Power Burst Facility/Boron Neutron Capture Therapy Program for Cancer Treatment

Volume 4, No. 8

Bulletin

MASTER

BNCT

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PBF/BNCT PROGRAM

MONTHLY BULLETIN

PRINCIPAL INVESTIGATOR'S HIGHLIGHTS

Highlights of the PBF/BNCT Program during August 1990 include progress within the areas of:

1. Project 1: Supporting Technology Development

- Task 1: Gross Boron Analysis in Tissue, Blood, and Urine - 450 samples were analyzed and approximately 700 samples await preparation and analysis. Current estimate of the boron detection limit for the ICP-MS is ≤ 0.1 ppb boron. Evaluation of this technology is continuing.
- Task 2: Analytical Methodologies Development for BSH (Borocaptate Sodium) Purity Determination - No reportable progress this month.
- Task 4: Boron Microscopic (subcellular) Analytical Development - The SIMS technology, developed at Cornell University, will be transferred to a support services laboratory. An RFP has been prepared.
- Task 5: Noninvasive Boron Quantitative Determination - Pharmacokinetic studies continue with software development that now permits data acquisition in 20 minutes vs 90 minutes.
- Task 6: Dosimetry - This task remains on hold because of continued unavailability of the Brookhaven Medical Research Reactor (BMRR).
- Task 7: Analytical Radiation Transport and Interaction Modeling for BNCT - A functional version of the `bnct_edit` reconstruction software (with documentation) has been received from the University of Utah. Effort will now begin on software to interface the reconstructed surfaces with the radiation transport calculational module.

2. Project 2: Large Animal Model Studies - All dogs in the 10-Gy dose-tolerance (no boron) group are doing well. Late effects due to the fast-neutron contamination in the BMRR beam are starting to develop.
3. Project 5: Neutron Source and Facility Preparation - An Environmental Assessment (EA) for the PBF/BNCT Program is being drafted in anticipation of authorization to modify the PBF reactor.
4. Core A: Administration and Common Support - The FY-91 funding for the PBF/BNCT Program was approved by the full United States Senate. Research efforts at BMRR remains on hold because of nonavailability of 3-MW operation. Meetings in August and September at Petten (The Netherlands) and Oregon Health Sciences University, respectively, will address potential collaboration.
5. Core B: PBF Operations - Safety, training, preventive maintenance, and routine stand-by activities continue.

Ronald V. Dorn III, M.D.
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PBF/BNCT Research Programs

ACRONYMS

AAPM	American Association of Physicists in Medicine
ACS	American Chemical Society
ASN	American Society of Neuroradiology
BMRR	Brookhaven Medical Research Reactor
BNL	Brookhaven National Laboratory
BNCT	Boron Neutron Capture Therapy
BPA	Boronophenylalanine
BSH	Borocaptate Sodium
BSS(B)	$B_{24}H_{22}SS^{4-}$
BSSO(B)	$B_{24}H_{22}S_2O^{4-}$
CCF	Change control form
COCA	Consent Order Compliance Agency
CSF	Cerebrospinal Fluid
CSI	Chemical shift imaging
CT	Computed tomography
DOE	Department of Energy
DOE-ER	Department of Energy-Energy Research
DOE-HERAC	Department of Energy-Health and Environmental Research Advisory Committee
DOE-HQ	Department of Energy-Headquarters
DOE-NE	Department of Energy-Nuclear Energy
DOE-OHER	Department of Energy-Office of Health and Environmental Research
DSPC	Distearoyl phosphatidyl choline
EA	Environmental Assessment
ECAG	European Concerted Action Group
EDF	Engineering Design File
EE	Environmental Evaluation
EGS	Engineering Graphics Systems
EIRMC	Eastern Idaho Regional Medical Center
EPA	Environmental Protection Agency
EPRO	Experimental Power Reactor Operator
ERDP	Exploratory Research and Development Project
FDA	Food and Drug Administration
FIA	Flow injection analysis
FMEA	Failure Mode and Effects Analysis
GE	General Electric
HFR	High flux reactor
HMPAO	Hexamethyl-Propylene-Amineoxime
HPLC	High Performance Liquid Chromatography
IACUC	Institutional Animal Care and Use Committee
ICP-AES	Inductively Coupled Plasma-Atomic Emission Spectroscopy

ICP-MS	Inductively Coupled Plasma-Mass Spectrometry
IM	Ion microscope
IND	Investigational New Drug exemption from FDA
INEL	Idaho National Engineering Laboratory
INPO	Institute of Nuclear Plant Operations
ISU	Idaho State University
IV	Intravenous
KURRI	Kyoto University Reactor Research Institute
LOFT/OECD	Loss-of-Fluid Test/Organization of Economic Cooperation and Development
MIT	Massachusetts Institute of Technology
MR	Magnetic resonance
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NCAR	National Center for Atmospheric Research
NCI	National Cancer Institute
NCS	Network computing system
NDE	New Device Exemption (FDA)
NEPA	National Environmental Policy Act
NESHAP	National Emission Standards for Hazardous Air Pollutants
NIST	National Institute of Science and Technology
NMR	Nuclear magnetic resonance
NWI	Northwest Imaging
OCT	A low-temperature adhesive
OHSU	Oregon Health Sciences University
ORAU	Oak Ridge Associated Universities
ORNL	Oak Ridge National Laboratory
PBF	Power Burst Facility
PDARS	Patient Data Acquisition and Retrieval System
PET	Position Emission Tomography
PMT	Photo multiplier tube
POM	Plant operating manual
RAP	Requirements Awareness Program
RBE	Relative Biological Effectiveness
RESL	Radiological and Environmental Sciences Laboratory
RF	Radiofrequency
RFP	Request for Proposal
SAR	Safety Analysis Report
SDD	System Design Description
SIMS	Secondary Ion Mass Spectrometry
TLD	Thermoluminescent dosimeter
TTAF	Test Train Assembly Area Facility
UCSF	University of California San Francisco
UofU	University of Utah
USDA	United States Department of Agriculture
WSU	Washington State University

PROJECT 1: SUPPORTING TECHNOLOGY DEVELOPMENT

Task 1: Gross Boron Analysis in Tissue, Blood, and Urine

A total of 273 samples were received for boron analysis during the month. Of these new samples, 26 were from nude mice involved in the melanoma project, 158 were from brain-tumor dogs, and 62 were from a normal laboratory dog in the plasmapheresis study. An additional 27 samples were from a dog head that was sectioned to determine normal levels of C, H, N, O, S, P, Ca, K, Na, B, Mg, and Cl in various tissues. A total of approximately 700 samples await preparation and analysis. 227 samples have been prepped and await analysis. Approximately 325 samples were prepared for analysis and over 450 were analyzed by Inductively Coupled Plasma-Atomic Emission Spectroscopy (ICP-AES) during the month.

