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/s/

Robert Yaes
8/10/04 04:57:23 PM
MEDICAL OFFICER

Sally Loewke
8/10/04 05:00:12 PM
MEDICAL OFFICER
Please see Deputy Director Memo

NDA # 21-749
Product: Ca-DTPA
Sponsor: Hameln Pharmaceuticals GmbH

MEDICAL OFFICER REVIEW

(Addendum to Ca, Zn-DTPA review)
July 19, 2004

1. Background Information:

This document is an addendum to the previous review, concerning the deaths and serious adverse events that were reported from a NDA application —— of another Ca-DTPA product. An overview was presented in a Medical Officer's Review dated 3/2/64. Ca-DTPA was considered as a possible treatment for ———— in the 1960s, and a NDA application ———— was filed for Ca-DTPA, under the brand name ————————
Three deaths and two serious adverse events were reported in a warning letter, dated June 14 1963, sent by the sponsor to physicians involved in clinical studies with ——

At UCLA medical center two patients with advanced liver disease and hemochromatosis were treated with Ca-DTPA 4g IM/day. One patient after receiving 14g Ca-DTPA became comatose and died 11 days later. A second patient also receiving 4g IM/day complained of nausea vomiting and pain and loss of sensation in the legs, but recovered after treatment was stopped. At the ———— two patients with severe hemochromatosis were treated with daily IM Ca-DTPA (the dose is not specified). After two weeks of treatment, both patients became obtunded and died. A third patient under treatment for auto-immune hemolytic anemia (dose and number of doses not specified) developed dysarthria, drowsiness, mouth ulcers, alopecia and drop in reticulocyte count platelet count and hematocrit. After cessation of treatment and treatment with prednisone, the patient recovered.

Pre clinical studies had shown;
Acute LD50 in mice and rats was 2800 and 2000 mg/kg respectively
Subacute toxicity studies in dogs showed
200 mg/kg/day IV x 4 weeks showed no evidence of toxicity

Reviewer's comment: 200 mg/kg/day would correspond to 14 g/day in a 70 kg man

500 mg/kg/day IV resulted in weight loss in 1 of 4 dogs

1000 mg/kg/day IV resulted in the death of 3 of 7 dogs by the third day of massive GI hemorrhage. Bone marrow aspirates demonstrated a cellular marrow in several dogs

The treatment of a total of 74 patients was reported in this NDA as shown in table 1 below

Table 1 Patients treated with Ca-DTPA reported in NDA

Diagnosis	Patients	Deaths
Hemochromatosis	19	2 (10.5%)
Transfusion Hemosiderosis	18	1 (5.6%)
Thalessemia Major	20	0
Acute Iron Overload	6	0
Acute or Chronic Lead Poisoning	6	0
Plutonium Inhalation	5	0
Total	74	3 (4%)

An additional three patients suffered serious adverse events including mental obtundation with ulceration of the lingual and buccal mucosa, Nausea and vomiting with lethargy weakness and paresthesias and nausea and vomiting with epistaxis, stomatitis and dermatitis. Symptoms in these three patients cleared when treatment was s discontinued.

Reviewer's comment; These symptoms are consistent with injury to organs with rapid cell turnover (bone marrow, skin and intestinal mucosa) due to impaired DNA synthesis from Zinc depletion. At the time of this review, the importance of zinc containing enzymes in DNA synthesis may not have yet been known.

One death and one SAE are described in detail in physician's notes. — was a 46 year old Hispanic female with advanced liver disease with persistent hyperbilirubinemia, hypoalbuminemia, PT varying between 8% and 31% of normal and recurrent bleeding from the nose gums and vagina, and mild diabetes. She had recurrent episodes of encephalopathy usually

associated with bleeding. She was started on treatment for hemochromatosis with 4g/day Ca-DTPA IM on —— The next day she developed nausea and vomiting. On day 4 she again developed nausea and vomiting and became stuperous. She began oozing blood from the nose gums and oropharynx DTPA was stopped after a total dose of 14g. She became comatose and died on —— The physician attributed death to hepatic coma.

Reviewer's comment: Given the history, cause of death could also have been an intracranial bleed. If Ca-DTPA produced a lower platelet count in a patient with an already low PT it could have been a contributing factor in her death.

— was a 53 year old white male with a history of heavy alcohol use and hepatic decompensation with ascites. A liver biopsy showed heavy infiltration with iron and the patient was treated for hemochromatosis with 4g Ca-DTPA IM /day. On the day after treatment patient complained of nausea, vomiting, lethargy and pain, weakness and numbness in the legs. Ca-DTPA was stopped after a total dose of 10 g and the symptoms slowly subsided.

Reviewer's comment: The fact that symptoms started soon after treatment began and subsided after treatment was stopped makes it likely that the symptoms were treatment related.

2. Assessment:

The toxicity of Ca-DTPA is well known from animal studies. Ca- DTPA is known to deplete trace metals, particular zinc, which is an essential component of enzymes involved in DNA synthesis. Consequently Ca-DTPA toxicity is manifested in organs with rapid cell turnover such as bone marrow and oral mucosa. The toxicity of Ca-DTPA increases with the protracted treatment and/or with multiple daily administration. While there is insufficient information available to definitely attribute these deaths and serious adverse events to Ca-DTPA, the severity of those adverse events is of concern. In addition to a higher dose and multiple administration, IM injection, with a slow release into the systemic circulation, would represent also a protracted treatment situation. At this time, it appears that those serious events only occurred in the patients with severe underling conditions (advanced liver disease and hemochromatosis) who were treated with multiple doses of IM Ca-DTPA at 4 grams per day.

On the other hand, before Zn-DTPA became available a number of patients, internally contaminated in occupational accidents at nuclear weapons laboratories, were treated by REAC/TS with multiple doses of Ca-DTPA with no reported adverse events attributed to the treatment. In one example one individual who was heavily contaminated with Am received 331 doses of Ca-DTPA during the first year of treatment without reported ill effect.

In the current submission (NDA 21-749), only a single initial dose of 1 gram Ca-DTPA is recommended intravenously. Treatment with Ca-DTPA in accordance with such a recommendation should be considered safe from a population perspective, given the safety information presented here, the REAC/TS data and potential benefit of the drug product. The product labeling, however, should be more specific to provide sufficient safety information and recommendations so that the health care professionals and patients who are exposed to the radioactive materials could make an informed decision regarding Ca-DTPA treatment (See recommendations below).

3. Recommendation:

- A statement that "IM injection is not ——— " should be added to the DOSAGE AND ADMINISTRATION section of the product labeling;
- The safety information presented here should be added to the OVERDOSAGE section of the product labeling. The following is the proposed statement:
  "In previous clinical studies, three deaths were reported in patients with sever ——— hemochromatosis who were treated with daily IM Ca-DTPA dosed at 4 gram per day. One patient became comatose and died after receiving a total of 14 gram Ca-DTPA, and the other two died after two weeks of treatment".

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/s/

Robert Yaes
8/10/04 03:50:15 PM
MEDICAL OFFICER

Sally Loewke
8/10/04 04:55:38 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Rockville MD 20857

Date: 01/29/03

To: Patricia Love, M.D.
Director, DMIRDP (HFD-160)

From: Mitchell Mathis, M.D.
Medical Officer
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Through: Brad Leissa, M.D.
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Dianne Murphy, M.D.
Director
Office of Counter-Terrorism and Pediatric Drug Development (HFD- 950)

Subject: Review of Radiation Emergency Assistance Center/Training Site (REAC/TS) clinical data on the use of Calcium DTPA and Zinc DTPA for the treatment of internal radiation contamination.

ABBREVIATIONS

AE	Adverse Event
Am	Americum
BUN	Blood Urea Nitrogen
Ca-DTPA	Calcium Diethylenetriaminepentaacetate
Cf	Californium
Cm	Curium
CNS	Central Nervous System
CRF	Case Report Form
Cs	Cesium
DOE	US Department of Energy
dpm	Decays per minute
EEF	Excretion Enhancement Factor
EEFD	Excretion Enhancement Factor Dose
g	Grams
GI	Gastrointestinal
GU	Genitourinary
hpf	High Power Field
IAEA	International Atomic Energy Agency
I.M.	Intramuscular
I.V.	Intravenous
lpf	Low Power Field
Micro	Microscopic examination
nCi	nanocurie
Neb	Nebulized
Np	Neptunium
NR	Not Recorded
ORISE	Oak Ridge Institute for Science and Education
PMHx	Past Medical History
Pu	Plutonium
RBC	Red Blood Cell
REAC/TS	Radiation Emergency Assistance Center/Training Site
RDD	Radiological Dispersal Device
SBP	Systolic Blood Pressure
U	Uranium
UA	Urinalysis
WBC	White Blood Cell
Y	Yttrium
Zn-DTPA	Zinc Diethylenetriaminepentaacetate
Zr	Zirconium

OCTAP/DCT Consultation Report
Ca/Zn-DTPA

IND: 4,041
14,603

Drugs: Generic: Ca-DTPA/Zn-DTPA
Chemical: Calcium or Zinc Diethylenetriaminepentaacetate
Trade: none

Pharmacological Category: Radioprotectant

Routes of Administration: IV

How Supplied: 1 g ampoules

Proposed Dose: 1 g IV or nebulized

Proposed Indication: [redacted] (Plutonium, Americium, Curium, [redacted]).

Sponsor: Oak Ridge Institute for Science and Education (ORISE)

Manufacturer: Heyl GMBH (Germany)

Related Drugs: Prussian Blue

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EXECUTIVE SUMMARY

Recommendations

Ca-DTPA and Zn-DTPA are safe and effective for the removal of internalized transuranic radionuclides.

A Phase 4 commitment should be required to monitor these products for adverse events and measures of efficacy post approval. This monitoring should include, at a minimum, those items listed on the attached Case Report Forms, as well as long-term follow up to evaluate the adverse consequences from exposure to internalized radiation sources.

Background

Transuranic radionuclides are radioactive isotopes with an atomic number greater than that of uranium. Military and civilian populations are at risk of internal exposure to particulate transuranic radioactive material. This risk comes from the potential use of the radiological dispersion device (RDD: "dirty bomb") as a terror weapon, as well as from nuclear fallout and nuclear power/weapons processing plant accidents.

Particulate radiation is a distinctly different clinical problem from penetrating radiation because particles of radioactive heavy metals can be internalized by inhalation, ingestion, or absorption from a wound. Internalized radioactive particles represent a health hazard because they continuously emit radioactivity to internal radiosensitive tissues.

Transuranic isotopes are absorbed from the exposure site (usually lung or wound) in ionic form. Ionized radioactive metals are transported in the blood and over time are deposited in the liver and bone[1]. Once internalized, normally tolerable amounts of alpha (short track length) radiation become toxic to internal tissue. Internal radiation exposure can result in acute changes (apoptosis or "cell death" and tissue fibrosis), and chronic health problems (mutagenesis, oncogenesis, and death).

Chelators are compounds that react with metals to form ionic complexes. Complexes of metal and chelator are less reactive than free metal ions and are more readily excreted in the urine. The elimination of chelated metals from the body is termed decorporation. Decorporation is the goal of chelation therapy.

Radiation-induced mutagenesis increases with radiation dose, and there is a body of evidence that supports using heavy metal chelators to remove circulating transuranic

1 Dolphin GW, Review of some problems associated with the use of chelating agents for the removal of incorporated radionuclides from humans, Diagnosis and treatment of incorporated radionuclides: proceedings of an international seminar organized by the International Atomic Energy Agency and the World Health Organization, 1976.

elements before they are deposited in the liver and bone[2,3]. Pre-clinical studies have shown that chelation therapy increases the latent period between plutonium exposure and death in dogs.[4] Chelation reduces the incidence of osteosarcoma in plutonium-contaminated mice[5].

Clinical experience of the effectiveness of chelators includes exposure and treatment data gathered by the Radiation Emergency Assistance Center/Training Site (REAC/TS) under contract with the Department of Energy (DOE), and it is the purpose of this review to examine and summarize these data for safety and efficacy information.

The DOE data derive from 685 accidental exposures to transuranic elements (primarily plutonium) treated with either zinc or calcium DTPA. No concurrent placebo control arm is available for comparison, a placebo control (no intervention) would be considered unethical based on the known morbidity and mortality of significant radiation exposure and the evidence of efficacy from pre-clinical studies. The database itself is comprised of the most complete set of data available to evaluate the safety and efficacy of DTPA in humans, and may be considered internally controlled given that pre- and post- treatment values for urinary radiation exretion have been obtained for the same (indivdual) patient.

NATURE OF REAC/TS DATA AND ANALYSIS

Primary data collected during the treatment of patients under the INDs held by the Oak Ridge Institute for Science and Education's (ORISE) REAC/TS were submitted to FDA. The REAC/TS data was collected over a period of 42 years and there was some variability in the format and content of the case report forms as would be expected given the extended time frame and changes in medical practice over the data collection period. Case report forms included clinical information, such as medical history, physical exam, vital signs, and clinical laboratory data.

The individual case report forms were entered into an MS Access database and descriptive queries were run to summarize the data. Additionally, summary statistics were calculated when the data were amenable to statistical analysis.

These data represent a cohort of cases with mild exposure to transuranic radionuclides. None of those exposed had symptoms consistent with acute radiation syndrome. They represent limited exposures to radioactive particulate material in a relatively conrolled environment.

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2 Breitenstein BD *et al*, DTPA Therapy: The U.S. experience, 1958-1987, International REAC/TS conference on the medical basis for radiation accident preparedness, proceedings of the second international conference, 1990.

