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ORAU-55

OAK RIDGE INSTITUTE OF SCIENCE AND EDUCATION

OAK RIDGE ASSOCIATED UNIVERSITIES/
OAK RIDGE NATIONAL LABORATORY
COMMITTEE ON HUMAN STUDIES
ACTIVE PROTOCOLS AND RELATED DOCUMENTS
FILE 3

1144560

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37830
Telephone 615 483-8411

Medical and
Health Sciences
Division

M E M O R A N D U M

TO: ORAU/ORNL COMMITTEE ON HUMAN STUDIES

FROM: Dianne Gresham, Secretary

DATE: December 8, 1978

SUBJECT: AMENDMENT TO IND FOR CA-DTPA TO ALLOW ITS USE IN AEROSOL FORM

Proposal #55 is enclosed for your review; this proposal is an amendment to an IND for Ca-DTPA. The consent form for Ca-DTPA is also included; however, it was considered and approved by the Committee as a separate item (Ident. #47) but not accompanied by a formal proposal on May 11, 1976.

A form accompanies this material for recording your vote. Please return the form in the enclosed self-addressed envelope no later than December 19. Your prompt response and cooperation will be appreciated.

dg

Enclosures: (4)

REPOSITORY Oak Ridge Institute for Science & Education
Medical Science Division
COLLECTION ORAU/ORNL Committee on Human Studies
BOX No
FOLDER ORAU-30019(1)

1144581

Ident. No. 55

APPLICATION FOR THE USE OF HUMANS AS EXPERIMENTAL SUBJECTS

TO: ORAU/ORNL COMMITTEE ON HUMAN STUDIES
Oak Ridge Associated Universities and
Oak Ridge National Laboratory

Date 12/8/78

Principal Investigator: Clarence C. Lushbaugh, Ph.D., M.D.

Co-Investigators: Approximately 40 physicians in charge of medical departments of contractors to the U.S. Department of Energy and the other facilities working with transuranium compounds.

Title of Project: Amendment to IND for Ca-DTPA to Allow Its Use in Aerosol Form

Ca-DTPA has been previously approved by FDA (IND #4041) as an agent for Phase II investigations of decorporation therapy of internally deposited actinide contamination. Approval has been previously given for administration either by slow intravenous infusion or by intramuscular injection. Investigators working on the study have, however, without FDA approval, also administered Ca-DTPA quite extensively as an aerosol. (Previous aerosol use occurred before management of the IND was transferred to Dr. Lushbaugh at ORAU). A total of 228 individuals have been treated with aerosol Ca-DTPA in the United States. Of these, 84 had more than one treatment. These 228 individuals were drawn from a total population of 334 persons who have reportedly been treated with Ca-DTPA in this country. Aerosol use of Ca-DTPA in the United States ceased in 1976, although it is still proceeding in other countries.

Aerosol Ca-DTPA was found in both preclinical and the previous clinical investigations to be quite useful as an agent for decorporation therapy. Reports of insignificant adverse reactions have been very infrequent.

A complimentary agent, Zn-DTPA, was recently approved by both the ORAU/ORNL Committee on Human Studies and FDA for administration either by intravenous infusion, intramuscular injection, or inhalation of an aerosol. Permission is requested to bring the flexibility for Ca-DTPA use up to the standards that have been approved for Zn-DTPA.

The principal investigator will follow the procedures of the Committee on Human Studies in obtaining "informed consent" from the subjects under study. The investigator

1144582

Title of Project: Amendment to IND for Ca-DTPA to Allow Its Use in Aerosol Form

Ident. No: 55

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 Chairman, Medical & Health Sciences Div.

Institution Oak Ridge Associated Universities

Date 12/8/78

1144583

Ident. # 47

INFORMED CONSENT FORM

FOR USE OF CA-DTPA, AN INVESTIGATIONAL DRUG

NAME:_____ AGE:_____ DATE:_____ TIME:_____AM/PM

I_____,hereby request and authorize_____M.D.
to give to_____the drug calcium-diethylenetriamine-pentaacetic
(myself)
acid (Ca-DTPA) in an attempt to enhance the removal of_____from my body.

I understand that I have been involved in an incident where I was exposed to radioactive _____and have been contaminated, to some degree, by this exposure. The above-named physician has consulted with me concerning this condition and has advised me that one method of treatment is the use of the drug Ca-DTPA. I understand that I may require repeated doses of this drug several times a week for up to several months depending on the level of contamination that I have experienced, should I decide to accept this method of treatment.

I understand that Ca-DTPA is an investigational drug and not available for general use. The term "investigational drug" means that the drug, Ca-DTPA, is undergoing investigation, under FDA control, to determine its effects on man. It has been explained to me that this compound has the property to bind with some heavy metals, including iron, lead, plutonium, americium, and the other heavy metals within the body and helps the body to excrete them. Some risks in taking Ca-DTPA with daily doses up to 1 gm are: Possible damage to the kidneys and the liver, or additional damage to those organs if they are already diseased. I understand that all risks are not known at this time. I have been fully informed of the known risks and possible consequences and understand that unforeseen results may occur. The alternative methods of treatment such as waiting for spontaneous excretion have been explained to me, and I realize that this drug (Ca-DTPA) is offered to me only after careful deliberation of Dr._____and his colleagues.

I am consenting to its use for the study and treatment of my condition with the understanding that the results of this treatment may not necessarily be of benefit to me. The use of Ca-DTPA in the treatment of internal radionuclide contamination is part of a national research program. I do not object if any information relating to my case is used in professional journals or medical books, or for any other purpose in the interest of medical education, knowledge, or research; provided, however, that it is specifically understood that in any such publication or use I shall not be identified in any way. I further agree that I will participate in whatever follow-up studies are deemed appropriate by my physician at whatever intervals are found suitable by the investigators. I am reserving the right to withdraw my permission at any time without prejudicing my further medical care. Dr. _____has also offered to answer any additional questions about this drug and possible delayed effects.

Signed:_____
(Patient)

Witness:_____

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:_____

Date:_____

1144501

(Revised form approved 2-2-77)

AMENDMENT TO IND FOR CA-DTPA TO ALLOW ITS USE IN

AEROSOL FORM

IDENTIFICATION # 55

I have reviewed this proposal and recommend

✓ Approval

_____ Disapproval

Comments:

Robert D. Fancy, MD

(Signature)

20 December 1978

(Date)

1144585

AMENDMENT TO IND FOR CA-DTPA TO ALLOW ITS USE IN

AEROSOL FORM

IDENTIFICATION # 55

I have reviewed this proposal and recommend

X Approval

_____ Disapproval

Comments:

(Signature)

12/18/78

(Date)

1144586

AMENDMENT TO IND FOR CA-DTPA TO ALLOW ITS USE IN

AEROSOL FORM

IDENTIFICATION # 55

I have reviewed this proposal and recommend

X Approval

_____ Disapproval

Comments:

William Hacker

(Signature)

Dec 18, 1978

(Date)

1144587

AMENDMENT TO IND FOR CA-DTPA TO ALLOW ITS USE IN

AEROSOL FORM

IDENTIFICATION # 55

I have reviewed this proposal and recommend

✓ Approval

_____ Disapproval

Comments:

(Signature)

12/12/78

(Date)

1144588

AMENDMENT TO IND FOR CA-DTPA TO ALLOW ITS USE IN

AEROSOL FORM

IDENTIFICATION # 55

I have reviewed this proposal and recommend

_X_ Approval

_____ Disapproval

Comments:

(Signature)

12/16/78

(Date)

1144589

AMENDMENT TO IND FOR CA-DTPA TO ALLOW ITS USE IN

AEROSOL FORM

IDENTIFICATION # 55

I have reviewed this proposal and recommend

✓ Approval

_____ Disapproval

Comments:

Ruby A. Miller

(Signature)

Dec. 13, 1978

(Date)

1144590

AMENDMENT TO IND FOR CA-DTPA TO ALLOW ITS USE IN

AEROSOL FORM

IDENTIFICATION # 55

I have reviewed this proposal and recommend

✓ Approval

_____ Disapproval

Comments:

Melvin E. Koons

(Signature)

Dec. 12, 1978

(Date)

1144591

AMENDMENT TO IND FOR CA-DTPA TO ALLOW ITS USE IN

AEROSOL FORM

IDENTIFICATION # 55

I have reviewed this proposal and recommend

✓ Approval

_____ Disapproval

Comments:

(Signature)

Dec. 9, 1978

(Date)

1144592

AMENDMENT TO IND FOR CA-DTPA TO ALLOW ITS USE IN

AEROSOL FORM

IDENTIFICATION # 55

I have reviewed this proposal and recommend

__x__ Approval

_____ Disapproval

Comments:

(Signature)

12/12/78

(Date)

1144593

AMENDMENT TO IND FOR CA-DTPA TO ALLOW ITS USE IN

AEROSOL FORM

IDENTIFICATION # 55

I have reviewed this proposal and recommend

_____ Approval

_____ Disapproval abstained

Comments:

Karl F. Hubner

(Signature)

12/11/78

(Date)

1144594

REVIEW AND ACTION

ORAU/ORNL Committee on Human Studies

Principal Investigator C. C. Lushbaugh Ident. No. 55

Project Title AMENDMENT TO IND FOR CA-DTPA TO ALLOW ITS USE IN AEROSOL FORM

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:

Approve X

Disapprove ____

Robert D. Lange, MD.
Chairman of Committee

7/27/79

Dr. Mathum

Department of Energy
Washington, D.C. 20545

December 20, 1978

Dr. William J. Gyarfas
Director, Division of Oncology
and Radiopharmaceutical Drug
Products
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Dear Dr. Gyarfas:

Enclosed is the amended IND 4041 as prepared by the Medical Health Sciences Divisipn of the Oak Ridge Associated Universities for your consideration.

Please feel free to call me if additional information is required.

Sincerely,

Walter H. Weyzen, Manager
Human Health Studies Programs
Division of Biomedical and
Environmental Research

Enclosure:
As stated

1114596

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37830
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Medical and
Health Sciences
Division

December 20, 1978

William J. Gyarfas, M.D., Director
Division of Oncology and Radiopharmaceutical
Drug Products
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Ref: IND 4041

Dear Dr. Gyarfas:

The following information, submitted in triplicate, constitutes an amendment to IND-4041, which was originally submitted by the Division of Operational Safety of the U.S. Atomic Energy Commission (now the U.S. Department of Energy) and is now managed for the U.S. Department of Energy by the Medical and Health Sciences Division of Oak Ridge Associated Universities. This proposed amendment will permit the administration of calcium trisodium diethylenetriaminepentaacetate (Ca-DTPA) by the aerosol route, in addition to the previously approved intravenous and intramuscular routes, for continued Phase 2 studies of Ca-DTPA as an agent for decorporation therapy of internally deposited actinide contamination.

