwise eligible for such an assurance, to submit special assurances.

§ 46.9 Obligation to obtain informed consent; prohibition of exculpatory clauses.

Any institution proposing to place any subject at risk is obligated to obtain and document legally effective informed consent. No such informed consent, oral or written, obtained under an assurance provided pursuant to this part shall include any exculpatory language through which the subject is made to waive, or to appear to waive, any of his legal rights, including any release of the institution or its agents from liability for negligence.

§ 46.10 Documentation of informed consent.

The actual procedure utilized in obtaining legally effective informed consent and the basis for Institutional Review Board determinations that the procedures are adequate and appropriate shall be fully documented. The documentation of consent will employ one of the following three forms:

(a) Provision of a written consent document embodying all of the basic elements of informed consent. This may be read to the subject or to his legally authorized representative, but in any event he or his legally authorized representative must be given adequate opportunity to read it. This document is to be signed by the subject or his legally authorized representative. Sample copies of the consent form as approved by the Board are to be retained in its records.

(b) Provision of a "short form" written consent document indicating that the basic elements of informed consent have been presented orally to the subject or his legally authorized representative. Written summaries of what is to be said to the patient are to be approved by the Board. The short form is to be signed

by the subject or his legally authorized representative and by the institution with the subject's signature. A copy of the approved summary, annotated to show any additions, is to be signed by the persons actually obtaining the consent and by the Institutional Review Board. The consent form and of the summaries as approved by the Board are to be retained in its records.

(c) Modification of either of the primary procedures defined in paragraphs (a) and (b) of this section. Granting of permission to use modified procedures imposes additional responsibility upon the Board and the institution to establish: (1) that the risk to any subject is minimal, (2) that use of either of the primary procedures for obtaining informed consent would surely invalidate objectives of considerable immediate importance, and (3) that any reasonable alternative means for attaining these objectives would be less advantageous to the subjects. The Board's reasons for permitting the use of modified procedures must be individually and specifically documented in the minutes and in reports of Board actions to the files of the institution. All such modifications should be regularly reconsidered as a function of continuing review and as required for annual review, with documentation of reaffirmation, revision, or discontinuation, as appropriate.

§ 46.11 Submission and certification of applications and proposals, general assurances.

(a) *Timely review.* Any institution having an approved general assurance shall indicate in each application or proposal for support of activities covered by this part (or in a separate document submitted with such application or proposal) that it has on file with DHEW such an assurance. In addition, unless the Secretary otherwise provides, each such application or proposal must be given review and, when found to involve subjects at risk, approval, prior to submission to DHEW. In the event the Secretary provides for the performance of institutional review of an application or proposal after its submission to DHEW, processing of such application or proposal by DHEW will under no circumstances be completed until such institutional review and approval has been certified. Except where the institution determines that human subjects are not involved, the application or proposal should be appropriately certified in the spaces provided on forms, or one of the following certifications, as appropriate, should be typed on the lower or right hand margin of the page bearing the name of an official authorized to sign or execute applications or proposals for the institution.

Human Subjects: Reviewed, Not at Risk.

(Date)
Human Subjects: Reviewed, At Risk, Approved

(Date)

(b) *Appropriate and proposal not certified.* Applications and proposals not properly certified, or submitted to not involving human subjects and found by the operating agency to involve human subjects, will be returned to the institution concerned.

§ 46.12 Submission and certification of applications and proposals, special assurances.

(a) Except as provided in paragraph (b) of this section, institutions not having an approved general assurance shall submit in or with each application or proposal for support of activities covered by this part a separate special assurance and certification of its review and approval.

(b) If the Secretary so provides, the assurance which must be submitted in or with the application or proposal under paragraph (a) of this section need satisfy only the requirements of § 46.7(a) and § 46.7(b) of this part. Under such circumstances, processing of such application or proposal by DHEW will not be completed until a further assurance satisfying the remaining requirements of § 46.7 has been submitted to DHEW.

(c) An assurance and certification prepared in accordance with this part and approved by DHEW shall be considered to have met the requirement for certification for the initial grant or contract period concerned. If the terms of the grant or contract recommend additional support periods, each application or proposal for continuation or renewal of support must satisfy the requirements of this section or § 46.11 whichever is applicable at the time of its submission.

§ 46.13 Applications and proposals lacking definite plans for involvement of human subjects.

Certain types of applications or proposals are submitted with the knowledge that subjects are to be involved within the support period, but definite plans for this involvement would not normally be set forth in the application or proposal. These include such activities as (a) institutional type grants where selection of projects is the responsibility of the institution, (b) training grants where training projects remain to be selected, and (c) research, pilot, or developmental studies in which involvement depends upon such things as the completion of instruments, or of prior animal studies, or upon the purification of compounds. Such applications or proposals shall be reviewed and certified in the same manner as more definitive applications or proposals. The initial certification indicates institutional approval of the applications or proposals as submitted, and commits the institution to later review of the plans when completed. Such later review and certification to DHEW should be completed prior to the beginning of the budget period during which actual involvement of human subjects is to begin. Review and certification to DHEW must in any event be completed prior to involvement of human subjects.

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§ 46.14 Applications and proposals submitted with the intent of not involving human subjects

If an application or proposal does not anticipate involvement of human subjects, no certification should be included with the initial submission of the application or proposal. In those instances, however, when later it becomes appropriate to use all or part of awarded funds for one or more activities which will involve subjects, each such activity shall be reviewed and approved in accordance with the assurance of the institution prior to the involvement of subjects. In addition, no such activity shall be undertaken until the institution has submitted to DHEW: (a) a certification that the activity has been reviewed and approved in accordance with this part, and (b) a detailed description of the proposed activity (including any protocol or similar document). Also, where support is provided by project grants or contracts, subjects shall not be involved prior to certification and institutional receipt of DHEW approval and, in the case of contracts, prior to negotiation and approval of an amended contract description of work.

§ 46.15 Evaluation and disposition of applications and proposals

(a) Notwithstanding any prior review, approval, and certification by the institution all applications or proposals involving human subjects at risk submitted to DHEW shall be evaluated by the Secretary for compliance with this part through such officers and employees of the Department and such experts or consultants engaged for this purpose as he determines to be appropriate. This evaluation may take into account, among other pertinent factors, the apparent risks to the subjects, the adequacy of protection against these risks, the potential benefits of the activity to the subjects and to others, and the importance of the knowledge to be gained.

(b) Disposition. On the basis of his evaluation of an application or proposal pursuant to paragraph (a) of this section and subject to such approval or recommendation by or consultation with appropriate councils, committees, or other bodies as may be required by law, the Secretary shall (1) approve, (2) defer for further evaluation, or (3) disapprove support of the proposed activity in whole or in part. With respect to any approved grant or contract, the Secretary may impose conditions, including restrictions on the use of certain procedures, or certain subject groups, or requiring use of specified safeguards or informed consent procedures when in his judgment such conditions are necessary for the protection of human subjects.

§ 46.16 Cooperative activities

Cooperative activities are those which involve institutions in addition to the grantee or prime contractor (such as a contractor under a grantee or a subcontractor under a prime contractor). If, in such instances, the grantee or prime contractor obtains access to all or some of

the subjects involved through one or more cooperating institutions, the basic DHEW policy applies and the grantee or prime contractor remains responsible for safeguarding the rights and welfare of the subjects.

(a) Institution with approved general assurance. Initial and continuing review by the institution may be carried out by one or a combination of procedures:

(1) Cooperating institution with approved general assurance. When the cooperating institution has on file with DHEW an approved general assurance, the grantee or contractor may, in addition to its own review, request the cooperating institution to conduct an independent review and to report its recommendations on those aspects of the activity that concern individuals for whom the cooperating institution has responsibility under its own assurance to the grantee's or contractor's Institutional Review Board. The grantee or contractor may, at its discretion, concur with or further restrict the recommendations of the cooperating institution. It is the responsibility of the grantee or contractor to maintain communication with the Boards of the cooperating institution. However, the cooperating institution shall promptly notify the grantee or contracting institution whenever the cooperating institution finds the conduct of the project or activity within its purview unsatisfactory.

(2) Cooperating institution with no approved general assurance. When the cooperating institution does not have an approved general assurance on file with DHEW, the DHEW may require the submission of a general or special assurance which, if approved, will permit the grantee or contractor to follow the procedure outlined in the preceding subparagraph.

(3) Interinstitutional joint review. The grantee or contracting institution may wish to develop an agreement with cooperating institutions to provide for an Institutional Review Board with representatives from cooperating institutions. Representatives of cooperating institutions may be appointed as ad hoc members of the grantee or contracting institution's existing Institutional Review Board or, if cooperation is on a frequent or continuing basis as between a medical school and a group of affiliated hospitals, appointments for extended periods may be made. All such cooperative arrangements must be approved by DHEW as part of a general assurance, or as an amendment to a general assurance.

(b) Institutions with special assurances. While responsibility for initial and continuing review necessarily lies with the grantee or contracting institution, DHEW may also require approved assurances from those cooperating institutions having immediate responsibility for subjects.

If the cooperating institution has on file with DHEW an approved general assurance, the grantee or contractor shall request the cooperating institution to conduct its own independent review of those aspects of the project or activity

which will involve human subjects for which it has responsibility. Such a request shall be in writing and should provide for direct notification of the grantee or contractor's Institutional Review Board in the event that the cooperating institution's Board finds the conduct of the activity to be unsatisfactory. If the cooperating institution does not have an approved general assurance on file with DHEW, it must submit to DHEW a general or special assurance which is determined by DHEW to comply with the provisions of this part.

§ 46.17 Investigational new drug 30-day delay requirement

Where an institution is required to prepare or to submit a certification under §§ 46.11, 46.12, 46.13, or 46.14 and the application or proposal involves an investigational new drug within the meaning of The Food, Drug, and Cosmetic Act, the drug shall be identified in the certification together with a statement that the 30-day delay required by 21 CFR 312.1(a)(2) has elapsed and the Food and Drug Administration has not, prior to expiration of such 30-day interval, requested that the sponsor continue to withhold or to restrict use of the drug in human subjects; or that the Food and Drug Administration has waived the 30-day delay requirement; provided, however, that in those cases in which the 30-day delay interval has neither expired nor been waived, a statement shall be forwarded to DHEW upon such expiration or upon receipt of a waiver. No certification shall be considered acceptable until such statement has been received.

§ 46.18 Institution's executive responsibility

Specific executive functions to be conducted by the institution include policy development and promulgation and continuing indoctrination of personnel. Appropriate administrative assistance and support shall be provided for the Board's functions. Implementation of the Board's recommendations through appropriate administrative action and followup is a condition of DHEW approval of an assurance. Board approvals, favorable actions, and recommendations are subject to review and to disapproval or further restriction by the institution officials. Board disapprovals, restrictions, or conditions cannot be rescinded or removed except by action of a Board described in the assurance approved by DHEW.