Analysis by ICP-AES slowed this month because of instrument downtime on the ARL-3410. A loss of cooling water to the radiofrequency coil caused it to overheat and damaged it beyond usefulness. A new coil was ordered and installed. The cooling water supply system was cleaned and a new socket for the power amplifier tube (which was causing some arcing and instability problems) was installed. The instrument is now back online.

A problem with the supply of ionized water for the Idaho National Engineering Laboratory (INEL) Research Center building caused additional delays. The only water available was insufficiently pure to be put through the instrument water-purification system that is designed only for the final polishing of relatively clean feedwater. Without the assurance of boron-free water, samples could not be prepped and new calibration standards could not be made. The problem has been corrected for the present, and additional steps are being taken to avoid shutdown in the future.

Evaluation of the boron analysis limits for the ICP-Mass Spectrometer, located at the INEL Environmental Chemistry Laboratory, continued. Unfortunately, the power supply to the instrument is plagued with problems that have caused several rather long down periods because of damaged components. A new power conditioner should be installed by the end of August. The instrument operator has determined that the cleanest water available to him, at this time, contains approximately 10-12 ppb of boron. Based on the signal-to-noise ratio with this background boron signal, he estimates the detection limit for boron to be ≤ 0.1 ppb boron. "Cleaner"

water (with respect to boron) will be provided to accurately assess the utility of this instrument.

Task 2: Analytical Methodologies for BSH (Borocaptate Sodium) Purity Determination

No reportable progress this month.

Task 3: Analytical Methodologies Development for Active Form Identification

This task is presently unfunded.

Task 4: Boron Microscopic (Subcellular) Analytical Development

The secondary ion mass spectroscopy (SIMS) technology, developed at Cornell University, will be transferred to a semiroutine, support services laboratory. A competitive request for proposal (RFP) has been prepared and it appears that three laboratories will respond.

Potential Participants: The Charles Evans Company was visited by Program participants to assess their capabilities for measuring boron distribution at the cellular level. The technical exchange was very encouraging.

Task 5: Noninvasive Boron Quantification Determination

Pharmacokinetic Studies: A boron-imaging study was performed on a dog with a choroid plexus papilloma tumor (dog #128). Two, three-dimensional, chemical shift imaging (3-D/CSI) sessions were conducted, and the usual spectroscopic pharmacokinetic data were obtained. The first 3-D/CSI used the protocol requiring 90 minutes for the scan. The second 3-D/CSI used a newer protocol requiring only 20 minutes to acquire the same amount of data. This study was the first conducted by newly-trained, Washington State University (WSU) researchers and technicians from Northwest Imaging (NWI).

Figures 1-4 display the pharmacokinetic data from studies conducted at NWI in July, 1990, using two normal dogs (28 and 68 lbs). These studies spanned approximately four hours following start of intravenous infusion of borocaptate sodium (BSH). Blood samples were analyzed by ICP-AES. All data have been normalized to the peak level observed during the time study. The spectra areas consist of the total boron signal coming from

the dog head (nose to part of the neck) and are not localized to any one tissue area.

Software Development: The 3-D/CSI protocols have been rewritten, reducing the scanning time from 90 minutes to approximately 20 minutes for the same amount of data. Scan time should be further reduced when the new imaging protocols, developed in conjunction with Stanford University, are used.

Task 6: Dosimetry

Because of Brookhaven Medical Research Reactor (BMRR) unavailability, there was no reportable progress.

Figure 1. Comparison of spectrum areas to boron levels in serum for 25-lb dog.

Figure 2. Comparison of spectrum areas to boron levels in serum for 68.2-lb dog.

Figure 3. Comparison of boron levels in serum for small and large dog.

Figure 4. Comparison of spectra areas of BSH for a 68.2-lb and 25-lb dog.

Task 7: Analytical Radiation Transport and Interaction Modeling for BNCT

Task 7A - Geometric Reconstruction Software: A functional version of the `bncd_edit` reconstruction software (complete with documentation) was received from the University of Utah (UofU). This will allow initiation of the task to generate interface software that will couple the reconstructed surfaces, produced by `bncd_edit`, with the radiation transport calculational module. This version of `bncd_edit` appears to address all of the original requirements specified in the RFP with one possible exception. Small, mathematically undefined areas (holes) can occasionally occur in the reconstructed surfaces. UofU has acknowledged the existence of this problem and Program participants are working with UofU to identify the conditions under which it occurs. Once the cause is identified, the problem will be corrected.

Radiation Transport Software Verification and Validation: Work is continuing to obtain more anatomical and geometric detail than is currently available for the dog head. Dr. Rhonda Aliah-Davis (Skyline Veterinary Clinic, Idaho Falls) obtained three dog heads for Program participants to section and examine to obtain accurate geometric and

compositional information for code modeling. One dog head was dissected and pictures, dimensions, and tissue samples were taken to improve the mathematical model of a representative Labrador Retriever. Sagittal and axial tissue samples have been submitted for elemental analysis to determine local concentrations of elements contributing to normal tissue dose (nitrogen, hydrogen, etc). Air volumes (sinuses), in the head of large dogs, will significantly affect the three-dimensional, thermal-neutron distributions.

Task 7B - Canine Dosimetry Because of BMRR unavailability, there was no reportable progress.

PROJECT 2: LARGE ANIMAL MODEL STUDIES

Normal Tissue Tolerance Studies: All dogs in the 10-Gy dose-tolerance (beam only - no boron) group are clinically well. Blood parameters remain normal, no new skin lesions have developed, and no neurological abnormalities have occurred. These dogs all had their six-month checkup this month, including computed tomography (CT) and magnetic resonance imaging (MRI) scans and cerebral spinal fluid analysis.