Background

Ca-DTPA has for the past decade been the agent of choice for chelation therapy of internally deposited actinide contamination. The analogous zinc trisodium diethylenetriaminepentaacetate (Zn-DTPA) has recently been approved for human use by the U.S. Food and Drug Administration (IND 14,603) as a complementary chelating agent. Zn-DTPA is approved for administration either intravenously, intramuscularly, or as an aerosol.

Ca-DTPA has been shown to cause excretion of the metabolically required metals, Zn [Ca68a, S173] and probably Mn [Ku69, Na71, P176b] but trace metal loss is ordinarily transient and of insufficient magnitude under the usual treatment protocols to cause harm. Only under conditions of, or approaching, constant infusion are toxic symptoms observed in animal studies [Su74, Ta74, P175]. Zn-DTPA is less toxic than Ca-DTPA and does not cause the loss of Zn and Mn [Ca66, Ha66, Ha67a,b, Ca68, Dv70, Na71, Co75, P176b]. Until the actinide becomes well-fixed to tissues, Ca-DTPA enhances the actinide excretion rate considerably more than equivalent amounts of Zn-DTPA; however, after approximately one day Zn-DTPA is for practical purposes as effective as the Ca salt [Se72,73, Vo74, L176, Se75,76, Vo76]. Thus in those cases which require multiple protracted treatment, initial treatment with Ca-DTPA followed by switching to Zn-DTPA after the first day should decrease the possibility of

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toxic effects due to trace metal depletion without affecting the efficacy of decontamination. Zn-DTPA can also be used in certain cases (minors, pregnant women, nephrotics, and persons with bone marrow depression) in which the use of Ca-DTPA is contraindicated. Therefore, the two agents are clearly complementary.

Ca-DTPA has been used successfully in man for decorporation of internally deposited americium [Sm72, Wr72, Co76a, Do76], plutonium [Sc73, Oh76a,b, Do76], californium, and curium. A summary of the recent usage of Ca-DTPA for chelation therapy in the United States (including records on one patient who received Zn-DTPA under an emergency IND) is given in Table 1.

Table 1

Recent U.S. DTPA Usage

Fiscal Year	No. Pts.	Doses	Route IV./I.M.	Route Aerosol
1971 - 1973	70	215	134	81
1973 - 1974	37	130	97	33
1974 - 1975	44	158	60	98
1975 - 1976	31	41	21	20
1976 - 1977	10	346*	346	0
Totals	192	890	658	232
Average/year	31	148	110	39

* One patient received 299 grams Zn-DTPA and 20 grams Ca-DTPA.

IND 4041 permits the use of Ca-DTPA for slow intravenous infusion and for intramuscular injection. As may be seen in Table 1, Ca-DTPA has also been administered quite extensively as an aerosol. Aerosol administration of Ca-DTPA in the United States has now ceased, although it is still proceeding in other countries.

Inhalation of Ca-DTPA has several advantages over treatment by intravenous or intramuscular administration of the agent. The inhalation route is usually less traumatic than injection from the patient's viewpoint, is more convenient for both the treating physician and the patient, might be more easily applied if a large number of individuals were involved in an exposure, and can be administered by less medically skilled persons [Sm76a]. Administration of the agent as an aerosol provides a longer presence of the agent in the body than does intravenous administration, offsetting the higher initial blood concentrations achieved intravenously [Sm74].

Availability of Drug

Calcium Chel 330 brand of Ca-DTPA is available as ampules containing one gram of $CaNa_3DTPA$ per four ml of solution (25.0% w/v, 0.50 M). The drug solution was formulated and packaged by Geigy Pharmaceuticals (Division of Ciba-Geigy Corporation, Ardsley, N.Y.), under contract with the U.S. Atomic Energy Commission (now U.S. Department of Energy, see Master File #1311). Although the drug was formulated over 10 years ago, periodic analyses have revealed no decomposition of the drug or loss of drug potency. A recent assay (October 1978) showed a DTPA concentration of 0.53 M. Tests for sterility and pyrogenicity by standard U.S.P. procedures have been negative.

Each investigator working under IND 4041 has in stock a small number of ampules of Ca-DTPA. In addition, over 2000 ampules are retained by Dr. C. C. Lushbaugh, Medical and Health Sciences Division, Oak Ridge Associated Universities, Oak Ridge, Tennessee. These are to be used for future distribution to the investigators.

Efficacy Studies in Animals

Inhaled DTPA was as effective as intraperitoneally injected DTPA in removing intramuscularly injected plutonium (in the form of the relatively soluble $^{238}Pu(NO_3)_4$ from the rat [Sm74]. Adult female rats were injected intramuscularly with 1.2 μCi $^{238}Pu(NO_3)_4$ in 25 μl of pH2 HNO_3. One hour later (prompt treatment conditions) the rats, in groups of eight, were treated with 0.5 or 0.035 mmol/kg (17.4 and 1.2 times the human dose) Ca- or Zn-DTPA intraperitoneally. The lower dose was also given by inhalation over a 30-minute period using a nebulizer representative of those used in human inhalation therapy. Plutonium-injected control rats were exposed to aerosols of, or injected with, 0.9% saline. Animals were sacrificed after 4 days. Controls retained an average of 23% of the plutonium dose in the liver, 41% in the skeleton, and 22% remained at the injection site. The effectiveness of the treatment procedures is summarized in Table 2. Best results were achieved with the 0.5 mmol/kg level, and under these prompt conditions the Ca salt is superior to the Zn salt. Inhalation was slightly, although not significantly, superior to injection at the lower dose of DTPA; again the Ca salt was more effective than the Zn salt although not to the same degree as at the higher dose. If one can assume similar effects in man and rat, the inhalation treatment should be as effective as treatment via the intravenous route.

Table 2

Retention of Intramuscularly Deposited $^{238}Pu(NO_3)_4$ in the Rat Four Days After Treatment with Inhaled or Injected Ca- or Zn-DTPA

	Percent of Control Retention[a]					
Treatment Route→	Intraperitoneal				Inhaled	
Treatment Level→	0.5 mmol/kg		0.035 mmol/kg		0.035 mmol/kg	
Agent→	Ca-DTPA	Zn-DTPA	Ca-DTPA	Zn-DTPA	Ca-DTPA	Zn-DTPA
Tissue						
Liver	9	20a	30b	57c	22ab	45c
Femur	17	57	40a	88b	31a	73b
Injection site	55a	82b	79b	92c	64a	84bc

[a] Numbers in the same row with the same letter (a, b or c) are not statistically different at 5% significance level according to Duncan's multiple range test.

Aerosol Ca-DTPA was found to be quite effective in removing inhaled soluble plutonium in rats [Ly66]. Plutonium-239 citrate (pH = 6.5) was administered to male rats of the Wistar line by a single 20-minute inhalation in a dynamic-type chamber designed for the simultaneous experimental poisoning of 15 animals. Atomization of the solutions (30 μCi/ml) was carried out in the aerosol generator with the aid of a jet of compressed air under a pressure of 1.5 kg/cm^2. Ca-DTPA was administered as an aerosol in a single 30-minute operation following periods of 5 minutes, 1, 4, and 24 hours, and 40 days from

the moment of inhalation of plutonium. During 10 minutes of inhalation, the lungs of the rat retained approximately 0.024 mmol/kg (0.8 times the human dose) of Ca-DTPA. The results are shown in Table 3. Inhalation of the Ca-DTPA aerosol after 5 minutes and 1 and 4 hours following inhalation of plutonium produced a smaller effect than the prophylactic administration of Ca-DTPA, but the treatment was still very effective. For the above periods the effectiveness of Ca-DTPA was virtually constant. When Ca-DTPA is given to the rats 24 hours after the inhalation of plutonium, the plutonium removal was significantly less, and inhalation of Ca-DTPA after 40 days did not alter the plutonium levels in the tissues of the rat, even when the Ca-DTPA dose was doubled.

Table 3

^{239}Pu Content (in Relation to Control Animals) in the Organs of Rats After Five Days from the Moment of Single-Dose Inhalation of DTPA, %

Time of Inhalation of DTPA before and after administration of ^{239}Pu	No. of Animals	Lungs	Skeleton
30 Min. before	5	8.2 ± 1.3	18.0 ± 3.3
5 Min. after	5	21.9 ± 3.0	51.9 ± 8.1
1 Hour after	5	20.4 ± 6.5	52.8 ±11.0
4 Hours after	5	16.6 ± 4.8	36.3 ±11.1
1 Day after	8	51.2 ± 9.8	64.8 ± 5.8
40 Days after*	4	87.6 ± 9.4	111.4 ±15.2
40 Days after*2	4	78.6 ±27.7	98.5 ±14.2
40 Days after*3	8	83.1 ±13.5	105.0 ±10.0

(continued)

		Liver	Kidneys	Organs
30 Min. before	5	15.3 ± 2.4	57.3 ±10.0	14.0 ± 2.2
5 Min. after	5	26.2 ± 0.6	93.2 ± 7.8	38.9 ± 4.5
1 Hour after	5	18.2 ± 5.3	48.5 ±13.6	45.0 ±14.2
4 Hours after	5	20.1 ± 7.3	57.9 ±17.4	28.3 ± 8.6
1 Day after	8	42.8 ±10.1	83.3 ±11.3	58.4 ± 6.8
40 Days after*	4	117.1 ±34.0	77.2 ± 8.8	100.5 ±10.7
40 Days after*2	4	70.9 ±10.0	122.1 ±21.5	94.8 ±15.1
40 Days after*3	8	94.0 ±18.5	99.6 ±13.7	97.6 ± 8.6

* DTPA inhalation for 10 minutes.
*2 DTPA inhalation for 20 minutes.
*3 Combined findings.

Inhaled Ca-DTPA was also quite effective in removing ^{91}Y [Sc64], ^{144}Ce [To62, To64], and ^{253}Es [Sm76b]. However, attempts to eliminate ^{239}Pu from the lungs of the dog following its penetration in insoluble form (dioxide) or in a form hydrolyzing to an insoluble form in vivo (plutonium nitrate and ammonium plutoniumpentacarbonate) resulted in failure even when the Ca-DTPA was administered over a prolonged period of time [To63, To64]. (Injected Ca-DTPA is also not effective at removing insoluble plutonium.)