3 Norwood WD, Therapeutic removal of plutonium in humans, Health Physics 1962; (8): 747-750

4 Bruenger *et al*, Effectiveness of DTPA treatments following the injection of particulate plutonium, Int. J. Radiat. Biol. 1991;(60): 803-818.

5 Jones CW *et al*, Reducing the cancer risk of 239-Pu by chelation therapy, Rad. Research 1986; (107): 296-306.

REVIEW OF THE REAC/TS DATABASE

The REAC/TS database consists of primary data collected for 685 exposures to transuranic radionuclides treated with Ca- and/or Zn-DTPA. The majority of the data collected are descriptive, and they are presented here in summary form so that generalizations can be made regarding various aspects of the population, the exposure to radionuclide, and the assessment and treatment of those exposed. Safety data were obtained from each case for which adverse events or abnormal laboratory values were reported. The criteria used to assess efficacy were prospectively defined.

Prior to entering the case reports into the database, an analysis plan was devised to identify cases suitable for efficacy analysis. The most informative cases were considered to be those with urine bioassay data recorded prior to chelation (i.e. those with a a pre-chelation baseline). Additional cases were considered supportive if there was a sufficient "wash out" period (at least 5 days) between chelation doses where a reasonably accurate baseline urine radioactivity level could be determined.

Of the 685 exposures, 18 had documented urine radiation concentrations measured prior to the first dose of chelator. These 18 "efficacy cases" are examined separately from the entire group. (See below.)

The descriptive data for the entire database are outlined below. Where applicable, similar data for the 18 efficacy cases are included for comparison to the entire group.

Demographics

The patient database consists of primarily white, middle-aged men employed in the nuclear processing industry in the United States. (See Tables 1 and 2.) Six hundred and forty-six (646) individuals received at least one dose of either Ca- or Zn-DTPA. The majority of the treatments occurred in white males. However, there are data for 30 female, 58 African American and 7 Hispanic exposures. The oldest exposure was 64 years old. The youngest exposure was 10 years old. The mean age of exposure is 37.7 years. One pediatric, no pregnant, no geriatric, and no hepatic/real failure patients were identified. Twenty-nine (29) patients received multiple (2 to 5) radiation exposures. The total number of radiation exposures was 685.

Table 1. Demographics (n=646)

		n	% (n/N)
Gender	Male	591	91.5
	Female	30	4.6
	Not Specified	25	3.9
Race	Caucasian	400	61.9
	Hispanic	7	1.1
	African-American	58	8.9
	Not Specified	181	28.0
Age (Years)	Maximum	64	--
	Minimum	10*	--
	Not Specified	98	--
	Mean**	37.7	--

*Only one pediatric patient reported.
**Of those cases reporting age data.

Table 2. Demographics for Efficacy Cases (n=18)

		n	% (n/N)
Gender	Male	16	88.9
	Female	2	11.1
Race	Caucasian	12	66.7
	Hispanic	0	0
	African-American	1	5.6
	Not Specified	5	27.8
Age (Years)	Maximum	55	--
	Minimum	23	--
	Age Not Specified	3	--
	Mean*	37.2	--

* Of those cases reporting age data.

Exposure Radionuclides

The population was primarily exposed to plutonium (See Tables 3 and 4). Multiple radionuclide exposures typically consisted of plutonium and americum. There were 48 primary exposures to curium, which represent only 7% of the total exposures.

Table 3. Primary Radionuclide Exposure (n=685)

	No. of Cases	% of Total Exposure Cases (n=685)
^{238,239}Pu	532	77.7
^{241}Am	24	3.5
^{244}Cm	48	7.0
^{137}Cs	1	0.1
^{235}U	4	0.6
^{252}Cf	2	0.3
^{95}Zr	2	0.3
^{237,238}Np	2	0.3
^{90}Y	1	0.1
Reported as "not known"	40	5.8
Not reported	29	4.2
TOTAL	685	

Table 4. Primary Radionuclide Exposure for Efficacy Cases (n=18)

	No. of Cases	% of Total Exposure Cases (n=18)
^{238,239}Pu	16	88.9
^{244}Cm	1	5.6
Reported as Unknown	1	5.6

Route of Exposure

The majority of cases (63.5% of all exposures) represent inhalational injuries. (See Table 5) A typical case history is a breech in a glove box (a glove box is a confined work area where workers access the radioactive material/equipment via arm-length protective gloves reaching into a transparent protective box), which allows radioactive particles to be suspended in breathable air, and then the particles are inhaled. (Note: The majority of radioactive fallout and RDD ["dirty bomb"] victims would also be contaminated via inhalational exposure.)

Wounds represent the second most common route of exposure (18.5% of all exposures). Wounds become contaminated when a worker's protective clothing is penetrated, usually by hand tools or broken glass, resulting in the introduction of contaminated material into the wound. (Note: Blast injuries from RDDs or nuclear explosions may well be expected to produce contaminated wounds among victims close to the detonation.)

Ingestion is an uncommonly reported route of contamination in the REAC/TS population because of the relatively contained environment of exposure. Inadvertent ingestion likely occurred with the inhalational route of exposure given that a substantial fraction of all

inhaled substances are actually swallowed. (Note: In contrast, fallout from a nuclear explosion would be expected to contaminate large agricultural areas, which would increase the possibility of ingestion of transuranic radionuclides.)

Table 5. Exposure: Primary Route (n=685)

	No. of Cases	% of Total Exposure Cases (n=685)
Inhalation	435	63.5
Wound	127	18.5
Skin	34	5.0
Burn	7	1.0
Ingestion	1	0.1
Reported as "not known"	30	4.4
Not Reported	51	7.4

Table 6. Primary Exposure Route for Efficacy Cases (n=18)

	No. of Cases	% of Total Exposure Cases (n=18)
Inhalation	10	55.6
Wound	5	27.8
Not Reported	3	16.7

Bioassay Data

The REAC/TS database is comprised of collected case report forms (CRFs) accrued over a period of 42 years. The data collected from case to case are variable, and commonly use different units of measurements for radiation amountsThese observations are not entirely unexpected given changes in the ractice of medicine over 4 decades.

The steps in treating a radioactive isotope exposure patient are to[6]: 1) document a credible exposure, 2) decontaminate externally, and 3) assess the patient for internal contamination. Assessment of internal contamination can take a variety of forms depending upon the route of exposure.

In an inhalational exposure, nasal swabs are taken and assessed for the presence of radionuclide via a radiation detection device. While this procedure is not quantitative and is dependent upon technique and available equipment, it does offer the treating physician a qualitative measure of presence or absence of inhaled radioactive particles.

6 Guidance for radiation accident management, REAC/TS web address www.orau.gov/reacts/guidance.htm

In a wound exposure, a radiation detection device is held over the wound (after external decontamination) to detect remaining (internal) contamination. If the wound is internally contaminated, surgical debridement is considered the primary intervention to impede the uptake of radionuclide from the wound into the systemic circulation.

Regardless of the route of exposure, a measure of internal contamination may be established by examination of the urine for the presence of radioactive material. Transuranic elements are eliminated by glomerular filtration as their primary route of excretion. There are 286 cases in the database where **urine bioassay** data exist. (See Table 7.) The Urine bioassayis considered the clinical "gold standard" to assess whether chelation treatment is effective for the individulal patient, as well as to determine when it is appropriate to discontiue treament. In this review, all cases examined for efficacy had urine bioassay data.

A number of cases report **fecal bioassay** data in addition to urine data. (See Table 7.) Transuranic elements are not absorbed in any appreciable amount from the gut, but radiation is found in the feces early after inhalation exposures.[7] The swallowing of radioactive material deposited in the oropharynx or elsewhere in the upper respiratory treact explans these findings. After the radionuclide is absorbed into the systemic circulation, it is renally excreted and is no longer found in the feces. The latter is the major reason why ingestion is not considered a major route of exposure for these isotopes.

There are limited reports of **whole body counts** in the database. This procedure is one in which a large radiation counter is maneuvered over the patient and the amount of emanating radiation can be quantified. This procedure may be unable to detect short path alpha particles that are located deep within the chest cavity, bones, or liver. Whole body counts were not routinely used in assessing the patients in the database, primarily because of technical difficulties and its impracticality.

Table 7. Bioassay Data (n=286)

	No. of Cases	% of Total Exposure Cases (n=685)	% of All Cases with bioassay Data (n=286)
Urine	286	41.8	100
Fecal	123	17.9	43.0
Whole Body Count	11	1.6	3.8

Chelation Doses

Prior to 1976 patients with internal radiation contamination were uniformly treated with Ca-DTPA. After 1976, with the introduction of Zn-DTPA, the practice evolved into treating first with a dose of Ca-DTPA, followed by Zn-DTPA for the duration of treatment. Ca-

7 ICRP Publication 19, The metabolism of compounds of plutonium and other actinides, International Commission on Radiological Protection, May 1972.

DTPA was recognized to be less well tolerated over a longer treatment duration, but it was also recognized to more effectively promote the urinary excretion of radionuclides (i.e. was noted to be a more effective chelator) if given early after exposure[8]. The increased relative toxicity of Ca-DTPA has been ascribed to its chelating trace minerals (primarily zinc) necessary for proper mitotic and other sub-cellular processes.[9]

Dosing amounts and routes have developed over time. The most recent cases in the database were treated with Ca-DTPA as soon as practical after internal contamination was confirmed; and this was followed with Zn-DTPA for protracted therapy until urine bioassay data supported discontinuing drug therapy. The route of administration was dependent upon the exposure route with nebulized dosing favored for inhalation injuries and IV doses for wounds. There were several cases of topically applied DTPA for wound irrigation, but these did not represent a substantial proportion of the cases to draw any conclusions of safety or efficacy.

DTPA treatment regimens vary greatly from case to case in the database. While the majority of patients received a single dose of chelator, the maximum number of doses of Ca-DTPA per patient administered was 338 one gram doses given over 6.5 years; Zn-DTPA maximum number of doses was 574 one gram doses given over approximately 3.5 years (See Table 8.)

8 Goans R, The Medical Basis for Radiation Preparedness, Proceedings of the Fourth International REAC/TS Conference, Orlando, FL, 2001.

9 Volf V, Treatment of Incoporated Transuranium Elements, International Atomic Energy Agency Technical Report #184, 1978.

Table 8. Chelation Doses (n=685 exposures)

	Total Doses	% of Total Doses Given (n=4166)	% of Ca-DTPA Doses	% of Zn-DTPA Doses	# of Patients Dosed*	Range of Dosing	Modal Dose per Patient (n)*
Ca-DTPA							
IV	1578	37.9	55.6		293	1-338	1 (156)
Neb	800	19.2	28.1		326	1-57	1 (240)
Topical	29	0.7	1.0		19	1-3	1 (13)
IM	11	0.3	0.4		8	1-3	1 (6)
Oral	48	1.2	1.7		1	48	48 (1)
Not Specified	374	9.0	13.2		32	1-198	1 (9)
TOTAL	2840	68.2	100		632	1-338	1 (393)
Zn-DTPA							
IV	1217	29.2		91.8	48	1-574	1 (12)
Neb	99	2.4		7.5	18	1-20	1 (7)
Topical	4	0.1		0.3	3	1-2	1 (2)
IM	4	0.1		0.3	3	1-2	1 (2)
Oral	0	0		0	0	0	0
Not Specified	2	0.05		0.2	2	1	1 (2)
TOTAL	1326	31.9		100	62	1-574	1 (23)

Unit Dose = 1 gram

*Some individuals received both chelators via multiple routes.

Table 9. Chelation Doses for Efficacy Cases (n=18 exposures)

	Total Doses	% of Total Doses Given (n=82)	% of Ca-DTPA Doses	% of Zn-DTPA Doses	# of Patients Dosed*	Range of Dosing
Ca-DTPA						
IV	29	35.4	52.7		9	1-13
Neb	26	31.7	47.3		10	1-15
TOTAL	55	67.1	100		17	1-17
Zn-DTPA						
IV	24	29.3		88.9	4	1-9
Neb	3	3.7		11.1	1	0-3
TOTAL	27	32.9		100	4	1-9

Unit Dose = 1 gram

*Some individuals received both chelators via multiple routes.

EFFICACY REVIEW

Prior to entering the case reports into the database, an analysis plan was devised to identify cases suitable for efficacy analysis. The most informative cases were considered to be those with urine bioassay data recorded prior to chelation so that the effect of chelator on urine radiation can be measured from a pre-chelation baseline. Additional cases were considered supportive if there was a sufficient "wash out" period (at least 5 days) between chelation doses. This was a very conservative strategy, given the relatively short t ½ (90 minutes) of these chelators, and the minor contribution of the terminal t ½ (<1% at 24 hours).

Of the 685 exposures, 18 had documented urine radiation concentrations measured prior to the first dose of chelator. These 18 cases are examined separately from the entire group. (See below.)

Urine Activity Analysis

An analysis was performed using the first chelator dose in each of the 18 cases (See Table 10.). Case 495 is included in this analysis because there was a 12 day delay between the first and second dose of chelator. In humans, 99% of Ca-DTPA is excreted renally within 24 hours[10], therefore 12 days is an adequate interval to establish a baseline urine radiation concentration. The urine activity numbers for case 495 are taken from around the second dose. The sole case of first dose Zn-DTPA (#327) is omitted in the summary statistical calculations.