Two of the dogs have begun to show delayed scalp damage (inflammation of the temporal muscles with varying amounts of fluid accumulation over the skull). As this was not seen in any of the dogs receiving boron, the response indicates that fast-neutron contamination is far more detrimental than anticipated. This further increases the advantages of PBF relative to other neutron sources. The two control dogs in this study were euthanized and necropsied August 8 and 13 and, as expected, gross necropsies were normal.

Spontaneously-Occurring Brain Tumors: "Brandy" Grudzinski (35447-93), suffered a recurrence of seizure activity starting August 25, 1990, and died August 27, nine months following treatment. At this time it is unknown whether the cause of death was because of recurrence of the tumor or radiation damage; however, death was accompanied by seizure activity inconsistent with tumor location, but consistent with radiation necrosis; likely indicating excessive irradiation. If confirmed by autopsy, this will be further evidence of the need to suppress the fast-neutron contamination to levels achievable only with PBF. Following fixation, the brain will be shipped to WSU for further evaluation.

Magnetic Resonance Spectroscopy: Whole-head boron spectroscopy was performed on "Niki" Fox (35447-128) on August 5, 1990, to monitor the uptake and distribution phases of boron assimilation. A single set of data was collected for 3-D/CSI. Indocyanine green was injected intravenously just prior to euthanasia to evaluate breaks in the blood-brain-barrier upon gross examination. On histologic examination the tumor was determined to be a choroid plexus papilloma.

Pharmacokinetics: A two-hour boron plasmapheresis exchange was performed on a normal Beagle on August 8, 1990.

"Shorty" Morgan (35447-121) entered a two-hour post-boron infusion kinetic study July 2, 1990, and was euthanized by injection of 2-ml sodium pentobarbital. Histological diagnosis was pituitary adenoma.

"Sam" Warner (35447-127) entered the project on July 23, 1990, with an enhancing cerebellar lesion. He entered the two-hour post-boron infusion kinetic study on July 31 and was given 20 ml of 2% Evans Blue dye to evaluate breaks in the blood-brain-barrier. He was euthanized at the end of the sampling time period. Histological diagnosis was reticulosis.

"Beau" Smith (35447-126) entered the two-hour post-boron infusion kinetic study July 26, 1990, and 5 ml 0.1% Evans Blue dye ten minutes prior to euthanasia. Histological diagnosis is pituitary adenocarcinoma.

Melanoma Project: Pharmacological participants from Idaho State University are assisting in the development of an experimental protocol to evaluate methods for increasing the biosolubility/availability of boronophenylalanine (BPA). Dog studies comparing the intravenous administration of BPA in a phosphate buffer (controls), diethanolamine, and cyclodextrin (Molecusol) will begin soon.

The latest information from large animal model experiments is summarized in Appendix A.

PROJECT 3: HUMAN STUDIES

This project is currently not funded.

PROJECT 4: STABILITY, PHARMACOLOGY, AND TOXICOLOGY OF DRUGS

This project is currently not funded.

PROJECT 5: PBF TECHNICAL SUPPORT

Analysis: An Environmental Evaluation (EE) for PBF/BNCT was developed and submitted to DOE for review in 1988 prior to the National Cancer Institute review of the Program. The EE was returned with comments to the effect that an Environmental Assessment (EA) was the proper National Environmental Policy Act (NEPA) documentation for program evaluation. Recent developments concerning the FY-91 funding of the PBF/BNCT Program prompted DOE-ID to direct that the documentation be developed in draft form for DOE review upon authorization to modify the PBF reactor. The EG&G Environmental Assessment Unit began developing an EA for the PBF/BNCT Program during the reporting period with the goal of providing a review draft of the NEPA document at the end of the fiscal year.

PBF Filter Model Upgrade: Work progressed on developing a new two-dimensional transport model of the PBF filter with all design changes incorporated. This model will be used to support the final filter design review. The objective is to have it ready to go by the end of September, 1990. Work will then be initiated on a three-dimensional transport model of the PBF reactor and bismuth shield to correctly represent the neutron and gamma source entering the filter.

PBF Design Bismuth Reflector: The current design of the bismuth reflector assemblies (bismuth contained in aluminum cans with coolant holes) specifies an overlapping geometry to reduce the gamma component in the therapy beam. The effectiveness of these overlaps had not been previously quantified because of difficulties in modeling each assembly discretely. An investigation was performed because of a large cost increment associated with fabricating these overlaps, reported at a recent design meeting.

The two-dimensional DOT model cannot represent the bismuth reflector discretely and a three-dimensional model is not currently available. A one-dimensional ANISN model was used to overestimate the effect of overlapping geometry and three cases were run:

1. Homogeneous reflector (design model)

- a. 84.0 volume percent B_i
- b. 12.5 volume percent Al
- c. 3.5 volume percent H₂O

2. Pure aluminum reflector

3. Aluminum reflector with 3.5% water.

The results, corrected for a fission-source shift were:

<u>Case</u>	<u>Relative Gamma Intensity</u>	<u>Relative Total Neutron Intensity</u>
1	1.0	1.0
2	1.20	1.28
3	1.17	1.10

These results indicate that the effect on the gamma component in the therapy beam will increase substantially less than 17%. A 17% increase in gamma component can be tolerated since the predicted gamma component is a factor of two less than the design requirements. A comparison of Case 2 with Case 3 shows the importance of minimizing water fraction in and around the reflector. A 3.5% water fraction reduces the neutron intensity by 16%.

CORE A: ADMINISTRATION AND COMMON SUPPORT

Funding: The full U.S. Senate approved the Water and Natural Resources Bill containing the FY-91 funding for the PBF/BNCT Program. The Bill will go to the Senate-House conferees to work out minor differences; then to the President.

Canine dose-tolerance research is on hold pending BMRR operability at full power (3 MW). BMRR can operate at powers up to 1 MW continuously with the present clean water supply. Testing above 1 MW is being delayed into September 1990 because of the large backlog of Brookhaven National Laboratory (BNL) work. BNL experiments use 1 MW or less power; operation at 3 MW is only required for the PBF/BNCT Program. All alternatives for

additional cooling water are on hold. This continues to be a serious concern for the PBF/BNCT Program. The Program would have doubled the epithermal-neutron biological database had BMRR been available for full power operation since March, 1990. DOE-CH has not yet approved the installation of the PBF/BNCT Program ${}^6\text{Li}$ dog shielding. INFL will not approve installation until BMRR can operate at 3 MW and provide a usable canine irradiation beam. BNL is ready to install the shielding when approved.