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Toxicity Studies in Animals

The acute toxicity of intratracheally instilled Ca-DTPA was determined in the rat [Ba72]. Female rats weighing 290 ± 10 grams were anesthetized with halothane and instilled with 0.45 ml of Ca-DTPA solutions of osmotic pressure 1650 mOs. Animals administered 50 mg (0.35 mmol/kg, 12.0 times the usual human dose) of Ca-DTPA every other day for a total of four instillations tolerated the dosage well. Doses of 75 mg and 87.5 mg every other day for a total of four instillations were each lethal to one of 10 animals. Control animals administered NaCl survived the treatment without deaths; however, sodium citrate (76 mg/instillation) was lethal to two of 10 animals after the second instillation. Animals died within minutes or hours after the final instillation due to suffocation induced by the instilled solutions. Animals were sacrificed for histopathologic examination immediately after the final treatment and after periods of recovery of 14 days and 30 days following the final instillation. Although lung, liver, spleen, kidney, and gastrointestinal tract were examined, only lesions in the lung were thought to be drug related. Rats receiving four treatments of 50 mg Ca-DTPA and sacrificed immediately following the last treatment showed only minimal histologic effects. A few small focal areas of fibroblastic activity were seen scattered throughout the lungs. These foci most often were adjacent to air passageways, vessels, and interlobular septa. The fibroblastic elements showed little collagenization. Hyperplasia and hypertrophy of alveolar lining cells were apparent in these lungs. This, along with infiltration of alveolar septa with mononuclear cells and slight fluid accumulation, caused moderate septal thickening. Alveoli were distended and occasional ruptured septa were present. Macrophages were accumulated along the septa within the alveolar spaces and sometimes were free within the spaces. At the 75 and 87.5 mg level of Ca-DTPA, the histopathologic changes were quite similar in detail to those described above, but with noticeable increase in number and size of fibroblastic foci. No obvious differences were observed between the severity of lesions in rats which received 75 mg and 87.5 mg Ca-DTPA. Surviving animals receiving higher doses of Ca-DTPA (100 mg or above) had lung lesions of much increased severity relative to those which received lower dosages. The lesions were patchy in distribution, affecting all lobes of the lungs and consisted of near total consolidation. This consolidation was produced by proliferations of fibroblastic tissue, histocytes, and epithelial tissue. Bronchiolization (cuboidal metaplasia) of alveolar lining epithelium was present along with alveolar cell hyperplasia, mononuclear cell infiltration of septa and perivascular areas, and fibroblastic activity. In areas of the lesions, edema fluid flooded alveolar spaces. In rats allowed two weeks of recovery before euthanasia, only minimal lesions were present in the lungs. These lesions consisted of a few focal areas of fibroplasia accompanied by lymphoid cell infiltration, a few scattered focal accumulations of macrophages, diffuse vesicular emphysema of varying severity, and scattered areas of atelectasis. Rats allowed to recover 4 weeks after treatment showed no histologic alterations in their lungs.

Since inhaled Ca-DTPA persists for a longer time in the rat than intravenously administered Ca-DTPA, there was some concern that the gastrointestinal syndrome, seen following continuous infusion of Ca-DTPA might also be produced upon repeated inhalation treatment. Two aspects of this problem have been studied [Sm74]: (1) do repetitive high doses produce the syndrome, and (2) what is the rate of recovery from any effects that may be produced? To study these questions, female rats weighing 260-320 grams were exposed to very dense Ca-DTPA

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aerosols (approx. 7 mg/l; MMAD [mass median aerodynamic diameter] 2.3 to 3.8 μm, σ g [geometric standard deviation] 2.1 to 2.6) for 15, 30, 60, or 120 minutes, twice daily. The exposure chamber was cooled to maintain internal temperatures below 25° over the longer exposure times. The average Ca-DTPA dose to the rat was 7.3 mg/exposure hour; daily doses were about 0.025, 0.05, 0.1, and 0.2 mmol/kg/day; the human dose is 0.028 mmol/kg. Four animals were sacrificed from each dose level after 1, 10, and 20 days of treatment, and after 1, 7, and 21 days of recovery following treatment. Control rats were treated with aerosolized 5% saline solution. No pathology was observed following the 1-day exposures. In the animals studied after longer exposures there was a slightly higher incidence and severity of vesicular emphysema in the DTPA-treated rats than in the saline-treated controls. After 7 or more days of treatment there was some emphysema in all groups; but except for the very lowest dose, there was no clear-cut correlation of incidence or severity with DTPA dose or recovery period out to 10 days. After 21 days recovery, only one of four rats from the highest DTPA-exposure group, and one of four rats from the saline group, showed emphysema. At the two highest doses a slight softening of the feces was noted but this was not confirmed as a gastrointestinal syndrome at the histopathological level, and may have simply reflected the amount of chelate going through the gut following the inhalation. By the end of each 30-minute or longer exposure, the nasal areas of the muzzle appeared red and slightly inflamed. This disappeared within about 10 minutes after removal from the chamber. The rats treated with DTPA rarely blinked or closed their eyes; however, this was even more common among rats treated with saline. No damage to the eyes was noted. No pathology of any consequence was found in the kidneys, ovaries, nares, pancreas, adrenals, urinary bladder, trachea, esophagus, cerebrum, cerebellum, or generally in the liver and gastrointestinal tract. In three animals the liver showed fatty change, i.e., small foci of hepatic parenchymal cells containing lipid vacuoles, after 10 days exposure at the 0.1 and 0.2 mmol/kg/day Ca-DTPA exposure levels. Two of four rats killed 1 day following the highest level of Ca-DTPA exposure showed a small increase in the number of goblet cells in the epithelial cells of the intestine. None of the fibrotic changes previously observed with intratracheally instilled Ca-DTPA at high dose levels were observed under the conditions of inhalation.

To test for early pathology associated with Ca-DTPA inhalation, male Wistar rats and Golden Syrian hamsters were exposed nose only to Ca-DTPA aerosols generated using a Retec nebulizer [Sm76a]. The aerosols in the rat exposure chamber averaged 4.7 mg Ca-DTPA/l, 3.25 μm MMAD, 2.4 σ g. Those in the hamster chamber averaged 3.9 mg Ca-DTPA/l, 3.86 μm MMAD, 2.4 σ g. The absorbed doses were estimated from chemical analyses of DTPA in the urine. The DTPA doses inhaled by the rats were 13 and 24 mg/kg for the two exposure times studied, and the doses for the hamster were 20 and 51 mg/kg. (The conventional intravenous dose in man is 14 mg/kg.) The animals were exposed to the aerosols during one week for a total of three times with the exposures spaced one day apart. Five animals from each group were killed after the first and third exposure and at weekly intervals for the following five weeks. The lungs, liver, kidneys, spleen, adrenals, turbinates, trachea, esophagus, stomach, duodenum, jejunum, ileum, eyes, and large intestine were examined histologically. The only pathology observed in this experiment considered ascribable to the Ca-DTPA treatments, was a transitory vesicular emphysema (Table 4).

Table 4

Transitory Vesicular Emphysema Occurrence in Rats and Hamsters Inhaling Ca-DTPA
(Animals with lesion per 5 animals sacrificed)

	Immediately after first exposure	After last inhalation exposure					
		Immediately	1 week	2 weeks	3 weeks	4 weeks	5 weeks
Rats:							
Shelf controls (a)	0	0	0	1			
Sham controls (b)	2	0	2	0			
Saline controls (c)	1	1	0	0	None	None	None
Ca-DTPA, 1 hr., 13 mg/kg (d)	3	4	4	2			
Ca-DTPA, 2 hr., 24 mg/kg (d)	0	2	2	0			
Hamsters:							
Shelf controls (a)	0	0					
Sham controls (b)	2	0					
Saline controls (c)	0	1	None	None	None	None	None
Ca-DTPA, 1 hr., 20 mg/kg (d)	5	0					
Ca-DTPA, 2 hr., 51 mg/kg (d)	5	0					

(a) Untreated animals held as controls for any caging or living conditions effects.
(b) Animals treated as the exposed animals but no aerosols delivered to the chamber.
(c) Animals treated as the exposed animals and with a 2-hr. exposure to aerosols generated from 0.9% saline.
(d) Animals exposed to Ca-DTPA aerosols.

Relative to the sham and saline treated controls, the occurrence of emphysema in rats after the first Ca-DTPA treatment was not significant, but in hamsters it was significant at $p > 0.999$. Immediately after the last treatment emphysema was present in rats with $p > 0.98$, and after one week recovery, with $p > 0.92$. The overall occurrence of emphysema in both treated groups compared to the three control groups, was significant at $p > 0.99$. Emphysema was not found in either species by three weeks postexposure. Body weight changes were not significantly different from the controls in any of the treated groups.

Further observations of the short-term toxicity of inhaled Ca-DTPA were made in the beagle dog [Sm76a]. Dogs were anesthetized and administered Ca-DTPA aerosols via an intratracheal catheter for 30 minutes/day for five consecutive days. The average dose/exposure was 60 mg/kg (range 24-92 mg/kg), approximately four times the usual human dose. One week after the last exposure, 3/4 treated dogs and 0/2 dogs exposed to Ca-DTPA aerosols showed enlargement and submucosal lymphoid follicles in the pyloric region of the stomach; this was not present in dogs sacrificed at 4, 8, or 18 weeks post-exposure. Epithelial atypica in the alveolar lining was noted in 5/16 dogs inhaling Ca-DTPA and in 1/8 dogs exposed to saline aerosols, and may or may not be treatment related. No emphysema, of the type observed in rats and hamsters, was seen in the dogs. No intestinal lesions were observed, such as occur when Ca-DTPA is given under

conditions approaching those of continuous administration. (These lesions result from Zn and Mn depletion when Ca-DTPA is continually infused.) Zinc levels in both plasma and in whole blood were not found to vary significantly from pre-treatment levels. Urinary Zn was increased on the days of treatment with Ca-DTPA from 30- to 40-fold but this was transitory and no effect was detected in fecal Zn output. Lost Zn was apparently quickly replaced from dietary sources.