10 Stather JW *et al*, The retention of ^{14}C-DTPA in human volunteers after inhalation or intravenous injection, Health Physics: (44-1); 45-52, 1983.

Table 10. Urine Activity Ratio Calculations (n=18)

Case Number	Radionuclide(s)	First Chelator Dose	Urine Activity Prior to First Dose of ChelatorΨ	Urine Activity After first Dose of ChelatorΦ	Ratio of Post to Pre Urine Activity (EEF)*
12	^{239}-Pu	Ca-DTPA I.V.	7.58E-05 pm/ml	7.09E-03 dpm/ml	93.54
	^{241}-Am	Ca-DTPA I.V.	2.55E-04 dpm/m	1.01E-01 dpm/ml	396.08
13	^{239}-Pu	Ca-DTPA I.V.	6.37E-05 dpm/m	9.52E-04 dpm/ml	14.94
	^{241}-Am	Ca-DTPA I.V.	5.38E-04 dpm/m	6.55E-03 dpm/ml	12.17
27	^{238}-Pu	Ca-DTPA I.V.	2.63E-05 nCi/m	1.96E-03 nCi/ml	74.50
	^{239}-Pu	Ca-DTPA I.V.	2.63E-04 nCi/m	1.64E-02 nCi/ml	62.36
	^{241}-Am	Ca-DTPA I.V.	1.04E-02 nCi/m	1.68E-02 nCi/ml	1.62
44	^{238,239}-Pu	Ca-DTPA I.V.	20 dpm/L	32 dpm/L	1.6
261	^{239}-Pu	Ca-DTPA Neb	85 dpm/day	553 dpm/day	6.51
	^{241}-Am	Ca-DTPA Neb	0.5 dpm/L	6.4 dpm/L	12.8
263	^{238}-Pu	Ca-DTPA Neb	0.2 dpm/1.5L	0.8 dpm/1.5L	4.00
264	^{238}-Pu	Ca-DTPA Neb	0.7 dpm/1.5L	0.8 dpm/1.5L	1.14
265	^{238}-Pu	Ca-DTPA Neb	2.0 dpm/1.5L	3.0 dpm/1.5L	1.5
327	^{238}-Pu	Zn-DTPA Neb	0.6 dpm/1.5L	0.5 dpm/1.5L	0.83
495	^{238}-Pu	Ca-DTPA I.V.	0.2 dpm/day	5.3 dpm/day	26.5
516	^{238}-Pu	Ca-DTPA Neb	0.4 dpm/day	7.7 dpm/day	19.25
519	^{238}-Pu	Ca-DTPA I.V.	0.2 dpm/day	16 dpm/day	80.00
568	^{238}-Pu	Ca-DTPA I.V.	0.5 dpm/L	31 dpm/L	62.00
578	^{244}-Cm	Ca-DTPA I.V.	3 dpm/1.5L	3.2 dpm/1.5L	1.07
621	^{238}-Pu	Ca-DTPA Neb	0.1dpm/1.5L	3.6 dpm/1.5L	36.00
622	^{239}-Pu	Ca-DTPA Neb	0.1dpm/1.5L	0.7 dpm/1.5L	7.00
626	UNKNOWN	Ca-DTPA Neb	4.4 dpm/1.5L	2.0 dpm/1.5L	0.45
669	^{238}-Pu	Ca-DTPA Neb	7.1 dpm/day	320 dpm/day	45.07

Ψ dpm = decays per minute *EEF = Excretion Enhancement Factor ΦSee text regarding Case #495

Summary Statistics for Ratio Data	
Mean (IV)*	25.93
Mean (Neb)**	25.42
SD (IV)*	33.76
SD (Neb)**	28.21
Median (IV)	12.485
Median (Neb)**	19.25
Range (IV)	(1.14,396.08)
Range (Neb)**	(0.45,80.00)
* Omits outlier case 12 for 241-Am ** Omits case 327	

A ratio is calculated around the first chelator dose in each case (except #495, detailed above). This ratio represents a relative change seen in urine activity (concentration of radiation bound to chelator) in response to the chelator. This value has been termed the Excretion

Enhancement Factor (EEF)[11]. The EEF represents multiples of the baseline (pre-treatment) urine radioactivity if it is larger than one and fractions of the same if it is less than one. Calculating the ratio allows a comparison of the observed urine changes without consideration of units of radiation measure. These data can then be combined to describe the population. The mean change (outliers excluded) in first dose urine activity ratios was 25.9 for I.V. Ca-DTPA, and 25.4 with nebulized Ca-DTPA. Therefore, the mean increase in urinary excretion (EEF) attributable to the first dose of chelator is greater than 25 times the baseline, pre-treatment excretion for this population.

Maintenance Dosing in Efficacy Cases

The urine radiation response to first dose of chelator is discussed above. Often patients received maintenance doses of chelator after the first dose. Six (6) of the 18 cases identified for efficacy analysis had doses of chelator delivered after the initial dose. The effect seen with the first dose of chelator (increased urine radiation concentration) was also seen with subsequent doses of chelator in the multi-dose cases. Many of these subsequent doses had interpretable urine data because doses were greater than 24 hours apart from each other and an inter-dose baseline could be established. This inter-dose baseline is understood to be a conservative measure of urine radiation concentration because the patients had had previous chelation with documented urine radiation concentration increases. Put differently, because the maintenance dose population of patients had already been chelated, their inter-dose urine radiation concentration troughs measured around doses subsequent to the first would likely be higher than if they had never been chelated. Maintenance dose details for the efficacy cases are listed in Appendix D.

Each evaluable chelator dose after the first dose has been identified, and the ratio of urine radiation concentration post-dose is divided by urine radiation concentration pre-dose. This allows the calculation of an EEF about subsequent doses in the efficacy cases. This EEF for each dose is termed an EEFD (Excretion Enhancement Factor--Dose). EEFDs have been calculated for the multi-dose efficacy cases (see Appendix D) and grouped together by chelator and route of delivery into populations. Each EEFD in a population is related to the others in the series by setting the date of pre-chelation urine as day zero. These data can be represented graphically with EEFD on the y-axis and time on the x-axis. It can be seen from the graphs that subsequent doses of chelator in multi-dose cases produced an increase in urine radiation concentration.

11 Volf V, Treatment of Incoporated Transuranium Elements, International Atomic Energy Agency Technical Report #184, 1978.

Figure 1. EEFD Plot for Ca-DTPA (IV)

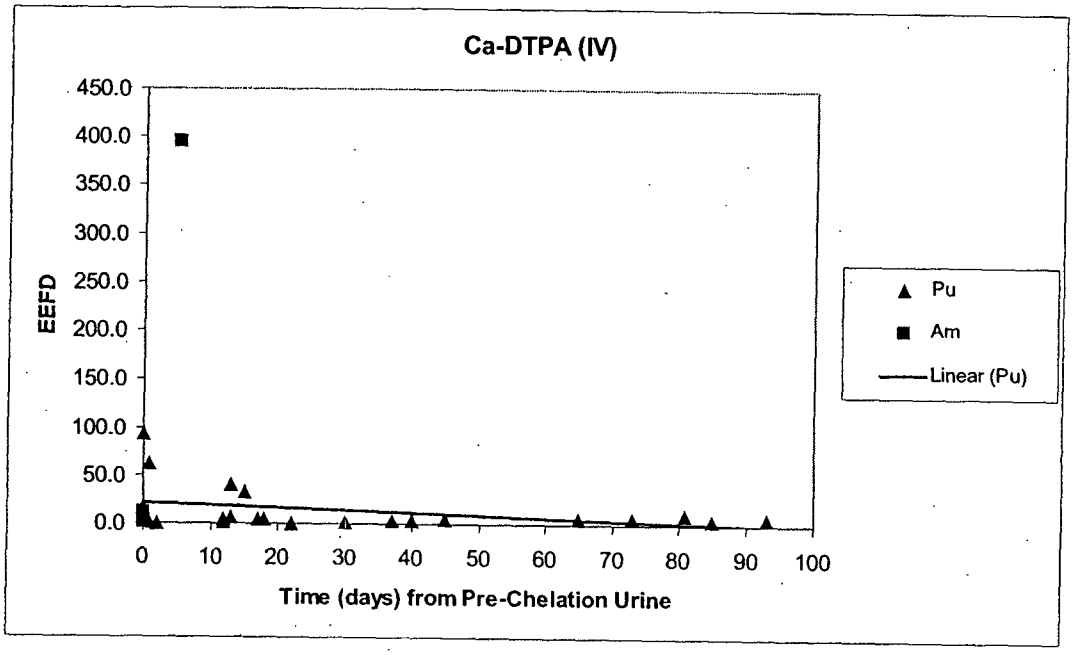


Figure 2. EEFD for Ca-DTPA (IV) with Single Outlier (case 12, 241-Am) Removed

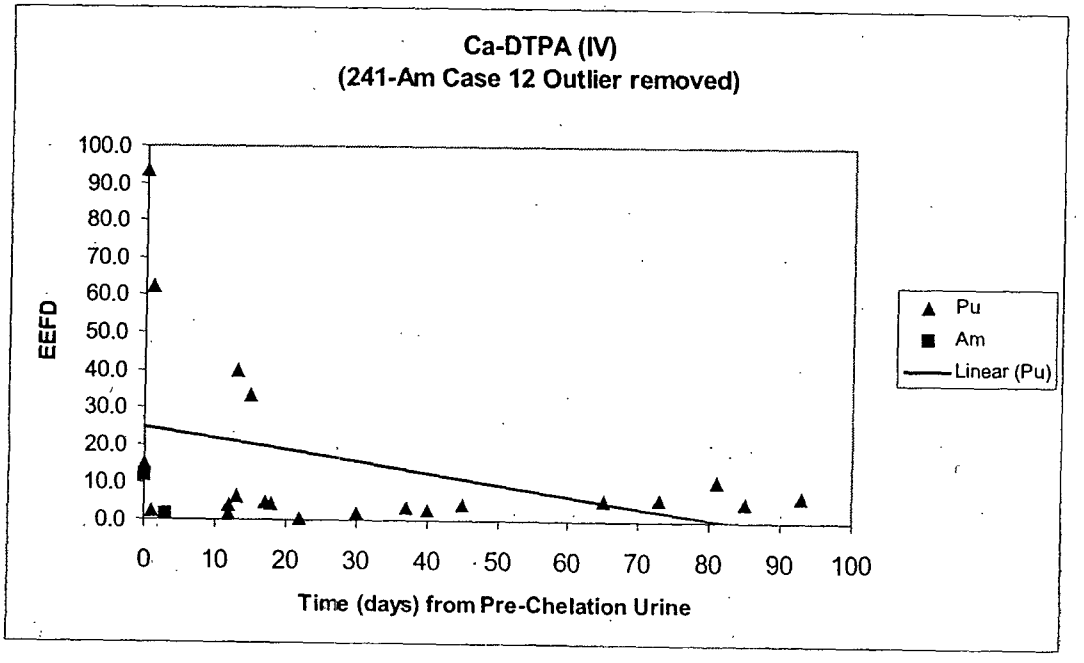


Figure 1 is a graphical representation of the Ca-DTPA (IV) given to the efficacy group patients. Both plutonium and americium are represented, but the plot is difficult to interpret because of the outlying americium point near day 0. Figure 2 is the same data with this outlying point removed. Figures 1 and 2 demonstrate that EEFDs for Ca-DTPA are greatest early in treatment and decrease over time for plutonium. The data for americium are not sufficient over time to draw the same conclusion.

Figure 3. EEFD Plot for Ca-DTPA (Neb)

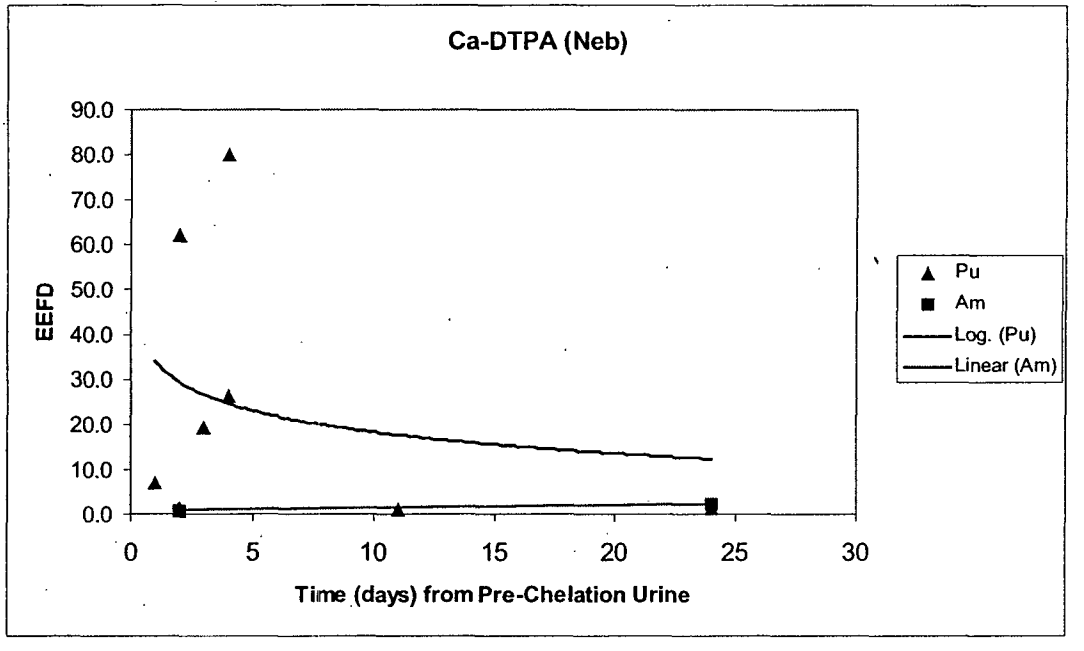


Figure 3 represents the graphical representation of the same type of data for the population receiving Ca-DTPA via nebulizer. Again, the greatest effect is seen in the first 5 days.