The PBF/BNCT Program fallback position will move the canine irradiation project to the Petten reactor in The Netherlands. An epithermal-neutron filter has been installed in the Petten high flux reactor and should produce a neutron beam superior to BMRR. The European program participants have offered free beam time (we now pay \$400/hour for BMRR beam time) and a sabbatical appointment for Dr. Gavin (WSU).

Meetings, Conferences, etc.: An oral presentation, "*In-Vivo* Chemical Shift Imaging of Canine Brain Tumors After Injection of $\text{Na}_2\text{B}_{12}\text{H}_{11}\text{SH}$," was presented at the Society of Magnetic Resonance in Medicine in New York City, NY, on August 23, 1990. Based upon the comments received after the presentation, there are several groups that are attempting to accomplish the same thing. The Emory University group, which is associated with the Georgia Tech reactor group, is just beginning MR development and is focusing on tagging the boron compounds with deuterium using deuterium spectroscopy. A Japanese group is also attempting boron spectroscopy, but has not had much success.

PBF/BNCT Program participants (Floyd Wheeler, Yale Harker, and Pat Gavin) were invited to participate in a normal-tissue, dose-tolerance workshop at the Petten High Flux Reactor (HFR) in The Netherlands September 6-7, 1990 and conduct neutron-beam spectrum and current measurements for intercomparison with BMRR. Because of travel restrictions imposed by DOE, only Floyd Wheeler and Pat Gavin were able to attend the meeting. The planning meeting agenda draws heavily on the PBF/BNCT Program's biological data base. The Europeans are looking to this Program for initial guidance and desire extensive collaboration. The BNCT beam at Petten HFR will be in operation by August 24, 1990, but the beam shielding will be incomplete. A pencil-size beam can be opened at full power allowing Program participants to take some preliminary spectrum measurements. Dr. Gavin will visit the large teaching veterinary hospital north of Amsterdam to determine the level of interest and potential support to a canine experimental project.

Potential Participants: Program participants will meet with biological researchers from Oregon Health Sciences University (OHSU) on September 4, 1990, to: (1) prepare a project plan for evaluating pituitary tumor BNCT,

and (2) assess OHSU interest in participating in the human BSH pharmacokinetic studies and utilizing the INEL-developed magnetic resonance capability.

Milestone Status:

<u>Milestone</u>	<u>Schedule</u>	<u>Actual</u>
a. Complete Phase I: Acute Canine Radiation Tolerance Study	6/90	6/27/90
b. Revise PBF/BNCT Program Plan	9/90*	--
c. Complete Noninvasive Boron Quantification Development for Clinical Use	10/90	--
d. Radiation Transport and Interaction Software Ready for Clinical Use	3/91	--
e. Complete Phase II: Acute Canine Radiation Tolerance Study	9/91	--
f. Complete Vessel Weld Mockup	9/91	--

* Revision to the Program Plan will be deferred until the FY-91 budget is established

CORE B: PBF OPERATIONS

The Plant Operating Manual was revised to delete the nonapplicable sections and update the operating sections that will be applicable to the PBF/BNCT Program.

The routine monthly safety walkthrough of the plant was completed. Those items identified during the walkthrough, that can be corrected within the maintenance budget, are being completed.

The scheduled preventative maintenance performed in the plant included: (1) control rod cooling air heat exchanger, (2) cooling tower, (3) secondary relief valves, (4) chemical treatment pump, (5) gas stack

monitor, (6) plant air compressor, (7) constant air monitor, (8) Building-619 fire protection system nitrogen, (9) 5/15-ton crane, (10) reactor building heating and ventilation system supply fans, (11) jib crane, (12) auxiliary compressor air aftercooler, and (13) utility cooling water pump.

A work authorization was released to have EG&G Engineering establish the requirements and design for installation of backflow preventers in the potable water system at the reactor, installation of additional fire protection sprinkler systems on the cooling tower stairs and installation of a fire protection system tie-in at the reactor.

Training conducted during the month consisted of: (1) satellite hazardous-waste accumulation area training for operations personnel, (2) ethics, (3) plant drills for reactor operators and health physics technician, (4) spill prevention and countermeasure control for reactor operators, (5) power burst specific hazard communication, and (6) occurrence reporting for Operations manager, shift supervisors, and reactor operators.