Of additional concern are both potential long-term effects of Ca-DTPA treatment and a possible synergism in effects of radionuclide insult and treatment, and this problem has been investigated [Ba77]. Male Wistar rats were exposed, nose only, to aerosols of $^{239}Pu(NO_3)_4$ generated from 0.27 N nitric acid solution. The initial lung burden was 78 $\pm$ 18 nCi ^{239}Pu. Twenty days later, and at five subsequent weekly intervals, rats both with and without the Pu burden were similarly exposed to Ca-DTPA aerosols (3 mg Ca-DTPA/rat/exposure) or to sham Ca-DTPA. Groups of animals were sacrificed at 30, 60, 100, and 150 days after Pu inhalation to determine possible effects of Ca-DTPA therapy, and Pu retention and distribution kinetics for dosimetric purposes. Appropriate control animals exposed to nitric acid aerosols, nitric acid in combination with Ca-DTPA or sham Ca-DTPA, and non-treated controls, completed the study. Delayed initial chelation therapy had little effect on Pu clearance from the lung. However, eventual deposition in skeleton and liver was decreased by 20% (significance level = 0.05). Treatment with Ca-DTPA had no significant effect on weight gain or survival or on the incidence of lung or bone tumors induced by plutonium inhalation. One rat exposed only to Ca-DTPA aerosols, and one rat exposed to nitric acid prior to Ca-DTPA aerosols, developed lung tumors. Although no lung tumors were observed in the control animals in this study, spontaneous lung tumors of the type reported have been found in this rat colony since this study was reported (J. E. Ballou, private communication, 1978), and the tumor incidence found with Ca-DTPA was not statistically significant.

Previous Human Studies with Aerosol Ca-DTPA

As stated in the background, Ca-DTPA has been administered as an aerosol quite extensively both in the United States and in other countries. A total of 228 individuals have been treated with Ca-DTPA by the aerosol route in the United States. Of these 84 had more than one treatment. These 228 individuals were drawn from a total population of 334 persons who have reportedly been treated with Ca-DTPA (B. Dupree, private communication, 1978).

Only a few cases of adverse reactions to aerosol Ca-DTPA have been reported. One patient experienced chills, feverishness (the patient did not measure his temperature), thirst, diuresis, myalgia, headaches, and paraesthesia, starting about 8 hours after the aerosol administration of one gram of Ca-DTPA [Li76]. The symptoms disappeared after about 4-5 hours, and the next day the patient felt no ill effects. There was no evidence of kidney or liver effects based on urinalysis and serum chemistry. This type of supersensitivity to Ca-DTPA is very rare and does not appear to be specific for inhaled Ca-DTPA. Similar reactions have been observed after intravenous infusion.

A second patient had 20-22 RBC/high power field in his urine on one occasion following months of intermittent aerosol Ca-DTPA therapy. This problem cleared four days after cessation and didn't reappear on resumption of

Ca-DTPA therapy (see Appendix). A third patient was reported to have experienced temporary side effects of hypogeusia and hyposmia (see Appendix). However, certainly the potential dianger of an internally deposited actinide compound far outweighs the risk of Ca-DTPA toxicity when the chelator is administered according to the established protocol.

Seven radiation workers who were involved in a minor plutonium accident were each treated with two 1-gram doses of aerosol Ca-DTPA at intervals of one or two days. During the three months following the incident, the workers were examined by a battery of medical tests which included urinalysis, 12 blood chemistries, hematology studies, and chest roentgenograms. No significant changes related to either the radiation exposure or the Ca-DTPA were observed (C. J. Sternhagen and G. J. Sinke, unpublished results).

Administration of Ca-DTPA as an aerosol was compared with intravenously administered Ca-DTPA by determining the concentration in the urine at various times following administration of identical quantities (i.e., 1 gram) of Ca-DTPA [Jo72]. The maximum concentration of DTPA in the urine (Fig. 1) following aerosol chelation was about 20% of the amount found after the same time following intravenous administration. This comparison could indicate a longer retention time in the body for DTPA administered by aerosol inhalation or, conversely, may imply that some DTPA is lost by exhalation and that only a fraction of the aerosol-administered DTPA was absorbed into the blood from the lung. After peak concentrations of DTPA in urine were reached, half-lives for DTPA concentration reduction by both methods of chelation were in the 1-3 hour range. In this study the efficacies of aerosol and intravenous Ca-DTPA treatments were identical, both increasing the plutonium excretion rate by a factor of about 35.

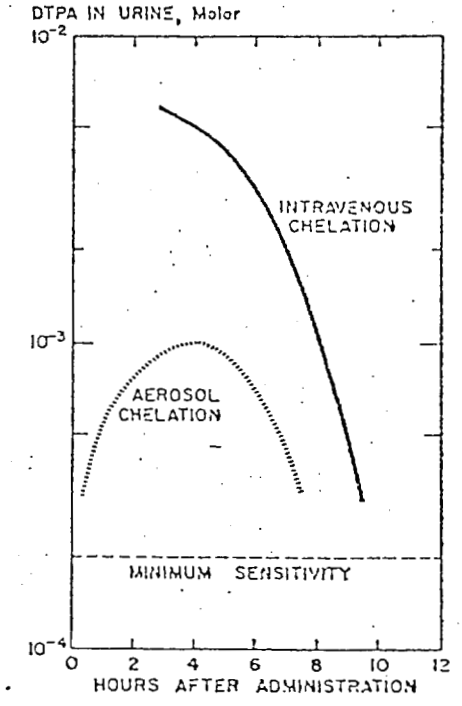

Fig. 1. DTPA elimination rate in urine.

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In another investigation J. C. Nénot, et al. [Ne71] indicated that aerosol inhalation of Ca-DTPA is more effective than intramuscular injection, because diffusion to the body from the lung is apparent slower than from the muscle, resulting in a longer lasting plasma burden. The same relationship apparently exists when comparing the effectiveness of aerosol inhalation of Ca-DTPA to intravenous injection [Jo72, J. C. Nénot, unpublished work].

The Appendix contains a list of the individual cases in which Ca-DTPA has been administered as an aerosol. The list includes the following information when available:

1. DTPA given (in grams)
   a. Total
   b. As aerosol

2. Body burden (in nCi unless otherwise noted)
   a. Initial estimate
   b. Final estimate
   c. Reduction in body burden; for an accident involving exposure to two radionuclides, the reduction in body burden represents a combined reduction for both isotopes.
   d. Radionuclide involved

3. Increased urinary excretion of the radionuclide above expected in the first day or two following DTPA treatment.

4. Comments
   a. Any adverse effects reported
   b. Any type of burden noted other than body burden

The information available on an individual case varies depending on the facility where the accident occurred. Some individuals had more than one incident involving exposure to radionuclides for which they received treatment with Ca-DTPA by aerosol. Such occurrences are bracketed on the left-hand column of the list. In no instance was an individual given an individual dose of more than one gram of Ca-DTPA.

Proposed Clinical Protocol

We propose to continue the Phase 2 study of the use of Ca-DTPA as a treatment for employees who accidentally receive internal depositions of plutonium or other transuranic heavy metals and to add administration of Ca-DTPA as an aerosol to the previously approved administration by intravenous infusion and intramuscular injection. The clinical use under investigation will be the chelation of the heavy metal nuclides to prevent deposition in bone and other body organs.

Because of the nature of the investigation, each case will be studied on an individual basis determined by the particular nuclide, its chemical form, the route of incorporation, the body burden, and the rate of excretion. Since the subjects in whom the drug is to be used are self-selected, it is not possible to characterize them beforehand. No controls are contemplated in the study. The number of cases expected and the duration of the investigation are undetermined at this time. The usage of Ca-DTPA over the last six years has been approximately 30 cases/year. Yearly progress reports will continue to be submitted by the sponsor to the Food and Drug Administration.

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The investigators in this study have been previously submitted to and approved by the Food and Drug Administration. An informed consent will be obtained from each patient using the previously approved consent form (which does not specify the route of administration). Patients shall not be identified by name in any reports of this work which may be published or presented at medical conferences.

The drug, supplied as ampules containing 4.0 ml of 0.50 M Ca-DTPA in water, is to be administered by either intramuscular injection of the undiluted solution, intravenous infusion (dose diluted with 250 ml of D_5W or normal saline) over a period of 60-90 minutes, or inhalation of the nebulized solution over a period of 15 minutes or longer. The route of administration will be dependent upon the particular nuclide, its chemical form, and the route of incorporation. Each dose of Ca-DTPA will be 4.0 ml (2.0 mmoles, 1.0 g of Ca-DTPA). No more than two doses of Ca-DTPA will be administered during each 24-hour period (see below).

Administration of Ca-DTPA by inhalation will be done using commercially available micro aerosol devices which develop a 1-3 micron size aerosol particle. The actual equipment to be used will be left to the discretion of the participating investigators and may include the Devilbiss 40 Atomizer, the Bird Respirator Model Mark 7, etc.

Before, during, and after chelation therapy, pertinent measurements for radioactivity will be made to determine the efficacy of treatment. These include assays of blood, urine, and feces and whole body and chest counting.

There are two distinct types of patients in whom Ca-DTPA will be investigated. One is the patient who has received questionable or minimal contamination, and the other is the patient who has received extensive contamination. In both types, immediate action is indicated due to the greater effectiveness of chelation therapy for prompt treatment.

Let us first consider a protocol for the first type of patients - those receiving questionable or minimal incorporation of actinides, who constitute the great majority of chelation therapy cases. The following standard protocol is proposed for these patients:

1. On assurance that a creditable incident has occurred and the person(s) at hand have in all likelihood received internal actinide contamination:

a. Obtain signature on informed consent form for Ca-DTPA therapy.
b. Obtain baseline blood and urine samples.
c. Administer one dose (4.0 ml of 0.50 M Ca-DTPA) by the most appropriate route for the particular case.
d. Begin collection of <u>all</u> urine and fecal samples for bioassay.
e. Whole body count and chest count assay.

2. By the fifth day evaluate bioassay data for body burden estimation and decide whether further chelation is necessary. If so,

a. Begin therapy regimen by repeating Ca-DTPA administration on a two dose per week basis until such time as excretion rate of actinide is not increased by Ca-DTPA administration.

b. Wait four to six months, re-establish baseline urinary excretion rate value and give a 4.0 ml Ca-DTPA dose by the appropriate route as initially. Obtain bioassay of urinary excretion to determine whether the Ca-DTPA increased excretion of the contaminant. If so,

c. Begin a second course of Ca-DTPA treatment on a two dose per week basis as in (a) above.

3. If bioassay data indicates that contamination was not in excess of minimally detectable amounts, then further therapy is not recommended.

4. When patient is released from further therapy, he should be followed at the routine intervals established by plant practice. At these exams urinalysis is recommended.

5. It is recommended that at the time of an employment termination the physician should ascertain at physical examination the person's plans so he can forward the history to an M.D. of the patient's choice. In addition, the M.D. should offer the person the opportunity to be followed medically by the U.S. Department of Energy follow-up system. This is to be done in order to help the individual in case there is an unexpected development of some medical problem or if the person again becomes contaminated and requires therapy at another plant site.