Figure 4. EEFD Plot for Zn-DTPA (IV)

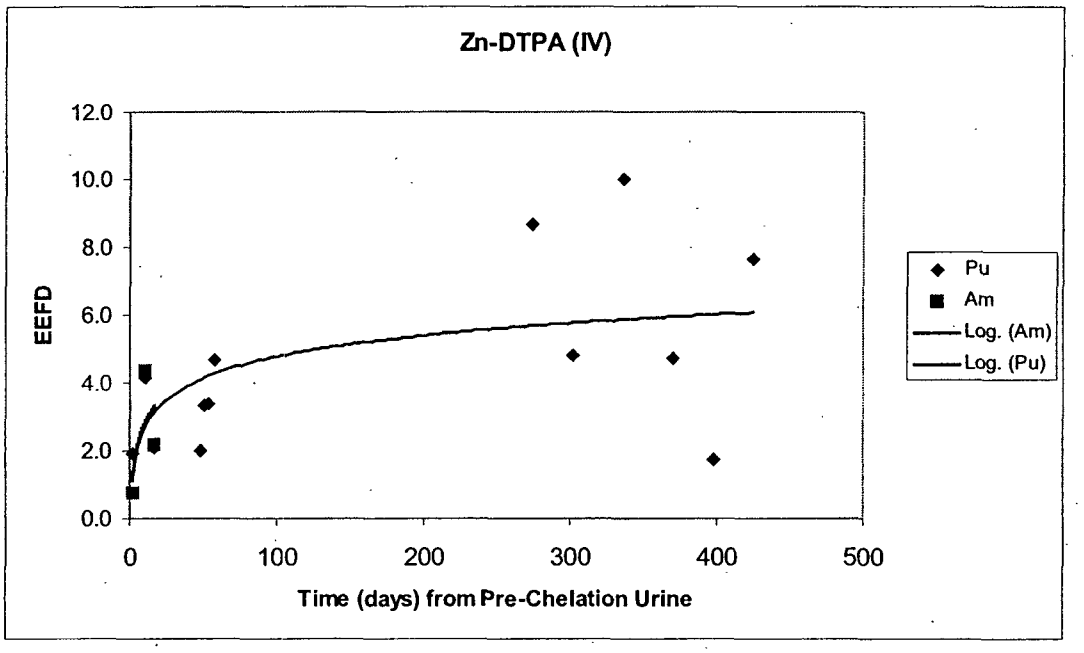
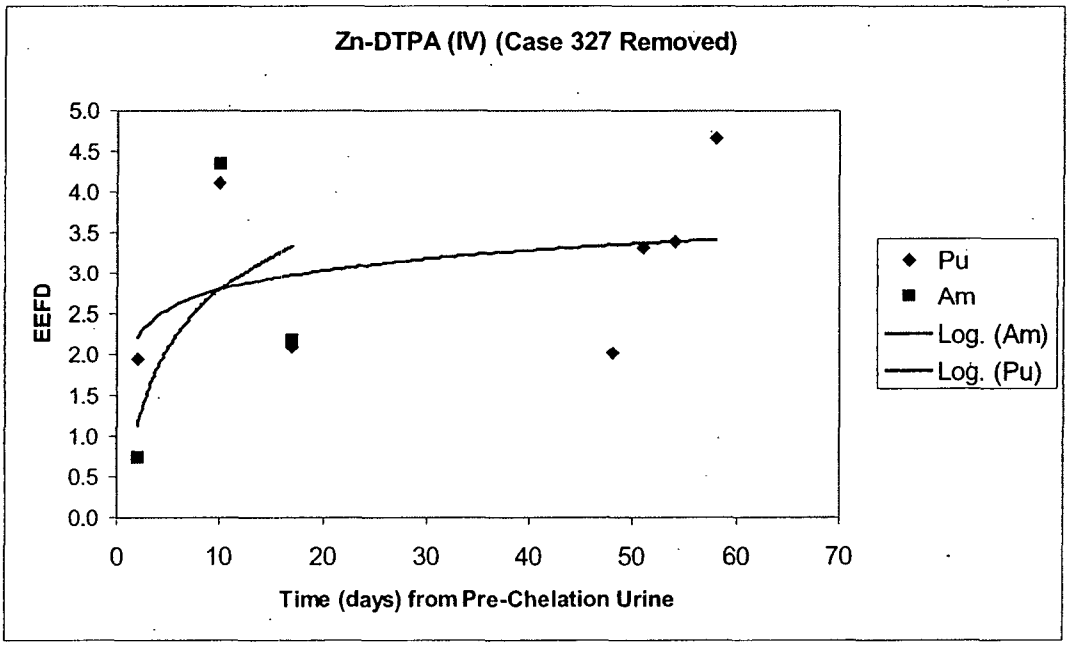


Figure 5. EEFD Plot for Zn-DTPA (IV) with Case 327 Removed



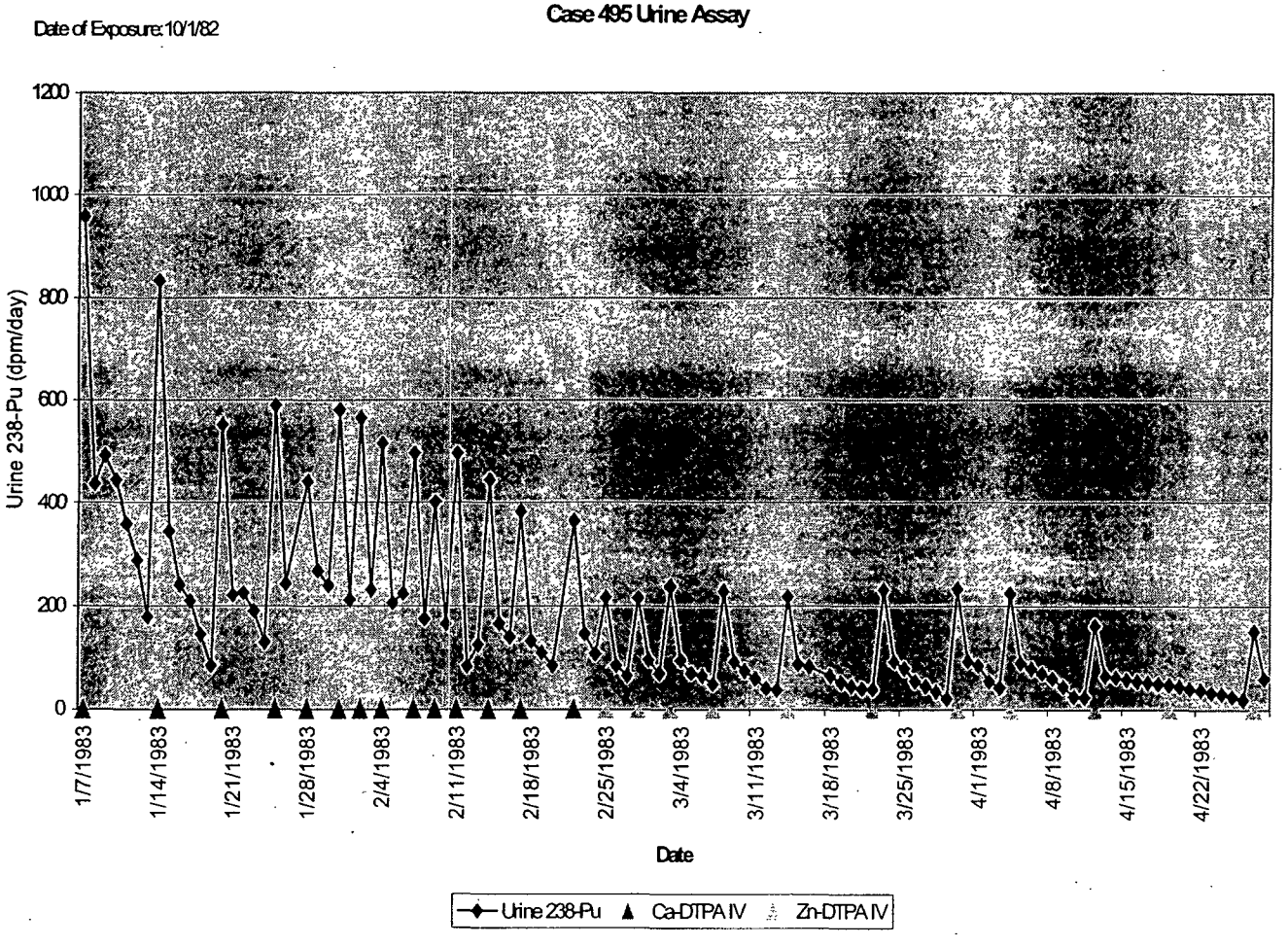
Figures 4 and 5 demonstrate the effect on EEFD of Zn-DTPA (IV). Increased excretion (greater EEFD) is seen over time in the population receiving Zn-DTPA (IV) for both plutonium and americium. The points in figure 4 after the 300-day mark are all from one case (#327). Data from case number 327 has been removed from the plot in figure 5.

There were insufficient data to draw conclusions for nebulized Zn-DTPA.

Graphical Representation of Individual Cases

The relationship of urine radiation concentration can be examined with regard to chelator dose timing over a treatment course. If urine concentration of radiation is plotted over time, a transient increase in urine radiation concentration can be seen to coincide with chelator dose. This relationship is clinically relevant because an increase in urine radiation concentration represents a decrease in body burden of radiation, which is the efficacy measure of interest. Data from three of the 18 cases are graphed in this manner below.

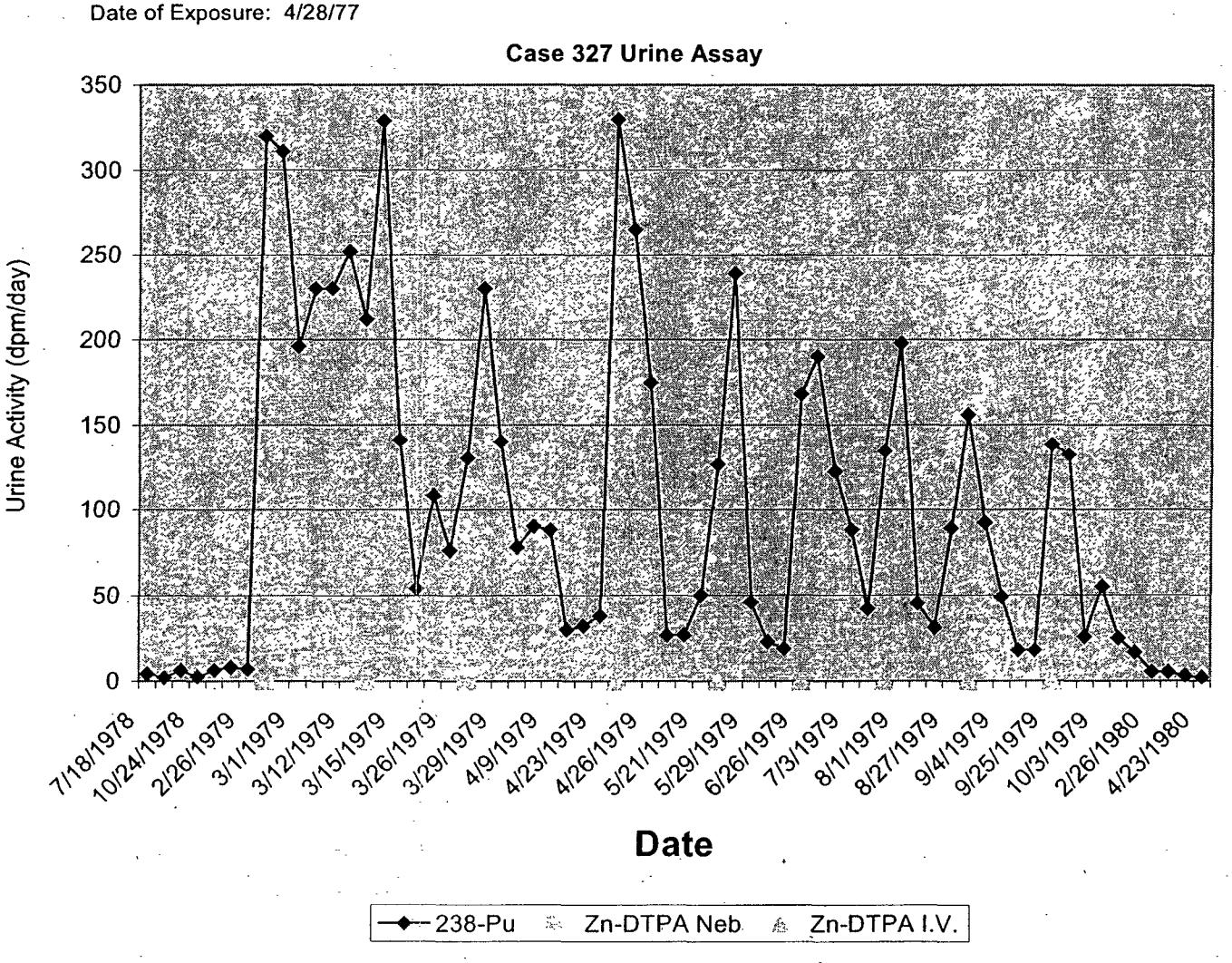
Figure 6. Case 495 Plot



Case 495 represents an example of the value of graphing these data as described. This patient was exposed on 10/1/1982 to Plutonium-238. The route of exposure was a contaminated wound. The y-axis represents urine concentration of radiation, measured in decays per minute per 24-hour urine. The x-axis is time with date of dosing and type of chelator dose indicated along the same axis.