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APPENDIX A

LARGE ANIMAL MODEL STUDIES

SUMMARY OF PATIENT DATA

PBF/BNCT CANINE PHARMACOKINETIC STUDY SUMMARY OF PATIENT DATA BSH INTRAVENOUS INJECTIONS STUDY

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ANIMAL	NAME OF DOG	EUTHANASIA		CASE SUMMARY	PATHOLOGY DIAGNOSIS	DOSE (mg/kg)	BLOOD SERUM AND URINE ANALYSIS	TISSUE ANALYSIS	CT		MRI	
		DATE	MIN						UNENH.	ENH	UNENH.	ENH
35447-1	"Muffy" Klugh	03/23/87	540	Yes	Pituitary adenoma	55	Yes	Yes	Yes	Yes	Yes	Yes
35447-2	"Stashi" Christensen	05/18/87	750	Yes	No tumor/positive boron control	57	Yes	Yes	N/P	N/P	No	No
35447-3	"King" Henry	05/18/87	Control	Yes	No tumor/negative boron control	0	Yes	N/P	N/P	No	No	No
35447-14	"Marsha" Despain	06/30/87	780	Yes	Invasive adenocarcinoma	62	Yes	Yes	Yes	Yes	Yes	Yes
35447-15A	"Amos" Vallangdigham	08/03/87	780	Yes	Invasive nasal carcinoma	59	Yes	Yes	Yes	Yes	Yes	Yes
35447-18	"Slim" Pozzobon	09/14/87	770	Yes	Invasive nasal adenocarcinoma	30	Yes	Yes	Yes	Yes	Yes	Yes
35447-20	"Mischief" Scott	11/02/87	90	Yes	Meningioma	55	Yes	Yes	Yes	Yes	Yes	Yes
35447-23	"Rocky" Christensen	11/13/87	780	Yes	Pituitary adenoma	55	Yes	Yes	Yes	Yes	Yes	Yes
35447-24	"Mariah" May	11/24/87	720	Yes	Subarachnoid cyst	55	Yes	Yes	Yes	Yes	Yes	Yes
36845-25	"Sandy" Frazier	01/26/88	780	Yes	Meningioma	53	Yes	Yes	Yes	Yes	Yes	Yes
35447-28	"Boots" Belisle	02/22/88	125	Yes	Regional demyelinating disease	55	Yes	Yes	Yes	Yes	Yes	Yes
35447-30	"Sunny" Seeley	03/01/88	420	Yes	Pituitary adenocarcinoma	55	Yes	Yes	Yes	Yes	Yes	Yes
35447-32	"Pip" Hahn	02/26/88	410	Yes	Meningioma	55	Yes	Yes	Yes	Yes	Yes	Yes
35447-33	"Coco" Pechtel	03/23/88	420	Yes	Nasal adeno carcinoma	56	Yes	Yes	Yes	Yes	Yes	Yes
35447-37	"Tucker" Reeves	04/14/88	420	Yes	No tumor/positive boron control	10	Yes	Yes	N/P	N/P	No	No
35447-39	"Fritts" Cogan	05/02/88	100	Yes	Meningioma	10	Yes	Yes	Yes	Yes	Yes	Yes
35447-40	"Rocky" Underwood	05/03/88	420	Yes	Fungal granuloma	30	Yes	Yes	Yes	Yes	Yes	Yes
35447-43	"Blue" Archer	05/23/88	420	Yes	Diffuse cortical astrocytoma	52	Yes	Yes	N/P	N/P	Yes	Yes
35447-49	"Jenny" Nelson	06/29/88	420	Yes	Diffuse astrocytoma	33	Yes	Yes	Yes	Yes	Yes	Yes
35447-50	"Caesar" Chenoweth	07/13/88	420	Yes	Meningioma	55	Yes	Yes	Yes	Yes	Yes	Yes
35447-54	"Licorice" Meyers	08/03/88	410	Yes	No tumor/positive boron control	55	Yes	Yes	Yes	Yes	Yes	Yes
35447-55	"Kelley" Langston	08/17/88	410	Yes	Diffuse astrocytoma	55	Yes	Yes	No	No	Yes	Yes
35447-57	"Rafferty" Reber	09/01/88	410	Yes	Meningioma (plasmapheresis)	50	Yes	Yes	No	No	Yes	Yes
35447-59	"Heidi" Boyer	09/12/88	180	Yes	Meningioma	55	Yes	Yes	No	No	Yes	Yes

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¹ Euthanasia time in minutes following start-of-boron administration. Boron administration requires approximately 50 minutes.

(P) Partial results
N/A Not applicable
N/P Not Performed

PBF/BNCT CANINE PHARMACOKINETIC STUDY

SUMMARY OF PATIENT DATA

BSH INTRAVENOUS INJECTIONS STUDY (CONTINUED)

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ANIMAL	NAME OF DOG	EUTHANASIA		CASE SUMMARY	PATHOLOGY DIAGNOSIS	DOSE (mg/kg)	BLOOD SERUM AND URINE ANALYSIS		TISSUE ANALYSIS		CT		MRI	
		DATE	MIN								UNENH.	ENH	UNENH.	ENH
35447-62	"Chester" Scott	10/09/88	180	Yes	Meningioma	55	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
35447-67	"Muffet" Hammel	11/01/88	180	Yes	Astrocytoma	55	Yes	Yes	Yes	Yes	No	Yes	N/P	N/P
35447-70	"Mac" Meyers	11/15/88	180	Yes	Fibrillary astrocytoma	55	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
35447-71	"Jake" Brede	01/04/89	180	Yes	Choroid plexus papilloma	55	Yes	Yes	Yes	Yes	Yes	Yes	N/P	N/P
35447-72	"Mandy" Ross	02/07/89	495	Yes	Choroid plexus papilloma	55	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
35447-76	"Scotty" Klemm	05/28/89	410	Yes	Protoplasmic astrocytoma	55	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
35447-86	"Brutus" Halverson	09/11/89	240	Yes	Pituitary adenocarcinoma	50	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
35447-88	"Scamper" Brewster	10/10/89	420	Yes	Pituitary adenocarcinoma	55	Yes	Yes	Yes	Yes	N/P	Yes	Yes	Yes
35447-97	"Kolsa" Joy	12/07/89	420	Yes	No tumor	55	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
35447-101	"Ginger" Mott	12/12/89	180	Yes	Choroid plexus papilloma	55	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
35447-104	"Killer" Divine	01/19/90	180	Yes	Choroid plexus papilloma	55	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
35447-117	"Toby" Page	04/27/90	180	No	Diencephalic mass	50	Yes	Yes	P	Yes	Yes	Yes	No	No
35447-116	"Taffy" Gruel ^{2,3}	05/05/90	300	No	Pending	55	Yes	Yes	P	Yes	Yes	Yes	Yes	Yes
35447-121	"Shorty" Morgan	07/02/90	180	Yes	Pituitary adenoma	55	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
35447-126	"Beau" Smith	07/26/90	180	Yes	Pituitary adenocarcinoma	55	No	No	No	No	Yes	Yes	Yes	Yes
35447-127	"Sam" Warner	07/31/90	180	Yes	Reticulosis	55	No	No	No	No	Yes	Yes	Yes	Yes
35447-128	"Niki" Fox ^{2,3}	08/05/90	297	Yes	Choroid plexus papilloma	55	No	No	No	No	Yes	Yes	Yes	Yes

1 Euthanasia or irradiation time in minutes following start-of-boron administration. Boron administration requires approximately 50 minutes.

2 Boron pharmacokinetic data obtained on these animals using MRS.

3 Three-dimensional chemical shift imaging (CSI).

(P) Partial results
N/A Not applicable
N/P Not Performed

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PBF/BNCT CANINE PHARMACOKINETIC STUDY SUMMARY OF PATIENT DATA BSH INTRA-ARTERIAL INJECTIONS STUDY

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<u>ANIMAL</u>	<u>SEX</u>	<u>DATE</u>	<u>EUTHANASIA (MIN)¹</u>	<u>BLOOD SERUM AND URINE ANALYSIS</u>	<u>TISSUE ANALYSIS</u>
2181	M	10/18/89	420	Yes	Yes
2067	F	10/26/89	420	Yes	Yes
2148	F	11/16/89	420	Yes	Yes

¹ Euthanasia or irradiation time in minutes following start-of-boron administration. Boron administration requires approximately 50 minutes.