Urinalyses and hemograms will be done on the day following each treatment with Ca-DTPA, and the patient's pulse and blood pressure will be measured to determine any effect of the drug. Any side effects will be noted and recorded.

Patients who have received extensive incorporation of actinides require unusual therapy and will be treated largely according to the discretion of the individual investigator. Treatment may involve Ca-DTPA for prompt therapy (up to one week), due to its greater chelating efficacy for early treatment, followed by switching to Zn-DTPA for protracted therapy, or it may involve treatment with Zn-DTPA from the beginning. No more than two 4-ml doses of 0.5 M Ca-DTPA or Zn-DTPA will be administered during any 24-hour period. Doses will be administered by the route considered most appropriate for the individual case - either intravenously, intramuscularly, or as an aerosol. Before, during, and after treatment, a complete history and physical examination will be performed. Urinalyses and hemograms will be done on the day following each treatment with DTPA, and the patient's pulse and blood pressure will be measured to determine any effect of the drug. Additional tests may be prescribed at the discretion of the investigator, such as other hematological studies, liver and kidney function profiles, etc. Any side effects will be noted and recorded. Items (4) and (5) in the above protocol for minimal contamination also apply in the case of extensive contamination.

This proposal has been approved by the Oak Ridge Associated Universities/Oak Ridge National Laboratory (ORAU/ORNL) Committee on Human Studies, which is organized in accordance with the Food and Drug Administration's guidelines for an institutional review committee. This committee will conduct reviews of the study at intervals not exceeding one year.

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The sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason therefor. The sponsor assures that the aerosol administration of Ca-DTPA will not be initiated prior to 30 days after the date of receipt of this proposed amendment by the Food and Drug Administration and that he will continue to withhold or to restrict aerosol use of Ca-DTPA if requested to do so by the Food and Drug Administration prior to the expiration of such 30 days.

Sincerely,

Walter H. Weyzen, M.D., Sponsor of IND 4041
Director, Division of Human Health Studies
Office of Environmental Research
U.S. Department of Energy

C. C. Lushbaugh, Ph.D., M.D., Manager of IND 4041
Director, Medical and Health Sciences Division
Oak Ridge Associated Universities

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INDIVIDUALS GIVEN Ca-DTPA BY AEROSOL BEFORE MAY 1, 1977

Ca-DTPA Given (g) Total	Aerosol	Body Burden (nCi) Initial	Final	Reduction	Radionuclide	Increased Urinary Excretion of Radionuclide	Comments
48.4	48.4						20-22 RBC/high power field in urine on one occasion following months of intermittent Ca-DTPA therapy. Cleared 4 days after cessation and didn't reappear on resumption of DTPA therapy.
6.0	6.0						
27.0	27.0						
0.5	0.5						
1.0	1.0						
7.0	7.0						
3.0	3.0						
1.0	1.0						
9.5	0.5	0.023 μCi	0.022 μCi	0.001 μCi	Pu α		
1.0	1.0						
1.0	1.0						
1.8	1.8						
1.8	1.8						
1.8	1.8						
3.0	2.0						
3.8	2.8						
1.8	1.8						
1.8	1.8						
3.0	3.0						
1.0	1.0						
1.0	1.0						
1.0	1.0						
2.0	2.0						
2.0	2.0						
1.0	1.0						
1.0	1.0						
1.0	1.0						
2.0	2.0						
2.0	2.0						
2.0	2.0						
1.0	1.0						
1.0	1.0						
3.0	3.0						
3.0	3.0						

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INDIVIDUALS GIVEN Ca-DTPA BY AEROSOL BEFORE MAY 1, 1977 (continued)

Ca-DTPA Given (g) Total	Aerosol	Body Burden (nCi) Initial	Final	Reduction	Radionuclide	Increased Urinary Excretion of Radionuclide	Comments
1.0	1.0						
3.0	3.0						
65.0	4.0						
2.0	2.0		neg				Whole body count
3.0	3.0		neg				Whole body count
2.0	2.0		neg				Whole body count
1.0	1.0		neg				Whole body count
1.0	1.0		neg				Whole body count
1.0	1.0		neg				Whole body count
1.0	1.0		neg				Whole body count
3.0	3.0		neg				Whole body count
1.0	1.0		neg				Whole body count
1.0	1.0		neg				Whole body count
10.0	10.0						
1.0	1.0						
-	-	0.0067	0.0064				
1.0	1.0	not detectable					
16.0	16.0			∿10% BB	Pu-soluble		
10.4	6.4						
2.0	2.0						
1.0	1.0						
53.0	28.0						
31.0	20.0						
1.0	1.0	< 0.1	< 0.1		^{238}Pu	5-15X	
1.0	1.0	< 0.1	< 0.1		^{238}Pu	20X	
20.0	20.0	15.0			^{239}Pu	50-100X	
1.0	1.0	< 0.1	< 0.1		^{239}Pu	10X	
1.0	1.0	4.0		∿ 0.1	^{239}Pu	∿40X	
1.0	1.0	0.3	0.2	0.1	^{238}Pu	100X	
1.0	1.0	< 0.1			^{239}Pu		
1.0	1.0	2.0		< 0.1	^{239}Pu		
		3.0			^{238}Pu		
1.0	1.0						
1.0	1.0	<sensitivity					Chest count measurement
1.0	1.0						
0.5	0.5	<sensitivity					
1.0	1.0						
1.0	1.0	0					Whole body count
23.0		< 0.94r		30 +%			Side effects - hypogeusia and hyposmia

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INDIVIDUALS GIVEN Ca-DTPA BY AEROSOL BEFORE MAY 1, 1977 (continued)

a-DTPA Given (g) otal	Aerosol	Body Burden (nCi) Initial	Final	Reduction	Radionuclide	Increased Urinary Excretion of Radionuclide	Comments
1.0	1.0	< 32					
1.0	1.0						
1.0	1.0						
1.0	1.0						
1.0	1.0						
1.0	1.0	<10% BB		up to 80%			
14.0	12.0	3.5 BB	1-1.75 BB			8-10X	
1.0	1.0			50-75%		up to 40X	
5.0	5.0	6.0	0.4		^{238}Pu		
9.0	5.0	4.55 mCi	<1 BB				
1.0	1.0		background				
2.0	2.0	11 μCi	<sensitivity				Lung measurements
1.0	1.0		background				
1.0	1.0	2.0		<0.1	^{244}Cm	30X	
		0.5			^{238}Pu		
2.0	2.0			50-75			
1.0	1.0						
1.0	1.0	3.0	1.0		^{244}Cm		
1.0	1.0		background				
1.0	1.0	<0.1			^{238}Pu	<5X	Excretion rate of ^{244}Cm from previous uptake enhanced by this DTPA treatment.
1.0	1.0	26 mCi	background		40 Kev		Chest count measurements
		144 mCi			17 Kev		
1.0	1.0	22 mCi	background		40 Kev		Chest count measurements
		35 mCi			17 Kev		
1.0	1.0	9-19 mCi	background				Chest count measurements
1.0	1.0	low level	background				
1.0	1.0	9 mCi	background		2° X ray		Lung measurement
1.0	1.0	11 mCi	background		2° X ray		Body counter measurement
1.0	1.0		background				
1.0	1.0	3.2	2.5		^{238}Pu	50-100X	
1.0	1.0	2 mCi			^{244}Cm		
		.035			^{144}Ce		
1.0	1.0	<10%BB					
1.0	1.0	<sensitivity	<1BB				Whole body γ
1.0	1.0	<sensitivity					Chest count measurement
1.0	1.0	< 1mCi/1.5L					
1.0	1.0	20.1					Whole body α
3.0	3.0						
1.0	1.0	9.8 mCi					Chest count - whole body γ

1194615

INDIVIDUALS GIVEN Ca-DTPA BY AEROSOL BEFORE MAY 1, 1977 (continued

Ca-DTPA Given (g) Total	Aerosol	Body Burden (nCi) Initial	Final	Reduction	Radionuclide	Increased Urinary Excretion of Radionuclide	Comments
2.0	2.0	4.0	3.0		^{244}Cm	20X	
1.0	1.0	<sensitivity					Whole body γ measurement
1.0	1.0	<sensitivity					Chest count measurement
1.0	1.0	<sensitivity					Chest count measurement
1.0	1.0	1.0		<0.1	^{239}Pu	20-30X	
1.0	1.0	0					Chest count measurement
4.0	4.0	2.0				100X	
2.0	2.0	2.0	2.0			0X	
1.0	1.0	2.0			^{239}Pu	10X	
1.0	1.0	<0.3			^{239}Pu		
0.75	0.75	0.5		<0.1	^{238}Pu	20X	
1.0	1.0	0.4		<0.1	^{238}Pu		
7.0	7.0	6.0	5.7		^{238}Pu	10X	
1.0	1.0	5.0	3.0-4.0		^{244}Cm		
1.0	1.0	2.0		<0.1	^{239}Pu		
1.0	1.0						
1.0	1.0	0.2		<0.1	^{239}Pu		
1.0	1.0	<0.3		<0.1	^{239}Pu	increased slightly	
1.0	1.0	0.3	0.3		^{239}Pu	increased slightly	
2.0	2.0	0.5		<0.1		10X	
1.0	1.0	2.0	1.9		^{238}Pu	5-10X	
14.0	14.0	13.0	3-8.0		^{238}Pu		
4.0	4.0	0.4		<0.1	^{238}Pu	10X	
1.0	1.0	0.4		<0.1	^{238}Pu	10X	
3.0	3.0	0.2		<0.1	^{238}Pu	20X	
1.0	1.0	3.0	3.0		^{244}Cm	0X	
1.0	1.0	5.0		<0.1	^{244}Cm		
1.0	1.0	3.0		<0.1	^{244}Cm		
1.0	1.0	5.0				10X	
1.0	1.0	<0.1			^{238}Pu		
1.0	1.0	0.2		<0.1	^{238}Pu		
1.0	1.0	0.4			^{239}Pu		
		0.5		<0.1	^{238}Pu		
1.0	1.0	0.2		<0.1	^{238}Pu		
1.0	1.0	<0.1	<0.1		^{239}Pu		
1.0	1.0	3.0	2.0		^{244}Cm	10X	
1.0	1.0	1.0		<0.1	^{244}Cm		
1.0	1.0	2.0				10-30X	
1.0	1.0	<23.0					Chest count measurements
1.0	1.0	<19.0			^{239}Pu		Whole body γ measurement