The relationship of increased urinary radiation concentration (radiation excreted) can be seen to correspond to chelation dose timing. This relationship is most evident later in the treatment course when the dosing interval was greater. Both Ca-DTPA and Zn-DTPA were used in this patient's treatment. A downward trend in urine radiation concentration is evident over the course of treatment.

Figure 7. Case 327 Plot



Case 327 represents the data collected from a patient exposed to Plutonium-238 in an inhalational injury sustained on 4/28/1977. The y-axis represents urine concentration in decays per minute per 24-hour urine. The x-axis is time with date of dosing and type of chelator dose indicated along the same axis.

The relationship of increased urinary radiation concentration (radiation excreted) can be seen to correspond to chelation dose timing. Zn-DTPA was delivered by nebulizer and I.V. in this example. A downward trend in urine radiation concentration is evident over the course of treatment.

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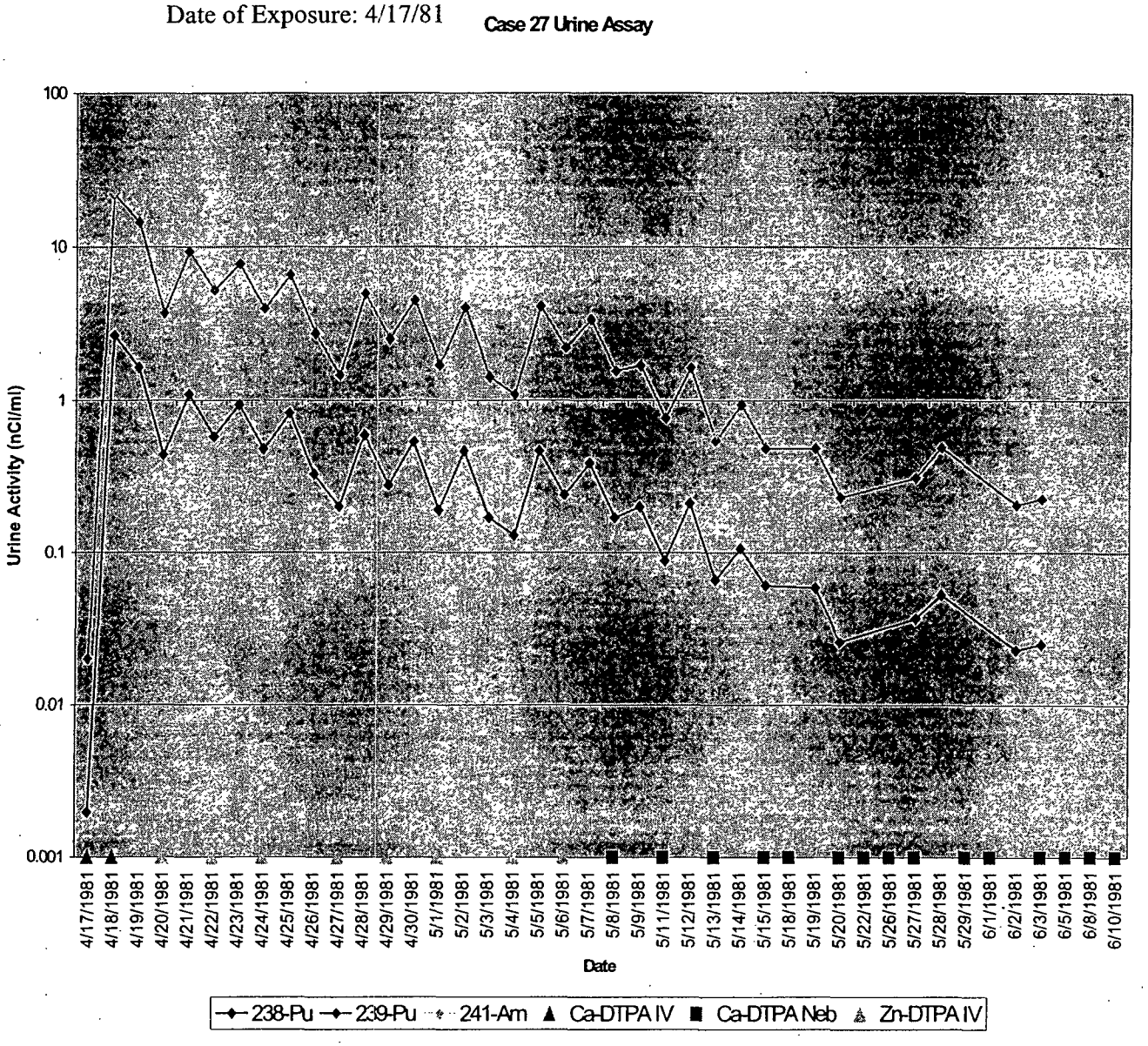
Figure 8. Case 27 Plot

Date of Exposure: 4/17/81



Case 27 represents the data collected from a patient exposed to Plutonium-238, Plutonium-239, and Americium-241 in a wound injury sustained on 4/17/1981. The y-axis represents urine concentration in nanocuries per milliliter. The x-axis is time with date of dosing and type of chelator dose indicated along the same axis.

The relationship of increased urinary radiation concentration (radiation excreted) of each radionuclide can be seen to correspond to chelation dose timing. Ca-DTPA and Zn-DTPA were used to treat this patient. A downward trend in urine radiation concentration is evident over the course of treatment.

Efficacy data from cases without first dose pre-chelation urine measurements

The majority of patients represented in the database were chelated as soon as possible after exposure to radionuclide, most often prior to collecting urine. This clinical procedure does not allow for the pre-chelation urine radiation excretion rate to be established, although to do so would be ethically questionable given that 24-hour urine collection would be required to establish such a "baseline". Calculations involving change of urine radiation from "baseline" cannot be performed in such cases, although a reasonable surrogate for the "baseline" might be urinary radiation excretion following chelator washout. The majority of the cases in the database were chelated prior to urine collection.

In addition, most cases in the database are single dose cases with the dose given prior to urine activity measurement. There is no interpretable efficacy data in these cases because there is no pre-chelation urine baseline to which effect of chelator can be compared.

To assess repeat-dose efficacy, inter-dose urine radiation excretion was used as a "baseline" to compare to post-dose urinary radiation excretion for the next dose of chelator given in a series. This procedure was followed above in evaluating maintenance doses in the 18 cases identified for efficacy analysis. Post-chelation divided by pre-chelation urine radiation concentrations provide a conservative calculation of enhanced excretion. The calculation is a conservative one because the pre-chelation inter-dose urine concentration of radiation is usually higher than baseline (untreated) excretion rate.

The database contains 288 cases with urine bioassay data. Eighteen (18) have pre-chelation urine radiation concentration measurements and are discussed above. Of the remaining 270 cases, 217 represent single-dose cases without pre-chelation urine radioactivity measurement. Without pre-chelation urine and with no second dose, a trough cannot be distinguished and the data are not interpretable.

Of the 53 remaining cases, 50 are unusable secondary to poor data quality or because of an undecipherable relationship between urine collection and chelator dosing. Some cases are missing urine radiation concentration measurements, in others chelator dose and urine radiation measurements are not temporally correlated. Also, daily chelation with 24-hour urine radiation measurements obscures the relationship of chelator to urine radiation concentration because each 24-hour urine represents both trough and peak readings between two doses.

The three cases (226, 418, and 490) that do contain usable data each have urine radiation measurements for 24-48 hours between chelation doses. This allows for an inter-dose baseline to be measured and for comparisons to be made with the next dose. Each of these cases demonstrates the same trend seen in the examples listed above. Urine radiation concentrations increase in response to dose of chelator, but without a clear baseline this increase cannot be quantified.

Efficacy Conclusions

Transuranic decorporation has been shown to reduce the incidence of primary bone tumors in animals by decreasing total body radiation. While not a placebo-controlled study, the evaluable patients served as their own control based on urinary radiation excretion pre- and post-chelator treatment. It can be seen from the efficacy cases in the REAC/TS population that an increase in urine radiation concentration is a consistent finding after treatment with Ca- and Zn-DTPA. Increased urine radiation excretion is an appropriate endpoint to assess efficacy because it represents elimination of total body radiation. Decreased total body radiation is a clinically meaningful endpoint in treating patients exposed to transuranic radionuclides.

Although there are few evaluable efficacy cases, these findings are consistent with the cases described in the published scientific literature.

SAFETY REVIEW

Each case in the database was examined for clinically relevant safety data. All recorded adverse events, abnormal clinical laboratory values, and abnormal vital signs (if available) have been considered without regard to causality.

Clinical Adverse Events

Nineteen (19) patients reported adverse events. (See Table 11.) Limited details are available, but available clinical descriptions are listed by case number in Appendix A. The majority of the comments are of minor clinical importance and of unclear relationship to treatment with DTPA. Of those adverse events that appear to be related to the drugs, the most serious events include an allergic reaction associated with IV Ca-DTPA, and respiratory distress associated with nebulized doses in two patients (one a known asthmatic). Pain was reported following intramuscular injection of Ca-DTPA.

Table 11. Clinical Adverse Events (n=685)

	Number of AEs Reported (n)*	% of Total Exposures (n/685)	% of Total Exposures Reporting AE Data (n/310)
AE Recorded			
CNS	7	1.0	2.3
Injection Pain	3	0.4	1.0
GI	2	0.3	0.6
Cardiovascular	2	0.3	0.6
Respiratory	2	0.3	0.6
Allergic	2	0.3	0.6
Dermatologic	1	0.1	0.3
GU	1	0.1	0.3
TOTAL	20	2.9	6.5
Recorded as "No AE"	290	42.3	93.5
Not Recorded	376	54.7	-

*One case (#204) reported 2 AEs: headache/lightheadedness and pelvic tenderness.

Clinical Laboratory Tests

Clinical laboratory data was not collected for all cases in the database. Of the total, 35% of the exposures had pre-chelation labs (blood chemistry, hematology, or urinalysis), and fewer had labs drawn following chelation. (See Table 12.) Abnormal post-chelation laboratory values are provided in Appendix B.

Table 12. Clinical Laboratory Tests (n=685)

	n	% of Total Cases (n/685)
Pre-chelation	240	35.0
Post-Chelation	162	23.6

Laboratory Adverse Events

The majority of laboratory adverse events in the database were referable to the renal system, and the majority of those were microscopic hematuria. (See Table 13.) Transuranic elements as well as DTPAs are excreted renally, and the kidneys are therefore exposed to both the radioactive isotope and the drug during chelation, regardless of the route of initial exposure. In effect, this potentially exposes the kidneys to higher doses of radioactivity than other organs. Details of laboratory adverse events are listed in Appendix B.

Table 13. Laboratory Adverse Events (n=685)

Post-chelation lab AE	Number of Events (n)	% of Total Exposures (n/685)	% of Total Events (n/34)
Total AEs Recorded	34	5.0	100.0
Renal	24	3.5	70.6
Proteinuria	2	0.3	5.9
Hematuria	14	2.0	41.2
Pyuria	5	0.7	14.7
Gluocosuria	3	0.4	9.1
Metabolic	5	0.7	14.7
Hyperkalemia	1	0.1	2.9
Hyperuricemia	3	0.4	8.9
Hypoglycemia	1	0.1	2.9
Hematologic	5	0.7	14.7
Leukocytosis	5	0.7	14.7
Recorded as Normal Post-chelation	131	19.1	--
Not Recorded	522	76.2	--

Vital Signs Data

About 11% of the patients in the database had vital sign data recorded before and after chelation, about 6% had vital signs recorded during the chelation (See Table 14.)

Table 14. Vital Signs (n=685)

	N	% of Total Cases (N/685)
Pre-chelation	81	11.8
During chelation	42	6.1
Post-chelation	77	11.2

Vital Signs Adverse Events

Very few patients had vital signs recorded prior to, during, or after chelation. Vital signs data for all patients in the database are listed below. (See Table 15.)

Table 15. Vital Signs (n=685)

	n	% of Total Cases (n/685)	% of Those Cases Reporting (n/total reporting that **set** of VS)
Pre-chelation	81	11.8	100.0
Normal	68	9.9	83.9
Abnormal	15	2.2	18.5
During chelation	42	6.1	100.0
Normal	35	5.1	83.3
Abnormal	7	1.0	16.7
Post-chelation	75	10.9	100.0
Normal	63	9.2	84.0
Abnormal	14	2.0	18.7

Several cases had abnormal pre-chelation vital signs. If only those cases are considered wherein a significant change in baseline prior to chelation is noted, the list of abnormal values that may be related to the chelation is reduced to four cases. The details of these four relevant clinical cases (192, 199, 683, and 687) are listed below. (See Table 16.) Four cases represent 0.6% of the total exposures. Three of these four have abnormal vital signs recorded during chelation, which represents 7.1% of all vital signs recorded during chelation. Three of these four clinically relevant cases have abnormal vital signs recorded after chelation, which represents 4% of all vital signs recorded post-chelation. For each case, there was an increase in systolic blood pressure, possibly related to the fluid bolus containing the chelator.