§ 46.19 Institution's records; confidentiality

(a) Copies of all documents presented or required for initial and continuing review by the Institutional Review Board, such as Board minutes, records of subject's consent, transmittals on actions, instructions, and conditions resulting from Board deliberations addressed to the activity director, are to be retained by the institution, subject to the terms and conditions of grant and contract awards.

(b) Except as otherwise provided by law information in the records or possession of an institution acquired in con-

knowledge of the Animal and Plant Health Inspection Service.

Therefore, pursuant to the authority conferred upon the Deputy Administrator, Veterinary Services, Animal and Plant Health Inspection Service by § 971 of the regulations concerning overtime services pertaining to, and amended by 9 CFR 972 (1976 ed.), as amended January 21, 1976 (41 FR 2074), April 16, 1976 (41 FR 16140), and July 23, 1976 (41 FR 27519), prescribing the commuted traveltime that shall be included in each period of overtime or holiday duty, are hereby amended by adding to or deleting from the respective lists therein as follows:

§ 972 Administrative instructions prescribing commuted traveltime.

WITHIN METROPOLITAN AREA

ONE HOUR

Add:

Los Angeles, California and Los Angeles Airport (served from Lawndale, California).

Add:

Madison, Wisconsin.

Delete:

Mobile, Alabama.

OUTSIDE METROPOLITAN AREA

TWO HOURS

Add:

Vernon, California (served from Lawndale, California).

Add:

Los Angeles Harbor San Pedro, California; including Long Beach, Wilmington, and Terminal Island (served from Lawndale, California).

Add:

Middleton, Wisconsin (served from Madison, Wisconsin).

Add:

Sauk City, Wisconsin (served from Madison, Wisconsin).

Add:

Watertown, Wisconsin (served from Madison, Wisconsin).

THREE HOURS

Add:

Chilton, Wisconsin (served from Markesan, Wisconsin).

Add:

Hartford, Wisconsin (served from Markesan, Wisconsin).

Add:

Mineral Point, Wisconsin (served from Madison and Waubesa, Wisconsin).

Add:

Monroe, Wisconsin (served from Madison, Wisconsin).

Add:

Ontario, California (served from Lawndale, California).

Add:

Waterford, Wisconsin (served from Markesan, Wisconsin).

FOUR HOURS

Add:

Lawrence Air Force Plant, California (served from Lawndale, California).

Add:

Hartford, Wisconsin (served from Madison, Wisconsin).

Add:

Escondido, California (served from Lawndale, California).

Add:

Milwaukee, Wisconsin (served from Madison, Wisconsin).

Add:

Newport Beach, California (served from Lawndale, California).

Add:

Sheboygan Falls, Wisconsin (served from Markesan, Wisconsin).

Delete:

Juda, Wisconsin (served from Madison, Wisconsin).

Delete:

Sheboygan Falls, Wisconsin (served from Milwaukee and Ripon, Wisconsin).

FIVE HOURS

Add:

March Field, California (served from Lawndale, California).

Delete:

Juda, Wisconsin (served from Sauk City, Wisconsin).

SIX HOURS

Add:

Antelope Wells, New Mexico (served from Roswell and Socorro, New Mexico).

Add:

Chilton, Wisconsin (served from Madison, Wisconsin).

Add:

Columbus, New Mexico (served from Roswell and Socorro, New Mexico).

Add:

San Luis Obispo, California (served from Lawndale, California).

TEN HOURS

Delete:

Barron, Wisconsin (served from Sauk City, Wisconsin).

(62 Stat. 561; 7 U.S.C. 2260.)

Effective date. The foregoing amendments shall become effective November 30, 1976.

It is to the benefit of the public that these instructions be made effective at the earliest practicable date. It does not appear that public participation in this rulemaking proceeding would make additional relevant information available to the Department.

Accordingly, pursuant to 5 U.S.C. 553 it is found upon good cause that notice and public procedure on these instructions are impracticable, unnecessary, and contrary to the public interest and

good cause is found for making them effective less than 30 days after publication in the FEDERAL REGISTER.

Done at Washington, D.C., this 26th day of November 1976.

NOTE—The Animal and Plant Health Inspection Service has determined that this document does not contain a major portion requiring preparation of an Information Statement under Executive Order 11735 and OMB Circular A-107.

PIERRE A. CHALOFF,
Acting Deputy Administrator,
Veterinary Services.

1 FR Doc 76-32184 Filed 11-27-76; 8:43 am

Title 10—Energy
CHAPTER III—ENERGY RESEARCH AND
DEVELOPMENT ADMINISTRATION
PART 745—PROTECTION OF HUMAN
SUBJECTS

Adoption of Final Regulations

On August 17, 1976, a document entitled, "Protection of Human Subjects Proposed Regulations," (10 CFR Part 705—now 10 CFR Part 745) was published in the FEDERAL REGISTER (41 FR 34778). These proposed regulations have been altered in §§ 705.6, 705.10, 705.705.16, and 705.19 (now 745.6, 745.745.11, 745.16, and 745.19) as a result of comments received.

The proposed regulations intend to ensure the rights and welfare of human subjects in research activities supported by ERDA. Adequate review and approval of activities involving human subjects, primarily the responsibility of the institution which receives or is accountable to ERDA for the funds awarded.

Although ERDA intended to substantially duplicate the policies and procedures adopted by HEW (40 FR 119 March 13, 1975), comments received in response to the proposed regulations identified differences that needed to be resolved between the two sets of regulations. The most significant issues were the membership requirements of the institutional review board (745.6) and retention of records (745.19). To eliminate the problems caused by these differences, these and other ERDA regulations have been altered to conform to the HEW regulations.

Accordingly, with the incorporated changes, the proposed regulations adopted as set forth below.

Effective date: November 30, 1976.

JAMES L. LIVERMAN,
Assistant Administrator
for Environment and Safety

The proposed regulations are adopted as follows:

Sec.	Applicability.
745.1	Applicability.
745.2	Policy.
745.3	Definitions.
745.4	Submission of assurances.
745.5	Types of assurances.
745.6	Minimum requirements for general assurances.
745.7	Minimum requirements for special assurances.

- 745.6 Evaluation and disposition of assurances.
- 745.9 Obligation to obtain informed consent; prohibition of a subpoena clause.
- 745.10 Documentation of informed consent.
- 745.11 Submission and certification of applications and proposals—general assurances.
- 745.12 Submission and certification of applications and proposals—special assurances.
- 745.13 Applications and proposals lacking definite plans for involvement of human subjects.
- 745.14 Applications and proposals submitted with the intent of not involving human subjects.
- 745.15 Evaluation and disposition of applications and proposals.
- 745.16 Cooperative activities.
- 745.17 Investigation; new drug 30-day delay requirement.
- 745.18 Institution's executive responsibility.
- 745.19 Institution's records; confidentiality.
- 745.20 Reports.
- 745.21 Early termination of awards; evaluation of subsequent applications proposals.
- 745.22 Conditions.

Authority: Sec. 105(a) Energy Reorganization Act of 1974, Pub. L. 93-492.

§ 745.1 Applicability.

(a) The regulations in this part are applicable to all Energy Research and Development Administration (ERDA) agreements including, but not limited to, grants and contracts supporting research, development, and related activities within the United States and its territories in which human subjects are involved.

(b) For agreements supporting activities outside the United States and its territories in which human subjects are involved, the requirements of this part shall apply to the maximum extent practicable as determined by the Administrator on a case-by-case basis, taking into account the relevant laws and practices of the foreign nation in which the activity will be conducted.

(c) The Administrator may, from time to time, determine in advance whether specific programs, methods, or procedures to which this part is applicable place subjects at risk, as defined in § 745.3(b). Such determinations will be published as notices in the FEDERAL REGISTER and will be included in an appendix to this part.

§ 745.2 Policy.

(a) Safeguarding the rights and welfare of subjects at risk in activities supported under ERDA agreements is primarily the responsibility of the institution which receives, or is accountable to ERDA for, the funds awarded for the support of the activity. In order to provide for the adequate discharge of this institutional responsibility, it is the policy of ERDA that no activity involving human subjects within the United States and its territories to be supported by ERDA agreements shall be undertaken unless an Institutional Review Board has reviewed and approved such activity, and the institution has submitted to ERDA a certification of such review and approval,

in accordance with the requirements of this part.

(b) This section shall determine whether the subjects will be placed at risk, and if not, it will be reviewed whether:

(1) the risks to the subject are so outweighed by the sum of the benefit to the subject and the importance of the knowledge to be gained as to warrant a decision to allow the subject to accept these risks;

(2) the rights and welfare of any such subjects will be adequately protected;

(3) legally effective informed consent will be obtained by adequate and appropriate methods in accordance with the provisions of this part; and

(4) the conduct of the activity will be reviewed at timely intervals.

(c) No agreement involving human subjects at risk shall be awarded to an individual unless he is affiliated with or sponsored by an institution which can and does assume responsibility for the subjects involved.

§ 745.3 Definitions.

(a) "Institution" means any public or private institution or agency (including Federal, State, and local government agencies).

(b) "Subject at risk" means any individual who may be exposed to the possibility of injury, including physical, psychological, or social injury, as a consequence of participation as a subject in any research, development, or related activity which departs from the application of those established and accepted methods necessary to meet his needs, or which increases the ordinary risks of daily life, including the recognized risks inherent in a chosen occupation or field of service.

(c) "Informed consent" means the knowing consent of an individual or his legally authorized representative so situated as to be able to exercise free power of choice without undue inducement or any element of force, fraud, deceit, duress, or other form of constraint or coercion. The basic elements of information necessary to such consent include:

(1) a fair explanation of the procedures to be followed, and their purposes, including identification of any procedures which are experimental;

(2) a description of any attendant discomforts and risks reasonably to be expected;

(3) a description of any benefits reasonably to be expected;

(4) a disclosure of any appropriate alternative procedures that might be advantageous for the subject;

(5) an offer to answer any inquiries concerning the procedures; and

(6) an instruction that the person is free to withdraw his consent and to discontinue participation in the project or activity at any time without prejudice to the subject.

(d) "ERDA" means the Energy Research and Development Administration.

(e) "Administrator" means the Administrator of ERDA or any other officer or employee of ERDA to whom authority has been delegated.

(f) "Agreement" means a grant, contract, cooperative agreement, or any other instrument under which ERDA provides funds, or other resources for projects or efforts involving human subjects.

(g) "Approved assurance" means a document that fulfills the requirement of this part and is approved by the Administrator.