1144616

INDIVIDUALS GIVEN Ca-DTPA BY AEROSOL BEFORE MAY 1, 1977 (continued)

a-DTPA Given (g) otal	Aerosol	Body Burden (nCi) Initial	Final	Reduction	Radionuclide	Increased Urinary Excretion of Radio-nuclide	Comments
3.0	3.0	<sensitivity					Chest count measurement
3.0	3.0	27					Chest count measurement
0.75	0.75						
1.0	1.0	<0.1		<0.1	^{238}Pu	OX	
		0.3			^{244}Cm		
1.0	1.0	0.2		<0.1	^{238}Pu	OX	
		0.4			^{244}Cm		
1.0	1.0						
1.0	1.0	1.0		<0.1		5-10X	
1.0	1.0	0.5		0.4		5-40X	
1.0	1.0	1.0		<0.1		5-10X	
1.0	1.0						
9.0	5.0						
4.0	2.0						
5.0	5.0						
7.0	5.0						
7.0	5.0						
5.0	3.0						
4.0	2.0						
4.0	2.0						
2.0	1.0						
0.0	10.0						
1.0		<10%MPBB				greatly increased	
1.0	1.0	<10%MPBB		evident		increased	
1.0	1.0	0					
1.0	1.0	<0.1					
1.0	1.0	<10%MPBB					
1.0	1.0	<10%MPBB					
1.0	1.0	<10%MPBB					
1.0	1.0	0.1		<0.1	^{239}Pu		
1.0	1.0	0.2		<0.1	^{239}Pu	little effect	
1.0	1.0	1.0		<0.1	^{239}Pu	increased	
1.0	1.0	0.8		<0.1	^{244}Cm	increased	
1.0	1.0	<10%MPBB			Pu		
1.0	1.0	<10%MPBB			Pu		
1.0	1.0	<0.1	<0.1		^{239}Pu		
1.0	1.0	0				OX	
2.0	2.0	0.4		0.5-1.0	^{239}Pu	increased	
		5.0			^{244}Cm		
2.0	2.0	0.5		0.5-1.0	^{239}Pu	increased	
		2.0			^{244}Cm		
1.0	1.0	2.0		<0.1	^{244}Cm		

1144617

INDIVIDUALS GIVEN Ca-DTPA BY AEROSOL BEFORE MAY 1, 1977 (continued)

Ca-DTPA Given (g) Total	Aerosol	Body Burden (nCi) Initial	Final	Reduction	Radionuclide	Increased Urinary Excretion of Radionuclide	Comments
1.0	1.0						
1.0	1.0	2.0		<0.1	^{244}Cm	increased	
1.0	1.0	2.0		<0.1	^{244}Cm		
1.0	1.0	2.0	1.5-1.9		^{244}Cm	increased	
1.0	1.0	<0.1	<0.1	<0.1	^{239}Pu		
1.0	1.0	0.2			^{239}Pu	little effect	
		<0.1			^{241}Am		
3.0	3.0						
1.0	1.0						
1.0	1.0						
1.0	1.0						
2.0	2.0						
2.0	2.0						
1.0	1.0						
1.0	1.0						
1.0	1.0						
2.0	2.0						
2.0	2.0						
2.0	2.0						
1.0	1.0						
1.0	1.0						
1.0	1.0						
1.0	1.0	22.0	<MDL		^{244}Cm		Whole body count
1.0	1.0	27.0	<MDL		^{244}Cm		Whole body count; some skin contamination initially
1.0	1.0	<MDL	<MDL				Whole body count
1.0	1.0	<MDL	<MDL				Whole body count
1.0	1.0	11.0	10.94		^{238}Pu		
1.0	1.0	14.0	13.98		^{238}Pu		
1.0	1.0	21.0	20.97		^{238}Pu		
10.0	10.0	2.0	0-1.0		^{238}Pu		
7.0	7.0	1.0	0.4-0.7		^{238}Pu		
13.0	13.0	5.0	0-2.0		^{238}Pu		
13.0	13.0	5.0	0-3.0		^{238}Pu		
1.0	1.0	<0.1	<0.1		^{239}Pu		
1.0	1.0	0.1	<0.1		^{239}Pu		
1.0	1.0	<0.1	<0.1		^{239}Pu		
1.0	1.0	2.0		<0.1	^{238}Pu		
1.0	1.0	2.0		<0.1	^{238}Pu		

1144618

INDIVIDUALS GIVEN Ca-DTPA BY AEROSOL BEFORE MAY 1, 1977 (continued)

Ca-DTPA Given (g) Total	Aerosol	Body Burden (nCi) Initial	Final	Reduction	Radionuclide	Increased Urinary Excretion of Radionuclide	Comments
1.0	1.0	4.0	3.9		^{238}Pu	20-30X	
1.0	1.0	0.7		<0.1	^{238}Pu		
1.0	1.0	0.2		<0.1	^{238}Pu		
1.0	1.0	0.1		<0.1	$^{238-240}Pu$		
1.0	1.0	0.3		<0.1	^{239}Pu		
		0.0067	0.0064				
1.0	1.0	<sensitivity					
1.0	1.0	0.2		0.1	^{239}Pu		
		0.4			^{241}Am		
4.0	4.0	0.8	0.3		^{238}Pu	100X	
4.0	4.0	0.5	0.2		^{238}Pu	100X	
1.0	1.0	0.04	0.02		^{238}Pu	50X	
1.0	1.0	0.05	0.02		^{238}Pu	50-100X	
1.0	1.0	0.3	0.1		^{238}Pu	500X	
0.5	0.5	2.0	2.0		^{238}Pu	100X	
1.0	1.0	0.3	0.1		^{238}Pu	100X	
1.0	1.0	0.01	0.005		^{238}Pu	50X	
1.0	1.0	0.05	0.02		^{238}Pu	50X	
		3.0	3.0		^{239}Pu		^{239}Pu is from previous incident
1.0	1.0	0.2	0.1		^{238}Pu	10X	
1.0	1.0	1.4	0.5		^{238}Pu	50-100X	
1.0	1.0	2.1	1.6		^{238}Pu	80X	
1.0	1.0	0.3	0.1		^{238}Pu	50-100X	
1.0	1.0	0.02	0.01		^{239}Pu	100X	
5.0	3.0	0.1	<0.1		^{238}Pu		
3.0	3.0						

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: C. C. Lushbaugh, M.D.

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: March 25, 1980

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by 4/4/80.
(If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to IND for Ca-DTPA to Allow Its Use in Aerosol Form

Proposal No.: 55 Date Approved: 1978

C. C. Lushbaugh M.D. 4/ /80

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

Several cases of Pu contamination were so treated in FY'80.

2. Report any complications.

None reported

1144620

3. Are there any planned changes?

No

4. Do you wish the project to be continued?

Yes

5. Comments.

A accumulation of clinical information is slow because less than 20 persons per year are so treated and in most cases therapy consists of only one injection

144621

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. C. C. Lushbaugh

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: 3/2/81

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by 3/17/81.
(If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: AMENDMENT TO IND FOR CA-DTPA TO ALLOW ITS USE IN AEROSOL FORM

Proposal No.: 55 Date Approved: 7/27/79

Signature of Principal Investigator — Date Signed 3/17/81

1. Report progress made in past year.
The most current information is for the period June 1, 1979-May 31, 1980. Information for the next annual period will be available in June 1981, when the physician co-investigators report their experience with the drug. During the aforementioned period, seven patients were treated with Ca-DTPA by the aerosol route. One additional physician requested authorization as a co-investigator on the Ca-DTPA IND, bringing the total number of co-investigators to 40.

2. Report any complications.

None.

1144622

3. Are there any planned changes?

Amendments to both the Ca-DTPA and Zn-DTPA IND's will be submitted to FDA to permit administration of both drugs by intravenous injection, in addition to the three previously approved routes (slow intravenous infusion, intramuscular injection, and inhalation of an aerosol). The proposed amendments are on the agenda for the April 1, 1981, meeting of the ORAU/ORNL Committee on Human Studies.

4. Do you wish the project to be continued?

Yes.

5. Comments.

None.

1144623

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. C. C. Lushbaugh

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: February 18, 1982

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by March 8, 1982. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to IND for Ca-DTPA to Allow Its Use in Aerosol Form

Proposal No.: 55 Date Approved: 7/27/79

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

2. Report any complications.

1144624

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. C. C. Lushbaugh

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: February 18, 1982

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by March 8, 1982. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to IND for Ca-DTPA to Allow Its Use in Aerosol Form

Proposal No.: 55 Date Approved: 7/27/79

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

In the reporting period 6/1/80 – 6/1/81 five patients were treated with Ca-DTPA by the aerosol route

2. Report any complications.

None

1144625

3. Are there any planned changes?

No

4. Do you wish the project to be continued?

Yes please

5. Comments.

1144626

Oak Ridge Associated Universities

MEMORANDUM

Dr. C. C. Lushbaugh **FROM** Dianne Gresham dg

DATE April 6, 1982 **COPIES TO** File, Committee on Human Studies

SUBJECT PROPOSALS REVIEWED BY COMMITTEE ON HUMAN STUDIES

Proposals 52, 55, and 60-64 were approved for continuation by the Committee on Human Studies on April 1, 1982. If there are any changes or problems with these proposals, please report them to the Committee Chairman. Thank you for your assistance and cooperation.

dg

1144627

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. C. C. Lushbaugh, M&HSD

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: March 23, 1983

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by April 6, 1983.
(If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to IND for Ca-DTPA to Allow its Use in Aerosol Form

Proposal No.: 55 Date Approved: 7/27/79

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

In the reporting period 6/1/81 - 5/31/82, three persons with real or suspected actinide contamination internally, were treated with the aerosol form of Ca-DTPA.

2. Report any complications.

None reported to ORAU.

1144628

3. Are there any planned changes?

No.

4. Do you wish the project to be continued?

Yes.

5. Comments.

None.

1144629

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. C. C. Lushbaugh, M&HSD

FROM: Dianne Gresham, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: March 23, 1983

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by April 6, 1983.
(If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to IND for Ca-DTPA to Allow its Use in Aerosol Form

Proposal No.: 55 Date Approved: 7/27/79

Signature of Principal Investigator Date Signed

1. Report progress made in past year.

[illegible]

3 persons with real or suspected actinide contamination internally, were treated with the aerosol form of Ca-DTPA.