Table 16. Clinically Relevant Abnormal Vital Signs (n=4)

Case Number	Pre-Chelation		During Chelation		Post-Chelation	
192	SBP	134	SBP	164	SBP	154
Ca-DTPA IV	DBP	84	DBP	80	DBP	84
	Pulse	76	Pulse	88	Pulse	76
	Resp	20	Resp	20	Resp	20
199	SBP	110	SBP	130	SBP	130
Zn-DTPA IV	DBP	84	DBP	94	DBP	94
	Pulse	100	Pulse	NR	Pulse	NR
	Resp	24	Resp	NR	Resp	NR
683	SBP	142	SBP	134	SBP	130
Ca-DTPA IV	DBP	88	DBP	102	DBP	84
	Pulse	60	Pulse	NR	Pulse	NR
	Resp	NR	Resp	NR	Resp	NR
687	SBP	140	SBP	NR	SBP	160
Ca-DTPA IV	DBP	84	DBP	NR	DBP	90
	Pulse	86	Pulse	NR	Pulse	NR
	Resp	NR	Resp	NR	Resp	NR

SBP = systolic blood pressure
DBP = diastolic blood pressure
Resp = respiratory rate
NR = not recorded

Safety Conclusions

The DTPAs have been used to treat internal contamination with transuranic radionuclides since the 1950's with hundreds of patients treated. While mild to moderate adverse events have been reported, there are no published reports of serious adverse events in humans.

The REAC/TS database contains nineteen clinical, 33 laboratory, and 4 clinically significant vital sign adverse events. Serious clinical events potentially related to DTPA include an allergic reaction requiring medical intervention and two episodes of respiratory distress with nebulized dosing (one of these patients had a past medical history of asthma). Each of these events was associated with Ca-DTPA.

Microscopic hematuria occurred in 13 patients. Twelve with Ca-DTPA and one with Zn-DTPA (this patient had RBCs in the urine prior to chelation). Four of the 12 Ca-DTPA patients had normal urinalyses recorded after microscopic hematuria was noted, which indicates the transient nature of the condition.

Mild hypertension was noted in 4 patients who had normal vital signs prior to chelation. Systolic and diastolic measurements were affected.

CONCLUSIONS

Safety

Each of the 685 exposures were analyzed for clinical and laboratory adverse events. Nineteen clinical and 33 laboratory adverse events were identified. The majority of patient complaints were of minor significance and transient. Potentially severe adverse events related to DTPA therapy include respiratory distress in one patient with known asthma treated with nebulized Ca-DTPA, and one systemic allergic reaction to nebulized Ca-DTPA. Transient microscopic hematuria was seen in 13 patients receiving DTPA. Four patients had hypertension during and after chelation therapy. There are no published reports of serious toxicity to DTPA. Had larger total body radiation exposure occurred, it is possible that more renal toxicity would be seen following chelation.

Efficacy

The principle toxicity of radioactive transuranic elements is an increase in the incidence of malignancy later in life. An increase in incidence of primary bone tumors has been documented in animals, but not in humans. As is blood pressure measurements for antihypertensive drugs, increased urinary excretion of transuranic elements is a clinically meaningful endpoint for efficacy of DTPA.

DTPA is effective in removal of transuranic heavy metals. From the 18 cases with the most complete urine bioassay data, the average increase in urine radiation in response to first dose of DTPA is 39.3 times higher than baseline excretion rate.

RECOMMENDATIONS

Ca- and Zn-DTPA should be approved for the treatment of internal contamination with transuranic radionuclides.

A Phase 4 commitment should be required to expand the database and monitor for adverse events. Urinalysis should be monitored for hematuria. Vital signs should be monitored for hypertension during and post-chelation (when feasible). Measures of efficacy should be collected in the form of pre-chelation and post-chelation urine concentrations of radiation (normalized to volume of urine). Patients receiving long term treatment should be followed for clinical signs of zinc deficiency, if Ca-DTPA is used.

APPENDIX A: DETAIL OF CLINICAL ADVERSE EVENTS

CNS

1. Case #13: lightheadedness and fatigue reported after first dose of Ca-DTPA.
2. Case #15: metallic taste in mouth after Ca-DTPA.
3. Case #27: numbness in fingers and nausea with aerosolized Ca-DTPA, resolved.
4. Case #172: headache, Chelator: Ca-DTPA 4 doses.
5. Case #204: "Patient complained of headache and light-headedness during treatments... complained of tenderness of the bladder region ... so (further continued treatment with) DTPA was not given". Chelator: Zn-DTPA doses 7,8, and 9 I.V..
6. Case #333: headache with dose four of five. Chelator: Ca-DTPA I.V..
7. Case #334: headache with dose eight of eight. Chelator: Ca-DTPA I.V..

PAIN

1. Case #329: I.M. injection site pain "severe". Chelator: Ca-DTPA single dose I.M..
2. Case #399: "Severe pain at site of injection..." Chelator: Ca-DTPA I.M..
3. Case #556: "Severe pain at site of injection." Chelator: Ca-DTPA I.M..

GASTROINTESTINAL

1. Case #15: metallic taste in mouth after Ca-DTPA.
2. Case #414: nausea/loose stool. Chelator: Ca-DTPA, single dose, I.V..

CARDIOVASCULAR

1. Case #25: chest pain, 49 year old male, "Employee stated had taken Nitroglycerin sublingual tablet... for angina pain; had relief after one tablet. Had not reported this event at the time to any medical personnel." Pt received first of two IV doses of Ca-DTPA earlier on the same day as the chest pain.
2. Case #380: "Rapid pulse because he was scared." No data given on vitals, not clear which dose associated with this problem... pt received both Zn- and Ca-DTPA.

RESPIRITORY

1. Case #288: "Employee was unable to complete medication as it made him cough and wheeze. This man is a chronic asthmatic who takes cortisone each day." Chelator: Ca-DTPA, single dose, nebulizer.
2. Case #601: "coughing paroxysms" with nebulized dose. Chelator: Ca-DTPA, single dose, nebulized.

ALLERGIC

1. Case #205: "... receiving an IV injection of Ca-DTPA flushed and began breaking out with (4mm) hives first on his forehead and then upper trunk. The reaction was similar to an IVP reaction. He was given Benadryl and adrenaline with immediate relief." Chelator: Ca-DTPA I.V., single dose.
2. Case #323: Right Chest "itching" seven days after last (fourth dose nebulized) Ca-DTPA.

DERMATOLOGIC

1. Case #390: "Two weeks after DTPA therapy a generalized dermatitis appeared including mucous membrane of mouth. Retardation of beard growth. Dermatitis and beard growth returned to normal after discontinuance of DTPA Therapy." Chelator: Ca-DTPA 28 doses I.V..

GENITOURINARY

1. Case #204: "Patient complained of headache and light-headedness during treatments... complained of tenderness of the bladder region ... so (further continued treatment with) DTPA was not given. Chelator: Zn-DTPA doses 7,8, and 9 I.V..

APPENDIX B: DETAIL OF LABORATORY ADVERSE EVENTS

RENAL

PROTEINURIA

1. Case #5: post-chelation UA with 30mg/dl protein.
2. Case #192: post-chelation urine protein to 2+ after normal pre-chelation UA. Chelator: single dose Ca-DTPA I.V..

HEMATURIA

3. Case #13: Pre and post-chelation urine with trace blood. Chelator: 1 dose Ca-DTPA I.V..
4. Case #68: transient hematuria, 22 RBCs seen on UA, which cleared when Ca-DTPA chelation halted and did not recur with resumption of chelation schedule. No dose number specified.
5. Case #84: transient hematuria in patient with PMHx of glomerular nephritis. Chelator: Ca-DTPA 3 doses, route not specified.
6. Case #141: hematuria, "DTPA was omitted on the 35th day due to red cells in the urine. On the 37th day urine was clear and DTPA started with no recurrence. Subsequent examination including — 12/60 did not reveal any abnormal findings." Note: no lab data provided with case. Chelator: 15 doses Ca-DTPA I.V..
7. Case #157: hematuria, 2-5 RBC in urine on 5 occasions with 13 other negative specimens. Chelator: 14 doses of Ca-DTPA, route not specified.
8. Case #223: multiple UA's with RBCs. Chelator: Ca-DTPA 147 total doses, 99 I.V. and 48 P.O..
9. Case #321: post-chelation urine with trace blood; pre-chelation negative excepting trace protein. Post-chelation BUN=21 and Creatinine 1.5 with no pre-values for comparison. Chelator: Ca-DTPA, 2 I.V. doses.
10. Case #327: pre-chelation UA abnormal: ++++ albumin, 1-2 WBC, 5-10 RBC... remains abnormal throughout treatment with RBCs to 10-20 after second nebulized dose of Zn-DTPA. Pt with history of chronic renal disease prior to chelation.
11. Case #396: pre-chelation UA with 20-25 RBCs.
12. Case #416: " (labs) negative except occasional Rbc/hpf." No abnormal lab data provided; no indication if pre- or post-chelation. Chelator: Ca-DTPA, 2 doses, I.V..
13. Case #417: "occasional RBCs" in urine with no indication if pre- or post-chelation. Chelator: Ca-DTPA, single dose I.V..
14. Case #455: post-chelation "trace blood in urine." Chelator Ca-DTPA, single dose, nebulized.

15. Case #554: post-chelation UA with 0-3 RBC/lpf and 25-50 WBC/lpf; pre-chelation urine micro not performed. Chelator: Ca-DTPA, two doses via nebulizer.
16. Case #568: pre-chelation urine 3-8 WBC/many epithelial cells; post-chleation urine 80-100 RBC/2-3 WBC/many epithelial cells. Female patient. Chelator: Ca-DTPA, single dose I.V..

PYURIA

17. Case #83: 8-10 "pus cells" on urinalysis, no further comment given.
18. Case #327: pre-chelation UA abnormal: ++++ albumin, 1-2 WBC, 5-10 RBC... remains abnormal throughout treatment with RBCs to 10-20 after second nebulized dose of Zn-DTPA. Pt with history of chronic renal disease prior to chelation.
19. Case #560: pre-chelation urine with 15-30 WBC/lpf; post-chelation urine with 10-15 WBC/lpf. Chelator: Ca-DTPA, single dose I.V..
20. Case #554: post-chelation UA with 0-3 RBC/lpf and 25-50 WBC/lpf; pre-chelation urine micro not performed. Chelator: Ca-DTPA, two doses via nebulizer.
21. Case #567: pre-chelation urine WBC 5-15/lpf; post-chelation urine WBC 25-50/lpf. Chelator: Ca-DTPA, single dose I.V..

GLUCOSURIA

22. Case #183: urine glucose to "1+" after Ca-DTPA, no medical history given. Chelator: single dose Ca-DTPA I.V..
23. Case #297: pre- and post-chelation urine with "++++ glucose." Pt. A known diabetic. Chelator: single dose Ca-DTPA nebulized.
24. Case #554: post-chelation UA with 0-3 RBC/lpf and 25-50 WBC/lpf; pre-chelation urine micro not performed. Chelator: Ca-DTPA, two doses via nebulizer.

METABOLIC

1. Case #184: post-chelation potassium to 6.3 mEq/L, some question about hemolysis of sample. Chelator: single dose Ca-DTPA I.V..
2. Case #187: post-chelation serum uric acid 8.5 mg/dl (normal reference range 3.2-8.3 mg/dl). Chelator: single dose Ca-DTPA I.V..
3. Case #188: post-chelation serum glucose 54 mg/dl (normal reference range 65-120mg/dl) with note that pt had a history of "low blood sugar pattern." Chelator: single dose Ca-DTPA I.V..
4. Case #205: post-chelation serum uric acid to 10.8 mg/dl (normal reference range 3.2-8.0 mg/dl). Uric acid crystals noted in pt's urine 9 months after chleation. Chelator: single dose Ca-DTPA I.V..
5. Case #209: post-chelation serum uric acid to 9.9 mg/dl (normal reference range 3.2-8.0 mg/dl). Uric acid pre-chelation 6.1. Chelator: single dose Ca-DTPA I.V..

HEMATOLOGIC

1. Case #270: post-chelation WBC to 14,700. No other labs detailed. Chelator: single dose Ca-DTPA nebulized.
2. Case #275: post-chelation WBC to 14,800. Pre-chelation WBC 9,101. Chelator: single dose Ca-DTPA nebulized.
3. Case #294: post-chelation WBC to 12,300. Pre-chelation WBC 9,943. Chelator: single dose Ca-DTPA nebulized.
4. Case #469: post-chelation WBC 12.4 (4.7 pre-chelation). Chelator Ca-DTPA, single dose, nebulized.
5. Case #639: pre chelation serum WBC 13,000; post-chelation serum WBC 13,300. Chelator: Ca-DTPA, single dose I.M..