(h) "Certification" means the official institutional notification to ERDA in accordance with the requirements of this part that a project or activity involving human subjects at risk has been reviewed and approved by the institution in accordance with the "approved assurance" on file at ERDA.

(i) "Legally authorized representative" means an individual or judicial, or other body authorized under applicable law to consent on behalf of a prospective subject to such subject's participation in the particular activity or procedure.

§ 745.4 Submission of assurances.

(a) Recipients or prospective recipients of ERDA support under any agreement involving subjects at risk shall provide written assurance acceptable to ERDA that they will comply with ERDA policy as set forth in this part. Each assurance shall embody (1) A statement of compliance with ERDA requirements for initial and continuing Institutional Review Board review of the supported activities; and (2) A set of implementing guidelines, including identification of the Board and a description of its review procedures; or, in the case of special assurance concerned with single activities or projects, a report of initial findings of the Board and of its proposed continuing review procedures.

(b) Such assurance shall be executed by an individual authorized to act for the institution and to assume on behalf of the institution the obligations imposed by this part, and shall be filed in such form and manner as the Administrator may require.

§ 745.5 Types of assurances.

(a) *General assurances.* A general assurance describes the review and implementation procedures applicable to all ERDA-supported activities conducted by an institution, regardless of the number, location, or types of its components or field activities. General assurances will be required from institutions having a significant number of concurrent ERDA-supported projects or activities involving human subjects.

(b) *Special assurances.* A special assurance will, as a rule, describe those review and implementation procedures applicable to a single activity or project. A special assurance will not be solicited or accepted from an institution which has on file with ERDA an approved general assurance.

§ 745.6 Minimum requirements for general assurances.

General assurances shall be submitted in such form and manner as the Administrator may require. The institution must include, as part of its general as-

1081087

assurance, implementing guidelines that specifically provide for:

(a) A statement of principles which will govern the institution in the discharge of its responsibilities for protecting the rights and welfare of subjects. This may include appropriate existing codes or declarations, or statements formulated by the institution itself. It is to be understood that no such principles supersede ERDA policy or applicable law.

(b) An Institutional Review Board or Board structure which will conduct initial and continuing reviews in accordance with the policy outlined in § 745.2. Such a Board or Board structure shall meet the following requirements:

(1) The Board must be composed of not less than five persons with varying backgrounds to assure complete and adequate review of activities commonly conducted by the institution. The Board must be sufficiently qualified through the maturity, experience, and expertise of its members, and diversity of its membership, to insure respect for its advice and counsel for safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific activities, the Board must be able to ascertain the acceptability of applications and proposals in terms of institutional commitments and regulations, applicable law, standards of professional conduct and practice, and community attitudes. The Board must, therefore, include persons whose concerns are in these areas.

(2) The Board members shall be identified to ERDA by name; earned degrees, if any; position or occupation; representative capacity; and by other pertinent indications of experience, such as board certification, licenses, etc., sufficient to describe each member's chief anticipated contributions to Board deliberations. Any employment or other relationship between each member and the institution shall be identified, i.e., full-time employee, part-time employee, member of governing panel or board, paid consultant, or unpaid consultant. Changes in Board membership shall be reported to ERDA in such form and at such times as the Administrator may require.

(3) No member of a Board shall be involved in either the initial or continuing review of an activity in which he has a conflicting interest, except to provide information requested by the Board.

(4) No Board shall consist entirely of persons who are officers, employees, or agents of, or are otherwise associated with, the institution, apart from their membership on the Board.

(5) No Board shall consist entirely of members of a single professional group.

(6) The quorum of the Board shall be defined, but may in no event be less than a majority of the total membership duly convened to carry out the Board's responsibilities under the terms of the assurance.

(c) Procedures which the institution will follow in its initial and continuing review of applications, proposals, and activities.

(d) Procedures which the Board will follow: (1) To provide advice and counsel to activity directors and investigators with regard to the Board's actions, (2) To insure prompt reporting to the Board of proposed changes in an activity, and of unanticipated problems involving risks to subjects or others, and (3) To insure that any such problems, including adverse reactions to biologicals, drugs, radioisotope-labelled drugs, or to medical devices, are promptly reported to ERDA.

(e) Procedures which the institution will follow to maintain an active and effective Board and to implement its recommendations.

§ 745.7 Minimum requirements for special assurances.

Special assurances shall be submitted in such form and manner as the Administrator may require. An acceptable special assurance shall:

(a) Identify the specific agreement involved by its full title and by the name of the activity or project director, principal investigator, fellow, or other person immediately responsible for the conduct of the activity.

(b) Include a statement, executed by an appropriate institutional official, indicating that the institution has established an Institutional Review Board satisfying the requirements of § 745.6(b).

(c) Describe the makeup of the Board and the training, experience, and background of its members as required by § 745.6(b)(2).

(d) Describe, in general terms, the risks to subjects that the Board recognizes as inherent in the activity, and justify its decision that these risks are so outweighed by the sum of the benefit to the subject, and the importance of the knowledge to be gained, as to warrant the Board's decision to permit the subject to accept these risks.

(e) Describe the informed consent procedures to be used, and attach documentation as required by § 745.10.

(f) Describe procedures which the Board will follow to insure prompt reporting to the Board of proposed changes in the activity, and of any unanticipated problems involving risks to subjects or others, to insure that any such problems, including adverse reactions to biologicals, drugs, radioisotope-labelled drugs, or to medical devices, are promptly reported to ERDA.

(g) Indicate at what time intervals the Board will meet to provide for continuing review. Such review must occur no less than annually.

(h) Be signed by the individual members of the Board and be endorsed by an appropriate institutional official.

§ 745.8 Evaluation and disposition of assurances.

(a) All assurances submitted in accordance with §§ 745.6 and 745.7 shall be evaluated by the Administrator through such officers and employees of ERDA as he determines to be appropriate. The Administrator's evaluation shall take into consideration, among other pertinent factors, the adequacy of the proposed In-

stitutional Review Board in light of anticipated scope of the applicant institution's activities and the types of subject populations likely to be involved; the appropriateness of the proposed initial and continuing review procedures in light of the probable risks, and size and complexity of the institution.

(b) On the basis of his evaluation, an assurance pursuant to paragraph (a) of this section, the Administrator shall: (1) Approve, (2) Enter into negotiations to develop a more satisfactory assurance, or (3) Disapprove. With respect to approved assurances, the Administrator may determine the period during which any particular assurance or class of assurances shall remain effective or otherwise condition or restrict his approval. With respect to negotiations, the Administrator may, pending completion of negotiations for a general assurance, require an institution, otherwise eligible for such an assurance, to submit special assurances.

§ 745.9 Obligation to obtain informed consent; prohibition of exculpatory clauses.

Any institution proposing to place a subject at risk is obligated to obtain a document legally effective informed consent. No such informed consent, oral or written, obtained under an assurance provided pursuant to this part shall include any exculpatory language through which the subject is made to waive, or appear to waive, any of his legal rights, including any release of the institution or its agents from liability for negligence.

§ 745.10 Documentation of informed consent.

The actual procedure utilized in obtaining legally effective informed consent and the basis for Institutional Review Board determinations that the procedures are adequate and appropriate shall be fully documented. The documentation of consent will employ one of the following three forms:

(a) Provision of a written consent document embodying all of the basic elements of informed consent. This may be read to the subject or to his legally authorized representative, but in any event he or his legally authorized representative must be given adequate opportunity to read it. This document is to be signed by the subject or his legally authorized representative. Sample copies of the consent form, as approved by the Board, to be retained in its records.

(b) Provision of a "short form" written consent document indicating that the basic elements of informed consent have been presented orally to the subject or his legally authorized representative. Written summaries of what is to be presented to the subject are to be approved by the Board. The short form is to be signed by the subject or his legally authorized representative and by an auditor who witnessed the oral presentation and to the subject's signature. A copy of the approved summary, annotated to show any additions, is to be signed by the persons officiating in obtaining the consent and by the auditor. Sample copies of the con-

form and of the summaries as approved by the Board are to be retained in its records.

(c) Modification of either of the primary procedures outlined in paragraphs (a) and (b) of this section. Granting of permission to use modified procedures imposes additional responsibility upon the Board and the institution to establish: (1) That the risk to the subject is minimal, (2) That use of either of the primary procedures for obtaining informed consent would surely invalidate objectives of considerable immediate importance, and (3) That any reasonable alternative means for attaining these objectives would be less advantageous to the subjects. The Board's reasons for permitting the use of modified procedures must be individually and specifically documented in the minutes and in reports and Board actions to the files of the institution. All such modifications should be regularly reconsidered as a function of continuing review and as required for annual review, with documentation of reaffirmation, revision, or discontinuation, as appropriate.

§ 745.11 Submission and certification of applications and proposals—general assurances.

(a) *Timely review.* Any institution having an approved general assurance shall indicate in each application or proposal for support of activities covered by this part (or in a separate document submitted with such application or proposal) that it has on file with ERDA such an assurance. In addition, unless the Administrator otherwise provides, each such application or proposal must be given review and, when found to involve subjects at risk, approval, prior to submission, or a written assurance must be submitted that a review is planned or in progress and that the results of the review will be received by the administrator no later than 60 days after the date of submission to ERDA. In the event the Administrator provides for the performance of institutional review of an application or proposal after its submission to ERDA, processing of such application or proposal by ERDA will under no circumstances be completed until such institutional review and approval has been certified. Except where the institution determines that human subjects are not involved, the application or proposal should be appropriately certified in the spaces provided on forms, or one of the following certifications, as appropriate, should be typed on the lower or right-hand margin of the page bearing the name of an official authorized to sign or execute applications or proposals for the institution.

Human Subjects: Reviewed, Not at Risk

(Date)

Human Subjects: Reviewed, at Risk, Approved.

(Date)

(b) *Applications and proposals not certified.* Applications and proposals not

properly certified, or submitted as not involving human subjects and found by the operating agency to involve human subjects, will be returned to the institution concerned.

§ 745.12 Submission and certification of applications and proposals, special assurances.

(a) Except as provided in paragraph (b) of this section, institutions not having an approved general assurance shall submit in or with each application or proposal for support of activities covered by this part a separate special assurance and certification of its review and approval.

(b) If the Administrator so provides, the assurance which must be submitted in or with the application or proposal under paragraph (a) of this section need satisfy only the requirements of § 745.7(a) and (b) of this Part. Under such circumstances, processing of such application or proposal by ERDA will not be completed until a further assurance satisfying the remaining requirements of § 745.7 has been submitted to ERDA.