PBF/BNCT CANINE TUMOR TREATMENT STUDY

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ANIMAL	SEX	NAME OF DOG	BIOPSY DIAGNOSIS	DATE	START TIME ³	DURATION MINUTES ¹	CALCULATED DOSE (cGy)	ESTIMATED ^{10B} AVG (ppm)	SURVIVING	DAYS	EUTHANASIA/DEATH	
											DATE	CAUSE
35447-79	F	"Pugee" Krebs	Astrocytoma ²	07/07/89	375	77.8	1923	18.5	No	343	06/20/90	Urinary Disfunction
35447-80	M	"Mugsy" Marshall	Astrocytoma ⁴	08/07/89	369	78.0	1722	21.6	No	12	08/19/89	Anesthesia
35447-83	M	"Rusty" Collins	Meningioma ⁴	08/25/89	430	68.5	1829	21.4	No	170	02/11/90	Unknown
35447-87	M	"Benji" Williams	Nasal adenocarcinoma ⁴	09/28/89	420	80.3	1653	20.6	No	140	02/14/90	Euthanasia
35447-93	F	"Brandy" Grudzinski	Meningioma ⁴	10/30/89	310	68.1	1912	24.9	No	300	08/27/90	Seizure
35447-94	F	"Brandy" Hoff	Meningioma ²	10/25/89	464	86.0	1887	14.3	Yes			
35447-95	M	"Godfrey" Beers	Meningioma ⁴	10/24/89	388	63.3	1743	24.5	No	0.5	10/25/89	Unknown
35447-100	F	"Juno" Bagley	Meningioma ⁴	11/30/89	315	73.0	2185	28.9	No ⁵	43	01/12/90	Euthanasia
35447-108	F	"Trixie" Herklotz	Papilloma ²	02/16/90	225	49.0	1900	51.9(?)	No ⁵	(a)	06/??/90	Unknown

- 1 Irradiation time in minutes.
 - 2 Diagnosis from CT and/or MRI scans.
 - 3 Time from start of boron injection to start of irradiation.
 - 4 Biopsy confirmed.
 - 5 Did not improve neurologic status.
- (a) The dog died sometime the week of June 11, 1990, was buried without necropsy, and the owner did not return messages or communicate with WSU.

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PBF/BNCT CANINE PLASMAPHERESIS STUDY

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GROUP	ANIMAL	SEX	PLASMA EXCHANGE			EUTHANASIA (MIN.)	BLOOD SERUM & URINE ANALYSIS	TISSUE ANALYSIS
			DATE	FIRST MIN ²	SECOND MIN ²	THIRD MIN ²		
1	2095 ¹	M	06/08/88	360	---	430	Yes	Yes
1	2084 ¹	M	06/09/88	360	---	446	Yes	Yes
1	2109 ¹	F	06/10/88	360	---	410	Yes	Yes
1A	2114 ¹	F	08/18/89	360	---	445	Yes	Yes
1A	2140 ¹	F	08/10/89	365	---	455	Yes	Yes
1A	2117 ¹	M	08/11/89	360	---	417	Yes	Yes
1B	2139 ¹	F	07/31/89	362	---	750	Yes	Yes
1B	2169 ^{1,3}	M	08/02/89	363	---	770	Yes	Yes
1B	2127 ¹	F	08/01/89	383	---	800	Yes	Yes
2	2097	M	06/14/88	360	---	413	Yes	Yes
2	2074	M	06/15/88	360	---	410	Yes	Yes
2	2092	F	06/16/88	360	---	400	Yes	Yes
2A	2066	F	08/17/89	360	---	390	Yes	Yes
2A	2145 ³	F	08/14/89	422	---	440	Yes	Yes
2A	2155	M	08/15/89	360	---	305	Yes	Yes
2A	1901	F	09/07/90	360	---	401	No	No
3	2103	M	06/20/88	360	---	755	Yes	Yes
3	2081	M	06/22/83	360	---	755	Yes	Yes
3	2089	F	06/24/88	360	---	790	Yes	Yes

¹ Control Animal (reinfused same boronated plasma that had just been extracted).

² Time from start of boron injection.

³ Dog went into respiratory arrest at 412 minutes, but was revived.

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PBF/BNCT CANINE PLASMAPHERESIS STUDY (CONTINUED)

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GROUP	ANIMAL	SEX	DATE	PLASMA EXCHANGE			EUTHANASIA (MIN.)	BLOOD SERUM & URINE ANALYSIS	TISSUE ANALYSIS
				FIRST MIN ²	SECOND MIN ²	THIRD MIN ²			
3A	2076	F	08/04/89	365	---	---	760	Yes	Yes
	2112	M	08/03/89	374	---	---	775	Yes	Yes
3A	2149	M	09/27/89	---	---	---	420	Yes	Yes
	2131	F	09/28/89	---	---	---	420	Yes	Yes
3A	2165	F	09/27/89	---	---	---	420	Yes	Yes
	2143	M	09/28/89	---	---	---	420	Yes	Yes
3A	2179	M	09/29/89	---	---	---	420	Yes	Yes
	2102	F	09/29/89	---	---	---	420	Yes	Yes
3A	2148	M	11/16/89	---	---	---	420	Yes	Yes
	2181	M	10/19/89	---	---	---	420	Yes	Yes
3A	2067	F	10/26/89	---	---	---	420	Yes	Yes
4	2096	M	06/27/88	360	470	600	640	Yes	Yes
	2104	M	06/28/88	360	480	600	660	Yes	Yes
4	2098	F	06/29/88	385	545	640	785	Yes	Yes
	2091	M	08/18/88	120	---	---	163	Yes	Yes
5	2073	F	09/08/88	130	---	---	160	Yes	Yes
	2090	M	09/09/88	129	---	---	180	Yes	Yes
5	2078 ¹	F	09/15/88	120	---	---	180	Yes	Yes
	2093	M	10/07/88	360	400	---	455	Yes	Yes
6	2086	F	10/13/88	360	401	---	480	Yes	Yes
	2068	M	09/23/88	405	505	---	560	Yes	Yes
6	2082 ¹	M	10/28/88	365	400	---	440	Yes	Yes

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¹ Control Animal (reinfused same boronated plasma that had just been extracted).