APPENDIX C: DETAIL OF VITAL SIGNS ADVERSE EVENTS

Case Number	Pre-chelation		During Chelation		Post-chelation	
5	SBP	NR	SBP	NR	SBP	158
Ca-DTPA Neb	DBP	NR	DBP	NR	DBP	96
	Pulse	NR	Pulse	NR	Pulse	96
	Resp	NR	Resp	NR	Resp	NR
20	SBP	146	SBP	134	SBP	122
Ca-DTPA I.V.	DBP	100	DBP	90	DBP	86
	Pulse	88	Pulse	80	Pulse	76
	Resp	18	Resp	NR	Resp	NR
25	SBP	154	SBP	NR	SBP	140
Ca-DTPA I.V.	DBP	108	DBP	NR	DBP	100
	Pulse	88	Pulse	NR	Pulse	84
	Resp	20	Resp	NR	Resp	20
37	SBP	146	SBP	134	SBP	122
Ca-DTPA I.V.	DBP	100	DBP	90	DBP	86
	Pulse	88	Pulse	80	Pulse	76
	Resp	18	Resp	NR	Resp	NR
183	SBP	150	SBP	154	SBP	154
Ca-DTPA I.V.	DBP	84	DBP	86	DBP	86
	Pulse	88	Pulse	80	Pulse	80
	Resp	18	Resp	18	Resp	18
187	SBP	108	SBP	NR	SBP	116
Ca-DTPA I.V.	DBP	66	DBP	NR	DBP	80
	Pulse	96	Pulse	NR	Pulse	64
	Resp	26	Resp	NR	Resp	18
192	SBP	134	SBP	164	SBP	154
Ca-DTPA I.V.	DBP	84	DBP	80	DBP	84
	Pulse	76	Pulse	88	Pulse	76
	Resp	20	Resp	20	Resp	20
199	SBP	110	SBP	130	SBP	130
Zn-DTPA I.V.	DBP	84	DBP	94	DBP	94
	Pulse	100	Pulse	NR	Pulse	NR
	Resp	24	Resp	NR	Resp	NR

Case Number	Pre-chelation		During Chelation		Post-chelation	
201	SBP	138	SBP	140	SBP	140
Zn-DTPA I.V.	DBP	80	DBP	80	DBP	80
	Pulse	92	Pulse	78	Pulse	80
	Resp	NR	Resp	NR	Resp	NR
205	SBP	140	SBP	140	SBP	130
Ca-DTPA I.V.	DBP	80	DBP	90	DBP	80
	Pulse	92	Pulse	88	Pulse	80
	Resp	NR	Resp	NR	Resp	NR
211	SBP	120	SBP	118	SBP	114
Ca-DTPA I.V.	DBP	96	DBP	84	DBP	82
	Pulse	84	Pulse	78	Pulse	78
	Resp	NR	Resp	NR	Resp	NR
321	SBP	154	SBP	140	SBP	140
Ca-DTPA I.V.	DBP	108	DBP	100	DBP	100
	Pulse	88	Pulse	82	Pulse	84
	Resp	20	Resp	20	Resp	20
419	SBP	140	SBP	142	SBP	138
Ca-DTPA Neb	DBP	96	DBP	88	DBP	88
	Pulse	80	Pulse	72	Pulse	76
	Resp	NR	Resp	NR	Resp	NR
421	SBP	130	SBP	140	SBP	140
Ca-DTPA Neb	DBP	100	DBP	100	DBP	100
	Pulse	NR	Pulse	NR	Pulse	NR
	Resp	NR	Resp	NR	Resp	NR
456	SBP	160	SBP	NR	SBP	142
Ca-DTPA Neb.	DBP	90	DBP	NR	DBP	70
	Pulse	72	Pulse	NR	Pulse	80
	Resp	NR	Resp	NR	Resp	NR
488	SBP	148	SBP	NR	SBP	130
Zn-DTPA I.V.	DBP	98	DBP	NR	DBP	90
	Pulse	100	Pulse	NR	Pulse	100
	Resp	NR	Resp	NR	Resp	NR

Case Number	Pre-chelation		During Chelation		Post-chelation	
491	SBP	148	SBP	NR	SBP	126
Zn-DTPA I.V.	DBP	108	DBP	NR	DBP	102
	Pulse	88	Pulse	NR	Pulse	88
	Resp	NR	Resp	NR	Resp	NR
514	SBP	NR	SBP	NR	SBP	150
Ca-DTPA I.V.	DBP	NR	DBP	NR	DBP	88
	Pulse	NR	Pulse	NR	Pulse	NR
	Resp	NR	Resp	NR	Resp	NR
515	SBP	NR	SBP	NR	SBP	140
Ca-DTPA I.V.	DBP	NR	DBP	NR	DBP	80
	Pulse	NR	Pulse	NR	Pulse	96
	Resp	NR	Resp	NR	Resp	NR
683	SBP	142	SBP	134	SBP	130
Ca-DTPA I.V.	DBP	88	DBP	102	DBP	84
	Pulse	60	Pulse	NR	Pulse	72
	Resp	NR	Resp	NR	Resp	NR
687	SBP	140	SBP	NR	SBP	160
Ca-DTPA I.V.	DBP	84	DBP	NR	DBP	90
	Pulse	86	Pulse	NR	Pulse	NR
	Resp	NR	Resp	NR	Resp	NR

SBP = systolic blood pressure
DBP = diastolic blood pressure
Resp = respiratory rate
NR = not recorded

APPENDIX D: DETAIL OF EEFD CALCULATIONS

ID	Date/Time	Cumulative Time (days)	Pu Urine	EEFD (Pu)	Am Urine	EEFD (Am)	Ca-DTPA	Zn-DTPA
12	2/2/99 11:30	0	0.0001		0.0003			
12	2/2/99 11:58	0		93.53562		396.0784	IV	
12	2/2/99 20:30	0	0.0071		0.1010			
12	2/3/99 0:40	1	0.0042		0.0690			
12	2/3/99 8:45	1	0.0012		0.0201			
12	2/4/99 7:00	2	0.0008		0.0042			
12	2/4/99 10:00	2	0.0003		0.0015			
12	2/4/99 12:05	2	0.0000		0.0023			
12	2/4/99 15:15	2	0.0008		0.0030			
12	2/4/99 19:30	2	0.0007		0.0022			
12	2/5/99 5:10	3	0.0009		0.0044			
12	2/5/99 8:10	3	0.0004		0.0023			
12	2/5/99 14:45	3	0.0005		0.0025			
12	2/5/99 20:40	3	0.0010		0.0043			
12	2/6/99 22:00	4	0.0007		0.0026			
12	2/7/99 22:00	5	0.0005		0.0039			
12	2/8/99 22:30	6	0.0004		0.0023			
12	2/14/99 12:00	12	0.0002		0.0013			
12	2/21/99 22:00	19	0.0001		0.0006			
12	2/28/99 18:00	26	0.0000		0.0007			
12	4/8/99 23:30	64	0.0000		0.0003			
12	5/28/99 16:30	114	0.0000		0.0001			
12	5/29/99 17:00	115	0.0000		0.0001			
12	5/30/99 17:00	116	0.0000		0.0001			
13	8/18/98 12:17	0	0.0001		0.0005			
13	8/18/98 12:25	0		14.94505		12.1747	IV	
13	8/18/98 16:47	0	0.0010		0.0066			
13	8/18/98 21:45	0	0.0214		0.0936			
13	8/19/98 6:45	1	0.1030		0.4470			
13	8/19/98 9:37	1	0.0744		0.4440			
13	8/19/98 12:30	1	0.0013		0.0084			
13	8/19/98 14:10	1	0.0014		0.0088			
13	8/19/98 16:11	1	0.0010		0.0071			
13	8/19/98 19:55	1	0.0010		0.0044			
13	8/19/98 23:00	1	0.0006		0.0035			
13	8/20/98 0:37	2	0.0005		0.0035			
13	8/20/98 8:03	2	0.0005		0.0041			
13	8/20/98 12:35	2		1.93015		0.7421		IV
13	8/21/98 6:47	3	0.0011		0.0031			
13	8/21/98 19:00	3	0.0020		0.0125			
13	8/23/98 7:30	5	0.0010		0.0055			
13	8/24/98 6:00	6	0.0005		0.0036			
13	8/31/98 5:30	13	0.0002		0.0015			

ID	Date/Time	Cumulative Time (days)	Pu Urine	EEFD (Pu)	Am Urine	EEFD (Am)	Ca-DTPA	Zn-DTPA
13	9/8/98 8:00	21	0.0001		0.0002			
13	9/21/98 7:30	34	0.0000		0.0002			
13	10/27/98 0:00	70	0.0000		0.0001			
13	11/21/98 0:00	94	0.0000		0.0001			
13	11/22/98 0:00	95	0.0000		0.0000			
13	11/24/98 5:00	97	0.0000		0.0001			
13	12/14/98 8:00	117	0.0000		0.0001			
27	4/17/1981	0	0.0003		0.0104			
27	4/17/1981	0					IV*	
27	4/18/1981	1	0.0164	62.35741	0.0168	1.6154	IV	
27	4/19/1981	2	0.0055		0.0020			
27	4/20/1981	3	0.0015	3.04054	0.0006	1.2018		IV*
27	4/21/1981	4	0.0045		0.0007			
27	4/22/1981	5	0.0015	1.77852	0.0004	1.8844		IV*
27	4/23/1981	6	0.0027		0.0008			
27	4/24/1981	7	0.0021	0.71981	0.0005	0.7816		IV*
27	4/25/1981	8	0.0015		0.0004			
27	4/26/1981	9	0.0008		0.0002			
27	4/27/1981	10	0.0006	4.11859	0.0002	4.3464		IV
27	4/28/1981	11	0.0026		0.0007			
27	4/29/1981	12	0.0008	2.52996	0.0002	2.4826		IV*
27	4/30/1981	13	0.0019		0.0004			
27	5/1/1981	14	0.0008	1.57143	0.0002	1.8827		IV*
27	5/2/1981	15	0.0012		0.0003			
27	5/3/1981	16	0.0004		0.0001			
27	5/4/1981	17	0.0010	2.08654	0.0002	2.1779		IV
27	5/5/1981	18	0.0022		0.0005			
27	5/6/1981	19	0.0008	1.09341	0.0002	1.2267		IV*
27	5/7/1981	20	0.0009		0.0002			
27	5/8/1981	21	0.0011	1.21577	0.0002	0.0163	Neb*	
27	5/9/1981	22	0.0005		0.0001			
27	5/10/1981	23	0.0001		0.0000			
27	5/11/1981	24	0.0007	1.45441	0.0001	2.2878	Neb	
27	5/12/1981	25	0.0010		0.0003			
27	5/13/1981	26	0.0005	0.85661			Neb*	
27	5/14/1981	27	0.0005					
27	5/15/1981	28	0.0002				Neb*	
27	5/18/1981	31					Neb*	
27	5/19/1981	32	0.0002		0.0000			
27	5/20/1981	33	0.0001		0.0000		Neb*	
27	5/22/1981	35					Neb*	
27	5/26/1981	39					Neb*	
27	5/27/1981	40	0.0002	0.91935			Neb*	
27	5/28/1981	41	0.0002					
27	5/29/1981	42					Neb*	
27	6/1/1981	44					Neb*	
27	6/2/1981	45	0.0001					
27	6/3/1981	46	0.0002				Neb*	
27	6/5/1981	48					Neb*	

ID	Date/Time	Cumulative Time (days)	Pu Urine	EEFD (Pu)	Am Urine	EEFD (Am)	Ca-DTPA	Zn-DTPA
27	6/8/1981	51					Neb*	
27	6/10/1981	53					Neb*	
44	9/11/67 22:15	0	7990.0000					
44	9/14/67 21:00	3	7730.0000					
44	9/15/67 13:30	4	7.3000					
44	9/16/67 22:00	5	10.5000					
44	9/21/67 8:00	10	10.7000					
44	9/21/67 19:00	10	20.0000					
44	9/22/67 22:00	11	20.0000				IV*	
44	9/23/67 11:00	12	32.0000	1.60000			IV	
44	9/23/67 22:00	12	0.3000					
44	9/24/67 22:00	13	12.0000	40.00000			IV	
44	9/25/67 20:00	14	12.0000					
44	9/26/67 16:00	15	0.3000	33.33333			IV	
44	9/27/67 8:00	16	10.0000					
44	9/28/67 3:30	17	0.3000	5.00000			IV	
44	9/29/67 0:00	18	1.5000					
44	10/1/67 0:00	20	3.2000					
44	10/1/67 12:00	20	0.3000					
44	10/7/67 7:00	26	0.4000					
44	10/8/67 20:00	27	2.8000					
44	11/27/67 0:00	76					IV*	
44	11/29/67 0:00	78					IV*	
44	12/1/67 0:00	80					IV*	
261	5/29/1974	0	2.0000		0.6000			
261	5/31/1974	2		1.50000		0.8333	Neb	
261	6/1/1974	3	3.0000		0.5000			
261	6/2/1974	4			0.3000			
261	6/6/1974	8	0.1000					
263	10/10/1974	0	0.2000					
263	10/14/1974	4	5.3000	26.50000			Neb	
263	10/24/1974	14	12.0000					
263	10/30/1974	20	6.6000					
264	10/11/1974	0	0.4000					
264	10/14/1974	3	7.7000	19.25000			Neb	
264	10/15/1974	4	5.5000					
264	10/30/1974	19	2.2000					
265	10/10/1974	0	0.2000					
265	10/14/1974	4	16.0000	80.00000			Neb	
265	10/15/1974	5	9.0000					
265	10/29/1974	19	1.6000					
327	7/18/1978	0	4.4000					
327	7/20/1978	2	2.1000					
327	10/23/1978	95	6.3000					
327	10/24/1978	96	2.7000					
327	10/28/1978	100	6.5000					
327	12/12/1978	144	8.2000					
327	2/26/1979	218	7.1000					
327	2/27/1979	219	320.0000	45.07042				Neb