(c) An assurance and certification prepared in accordance with this part and approved by ERDA shall be considered to have met the requirement for certification for the initial agreement period concerned. If the terms of the agreement recommend additional support periods, each application or proposal for continuation or renewal of support must satisfy the requirements of this section or 745.11, whichever is applicable at the time of its submission.

§ 745.13 Applications and proposals lacking definite plans for involvement of human subjects.

Certain types of applications or proposals are submitted with the knowledge that subjects are to be involved within the support period, but definite plans for this involvement would not normally be set forth in the application or proposal. These include such activities as (a) Institutional-type grants where selection of projects is the responsibility of the institution, (b) Training grants where training projects remain to be selected, and (c) Research, pilot, or developmental studies in which involvement depends upon such things as the completion of instruments, or of prior animal studies, or upon the purification of compounds. Such applications or proposals shall be reviewed and certified in the same manner as more definitive applications or proposals. The initial certification indicates institutional approval of the applications or proposals as submitted and commits the institution to later review of the plans when completed. Such later review and certification to ERDA should be completed prior to the beginning of the budget period during which actual involvement of human subjects is to begin. Review and certification to ERDA must in any event be completed prior to involvement of human subjects.

§ 745.14 Applications and proposals submitted with the intent of not involving human subjects.

If an application or proposal does not anticipate involving or intend to involve human subjects, no certification should be included with the initial submission of the application or proposal. In those instances, however, when later it becomes appropriate to use all or part of awarded funds for one or more activities which will involve subjects, each such activity shall be reviewed and approved in accordance with the assurance of the institution prior to the involvement of subjects. In addition, no such activity shall be undertaken until the institution has submitted to ERDA: (a) A certification that the activity has been reviewed and approved in accordance with this part, and (b) A detailed description of the proposed activity (including any protocol, revised statement of work or similar document). Also, where support is provided by project grants or contracts, subjects shall not be involved prior to certification and institutional receipt of ERDA approval and, in the case of contracts, prior to negotiation and formal amendment of the contract statement of work.

§ 745.15 Evaluation and disposition of applications and proposals.

(a) Notwithstanding any prior review, approval, and certification by the institution, all applications or proposals submitted to ERDA involving human subjects at risk shall be evaluated by the Administrator for compliance with this part through such officers and employees of ERDA as he determines to be appropriate. This evaluation may take into account, among other pertinent factors, the apparent risks to the subjects, the adequacy of protection against these risks, the potential benefits of the activity to the subjects and to others, and the importance of the knowledge to be gained.

(b) *Disposition.* On the basis of his evaluation of an application or proposal, pursuant to paragraph (a) of this section, and subject to such approval or recommendation by or consultation with appropriate councils, committees, or other bodies as may be required by law, the Administrator shall (1) Approve, (2) Defer for further evaluation, or (3) Disapprove support of the proposed activity in whole or in part. With respect to any grant or contract award or other agreement, the Administrator may impose conditions, including restrictions on the use of certain procedures or certain subject groups, or requiring use of specified safeguards or informed consent procedures when in his judgment such conditions are necessary for the protection of human subjects.

§ 745.16 Cooperative activities.

Cooperative activities are those which involve institutions in addition to the institution having an agreement with ERDA (herein referred to as, though not limited to, a grantee or prime contractor). Examples of cooperative activities are those of a contractor under a grantee or of a subcontractor under a

1081089

prime contractor. If, in such instances, the grantee or prime contractor obtains access to all or some of the subjects involved through one or more cooperating institutions, the basic ERDA policy applies and the grantee or prime contractor remains responsible for safeguarding the right and welfare of the subjects.

(a) *Institutions with approved general assurances.* Initial and continuing review by the institution may be carried out by one or a combination of procedures:

(1) *Cooperating institution with approved general assurance.* When the cooperating institution has on file with ERDA an approved general assurance, the grantee or prime contractor may, in addition to its own review, request the cooperating institution to conduct an independent review, and to report its recommendations on those aspects of the activity that concern individuals for whom the cooperating institution has responsibility under its own assurance to the grantee's or prime contractor's Institutional Review Board. The grantee or prime contractor may, at its discretion, concur with or further restrict the recommendations of the cooperating institution. It is the responsibility of the grantee or prime contractor to maintain communication with the Boards of the cooperating institution. However, the cooperating institution shall promptly notify the grantee or contracting institution whenever the cooperating institution finds the conduct of the project or activity within its purview to be unsatisfactory.

(2) *Cooperating institution with no approved general assurance.* When the cooperating institution does not have an approved general assurance on file with ERDA, ERDA may require the submission of a general or special assurance which, if approved, will permit the grantee or prime contractor to follow the procedure outlined in the preceding subparagraph.

(3) *Interinstitutional joint review.* The grantee or prime contracting institution may wish to develop an agreement with cooperating institutions to provide for an Institutional Review Board with representatives from cooperating institutions. Representatives of cooperating institutions may be appointed as ad hoc members of the grantee or contracting institution's existing Institutional Review Board or, if cooperating is on a frequent or continuing basis, as between a medical school and a group of affiliated hospitals, appointments for extended periods may be made. All such cooperative arrangements must be approved by ERDA as part of a general assurance, or as an amendment to a general assurance.

(b) *Institutions with special assurances.* While responsibility for initial and continuing review necessarily lies with the grantee or prime contracting institution, ERDA may also require approved assurance from those cooperating institutions having immediate responsibility for subjects. If the cooperating institution has on file with ERDA an approved general assurance, the grantee or prime

contractor shall request the cooperating institution to conduct its own independent review of those aspects of the project or activity which will involve human subjects for which it has responsibility. Such a request shall be in writing and shall provide for direct notification of the grantee or prime contractor's Institutional Review Board in the event that the cooperating institution finds the conduct of the activity to be unsatisfactory. If the cooperating institution does not have an approved general assurance on file with ERDA, it must submit to ERDA a general or special assurance which is determined by ERDA to comply with the provisions of this part.

§ 745.17 Investigational new drug 30-day delay requirement.

Where an institution is required to prepare or to submit a certification under §§ 745.11, 745.12, 745.13, or 745.14, and the application or proposal involves an investigational new drug within the meaning of The Food, Drug, and Cosmetic Act, the drug shall be identified in the certification, together with a statement that the 30-day delay required by 21 CFR 312.1(a)(2) has elapsed and the Food and Drug Administration has not, prior to expiration of such 30-day interval, requested that the sponsor continue to withhold or to restrict use of the drug in human subjects; or that the Food and Drug Administration has waived the 30-day delay requirement, provided, however, that in those cases in which the 30-day delay interval has neither expired nor been waived, a statement shall be forwarded to ERDA upon such expiration, or upon receipt of a waiver. No certification shall be considered acceptable until such statement has been received.

§ 745.18 Institution's executive responsibility.

Specific executive functions to be conducted by the institution include policy development and promulgation and continuing indoctrination of personnel. Appropriate administrative assistance and support shall be provided for the Board's functions. Implementation of the Board's recommendations through appropriate administrative action and follow-up is a condition of ERDA approval of an assurance. Board approvals, favorable actions, and recommendations are subject to review and to disapproval or further restriction by the institution officials. Board disapprovals, restrictions, or conditions cannot be rescinded or removed except by action of a Board described in the assurance approved by ERDA.

§ 745.19 Institution's records: confidentiality.

(a) Copies of all documents presented, or required for initial and continuing review by the Institutional Review Board, and documents such as Board minutes, records of subject's consent, transmittals on actions, instructions, and conditions resulting from Board deliberations addressed to the activity director, are to be retained by the institution permanently unless permission is obtained from the Administrator to destroy specific records.

(b) Except as otherwise provided, law, information in the records or possession of an institution acquired in connection with an activity covered by this part, which information refers to or is identifiable with a particular subject, may not be divulged except:

(1) with the consent of the subject or his legally authorized representative;

(2) as may be necessary for the administrator to carry out his responsibilities under this part.

§ 745.20 Reports.

Each institution with an approved assurance shall provide the Administrator with such reports and other information as the Administrator may, from time to time, prescribe.

§ 745.21 Early termination of award evaluation of subsequent applications and proposals.

(a) If, in the judgment of the Administrator, an institution has failed materially to comply with the terms of policy with respect to a particular ERDA agreement, he may require that agreement be terminated or suspended in the manner prescribed in applicable regulations.

(b) In evaluating applications or proposals for support of activities covered by this part, the Administrator may take into account, in addition to all other eligibility requirements and program terms, such factors as: (1) Whether applicant or offeror has been subject to a termination or suspension under paragraph (a) of this section, (2) Whether the applicant, offeror, or the person who would direct the scientific and technical aspects of an activity has, in the judgment of the Administrator, failed materially to discharge his, her, or its responsibility for the protection of the health and welfare of subjects in his, her, or their care (whether or not ERDA funds are involved), and (3) Whether, where deficiencies have existed in carrying out such responsibility, adequate steps have been taken to eliminate these deficiencies.

§ 745.22 Conditions.

The Administrator may, with respect to any agreement or any class of agreements, impose additional conditions, to or at the time of any award of his judgment such conditions are necessary for the protection of human subjects.

[FR Doc 75-30154 Filed 11-20-70; 8:45

Title 12—Banks and Banking

CHAPTER I—COMPTROLLER OF THE TREASURY, DEPARTMENT OF THE TREASURY

PART 4—DESCRIPTION OF OFFICE PROCEDURES, PUBLIC INFORMATION

Revision of List of Forms Currently

This amendment is issued under authority of the National Bank Act, U.S.C. 1 et seq., pursuant to the request of 5 U.S.C. 552 that each agency publish in the Federal Register descriptions of agency forms and instructions which are available to and which are obtained by the public. The amend-

CV's - ORAU/ORNL Committee on Human Studies

10/14/76

Name: Gould A. Andrews
 Position: [REDACTED]
 School: [REDACTED]

Licensure: Tennessee
 Boards: Internal Medicine, Nuclear Medicine
 Memberships: Society for Experimental Biology and Medicine
 American Association for Cancer Research
 American Thyroid Association
 Society of Nuclear Medicine
 Southern Society for Clinical Research
 American Medical Association
 American Association for the Advancement of Science
 American Federation for Clinical Research
 Fellow, American College of Physicians
 American Society of Hematology (1968)
 Health Physics Society, East Tennessee Chapter
 Tennessee Academy of Science
 Tennessee Blood Club

Name: A. Bertrand Brill
 Position: Associate Professor of Medicine and Radiology,
 Vanderbilt School of Medicine
 School: [REDACTED]

Licensure: Tennessee
 Memberships: American Association for the Advancement of Science
 Society of Nuclear Medicine
 Radiation Research Society
 American Thyroid Association

Other Indication of Experience and Competence:
 Medical Director, Division of Radiological Health,
 U.S. Public Health Service, 1957-1964, Rockville, Md.