2. Report any complications.

[illegible]

1144630

3. Are there any planned changes?

No

4. Do you wish the project to be continued?

Yes

5. Comments.

1144631

Oak Ridge Associated Universities

Memorandum

To Dr. C. C. Lushbaugh

From Dianne Gresham

Date June 22, 1983

Copies to Dr. Fry, Dr. Lange, File

Subject APPROVAL OF CONTINUATION OF PROPOSALS REVIEWED BY COMMITTEE ON HUMAN STUDIES

The Committee on Human Studies approved for continued study Proposals 52, 55, and 60-64. Your request to name Dr. Shirley Fry as principal investigator on Proposals 60, 62, and 63 was approved by the Committee; Dr. Fry is aware of the change in responsibility and will be requested to submit a progress report next year and to notify the Committee Chairman immediately of any changes or problems should they occur.

Thank you for your assistance and cooperation.

dg

1144632

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. C. C. Lushbaugh

FROM: Blanche Carden, Secretary - Committee on Human Studies

RE: Progress Reports

DATE: April 23, 1984

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 7, 1984.
(If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to IND for Ca-DTPA to Allow its Use in Aerosol Form

Proposal No.: 55 Date Approved: 7/27/79

Signature of Principal Investigator — Date Signed: May 9, 1984

1. Report progress made in past year.

In the reporting period 6/1/82 - 5/31/83, one person with real or suspected actinide contamination internally, was treated with the aerosol form of Ca-DTPA.

2. Report any complications.

None reported to ORAU.

1144633

3. Are there any planned changes?

No.

4. Do you wish the project to be continued?

Yes.

5. Comments.

None.

1144634

Oak Ridge Associated Universities

Memorandum

To Dr. C. C. Lushbaugh

From Blanche Carden B. Carden

Date June 12, 1984

Copies to File, Committee on Human Studies

Subject PROPOSALS REVIEWED BY COMMITTEE ON HUMAN STUDIES

Proposals 55, 61 and 64 were approved for continuation by the Committee on Human Studies on May 25, 1984. If there should be any changes or problems with these proposals, please report them to the Committee Chairman.

bbc

1144635

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

March 20, 1985

M E M O R A N D U M

To: Dr. Lushbaugh

From: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

Subject: PROGRESS REPORTS

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a yearly progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue.

Please answer the questions below and add any other information you feel pertinent and return by April 10, 1985. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to IND for Ca-DTPA to Allow Its Use in Aerosol Form

Proposal No.: 55 Date Approved: 1978

Signature of Principal Investigator Date Signed 3/25/85

1. Report progress made in past year:

   In the reporting period 6/1/83 - 5/31/84 seven persons with real or suspected actinide contamination internally were treated with the aerosol form of Ca-DTPA.

2. Report any complications:

   None reported.

1144636

3. Are there any planned changes?

No.

4. Do you wish the project to be continued?

Yes.

5. Comments:

-

1144637

STATUS REPORT ON RESEARCH PROPOSALS PREVIOUSLY REVIEWED AND APPROVED BY THE ORAU/ORNL COMMITTEE ON HUMAN STUDIES

(April 26, 1985)

55 Amendment to IND for Ca-DTPA to Allow Its Use in Aerosol Form (Lushbaugh)

Change in Committee 5/6/85

Progress

In the reporting period 6/1/83-5/31/84 ~~seven~~ 9 persons with real or suspected actinide contamination internally were treated with the aerosol form of Ca-DTPA.

Complications

None reported.

Changes

No changes.

Continuation

Keep active.

Comments

None.

1144638

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

April 17, 1986

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. C. C. Lushbaugh

FROM: Lynn Reeves, Secretary
ORAU/ORNL Committee on Human Studies

SUBJECT: PROGRESS REPORTS

The guidelines for the ORAU/ORNL Committee on Human Studies require that yearly all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by ~~May 5,~~ 1986. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to IND for CA-DTPA to Allow Its Use in Aerosol Form

Proposal No. 55 Date 1978

Signature of Principal Investigator Date Signed 4/18/86

1. Report progress made in the past year.

2. Report any complications.

1144639

3. Are there any planned changes?

see proposal no 52

4. Do you wish the project to be continued?

Yes

5. Comments.

1144640

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. C. C. Lushbaugh

FROM: Becky Hawkins/Secretary, Committee on Human Studies B. Hawkins

RE: Status Reports on Active Proposals

DATE: May 1987

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 1, 1987. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 55 Amendment to IND for CA-DTPA to Allow Its Use in Aerosol Form

Proposal No. 55 Date Approved: 1978

Signature of Principal Investigator Date Signed

1. Report progress made in the past year.

28 patients received CA-DTPA in aerosol form.

2. Report any complications.

none

1144641

3. Are there any planned changes?

4. Do you wish the project to be continued?

5. Comments.

1144642

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. C. C. Lushbaugh

FROM: Becky Hawkins/Secretary, Committee on Human Studies B Hawkins

RE: Status Reports on Active Proposals

DATE: June 1988

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by June 17, 1988. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 55 Amendment to IND for CA-DTPA to Allow Its Use in Aerosol Form

Proposal No. 55 DATE APPROVED: 1978

Signature of Principal Investigator Date Signed

1. Report progress made in the past year.

4 doses By Aerosol were given

2. Report any complications.

none

1144643

3. Are there any planned changes?

No

4. Do you wish the project to be continued?

Yes

5. Comments.

1144644

June 30, 1988

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. C. C. Lushbaugh

Title of Project: 55 Amendment to IND for CA-DTPA to Allow Its Use in Aerosol Form

Date Approved: 1978

1. Report progress made in the past year.

   4 Doses of CA DTPA were used in its aerosol form

2. Report any complications.

   None

3. Are there any planned changes:

   No

4. Do you wish the project to be continued?

   Yes

5. Comments.

1144645

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical and Health Sciences Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. C. C. Lushbaugh

FROM: Becky Hawkins/Secretary, Committee on Human Studies

RE: Status Reports on Active Proposals

DATE: April 6, 1989

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 8, 1989. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 55 Amendment to IND for CA-DTPA to Allow Its Use in Aerosol Form

Proposal No. 55 DATE APPROVED: 1978

Signature of Principal Investigator Date Signed

1. Report progress made in the past year.

10 pts received 11 Treatments with aerols.

Savannah River

2. Report any complications.

1144646

3. Are there any planned changes?

4. Do you wish the project to be continued?

5. Comments.

1144647

Oak Ridge Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical Sciences Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. C. C. Lushbaugh

FROM: Becky Hawkins/Secretary, Committee on Human Studies

RE: Status Reports on Active Proposals

DATE: May 2, 1990

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 17. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: 55 Amendment to IND for CA-DTPA to Allow Its Use in Aerosol Form

Proposal No. 55 DATE APPROVED: 1978

Signature of Principal Investigator

5/18/90
Date Signed

1. Report progress made in the past year.

   Single (1 gm) doses of Ca-DTPA were administered in aerosol form to each of 18 individuals with real or suspected actinide contamination.

2. Report any complications.

   None

1144648

3. Are there any planned changes?

   We plan to transfer responsibility for the Principal Investigator on this proposal from C. C. Lushbaugh, Ph.D., M.D., to another ORAU physician (TBA).

4. Do you wish the project to be continued?

   Yes, please

5. Comments.

1144649

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical
Sciences
Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. C. C. Lushbaugh

FROM: Karl Hubner/Chairman, Committee on Human Studies KH

RE: Committee Action on Active Proposals

DATE: June 28, 1990

Your project number 55 "Amendment to IND for CA-DTPA to Allow Its Use in Aerosol Form" was reviewed and approved at our last meeting on June 28, 1990.

Progress reports of all active proposals will again be reviewed at our next meeting to be held in the spring of 1991.

bh

1144650

June 28, 1990
ORAU/ORNL COMMITTEE ON HUMAN STUDIES

STATUS REPORTS ON ACTIVE PROPOSALS

Investigator: Dr. C. C. Lushbaugh

Title of Project: 55 Amendment to IND for CA-DTPA to Allow Its Use in Aerosol Form

Date Approved: 1978

1. Report progress made in the past year.

   Single (1 gm) doses of Ca-DTPA were administered in aerosol form to each of 18 individuals with real or suspected actinide contamination.

2. Report any complications.

   None

3. Are there any planned changes:

   We plan to transfer responsibility for the Principal Investigator on this proposal from C. C. Lushbaugh, Ph.D., M.D., to another ORAU physician (TBA).

4. Do you wish the project to be continued?

   Yes, please

5. Comments.

   None

1144621

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical
Sciences
Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Fun Fong

FROM: Dr. Karl Hubner/Chairman, Committee on Human Studies

RE: COMMITTEE ACTION ON ACTIVE PROPOSALS

DATE: September 7, 1991

Your project number 55 "Amendment to IND for CA-DTPA to Allow Its Use in Aerosol Form" was reviewed and approved at our last meeting on June 6, 1991. The committee has no objection to the continuation of this project.

Progress reports of all active proposals will again be reviewed at our next meeting to be held in the spring of 1992.

bh

1144652

Oak Ridge
Associated
Universities

Post Office Box 117
Oak Ridge, Tennessee 37831-0117

Medical
Sciences
Division

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Fun Fong

FROM: Marta V. Rivera/Secretary, Committee on Human Studies

RE: Status Reports on Active Proposals

DATE: May 12, 1992

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by May 26. (If additional space is needed, please use the back of this form or attach extra sheets.)

Title of Project: Amendment to IND for CA-DTPA to Allow Its Use in Aerosol Form

Proposal No. 55 DATE APPROVED: 1978

Fun Fong/MD
Signature of Principal Investigator

6/26/92
Date Signed

1. Report progress made in the past year.

See attached

2. Report any complications.

1144653

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

To: Dr. Fun H. Fong/Robert C. Ricks

From: Dr. Karl Hubner, Chairman
Committee on Human Studies

Date: August 5, 1992

Re: Committee Action on Active Proposals

Your project number 55 "Amendment to IND for Ca-DTPA to Allow Its Use in Aerosol Form" was reviewed and approved for continuation at our last meeting on July 31, 1992.

Progress reports of all active proposals will again be reviewed at our next meeting to be held in the fall of 1992.

/mvr

1144654

Proposal No. 55: Ca-DTPA IND Amendment for Aerosol Administration

1. Report progress made in the past year.

   Clinical Experience:

   For the reporting period June 1, 1991 - May 31, 1992, 52 physicians (ORISE's Principal Investigators plus 47 co-investigators in the U.S. and 1 each in Canada, England, Brazil, Japan, and Spain) were authorized on DOE's IND to administer Ca-DTPA for treatment by aerosol for real or suspected internal contamination with transuranic elements.

   Six patients received Ca-DTPA by aerosol for a single dose for treatment of suspected plutonium or americium internal contamination. Two of these six patients received additional Zn-DTPA chelation therapy by aerosol.