ID	Date/Time	Cumulative Time (days)	Pu Urine	EEFD (Pu)	Am Urine	EEFD (Am)	Ca-DTPA	Zn-DTPA
327	2/28/1979	220	311.0000					
327	3/1/1979	221	196.0000					
327	3/5/1979	225	230.0000					
327	3/6/1979	226	230.0000					
327	3/12/1979	232	252.0000					
327	3/13/1979	233	212.0000	1.55189				Neb
327	3/14/1979	234	329.0000					
327	3/15/1979	235	141.0000					
327	3/19/1979	239	54.0000					
327	3/20/1979	240	108.0000					
327	3/26/1979	246	76.0000					
327	3/27/1979	247	130.0000	1.76923				Neb
327	3/28/1979	248	230.0000					
327	3/29/1979	249	140.0000					
327	4/3/1979	253	78.0000					
327	4/4/1979	254	90.0000					
327	4/9/1979	259	88.0000					
327	4/10/1979	260	30.0000					
327	4/17/1979	267	32.0000					
327	4/23/1979	273	38.0000					
327	4/24/1979	274	330.0000	8.68421				IV
327	4/25/1979	275	265.0000					
327	4/26/1979	276	175.0000					
327	5/15/1979	295	27.0000					
327	5/16/1979	296	27.0000					
327	5/21/1979	301	50.0000					
327	5/22/1979	302	126.0000	4.78000				IV
327	5/23/1979	303	239.0000					
327	5/29/1979	309	46.0000					
327	5/30/1979	310	23.0000					
327	6/25/1979	335	19.0000					
327	6/26/1979	336	168.0000	10.00000				IV
327	6/27/1979	337	190.0000					
327	7/2/1979	342	122.0000					
327	7/3/1979	343	88.0000					
327	7/30/1979	370	42.0000					
327	7/31/1979	370	134.0000	4.71429				IV
327	8/1/1979	371	198.0000					
327	8/7/1979	377	45.0000					
327	8/8/1979	378	31.0000					
327	8/27/1979	397	89.0000					
327	8/28/1979	398	156.0000	1.75281				IV
327	8/29/1979	399	92.0000					
327	9/4/1979	404	49.0000					
327	9/5/1979	405	18.0000					
327	9/24/1979	424	18.0000					
327	9/25/1979	425	138.0000	7.66667				IV
327	9/26/1979	426	132.0000					
327	10/2/1979	432	26.0000					

ID	Date/Time	Cumulative Time (days)	Pu Urine	EEFD (Pu)	Am Urine	EEFD (Am)	Ca-DTPA	Zn-DTPA
327	10/3/1979	433	55.0000					
327	10/9/1979	439	25.0000					
327	10/16/1979	446	17.0000					
327	2/26/1980	576	5.4000					
327	2/27/1980	577	5.3000					
327	4/22/1980	632	3.1000					
327	4/23/1980	633	2.2000					
495	1/7/1983	0	958.0000	0.45616			IV*	
495	1/8/1983	1	437.0000					
495	1/9/1983	2	492.0000					
495	1/10/1983	3	445.0000					
495	1/11/1983	4	360.0000					
495	1/12/1983	5	288.0000					
495	1/13/1983	6	179.0000					
495	1/14/1983	7	833.0000					
495	1/15/1983	8	346.0000					
495	1/16/1983	9	241.0000					
495	1/17/1983	10	210.0000					
495	1/18/1983	11	145.0000					
495	1/19/1983	12	85.0000					
495	1/20/1983	13	553.0000	6.50588			IV	
495	1/21/1983	14	221.0000					
495	1/22/1983	15	226.0000					
495	1/23/1983	16	190.0000					
495	1/24/1983	17	130.0000					
495	1/25/1983	18	589.0000	4.53077			IV	
495	1/26/1983	19	243.0000					
495	1/28/1983	21	442.0000					
495	1/29/1983	22	268.0000	0.60633			IV	
495	1/30/1983	23	240.0000					
495	1/31/1983	23	581.0000	2.42083			IV*	
495	2/1/1983	24	212.0000					
495	2/2/1983	25	566.0000	2.66981			IV*	
495	2/3/1983	26	232.0000					
495	2/4/1983	27	515.0000	2.21983			IV*	
495	2/5/1983	28	206.0000					
495	2/6/1983	29	224.0000					
495	2/7/1983	30	496.0000	2.21429			IV	
495	2/8/1983	31	174.0000					
495	2/9/1983	32	402.0000	2.31034			IV*	
495	2/10/1983	33	165.0000					
495	2/11/1983	34	496.0000	3.00606			IV*	
495	2/12/1983	35	84.0000					
495	2/13/1983	36	125.0000					
495	2/14/1983	37	445.0000	3.56000			IV	
495	2/15/1983	38	166.0000					
495	2/16/1983	39	140.0000					
495	2/17/1983	40	383.0000	2.73571			IV	
495	2/18/1983	41	133.0000					

ID	Date/Time	Cumulative Time (days)	Pu Urine	EEFD (Pu)	Am Urine	EEFD (Am)	Ca-DTPA	Zn-DTPA
495	2/19/1983	42	110.0000					
495	2/20/1983	43	85.0000					
495	2/22/1983	45	365.0000	4.29412			IV	
495	2/23/1983	46	146.0000					
495	2/24/1983	47	108.0000					
495	2/25/1983	48	217.0000	2.00926				IV
495	2/26/1983	49	85.0000					
495	2/27/1983	50	65.0000					
495	2/28/1983	51	216.0000	3.32308				IV
495	3/1/1983	52	96.0000					
495	3/2/1983	53	70.0000					
495	3/3/1983	54	238.0000	3.40000				IV
495	3/4/1983	55	95.0000					
495	3/5/1983	56	70.0000					
495	3/6/1983	57	65.0000					
495	3/7/1983	58	49.0000	4.67347				IV
495	3/8/1983	59	229.0000					
495	3/9/1983	60	92.0000					
495	3/10/1983	61	75.0000					
495	3/11/1983	62	60.0000					
495	3/12/1983	63	40.0000					
495	3/13/1983	64	38.0000					
495	3/14/1983	65	219.0000	5.76316			IV	
495	3/15/1983	66	88.0000					
495	3/16/1983	67	83.0000					
495	3/18/1983	69	65.0000					
495	3/19/1983	70	53.0000					
495	3/20/1983	71	45.0000					
495	3/21/1983	72	40.0000					
495	3/22/1983	73	39.0000	5.94872			IV	
495	3/23/1983	74	232.0000					
495	3/24/1983	75	93.0000					
495	3/25/1983	76	80.0000					
495	3/26/1983	77	55.0000					
495	3/27/1983	78	45.0000					
495	3/28/1983	79	35.0000					
495	3/29/1983	80	21.0000					
495	3/30/1983	81	233.0000	11.09524			IV	
495	3/31/1983	81	93.0000					
495	4/1/1983	82	85.0000					
495	4/2/1983	83	55.0000					
495	4/3/1983	84	42.0000					
495	4/4/1983	85	225.0000	5.35714			IV	
495	4/5/1983	86	90.0000					
495	4/6/1983	87	80.0000					
495	4/7/1983	88	70.0000					
495	4/8/1983	89	60.0000					
495	4/9/1983	90	45.0000					
495	4/10/1983	91	25.0000					

ID	Date/Time	Cumulative Time (days)	Pu Urine	EEFD (Pu)	Am Urine	EEFD (Am)	Ca-DTPA	Zn-DTPA
495	4/11/1983	92	24.0000					
495	4/12/1983	93	162.0000	6.75000			IV	
495	4/13/1983	94	65.0000					
495	4/14/1983	95	62.0000					
495	4/15/1983	96	58.0000					
516	5/13/1986	0	0.5000					
516	5/14/1986	1	0.5000					
516	5/15/1986	2	31.0000	62.00000			Neb	
516	5/16/1986	3	15.0000					
516	5/18/1986	5	19.0000					
516	5/19/1986	6	8.0000					
516	5/23/1986	10					IV*	
519	4/6/1986	0	2.8000					
519	4/7/1986	1	0.5000	2.28571			IV	
519	4/8/1986	2	6.4000					
519	4/9/1986	3	1.9000					
568	5/19/1978	0	0.2000					
568	6/1/1978	12	0.8000	4.00000			IV	
568	6/7/1978	18	0.4000					
568	10/25/1978	156	0.1000					
621	7/12/1971	0	0.9000					
621	7/13/1971	1	0.4000					
621	7/22/1971	10	3.0000					
621	7/23/1971	11	3.2000	1.06667			Neb	
621	7/24/1971	12	2.1000					
621	8/6/1971	24					Neb*	
621	8/9/1971	27					Neb*	
621	8/11/1971	29	4.9000					
622	1/23/1969	0	0.4000					
622	4/11/1969	78	0.1000					
622	9/19/1969	236	0.1000					
622	9/26/1969	243	3.6000	36.00000			Neb	
622	10/8/1969	255	1.0000					
622	12/8/1969	315	0.0100					
622	12/23/1969	330	0.4000					
622	2/5/1970	372	0.1000					
622	2/18/1970	385	0.2000					
626	8/1/1971	0	0.1000					
626	8/2/1971	1	0.7000	7.00000			Neb	
626	8/20/1971	19	0.1000					
626	8/23/1971	22	0.1000					
626	12/30/1971	149	0.1000					
629	7/12/1971	0	0.9000					
629	7/13/1971	1	4.4000					
629	7/22/1971	10					Neb*	
629	7/23/1971	11	2.0000					
629	7/24/1971	12	0.8000					
629	9/17/1971	65	0.1000					

* EEFD not calculated at this dose due to; 1) missing urine values around time of dose, 2) 24-hr urine between two doses.

ATTACHMENT 1: CASE REPORT FORM FOR USE IN AN EMERGENCY EVENT

Chelation Therapy Emergency Case Report
For use with the administration of heavy metal chelators
Ca-DTPA, Zn-DTPA, or Prussian Blue in a mass casualty radiation exposure event

Date of report: _____ Unique Patient Identifier: _____

Patient ID
Name:_____ **Date of Birth:** _____ **Sex: Male Female**
Address: _____
Phone: (_____)_____ If hospitalized, where? _____
Criteria for Diagnosis **Details/Dates**
History of Exposure _____
Lab/Field confirmed exposure _____
Symptoms of Acute Rad Syndrome _____
Contamination Place/ Date/Time of Exposure: _____
Radionuclide(s): confirmed suspected _____
Route (check all that apply): Skin, Inhalation, Wound, Burn, Ingestion
Initial Radioactivity Deposited: _____
How measured: _____
Decontamination
External: Skin washed with: _____
Wound excised/washed: _____
Contraindications to aerosolized treatment (h/o lung disease, cough, syspnea, chest tightness, wheezing)? _____
Internal: Ca-DTPA Date/Time of initial dose: _____
Amount: _____ Route: _____ Total Doses: _____
Zn-DTPA Date/Time of initial dose: _____
Amount: _____ Route: _____ Total Doses: _____
Prussian Blue Date/Time of initial dose: _____
Amount: _____ Route: _____ Total Doses: _____

Adverse Reaction(s) to Treatment? _____
_____
Vital Signs: Stable Unstable: _____
Disposition of Pt/Outcome: _____
_____
Report Completed By: _____ Title: _____
Phone: (____)_____ Email: _____@_____
Address: _____

Attach Copy of Emergency Records to this Form

ATTACHMENT 2: CASE REPORT FORM FOR USE IN A CONTROLLED EVENT

Radiopharmaceutical Therapy Case Report Form
For use with the administration of Ca-DTPA/ Zn-DTPA/Prussian Blue
in a contained radiation exposure event

Date of report: _____Unique Patient Identifier: _____

Patient ID:
Name:_____ **Date of Birth:** _____ **Sex: M F**
Address: _____
Phone: (_____**)**_____ **If hospitalized, where?** _____

Past Medical Hx: _____
_____
_____
_____

Current Medications: _____
_____
_____
_____

Evidence of Acute Radiation Syndrome:
_____
_____

DATE AND TIME OF EXPOSURE: _____

Type of Radiation Exposure (check all that apply):

___ Skin Contamination; ___ Inhalation; ___ Wound; ___ Burn;
___ Ingestion; ___ Other (give details):

Initial Radioactivity Deposited: (include activity measure, anatomic location, and specific radionuclides if known for each)
Skin: _____
Wound: _____

Nares: Right _____ Left _____ Other: _____

EXTERNAL DECONTAMINATION AGENTS/METHODS:

Skin: _____
Wound (include excision):_____
Other: _____

Adverse Reaction to Treatment:

1._____
_____
2._____
_____
3._____
_____

Notes: Use Treatment Log to detail chelator doses.
Use Pre/Post Chelation Data Sheet to record vitals/labs
Use BioAssay Log for post-chelation monitoring of urine/fecal samples

Patient Disposition/Outcome: _____
_____
_____

Other Treatment Rendered: KI
(dose/route/date/time):_____
Other: _____

Report Completed By: _____ Title: _____
Facility: _____
Phone: (_____)_____ Email: _____
Address: _____

Attach Copy of Emergency Records to this Form

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mitchell Mathis
2/4/03 05:35:10 PM
MEDICAL OFFICER

Brad Leissa
2/4/03 05:41:56 PM
MEDICAL OFFICER

Mary Purucker
2/4/03 06:06:12 PM
MEDICAL OFFICER
Concur with Dr. Mathis' consult

Dianne Murphy
2/5/03 06:14:25 PM
MEDICAL OFFICER