Name: Donald W. Goodwin
 Position: Minister, United Church, Chapel-on-the-Hill
 School: [REDACTED]

Memberships: Ministerial Standing, United Church of Christ
 Additional Information:
 Member of various boards which change from time to time

1081091

Name: Karl F. Hübner
Position: [REDACTED]
School: [REDACTED]
Licensure: Tennessee
Memberships: Roane-Anderson County Medical Society
Tennessee Medical Association
American Medical Association

Name: Melvin E. Koons
Position: Executive Assistant to President, Union Carbide
Corporation Nuclear Division
School: [REDACTED]
Admitted to Practice of Law: North Dakota 1961; Tennessee 1964; Federal District Court,
North Dakota 1961; East Tennessee 1964; U. S. Supreme Court,
1966
Memberships: American Bar Association
Public Contracts Section
Federal Bar Association
Government Contracts Committee
R & D Contracts Subcommittee
Tennessee Bar Association
North Dakota Bar Association, Ward County

Name: Robert Lange
Position: Research Professor; Assistant Director, University of
Tennessee Memorial Research Center
School: [REDACTED]
Licensure: Tennessee, Minnesota, Missouri, Georgia
Board: Internal Medicine
Memberships: American Association for the Advancement of Science
American Medical Association
Knoxville Academy of Medicine
Southern Society of Research
Central Society of Clinical Research
American College of Physicians
International Society of Hematology

Name: Michael Scott Lawyer
Position: Staff Attorney, Oak Ridge Associated Universities
School: [REDACTED]
Admissions: Mississippi, 1970; U. S. District Court, Northern District
of Mississippi, 1970
U. S. Court of Military Appeals, 1971
U. S. Tax Court, 1975
U. S. Court of Claims, 1975
U. S. Supreme Court, 1975
Memberships: Federal Bar Association
Government Contracts and Administrative Law Committees
Mississippi Bar Association

1081092

Name: Thomas A. Lincoln
Position: Director, Health Division, Oak Ridge National Laboratory
School: [REDACTED]

Licensure: Tennessee, Minnesota
Board: American Board of Preventive Medicine, by examination,
June 5, 1963
Memberships: Fellow Industrial Medical Association
Past President, Tenn. Industrial Medical Association
American Academy of Occupational Medicine
American Medical Association
Past President, Roane-Anderson County Medical Society
Treasurer, Board of Directors, Oak Ridge Regional Mental
Health Center

Name: Clarence C. Lushbaugh
Position: Chairman, Medical and Health Sciences Division
Director, Radiation Emergency Assistance Center/
Training Site (REAC/TS)
School: [REDACTED]

Licensure: Tennessee
Memberships: American Association for the Advancement of Science
American Society for Experimental Pathology
Associated Researchers and Clinicians in Cancer
Society for Experimental Biology and Medicine
Health Physics Society
Radiation Research Society
Society of Nuclear Medicine
American Medical Society
Tennessee State Medical Society

Name: John B. Storer
Position: Director, Biology Division, Oak Ridge National Laboratory
School: [REDACTED]
Memberships: American Association for Cancer Research
American Society for Experimental Pathology
Radiation Research Society
Society for Experimental Biology and Medicine
National Council on Radiation Protection and Measurements

Name: Joan B. Woods
Position: Psychiatrist, Veterans Administration Hospital,
Murfreesboro, Tennessee
School: [REDACTED]
Licensure: Tennessee
Boards: American Board of Psychiatry and Neurology
Memberships: American Psychiatric Association
American Medical Association and Subsidiaries

Name: Edythelena Tompkins
Position: Chief Epidemiologist, ORAM
School: [REDACTED]

Memberships: American Public Health Association
Society for Epidemiological Research
Society for Occupational and Environmental Health
American Thyroid Society

Committee Members and Their Responsible Area

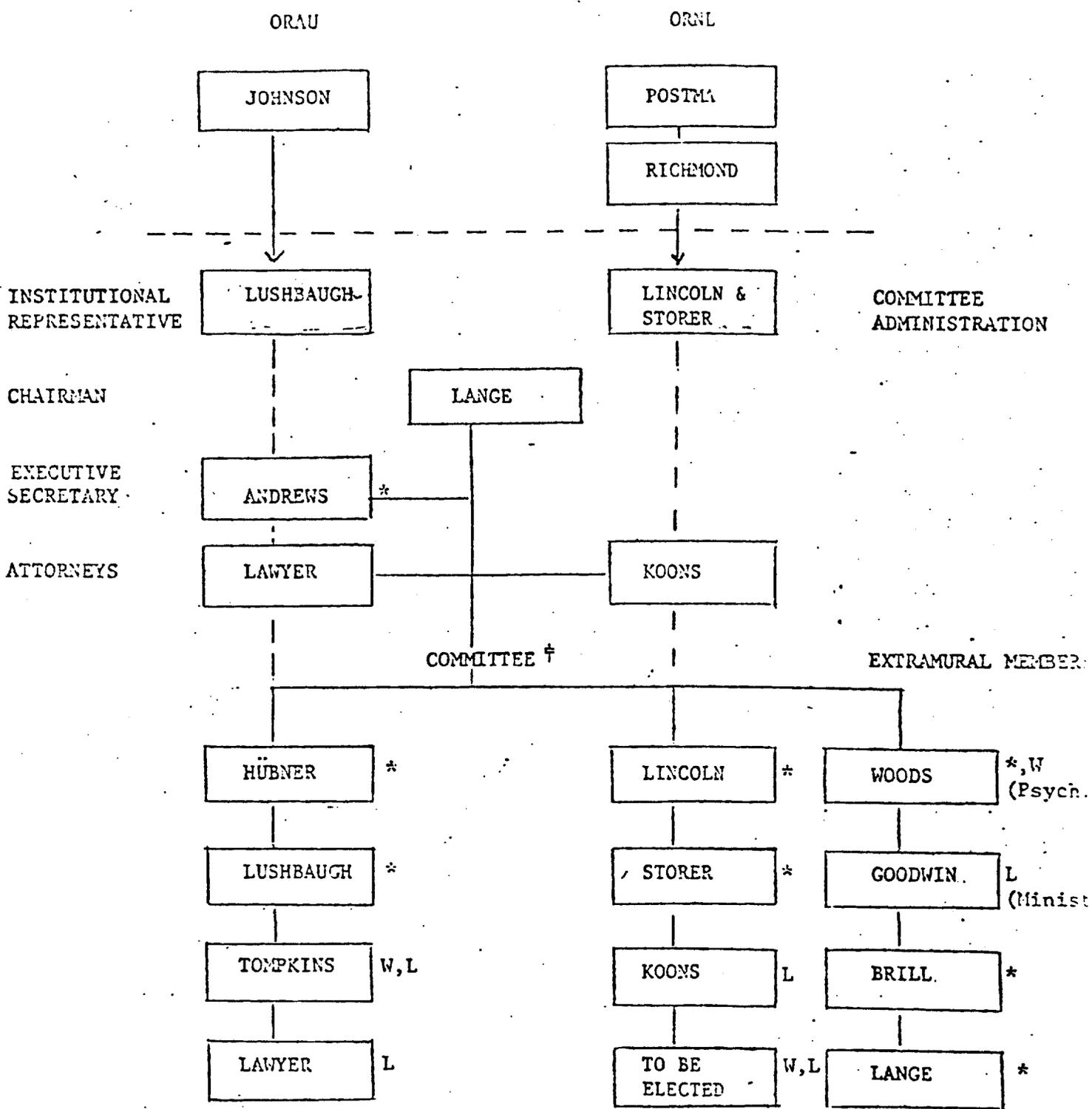
(On January 1, 1977, the following members constituted the Committee and had these stated responsibilities.)

- O Robert Lange, M.D. (Univ. Tenn.), Chairman, Extramural Representative
- Gould A. Andrews, M.D. (ORAU), Secretary
- OO John B. Storer, M.D., Official ORNL Representative
- OO C. C. Lushbaugh, Ph.D., M.D., Official ORAU Representative
- O A. Bertrand Brill (Vanderbilt Univ.), Extramural Representative
- * Melvin E. Koons (UCNC), Lawyer
- * M. Scott Lawyer (ORAU), Lawyer
- O* Donald W. Goodwin, Ph.D. (United Church, O.R.), Minister
- OW Joan B. Woods, M.D. (VA Hosp., Murfreesboro), Psychiatrist
- Thomas A. Lincoln, M.D. (ORNL), Occupational Medicine
- Karl F. Hübner, M.D. (ORAU), Clinical Research
- *W Edythalena Tompkins, A.B. (ORAU), Epidemiology

-
- O - Extramural member
 - OO - Institutional representative
 - * - Non-M.D. member
 - W - Woman member

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

INSTITUTIONAL DIRECTORS



* = M.D.
 W = Woman
 L = Lawyer

1081096

† ON ORNL PROPOSALS, ORNL AFFILIATES DO NOT VOTE:
 ON ORAU PROPOSALS, ORAU AFFILIATES DO NOT VOTE.

Ident. No. _____

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

To: COMMITTEE ON HUMAN STUDIES
Oak Ridge Associated Universities and
Oak Ridge National Laboratory

Date _____

Principal Investigator: _____

Co-Investigators: _____

Title of Project: _____

Use Following Format (Submit Original and 8 Copies)

I. Objectives of Experiment:

(Include statement why experiment must be done in humans, and expected benefits from the knowledge.)

II. Methods of Procedure:

Brief description of methods, all medications including name and dose range, number and types of subjects anticipated, time for single session, total number of sessions, total duration of study, methods used to screen subjects, etc.

III. Possible Hazards and their Evaluation:

IV. Radioisotopes and New Drugs

If the study involves radioisotopes, indicate action of the Isotopes Committee. If new drugs are involved, indicate that appropriate application to FDA has been made.

See page 2

1081097

Title of Project: _____

Ident. No. _____

V. Responsibility of Principal Investigator:

Include statement of your procedures for protecting rights of the patients and gaining informed consent.

The principal investigator will follow the procedures of the Committee on Human Studies in obtaining "informed consent" from the subjects under study. The investigator recognizes that he retains the primary responsibility for safe-guarding the interests of the participants under study. Any significant changes in methods of procedure or of the development of unexpected risks will be brought to the attention of the Committee on Human Studies.

Starting Date _____

Signatures: _____ Principal Investigator

_____ Co-Investigator

_____ "

_____ "

_____ "

_____ "

DIVISION REVIEW:

The application described above has been reviewed and approved.