2. Report any complications.

   There were no adverse effects from these administrations.

3. Are there any planned changes?

   No.

4. Do you wish the project to be continued.

   Yes. Collection of data from aerosol inhalation of Ca-DTPA must continue until a clearly superior route is found. A comprehensive study of Ca-DTPA and Zn-DTPA excretion data mentioned in previous proposals (47, 61) will also reflect the effects of aerosol administration and give an indication as to the ultimate duration of this study.

5. Comments.

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ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Fun H. Fong/ Dr. Robert C. Ricks

From: Marta Rivera, Secretary Committee on Human Studies

RE: Status Report on Active Proposals

Date: April 28, 1993

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposal present a progress report to the Committee on the status of the proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions and add other information you feel pertinent and return by May 14. (If additional space is needed, please use the back of this form or attach extra sheets).

Title of Project: "Amendment to IND for Ca-DTPA to Allow Its Use in Aerosol Form"

Proposal No. 55

RCRicks, PhD
Signature of Co-Principal Investigator

6/1/93
Date Signed

Signature of Co-Principal Investigator

6 Jun 93
Date Signed

1. Report progress made in the past year.

   Please see pages attached.

2. Report any complications.

   Please see pages attached.

1144656

Proposal No. 55: Ca-DTPA IND Amendment for Aerosol Administration

1. Report progress made in the past year.

   Clinical Experience:

   For the reporting period June 1, 1991 - May 31, 1992, 52 physicians (ORISE's Principal Investigators plus 47 co-investigators in the U.S. and 1 each in Canada, England, Brazil, Japan, and Spain) were authorized on DOE's IND to administer Ca-DTPA for treatment by aerosol for real or suspected internal contamination with transuranic elements.

   Six patients received Ca-DTPA by aerosol for a single dose for treatment of suspected plutonium or americium internal contamination. Two of these six patients received additional Zn-DTPA chelation therapy by aerosol.

2. Report any complications.

   There were no adverse effects from these administrations.

3. Are there any planned changes?

   No.

4. Do you wish the project to be continued.

   Yes. Collection of data from aerosol inhalation of Ca-DTPA must continue until a clearly superior route is found. A comprehensive study of Ca-DTPA and Zn-DTPA excretion data mentioned in previous proposals (47, 61) will also reflect the effects of aerosol administration and give an indication as to the ultimate duration of this study.

5. Comments.

Oak Ridge
Associated Universities
Post Office Box 117
Oak Ridge, Tennessee 37831-0117

To: Dr. Fun H. Fong/Robert C. Ricks

From: Dr. William Calhoun, Chairman
Committee on Human Studies

Date: June 29, 1993

Re: Committee Action on Active Proposals

Your project number 55 "Amendment to IND for Ca-DTPA to Allow Its Use in Aerosol Form" was reviewed and approved for continuation at our last meeting on June 25, 1993.

Progress reports of all active proposals will again be reviewed at our next meeting to be held in the fall of 1993.

/mvr

1144658

Proposal No. 55

1. Report progress made in the past year.
   Clinical Experience:

   For the reporting period June 1, 1990 - May 31, 1991, 52 physicians (ORISE's Principal Investigators plus 47 co-investigators in the U.S. and 1 each in Canada, England, Brazil, Japan, and Spain) were authorized on DOE's IND to administer Zn-DTPA for treatment of real or suspected internal contamination with transuranic elements.

   Six patients received Ca DTPA by inhalation for a single dose by aerosol for treatment of suspected plutonium or americium internal contamination.

2. Report any complications.

   None

3. Are there any planned changes?

   No.

4. Do you wish the project to be continued.

   Yes. Collection of data from aerosol inhalation of Ca DTPA and Zn DTPA must continue until a more clearly superior route is developed. A comprehensive study of Ca DTPA and Zn DTPA excretion data mentioned in previous proposals (47, 61) will also reflect the effects of aerosol administration and give an indication as to the ultimate duration of this study.

5. Comments.

1144659

ORAU/ORNL COMMITTEE ON HUMAN STUDIES

TO: Dr. Robert C. Ricks

FROM: Marta V. Rivera/Secretary, Committee on Human Studies

RE: Status Reports on Active Projects

DATE: July 11, 1994

The guidelines for the ORAU/ORNL Committee on Human Studies require that all principal investigators of ongoing proposals present a progress report to the Committee on the status of their proposals each year. Each proposal must be reviewed by the Committee yearly for research projects to continue. Please answer the questions below and add any other information you feel pertinent and return by July 20. (If additional space is needed, please use the back of this form or attach extra sheets. Please include your name, project number, and date on additional sheets)

Title of Project: Amendment to IND for Ca DTPA to Allow its Use on Aerosol Form

Project No. ORAU-55

First approved: June 6, 1991
Most recent re-approval for continuation: June 25, 1993.

RCRicks
Signature of Principal Investigator

7/27/94
Date/Signed

1. Report progress made in the past year.

   There were no administrations of Ca DTPA in the aerosol form during the FY 92/93 DTPA reporting period.

2. Report any complications.

   N/A

1144660

3. Are there any planned changes?

   See cover memorandum dated July 25, 1994, requesting consolidation of Ca DTPA Project numbers and consolidation of Zn DTPA Project numbers.

4. Do you wish the project to be continued?

   Yes

5. Comments.

   None.

PROTECTING HUMAN SUBJECTS

Office of Health and Environmental Research — U.S. Department of Energy

PROJECT SUMMARY

Policy: Research activities that involve human subjects and that are funded by the U.S. Department of Energy (DOE), conducted in DOE facilities, or conducted by DOE personnel must be approved or exempted from review in accord with 10 CFR Part 745. Failure to comply with these regulations may prevent DOE from authorizing or funding an activity, or may lead the Department to suspend or terminate the project.

Directions: Institutions must complete this form, providing the data listed below in the format indicated, for each research activity each year. Forms must be sent to the appropriate DOE Field Office, which will forward them to DOE Headquarters (Protection of Human Subjects, Mail Station ER-70, Office of Health and Environmental Research, U.S. Department of Energy, Washington, DC 20585).

1. Project Title: Amendment to IND for Ca-DTPA to Allow its Use in Aerosol Form

2. Principal Investigator: J. Glenn Davis, M.D., M.P.H.
Telephone Number: (615) 576-3090

Mailing Address — Include full name of performing institution.
Oak Ridge Institute for Science and Education, Medical Sciences Division,
P.O. Box 117, Oak Ridge, TN 37831-0117

3. Institutional Assurance Number (if issued)[1]: MPA 1394

4. Project Number[2]: ORAU 55

5. Annual Funding: Subproject of ORAU 47
Give actual funding or check the amount closest to the estimated total for the current Federal fiscal year, whether requested or obtained. Include both direct and indirect costs.

☒ Actual Funding $ 17,500 (ORAU 47)

☐ $10,000 ☐ $100,000 ☐ $500,000 ☐ $1,000,000 ☐ $5,000,000

6. Funding Sources
A. Name DOE Program Office (see list in attachment), if applicable.
B. Name non-DOE sources of funding (up to two), if applicable.

A. DOE Program Office: Office of Occupational Medicine (EH 43)

Contact Person: Agatha Francis
Telephone Number: (301) 903-5591

B. Non-DOE Source

Non-DOE Source

[1] Under 10 CFR Part 745, institutions are required to file an assurance of compliance with the regulations with DOE or the Department of Health and Human Services. The Department involved may then issue an assurance number.

[2] Each project must have a unique identification number assigned by the institution—for example, ANL-94/101.

1144662

7. The Project has been reviewed and approved by the Institutional Review Board (IRB) as required under 10 CFR Part 745.

A. Type of Review

☒ Full Board
For a list of research not requiring IRB review, see Attachment.

☐ Expedited
For an explanation of projects that qualify for expedited reviews, see Attachment.

B. Type of Approval

☐ New ☐ Annual Renewal ☐ Other

C. IRB Approval Date

1978, reviewed and approved for continuation annually through June 1994.

8. This Project involves the following collaborating institutions (list a maximum of two):

None

9. Vulnerable Populations

☒ This project does not involve vulnerable populations.

☐ This project involves the following vulnerable populations:

☐ Minors ☐ Mentally Disabled ☐ Prisoners
☐ Fetuses, Pregnant Women, In Vitro Fertilization ☐ Economically or Educationally Disadvantaged

10. Type of Research

Check all categories that apply.

☐ Epidemiology (using personally identifiable data)--
- ☐ Using data collected directly from human subjects.
- ☐ Using existing data.

☐ Diagnostic studies using radiation or chemical agents in tracer amounts.

☐ Therapeutic studies using radiation or chemical agents.

☐ Studies of exposure, effects, health, or monitoring using human urine, blood, other body fluids, cells, or tissues--
- ☐ Specimens collected directly from human subjects for this project.
- ☐ Specimens obtained from secondary sources (e.g., hospitals, laboratories).

☐ Instrument development and testing using human subjects.

☒ Surveys that collect personally identifiable data.

☐ Environmental studies using human subjects to evaluate weatherization options, habitat alteration, or similar.

☒ Other. Please identify Therapeutic pharmacologic agent

1144663

11. Abstract

Provide a brief abstract that includes the following information:

A. Summarize the objectives and methodology of this research project. (Explain clearly why it belongs in the categories checked in Item 10).

Amends IND for Ca-DTPA to include the use of Ce-DTPA in aerosol form

B. Specify the number of human subjects involved each year.

Variable, generally less than 10

C. Describe the involvement of human subjects and the risks, if any, to which they are exposed.

See ORAU-47

Ca-DTPA was previously approved by FDA (INDA 4041) for Phase 2 investigations of decorporation of internally deposited actinide contaminants by slow IV infusion or IM injection. This project amends the INDA to include administration of Ca-DTPA in aerosol form. Data are compiled by ORISE and maintained for DOE in DOE System of Records #73 (DTPA Registry; see ORAU 61)

D. List the chemical or radioactive materials, if any, that are used in the study, and identify the route of exposure.

Ca-DTPA: a non-radioactive therapeutic pharmaceutical administered by inhalation via a nebulizer.

See reverse for approval signatures.

The official signing below confirms that the information provided on this form is correct and that the institution assumes responsibility for future reviews, approvals, and submissions of project summaries, which are all required at least once a year.	
Signature of Institution Official	Date 2/28/94
Printed or Typed Name J. Glenn Davis, M.D., M.P.H.	Telephone Number (615) 576-3090

For DOE USE Only

Date Received by ER-70	Date Accepted _____ Returned to Originator _____
Reason for Return	
DOE Reviewers	

1144665