² Time from start of boron injection.

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GROUP	ANIMAL	SEX	DATE	PLASMA EXCHANGE			EUTHANASIA (MIN.)	BLOOD SERUM & URINE ANALYSIS	TISSUE ANALYSIS
				FIRST MIN ²	SECOND MIN ²	THIRD MIN ²			
A	IT79	F	07/20/90	120	---	---	180	Yes	No
A	EG79	M	07/23/90	120	---	---	180	No	No
A	ACK79	M	08/08/90	120	---	---	180	No	No
B	G-1	F	03/16/90	145	---	---	225	No	Yes
B	G-8	F	03/22/90	120	---	---	180	Yes	No
B	G-10	F	05/04/90	120	---	---	280	No	No
B	G-11	F	06/06/90	120	---	---	255	Yes	Yes
B	2146	F	09/01/90	155	---	---	205	No	No
C	G-2	F	03/23/90	360	---	---	440	No	No
C	G-6	F	03/23/90	370	---	---	440	Yes	P
C	G-7	F	04/06/90	360	---	---	460	Yes	No
E*	2174	F	05/24/90	---	---	---	420	Yes	N/A
E*	1846	F	05/23/90	---	---	---	420	Yes	N/A
E*	2173	F	05/24/90	---	---	---	420	Yes	N/A

1 Control Animal (reinfused same boronated plasma that had just been extracted).

2 Time from start of boron injection.

* Dosage was 100 mg boron/kg body weight.

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PBF/BNCT CANINE DOSE-TOLERANCE STUDY

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ANIMAL	SEX	DATE	IRRADIATION		10 ¹⁰ B EST AVG	BLOOD SERUM URINE ANAL.	SURVIVING	DAYS	EUTHANASIA/DEATH		TISSUE ANALYSIS
			START TIME ³	DURATION (MINS)					DATE	CAUSE	
1592 ¹	M	01/11/89	345	58.0	1273	Yes	No	0	01/11/89	Euthanasia	Yes
1587 ¹	M	01/12/89	21	36.0	1275	Yes	No	0	01/12/89	Euthanasia	Yes
966	M	02/08/89	235	48.0	1453	Yes	No	365	02/08/90	Euthanasia	N/A
1588	M	02/09/89	220	49.0	1258	Yes	No	368	02/12/90	Euthanasia	N/A
995	M	02/09/89	238	42.0	1275	Yes	No	365	02/09/90	Euthanasia	N/A
1591	M	02/10/89	194	90.0	2629	Yes	No	368	02/13/90	Euthanasia	N/A
1564	M	02/28/89	204	87.0	2545	Yes	No	379	03/14/90	Euthanasia	N/A
997	M	03/02/89	190	74.0	2687	Yes	No	375	03/12/90	Euthanasia	N/A
983	M	03/02/89	160	149.0	3834	Yes	No	128	07/08/89	Seizures	N/A
1590	M	03/01/89	176	140.0	3800	Yes	No	155	08/05/89	Seizures	N/A
946	M	04/11/89	195	109.0	3821	Yes	No	137	08/26/89	Neurologic Disease	N/A
985	M	04/13/89	170.0	168.0	6363	Yes	No	153	09/13/89	Neurologic Disease	N/A
1700	M	04/12/89	182.0	166.5	6374	Yes	No	158	09/17/89	Neurologic Disease	N/A
980 ²	M	04/11/89	155.0	120.0	Sham	Yes	No	372	04/18/90	Euthanasia	N/A
1589 ²	M	04/15/89	125.0	120.0	Sham	Yes	No	370	04/20/90	Euthanasia	N/A

¹ Dosimeter animals euthanized after irradiation.

² Control dogs given sham irradiations (0 cGy)

³ Time from start of boron administration

N/A Not applicable

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PBF/BNCT CANINE DOSE-TOLERANCE STUDY (CONTINUED)

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ANIMAL	SEX	IRRADIATION			10B ppm EST. AVG	BLOOD SERUM		SURVIVING	DAYS	EUTHANASIA/DEATH		TISSUE ANALYSIS
		START TIME ³	DURATION (MINS)	CALCULATED DOSE (cGy)		URINE	ANAL.			DATE	CAUSE	
2255	M	N/A	157.0	1000	0	No	No	Yes	90	04/30/90	Euthanasia	Yes
2256	M	N/A	236.0	1500	0	No	No	No				
2257	M	N/A	157.0	1000	0	No	No	Yes				
2258	M	N/A	236.0	1500	0	No	No	No	91	05/02/90	Euthanasia	Yes
2259	M	N/A	157.0	1000	0	No	No	Yes				
2260	M	N/A	236.0	1500	0	No	No	No	101	04/14/90	Euthanasia	Yes
2261 ²	M	N/A	N/A	N/A	N/A	No	No	No	N/A	08/08/90	Euthanasia	
2262	M	N/A	157.0	1000	0	No	No	Yes				
2263	M	N/A	236.0	1500	0	No	No	No	98	04/14/90	Euthanasia	Yes
2264	M	N/A	236.0	1500	0	No	No	No	88	05/01/90	Euthanasia	Yes
2265	M	N/A	157.0	1000	0	No	No	Yes				
2266 ²	M	N/A	N/A	N/A	N/A	No	No	No	N/A	08/13/90	Euthanasia	No

¹ Dosimeter animals euthanized after irradiation.