Official signing for the institution:

Signature _____

Title _____

Institution _____

Date _____

1081098

MEDICAL AND HEALTH SCIENCES DIVISION
OAK RIDGE ASSOCIATED UNIVERSITIES
Oak Ridge, Tennessee
Consent for Experimental Test

Annex 8 Example
of a typical informed
consent form for a
specific project

I authorize the performance upon _____
(myself or name of patient)
of the following test: Phase I radiopharmaceutical tests of DL-valine-1-¹¹C
for pancreas visualization.

The nature and purpose of the test, the risks involved, and the possibilities of complications have been explained to me. I understand that this test is not a treatment for my disorder nor is it being done primarily for my benefit, rather that the test is for experimental purposes. Further, I understand that any information gained from doing this test becomes the property of ORAU and may be published in the scientific literature at the discretion of the staff of the Medical and Health Sciences Division, Oak Ridge Associated Universities.

DATE _____

(Patient or person authorized to consent for patient)

WITNESS: _____

I have talked with _____ about the proposed test to be given including the following:

1. This is a new radioactive drug: DL-Valine-1-¹¹C.
2. The drug contains the radioactive isotope ¹¹C and an organic chemical in quantities much less than those required to produce any measurable chemical effect in the body. Patient should feel no effect from the drug.
3. The radiation dose will be approximately 0.25-0.5 rad to the whole body.
4. Blood samples (2 ml) will be drawn at intervals during a period of 1-1/2 hours after administration.
5. Whole body counts and scans will be made over a 2-hr period.
6. The patient may withdraw from the test at any time.

DATE: _____

Investigator

1081099

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

PROTECTION OF HUMAN SUBJECTS
ASSURANCE/CERTIFICATION DECLARATION

ORIGINAL FOLLOW-UP REVISION

GRANT CONTRACT FELLOW OTHER

NEW RENEWAL CONTINUATION
APPLICATION IDENTIFICATION NUMBER (if known)

STATEMENT OF POLICY: Safeguarding the rights and welfare of subjects at risk in activities supported under grants and contracts from DHEW is primarily the responsibility of the institution which receives or is accountable to DHEW for the funds awarded for the support of the activity. In order to provide for the adequate discharge of this institutional responsibility, it is the policy of DHEW that no activity involving human subjects to be supported by DHEW grants or contracts shall be undertaken unless the Institutional Review Board has reviewed and approved such activity, and the institution has submitted to DHEW a certification of such review and approval, in accordance with the requirements of Public Law 93-348, as implemented by Part 46 of Title 45 of the Code of Federal Regulations, as amended, (45 CFR 46). Administration of the DHEW policy and regulation is the responsibility of the Office for Protection from Research Risks, National Institutes of Health, Bethesda, Md 20014.

1. TITLE OF PROPOSAL OR ACTIVITY

2. PRINCIPAL INVESTIGATOR/ACTIVITY DIRECTOR/FELLOW

3. DECLARATION THAT HUMAN SUBJECTS EITHER WOULD OR WOULD NOT BE INVOLVED

A. NO INDIVIDUALS WHO MIGHT BE CONSIDERED HUMAN SUBJECTS, INCLUDING THOSE FROM WHOM ORGANS, TISSUES, FLUIDS, OR OTHER MATERIALS WOULD BE DERIVED, OR WHO COULD BE IDENTIFIED BY PERSONAL DATA, WOULD BE INVOLVED IN THE PROPOSED ACTIVITY. (IF NO HUMAN SUBJECTS WOULD BE INVOLVED, CHECK THIS BOX AND PROCEED TO ITEM 7. PROPOSALS DETERMINED BY THE AGENCY TO INVOLVE HUMAN SUBJECTS WILL BE RETURNED.)

B. HUMAN SUBJECTS WOULD BE INVOLVED IN THE PROPOSED ACTIVITY AS EITHER: NONE OF THE FOLLOWING, OR INCLUDING: MINORS, FETUSES, ABORTUSES, PREGNANT WOMEN, PRISONERS, MENTALLY RETARDED, MENTALLY DISABLED. UNDER SECTION 6. COOPERATING INSTITUTIONS, ON REVERSE OF THIS FORM, GIVE NAME OF INSTITUTION AND NAME AND ADDRESS OF OFFICIAL(S) AUTHORIZING ACCESS TO ANY SUBJECTS IN FACILITIES NOT UNDER DIRECT CONTROL OF THE APPLICANT OR OFFERING INSTITUTION.

4. DECLARATION OF ASSURANCE STATUS/CERTIFICATION OF REVIEW

A. THIS INSTITUTION HAS NOT PREVIOUSLY FILED AN ASSURANCE AND ASSURANCE IMPLEMENTING PROCEDURES FOR THE PROTECTION OF HUMAN SUBJECTS WITH THE DHEW THAT APPLIES TO THIS APPLICATION OR ACTIVITY. ASSURANCE IS HEREBY GIVEN THAT THIS INSTITUTION WILL COMPLY WITH REQUIREMENTS OF DHEW Regulation 45 CFR 46, THAT IT HAS ESTABLISHED AN INSTITUTIONAL REVIEW BOARD FOR THE PROTECTION OF HUMAN SUBJECTS AND, WHEN REQUESTED, WILL SUBMIT TO DHEW DOCUMENTATION AND CERTIFICATION OF SUCH REVIEWS AND PROCEDURES AS MAY BE REQUIRED FOR IMPLEMENTATION OF THIS ASSURANCE FOR THE PROPOSED PROJECT OR ACTIVITY.

B. THIS INSTITUTION HAS AN APPROVED GENERAL ASSURANCE (DHEW ASSURANCE NUMBER _____) OR AN ACTIVE SPECIAL ASSURANCE FOR THIS ONGOING ACTIVITY, ON FILE WITH DHEW. THE SIGNER CERTIFIES THAT ALL ACTIVITIES IN THIS APPLICATION PROPOSING TO INVOLVE HUMAN SUBJECTS HAVE BEEN REVIEWED AND APPROVED BY THIS INSTITUTION'S INSTITUTIONAL REVIEW BOARD IN A CONVENED MEETING ON THE DATE OF _____ IN ACCORDANCE WITH THE REQUIREMENTS OF THE Code of Federal Regulations on Protection of Human Subjects (45 CFR 46). THIS CERTIFICATION INCLUDES, WHEN APPLICABLE, REQUIREMENTS FOR CERTIFYING FDA STATUS FOR EACH INVESTIGATIONAL NEW DRUG TO BE USED (SEE REVERSE SIDE OF THIS FORM).

THE INSTITUTIONAL REVIEW BOARD HAS DETERMINED, AND THE INSTITUTIONAL OFFICIAL SIGNING BELOW CONCURS THAT:

EITHER HUMAN SUBJECTS WILL NOT BE AT RISK; OR HUMAN SUBJECTS WILL BE AT RISK.

5. AND 6. SEE REVERSE SIDE

7. NAME AND ADDRESS OF INSTITUTION

8. TITLE OF INSTITUTIONAL OFFICIAL

TELEPHONE NUMBER

SIGNATURE OF INSTITUTIONAL OFFICIAL

DATE

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator _____ Ident. No. _____

Project Title _____

1. In the opinion of this committee the risks to the rights and welfare of the subjects in this project or activity are:

The committee states that adequate safeguards against these risks have been provided.

2. In the opinion of the committee the potential benefits of this activity to the subjects outweigh any probable risks. This opinion is justified by the following reasons:

3. In the opinion of the committee the following informed consent procedures will be adequate and appropriate:

4. The committee seeks continuing communication with the investigator(s) on this project along the following lines:

5. Other committee comments:

Approve _____

Chairman of Committee

Disapprove _____

Date

1081101

JUL 21 1980

Union Carbide Corporation
Nuclear Division
ATTN: Dr. Herman Postma, Director
Oak Ridge National Laboratory
Post Office Box X
Oak Ridge, Tennessee 37830

Gentlemen:

ORNL HUMAN USE EXPERIMENTAL PROCEDURES

We have recently been contacted by the Office for Protection from Research Risks in the Office of the Director of NIH concerning the exposure of one or more ORNL employees to 12-O-tetradecanoyl phorbol 13-acetate (TPA) in the spring of 1979. This incidence is viewed by ORO with considerable concern for several reasons:

1. It indicates that the ORNL procedures for human use experiments are either inadequate, not being followed, or that ORNL employees are not aware of them.
2. In response to an inquiry from the National Cancer Institute, ORNL acknowledged by letter of February 28, 1980, that an exposure did occur. The ORNL response also indicated that the "in vitro studies using TPA are not associated with my NIH grant or my NIH contract but rather with Department of Energy funding." This statement implies that DOE would condone such activities. On the contrary, the Department of Energy imposes the same requirements as does NIH. In any case, the source of funding is immaterial since NCI work at ORNL is conducted for DOE under the DOE/UCC-ND contract.
3. The concern by NCI was raised some months ago yet we are unaware of any steps taken by ORNL to prevent recurrences. Moreover, ORO became aware of the February 28 ORNL letter to NCI only when requested by the Office for Protection from Research Risks to

CONCURRENCE	
RTG. SYMBOL	
INITIALS/SIG.	
DATE	
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Union Carbide Corporation

-2-

obtain a more responsive attitude from ORNL. This cannot be considered a program matter and ORNL should have involved ORO at an early date.

In order that we may be assured that ORNL practices and procedures concerning research involving human subjects may reasonably be expected to prevent such occurrences in the future, we need the following information:

- (1) Confirmation from ORNL of the reported incident including whether formal institutional review of the activities took place and, if so, results of the review.
- (2) If there was no prior approval, a report of any followup or corrective actions taken by ORNL including measures to prevent the occurrence of similar incidents.
- (3) A copy of the ORNL procedures and policies regarding review of proposed research involving human subjects and what has been done or is planned to assure understanding of and compliance with this policy on the part of individuals conducting research at ORNL.

Your response to the above is requested by August 15, 1980.

Sincerely,

Original Signed by
Joseph A. Lenhard
Joseph A. Lenhard
Assistant Manager for Energy
Research and Development

ER-13:WRB

cc: R. F. Hibbs, UCC-ND

JUL 15 4 12 PM '80

EOB ENERGY B&D
OFFICE OF A221-MCB

1081103

CONCURRENCES	
RTG. SYMBOL	ER-13
INITIALS/SIG.	WRB
DATE	7-18
RTG. SYMBOL	ER-10
INITIALS/SIG.	WRB
DATE	JUL 18 1980
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DEPARTMENT OF HEALTH, EDUCATION AND WELFARE

June 17, 1980

74 S. Cent. Hwy
496-7005

C. C. Lushbaugh
Medical and Health sciences Division
Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37830

Dear Dr. Lushbaugh:

This letter is an official request from the Office for Protection from Research Risks (OPRR) for an investigation and report concerning the involvement of individuals as subjects of research that had not been reviewed and approved by the institutional review board (IRB) at Oak Ridge National Laboratories. The incidents are described in the enclosed report to Dr. Thaddeus J. Donanski of the National Cancer Institute.

The General Assurance of Oak Ridge Associated Universities (G01716) with the Department requires review and approval of all research activities that involve human subjects conducted at or supported by Oak Ridge National Laboratories. The activities of Dr. Thomas J. Slaga and his colleagues, described in the enclosed letter, in applying 12-0-tetradecanoylphorbol-13-acetate (TPA) to themselves, were required to be reviewed and approved in advance by the IRB.

This office requests information on the following points:

1. confirmation from the institution of the reported incidents, including whether or not IRB review of the activities took place, and if so, minutes of the review;
2. in the event that there had been no prior IRB approval, a report of any follow-up or corrective action taken by the institution, including measures to prevent the recurrence of similar incidents;
3. a statement of the institutional policy regarding IRB review of such activities and what is being done administratively to insure understanding of, and compliance with, the policy on the part of researchers;

1081104

JUN 20 1980

Page 2 - C. C. Lushbaugh

4. how the current institutional policies regarding use and handling of known carcinogenic and other hazardous materials adequately cover research involving human subjects.

The enclosed letter to NCI states that the incidents were connected with research supported by the Department of Energy. It is important to note that, in addition to the Department of Health and Human Services requirement for IRB review of all research involving human subjects, the Department of Energy imposes the same requirements for research which it supports. The Department of Energy may take steps independently of this office to determine whether Oak Ridge National Laboratories is materially fulfilling its responsibilities for protection of human subjects.

Thank you for your cooperation in this matter. I look forward to your prompt response.

Sincerely yours,

Charles R. Mackay, Ph.D.
Deputy Director
Office for Protection
from Research Risks
Office of the Director

Enclosure

cc: Dr. Domanski, NCI
Dr. Slaga, ORNL
Dr. Fry, ORNL
Dr. Richmond, ORNL
Dr. Herman Postma
Ms. Dianne Gresham ✓

1081105

OAK RIDGE NATIONAL LABORATORY

OPERATED BY
UNION CARBIDE CORPORATION
NUCLEAR DIVISION



POST OFFICE BOX Y
OAK RIDGE, TENNESSEE 37830

February 28, 1980

Dr. Thaddeus J. Domanski
Division of Cancer Research, Resources
and Centers
National Cancer Institute
National Institutes of Health
Westwood Building
Bethesda, Maryland 20014

Dear Thad:

In response to your recent telephone inquiry concerning alleged TPA experiments using human subjects, it is hoped the following explanations will provide you with sufficient information. I might add that I, too, received a telephone call, from probably the same individual who contacted you, accusing me of treating people with TPA.

First, I would like to state emphatically that I have never treated anyone other than myself with the agent, TPA, nor do I have plans to initiate such investigations using human subjects. I did on one occasion in the spring of 1979 apply a very small amount of TPA to my own skin. This was done primarily out of curiosity outside the laboratory and after hours. In addition, four other individuals in my research group also applied a small amount of TPA to their own skin one time. I neither asked them to do such nor did I apply the agent. Since TPA had been found to cause inflammation and hyperplasia in mouse skin, I was interested in determining the effect on human skin especially since there were reports suggesting TPA might inhibit growth in human cells. Our laboratory had determined, for example, that TPA inhibited human foreskin growth in culture. These in vitro studies using TPA are not associated with my NIH grant or my NIH contract but rather with Department of Energy funding. Croton oil, the source of TPA, has been and still is, to a certain degree, used for a variety of reasons on both humans and in veterinary medicine.

I would like to point out that it was suggested that perhaps such studies on a very small scale were warranted. I therefore applied for permission to perform such studies using humans and presented the proposed research to our local Committee for Human Rights which reviews such work. The Committee felt the proposed investigation had definite scientific merit but opposed the selection of voluntary laboratory personnel as subjects. They also encouraged

3/11/80 - Copies to: Mr. Namovicz
File CA 20076 (official + mini)
1081106 File Y01 CP-70227 (official + mini)

JUN 20 1980

a more extensive investigation than I was interested in pursuing. They asked that I resubmit the proposal although I never did so. I simply never got around to it, and I must confess I have now lost all interest.

Above all, I must emphasize that this has nothing to do with my NIH grant supported research which concerns polycyclic hydrocarbon metabolism in mice or my NIH contract which concerns in vitro transformation of mouse epidermal cells. I am certainly well aware of the NIH rules and regulations governing research involving human subjects and would never abuse that.

I am indeed sorry this incident has developed to such a point and sincerely hope it can now be put to rest. Should you desire more information, please do not hesitate to contact me. In addition, Dr. R. J. M. Fry, Head, Cancer and Toxicology Program, ORNL and/or Dr. C. R. Richmond, Acting Director, Biology Division, ORNL are both very familiar with the situation and would be happy to talk with you.

Thank you very much.

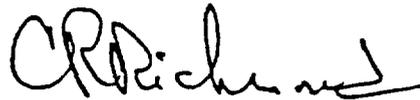
Sincerely,



Thomas J. Slaga, Ph.D.
Senior Staff, ORNL



R. J. M. Fry, M.D.
Head, Cancer and Toxicology Program
Biology Division, ORNL



C. R. Richmond, Ph.D.
Acting Director, Biology Division
ORNL

TJS:ms

1081107

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

To: COMMITTEE ON HUMAN STUDIES
Oak Ridge Associated Universities and
Oak Ridge National Laboratory

Date: June 7, 1979

Principal Investigator: Dr. Thomas J. Slaga

Co-Investigators: Dr. Susan M. Fischer
Dr. Andre Klein-SzantoTitle: In Vivo Effects of TPA on Adult Human SkinI. Objectives of Experiment:

Previous work with 12-O-tetradecanoyl phorbol 13-acetate (TPA) has shown it to be a noncarcinogenic tumor promoting agent on mouse skin. A recent study on cultured human foreskin epidermis, however, suggests that this agent may be inactive in humans, although culture effects can not be ruled out. As differences exist between newborn and adult mice (in vivo but not in vitro) with respect to TPA activity, it is necessary to determine whether TPA is active in adult human skin both in vivo as well as in culture. The data from this study is extremely important in determining the relevancy of mouse skin tumorigenesis studies as models for human carcinogenesis.

II. Methods of Procedure

TPA will be applied in acetone in single 10 and 20 ug doses to the skin on the inside of the lower forearm (dime size area) 4 or 2 days prior to biopsy. Skin punch biopsies (3mm in diameter) of these areas will be performed by a local dermatologist, Tiovo Rist, M.D. in his office, using standard procedures including local anethetization and sutures if needed. The removed tissues will be fixed and processed for histological examination since the key feature of TPA activity is local inflammation and hyperplasia. Five volunteers will participate in this study: All are members of this laboratory and have prior knowledge and experience with the agent under investigation.

III. Possible Hazards and their Evaluation

We anticipate no adverse effects other than minor skin irritation as a result of TPA application. While infection of the biopsied area is possible, it is unlikely and would be under immediate and constant care of the dermatologist.

IV. Radioisotopes and New Drugs

This study does not involve the use of radioisotopes in human subjects. TPA is an ingredient of croton oil which has been used topically as a counterirritant in veterinary medicine.

1081108

V. Responsibility of Principal Investigator

Copies of this application will be read to each volunteer as will be the informed consent form, which will be signed by the volunteer and 2 witnesses to assure full understanding of the project. The attending dermatologist will see to the safety and well-being of the volunteers. Any changes in methods of procedure or in the development of unexpected risks will be brought to the attention of the Committee on Human Studies.

Starting Date: To be determined (summer 1979)

Signatures; Thomas J. Slaga Principal Investigator

Susan M. Fischer Co-Investigators

A. W. L. Sato "

DIVISION REVIEW:

The application described above has been reviewed and approved for submission to the Committee on Human Studies, Official signing for the institution:

Signature J. R. Storey

Title Director

Institution Biology Division ORNL

Date 6/11/79

Oak Ridge National Laboratory
Biology Division

CONSENT FOR USE OF TISSUES IN RESEARCH PROJECT

Subject: _____ Age: _____ Sex: _____

Date: _____

I hereby authorize the following procedure:

- (1) Application of the agent 12-O-tetradecanoyl phorbol 13-acetate (TPA) to small areas of the skin of the lower forearm. The doses to be used are 10 and 20 ug in acetone.
- (2) Removal of a small segment of skin (3mm) from the treated areas by punch biopsy will be performed by the dermatologist, Toivo E. Rist, M.D.

I understand that the above biopsy procedure is a routine diagnostic procedure commonly used in studies of skin diseases. The risks involved in these procedures are very minimal.

I have been informed and understand that my consent to be treated as described above will not present any risks to me.

Signed _____

Date _____

The foregoing consent was read, discussed and signed in my presence, and in my opinion the person so signing did so freely and with full knowledge and understanding.

Witness _____

Witness _____

Date _____

Date _____

1081110

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator Dr. Thomas J. Slaga Ident. No. 56

Project Title IN VIVO EFFECTS OF TPA ON ADULT HUMAN SKIN

1. In the opinion of this committee the rights and welfare of the subjects in this project or activity will be protected. The committee states that adequate safeguards against any untoward effects have been provided.

2. In the opinion of the committee the informed consent procedures to be used in this project will be both appropriate and adequate. The committee also finds that no inappropriate psychological or sociological risks will exist for the subjects involved in this project.

3. The committee seeks continuing communication with the investigator(s) on this project along the following lines:

4. Other committee comments:
The study should not be carried out as designed. If the investigator so desires, the study should be redesigned and resubmitted. A letter was sent to Dr. Slaga explaining the basis for the disapproval of the Committee.

Approve _____

Disapprove _____

1081111

Robert Slaga MD
Chairman of Committee

7/27/79

Date

ORAU- .L COMMITTEE ON HUMAN STUDIES V ING RECORD

Proposal Number and Title #56 IN VIVO EFFECTS OT TPA ON ADULT HUMAN SKIN

Principal Investigator Dr. Thomas J. Slaga

VOTE OF COMMITTEE

Signature	Approve	Disapprove	Comment	Date
1. <i>[Signature]</i>		X		7/27/79
2. <i>[Signature]</i>		X		7/27/79
3. <i>[Signature]</i>		✓		7/27/79
4. <i>[Signature]</i>		X		7-27-79
5. <i>[Signature]</i>		X		7/27/79
6. <i>[Signature]</i>		✓		7/27/79
7. <i>[Signature]</i>		✓		7/27/79
8. <i>[Signature]</i>		✓		7-27-79
9. <i>[Signature]</i>		✓		7-27-79
10.				
11.				
12.				
13.				
14.				