² Control dogs given sham irradiations (0 cGy)

³ Time from start of boron administration

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PBF/BNCT BMRR CALCULATED DOSE CONTRIBUTIONS AT LOCATION OF THE PEAK BLOOD-VOLUME DOSE (DOSE RATE COMPONENTS AT PEAK DOSE LOCATION)

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DATE	SUBJECT	Beam Size (cm)	$\bar{d}_b$	$\bar{d}_f$	$\bar{d}_g$	$\bar{d}_n$	$\bar{d}_r$
12/16/88	Dog head phantom						
01/10/89	Dog head phantom						
01/11/89	Dog 1592	5 x 10	0.1680	0.1600	1.6700	0.2620	2.0920
01/12/89	Dog 1587	5 x 10	0.1680	0.1600	1.6700	0.2620	2.0920
02/08/89	Dog 966	5 x 10	0.1680	0.1600	1.6700	0.2620	2.0920
02/09/89	Dog 1588	5 x 10	0.1680	0.1600	1.6700	0.2620	2.0920
02/09/89	Dog 995	5 x 10	0.1680	0.1600	1.6700	0.2620	2.0920
02/10/89	Dog 1591	5 x 10	0.1680	0.1600	1.6700	0.2620	2.0920
02/28/89	Dog 1564	5 x 10	0.1680	0.1600	1.6700	0.2620	2.0920
03/01/89	Dog 1590	5 x 10	0.1680	0.1600	1.6700	0.2620	2.0920
03/02/89	Dog 983	5 x 10	0.1680	0.1600	1.6700	0.2620	2.0920
03/02/89	Dog 997	5 x 10	0.1680	0.1680	1.6700	0.2600	2.0920
04/11/89	Dog 946	5 x 10	0.1680	0.1600	1.6700	0.2620	2.0920
04/12/89	Dog 1700	5 x 10	0.1680	0.1600	1.6700	0.2620	2.0920
04/13/89	Dog 985	5 x 10	0.1680	0.1600	1.6700	0.2620	2.0920
07/07/89	Dog 35447-079, "Pugee"	10 x 10	0.2750	0.3000	2.4200	0.4300	3.1500
08/07/89	Dog head phantom	10 x 10	0.3480	0.3580	3.1200	0.6070	4.0850
08/07/89	Dog 35447-080, "Mugsy"	10 x 10	0.2310	0.3000	1.9210	0.4030	2.6240
08/25/89	Dog 35447-081, "Rusty"	10 x 10	0.2660	0.3000	2.4800	0.4280	3.2080
09/28/89	Dog 35447-087, "Benji"	10 x 10	0.2160	0.3000	1.735	0.3770	2.4120
10/24/89	Dog 35447-095, "Godfrey"	10 x 10	0.2580	0.3000	2.1500	0.4505	2.9005
10/25/89	Dog 35447-094, "Brandy"	10 x 10	0.2920	0.3000	2.3300	0.5090	3.1390
10/31/89	Dog 35447-093, "Brandy"	10 x 10	0.2521	0.3000	2.3000	0.4396	3.0396
11/30/89	Dog 35447-100, "Juno"	10 x 10	0.2430	0.3000	2.2300	0.4250	2.9550
02/16/90	Dog 35447-108, "Trixie"	10 x 10	0.2630	0.3000	2.092	0.4580	2.8500

$\bar{d}_b$ = Dose rate (cGy/(min·MW·ppm)) from the $^{10}\text{B}(n,\alpha)^7\text{Li}$ reaction.

$\bar{d}_f$ = Dose rate (cGy/(min·MW)) from above-thermal neutron (primarily hydrogen recoil).

$\bar{d}_g$ = Gamma dose rate (cGy/min·MW).

$\bar{d}_n$ = Dose rate (cGy/min·MW) from the $^{14}\text{N}(n,p)^{14}\text{C}$ reaction, assuming 1.87 weight percent nitrogen in brain tissue (also a peak location).

$\bar{d}_r = \bar{d}_f + \bar{d}_g + \bar{d}_n$

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PBF/BNCT CANINE MELANOMA PHARMACOKINETIC STUDY

SUMMARY OF PATIENT DATA

D, L-BPA STUDY

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ANIMAL	NAME OF DOG	DATE	BORON DOSE	FORM OF BPA**	ADMINISTRATION ROUTE*	COLLECTION LENGTH	SURGERY OR EUTHANASIA	DATE
39412-001	"Cindy" Coyne	01/11/89	50 mg/kg	D, L HCl	Orally	6 hrs	Euthanasia	01/11/89
39412-002	"Smokey" Griffith	01/18/89	50 mg/kg	D, L HCl	Orally	6 hrs	Euthanasia	01/18/89
39412-003	"Minnie" Martin	02/10/89	50 mg/kg	D, L HCl	Orally	6 hrs	Euthanasia	02/10/89
39412-004	"Tracker" Gill	04/25/89	200 mg/kg	D, L Nat	SQ, QID	36 hrs	Euthanasia	04/26/89
39412-005	"Percie" Nissley	06/07/89	200 mg/kg	D, L Nat	SQ, QID	48 hrs	Surgery	06/09/89
39412-006	"Haidi" Meshishnek	08/16/89	200 mg/kg	D, L Nat	SQ, QID	48 hrs	Surgery	08/18/89
39412-007	"Corky" Treadway	08/21/89	200 mg/kg	D, L Nat	SQ, QID	48 hrs	Surgery	08/23/89
39412-008	"Lucy" Dowling	10/27/89	500 mg/kg	D, L Nat	Orally	6 hrs	Euthanasia	10/27/89
39412-009	"Peanuts" Wetterayer	08/22/89	203 mg/kg	D, L Nat	SQ, QID	48 hrs	Surgery	08/24/89
39412-010	"Mindy" Sachtjen	09/05/89	250 mg/kg	D, L Nat	SQ, QID	12 hrs	Euthanasia	09/06/89
39412-011	"Benji" Gebhard	09/14/89	750 mg/kg	D, L Nat	SQ, QID	48 hrs	Euthanasia	09/16/89
39412-012	"Muff" Hoglund	10/28/89	400 mg/kg	D, L Nat	SQ, QID	48 hrs	Surgery	10/04/89
39412-013	"Corky" Newby	10/11/89	491 mg/kg	D, L Nat	Oral, QID	48 hrs	Euthanasia	10/13/89
39412-015	"Missy" Freeman	11/14/89	750 mg/kg	D, L Nat	Orally	6 hrs	Euthanasia	11/14/89
39412-016	"Lucky" Nisonger	03/29/90	250 mg/kg	D, L Nat	Orally	6.5 hrs	Surgery	03/29/90
39412-017	"Winston" Sisteck-Lane	04/10/90	250 mg/kg	D, L Nat	Orally	5.5 hrs	Surgery	04/10/90
		04/26/90	250 mg/kg	D, L Nat	Orally	6.5 hrs	Surgery	04/26/90

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* SQ = subcutaneously
QID = four times per day
BID = two times per day
** 3-p-Boronophenylalanine

END

DATE FILMED

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