Chairman's statement of Committee consensus:

Ex. Study as designed should not be carried out. Should be redesigned & resubmitted

7/27/79
DATE

Acknowledgment of submitter:

See letter dated 8/13/79.

1081112

Thomas J. Slaga
DATE



UNION CARBIDE CORPORATION
NUCLEAR DIVISION
P. O. BOX X, OAK RIDGE, TENNESSEE 37830

Ms. Dianne Gresham, Secretary
ORAU/ORNL Human Studies Committee
Oak Ridge Associated Universities
Medical and Health Sciences Division
Oak Ridge, Tenn. 37830

Dear Dianne:

I am sorry I will be unable to attend the committee meeting on Friday.

I have reviewed the proposal on "In Vivo Effects of TPA on Adult Human Skin" (No. 56) and would like to have my vote recorded in favor of the experiments.

Sincerely,

A handwritten signature in cursive script that reads "Ruby".

Ruby A. Miller
Assistant Director
Public Relations

1081113

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37830

Medical and
Health Sciences
Division

(615) 576-3098

February 21, 1980

Dr. Thomas J. Slaga
Biology Division
ORNL
P. O. Box Y
Oak Ridge, TN 37830

Dear Dr. Slaga:

I am enclosing a copy of a letter sent to you in August from Dr. Lange notifying you of the ORAU/ORNL Committee on Human Studies' findings at their July 27, 1979, meeting.

It is with regards to this letter that the attached copy of the voting form is to be signed by you. Please return it to me in the enclosed, self-addressed envelope at your earliest convenience for the purposes of keeping our records updated.

Your assistance and cooperation will be appreciated.

Sincerely,



Dianne Gresham, Secretary
ORAU/ORNL Committee on Human
Studies

dg

Enclosures: 3

1081114



1924 ALCOA HIGHWAY
KNOXVILLE, TENNESSEE 37920
OFFICE OF THE CHAIRMAN AND DIRECTOR
(615) 971-3165

THE UNIVERSITY OF TENNESSEE
MEMORIAL RESEARCH CENTER

DEPARTMENT OF MEDICAL BIOLOGY

August 13, 1979

Dr. Thomas J. Slaga
Biology Division
ORNL
P. O. Box Y
Oak Ridge, TN 37830

Dear Dr. Slaga:

The Human Participation Committee appreciated the time you took to discuss your project "In Vivo Effects of TPA on Adult Human Skin." Although the project was thought to be meritorious, there were some questions regarding the selection of subjects and the consent form. The committee voted not to approve the project at this time, but would be willing to reconsider a revised proposal. I hope you will see your way clear to resubmit.

Sincerely,

Robert D. Lange, M.D.
Chairman

nhp
cc: Ms. Dianne Gresham

1081115

cc by CRRichmond 2/13/80:

T. Slaga H. stma
J. Storer L. Lushbaugh (ORAU)
T. T. Odell
S. Garrett

cc made for 1151 Dr. ...

top of the news

basis of safety and health.

Attention has been focused on the issue recently since OSHA cited American Cyanamid on charges of forcing female employees at one unit of its Willow Island, W.Va., plant to choose between their jobs and their child-bearing capability. The company has protested the ruling (*CW*, Jan. 9, p. 22).

The proposed guidelines would give the employer the opportunity to submit information or conduct studies to prove that certain women should be treated differently for health reasons and that men's health is not affected by similar exposure.

For example, employers who want to determine the reproductive effects of a particular exposure on pregnant females would also have to study nonpregnant females and males. The agencies said they recognize that temporary policies might have to be adopted, but only after other alternatives have been considered and the policy is tailored specifically for the group affected and provides for research on possible health effects to other workers. The research would have to be completed within two years. Firms without the resources for the research, the proposal adds, could ask OSHA to carry it out.

Written comments on the proposed guidelines must be received by EEOC by June 2.

Stauffer cited for air pollution violation

An emission from Stauffer Chemicals's Manchester plant in Houston last week caused 53 persons to seek hospital treatment. Fire Dept. officials identified the substance spewed from the plant's No. 8 stack as sulfur dioxide, a nontoxic irritant, but Stauffer representatives at the plant would neither confirm nor deny the identification.

Elwood Lentz, senior vice-president for the company's Southwest regional office, blamed employees who failed to report a jammed air-control valve on the furnace.

The incident took place shortly before 6 p.m. on Feb. 5, and amounted to a "puff of smoke" that drifted from the stack and dissipated minutes later. Eugene New, an enforcement officer for Houston's Health Dept., was unable to reach management at the plant to determine the cause, and issued Stauffer a citation for air pollution. Violations carry a maximum fine of \$1,000. The company has 10 days to answer.

NIH probes tumor testing at Oak Ridge

Several Union Carbide employees at Oak Ridge National Laboratory are suspected of having tested a potent tumor promoter on themselves without authorization. An inquiry is under way by the National Institutes of Health to determine whether the suspected testing violated the lab's agreement to use federal grant money in conformity with NIH's guidelines for research with human subjects.

Chester Richmond, acting director of the Biology Division at Oak Ridge, says that it is his understanding that about a year ago, researcher Thomas J. Slaga and "several individuals" believed to be co-workers in Slaga's lab, applied 12-O-tetradecanoylphorbol-13-acetate to their skin. Richmond asserts that Slaga and the others applied the compound to themselves, not to each other, and that they did so outside the laboratory, on their own time, and without any authorization from Oak Ridge. A tumor promoter, such as the compound in question, induces tumor formation when acting in conjunction with a carcinogen.

Slaga told *CW* he applied the tumor promoter to himself, and that some other people in the lab applied it to themselves. Slaga said that the compound has opposite effects on mice and human cells *in vitro*. "I was just very curious to see if it would produce a little welt on the skin," he said. "I look at it as absolutely nothing." Co-workers in the same lab as Slaga declined comment.

C.C. Lushbaugh, chairman of the Medical and Health Sciences Division at Oak Ridge Associated Universities and a member of Oak Ridge's board that reviews human-subject research proposals, says Slaga submitted a proposal to the committee on June 7, 1979, to allow him to experiment on human subjects with the tumor promoter. His request was discussed, but denied, at the July 27, 1979 meeting. The committee suggested that Slaga revise his proposal. Slaga's formal request apparently came several months after the human testing allegedly occurred.

Charles MacKay, deputy director of the Office for Protection From Research Risks at NIH, says his office has no record that Slaga's research was to involve human subjects.

Slaga is working under a grant from the National Cancer Institute to test the tumor promoter on mice as part of a larger research project. On Jan. 21, NIH's program officer, Thaddeus Do-

manski, told Slaga to submit, as soon as possible, a written statement testifying that the alleged use of the tumor promoter on humans had nothing to do with the grant. The statement must be signed by Slaga and the Oak Ridge administrator for government grants. Slaga said he has sent the letter to NIH.

Oak Ridge National Lab is owned by the federal government and operated by Union Carbide, which employs the workers at the lab. Both the lab and Union Carbide abide by NIH guidelines for experimentation with human subjects. Oak Ridge has an agreement with NIH that stipulates that all human-subject research proposals first will be cleared through an institutional review board at the lab. Proposals are then reviewed for approval at NIH.

New EPA rules aim at particulate emissions

New ammonium sulfate plants would have to remove up to 99.9% of their particulate emissions under rules proposed by the Environmental Protection Agency.

The proposed rules would require venturi scrubbing or fabric filtration to control particulates. The EPA estimates that the capital costs would add less than 0.01% to the wholesale price of ammonium sulfate.

In spite of the relatively low cost, the EPA estimates that the rules would reduce particulates from ammonium sulfate dryers from 737 tons/year, the amount estimated for 1985 if no federal rules were established, to 144 tons/year. Compliance would amount to an 80% reduction of particulate emissions under a state implementation plan.

The proposed rules would limit exhaust emissions from the dryers to 0.15 kilogram of particulate matter per megagram of ammonium sulfate. The rules would require continuous monitoring of the pressure drop across the control system to ensure proper operation and maintenance.

The rules would apply to new, modified and reconstructed ammonium sulfate dryers at caprolactam by-product ammonium sulfate plants, synthetic ammonium sulfate plants, and coke oven by-product ammonium sulfate plants.

EPA puts the compliance cost for the ammonium sulfate industry at about \$1 million/year by 1985. Annualized cost to the industry in the fifth year would amount to \$500,000. The rules are open for comment until April 5.

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basis of safety and health.

Attention has been focused on the issue recently since OSHA cited American Cyanamid on charges of forcing female employees at one unit of its Willow Island, W.Va., plant to choose between their jobs and their child-bearing capability. The company has protested the ruling (*CW*, Jan. 9, p. 22).

The proposed guidelines would give the employer the opportunity to submit information or conduct studies to prove that certain women should be treated differently for health reasons and that men's health is not affected by similar exposure.

For example, employers who want to determine the reproductive effects of a particular exposure on pregnant females would also have to study nonpregnant females and males. The agencies said they recognize that temporary policies might have to be adopted, but only after other alternatives have been considered and the policy is tailored specifically for the group affected and provides for research on possible health effects to other workers. The research would have to be completed within two years. Firms without the resources for the research, the proposal adds, could ask OSHA to carry it out.

Written comments on the proposed guidelines must be received by EEOC by June 2. □

Stauffer cited for air pollution violation

An emission from Stauffer Chemicals's Manchester plant in Houston last week caused 53 persons to seek hospital treatment. Fire Dept. officials identified the substance spewed from the plant's No. 8 stack as sulfur dioxide, a nontoxic irritant, but Stauffer representatives at the plant would neither confirm nor deny the identification.

Elwood Lentz, senior vice-president for the company's Southwest regional office, blamed employees who failed to report a jammed air-control valve on the furnace.

The incident took place shortly before 6 p.m. on Feb. 5, and amounted to a "puff of smoke" that drifted from the stack and dissipated minutes later. Eugene New, an enforcement officer for Houston's Health Dept., was unable to reach management at the plant to determine the cause, and issued Stauffer a citation for air pollution. Violations carry a maximum fine of \$1,000. The company has 10 days to answer. □

NIH probes tumor testing at Oak Ridge

Several Union Carbide employees at Oak Ridge National Laboratory are suspected of having tested a potent tumor promoter on themselves without authorization. An inquiry is under way by the National Institutes of Health to determine whether the suspected testing violated the lab's agreement to use federal grant money in conformity with NIH's guidelines for research with human subjects.

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