Column E Explanation

1. Registration Number: Armed Forces Radiobiology Research Institute, Registration #51-F-0003

2. Number of animals used in this study: 11

3. Species (common name) of animals used in the study: Nonhuman primates

4. Explain the procedure causing more than slight or momentary pain and/or distress.

Pain is not expected from the irradiation procedure itself, but the sequelae of radiation exposure at the levels used in this study can cause pain and distress. Animals were sedated with an anesthetic agent throughout the irradiation procedure to reduce stress. Seven to ten days post-irradiation, various changes occur in the body (*e.g.* compromised immune system leading to immunosuppression, bone marrow suppression, gastrointestinal upset, etc.). These changes can potentially lead to bacterial infections, fever, anorexia, bleeding, nausea, vomiting, constipation, and diarrhea which can cause pain and distress in the animal. If pain or distress was observed, the principal investigator and attending veterinarian were notified to evaluate and determine the appropriate treatment.

5. Provide scientific justification why pain and/or distress could not be relieved.

Nonhuman primates are necessary for the pre-clinical development of radiation countermeasures intended for use in humans because drug metabolism and physiology in nonhuman primates are similar to humans. There is a greater than 95% DNA sequence similarity between nonhuman primates and humans. This animal model is considered as the gold standard by the US Food and Drug Administration (FDA) for drug development. There are no *in vitro* techniques available to demonstrate that any drug will counter the effects of whole-body irradiation in humans. Testing a drug with potential for human application in nonhuman primates ensures safety and specificity prior to the drug entering into the clinic for human trials. Rhesus macaques are the model of choice for investigations of radiation injury and countermeasures because of the large database available from the existing literature that allows for robust comparison. The FDA has accepted rhesus macaques as the appropriate animal model for pilot and pivotal efficacy testing of radiation countermeasures under the Animal Efficacy Rule, where drug efficacy cannot be performed in humans.

For efficacy studies, the endpoint currently mandated by the FDA for approval of radiation countermeasures is mortality. Moribundity was used as a surrogate for mortality and veterinary treatments and euthanasia were used in order to minimize pain and distress, through use of an extensive set of humane endpoint criteria. Studies were conducted using full supportive care suggesting that treatment methods were provided to relieve more than slight or momentary pain and distress. Antibiotics, analgesics, antipyretic agents, nutritional supplements, and oral electrolyte supplements were given to provide relief from discomfort or pain. Blood transfusion, intravenous fluids, anti-diarrheal, anti-ulcer, and anti-emetics were also provided to all animals; however, the methods used were not necessarily substantively effective in alleviating pain and distress such to change the categorization to a Column D.

According to the Paperwork Reduction Act of 1995, an agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a valid OMB control number. The valid OMB control number for this information collection is 0579-0036. The time required to complete this information collection is estimated to average 2 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

OMB APPROVED
0579-0036

This report is required by law (7 U.S.C. 2143). Failure to report according to the regulations can result in an order to cease and desist and to be subject to penalties as provided for in Section 2150.

Interagency Report Control No. 0180-DOA-AN

Fiscal Year: 2018

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

ANNUAL REPORT OF RESEARCH FACILITY

(TYPE OR PRINT)

REGISTRATION NUMBER: 51-F-0003

Customer Number: 443

2. HEADQUARTERS RESEARCH FACILITY *(Name and Address, as registered with USDA, include ZIP Code)*

Armed Forces Radiobiology Research Institute
Veterinary Sciences Department
4555 South Palmer Road
Bethesda, MD 20889-5648

Telephone: 301-295-1365

3. REPORTING FACILITY *(List all locations where animals were housed or used in actual research, testing, teaching, or experimentation, or held for these purposes. Attach additional sheets if necessary.)*

FACILITY LOCATIONS *(Sites)* *See Attached Listing*

REPORT OF ANIMALS USED BY OR UNDER CONTROL OF RESEARCH FACILITY *(Attach additional sheets if necessary or use APHIS FORM 7023A.)*

A. Animals Covered By The Animal Welfare Regulations	B. Number of animals being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not yet used for such purposes.	C. Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use of pain-relieving drugs.	D. Number of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic, or tranquilizing drugs were used.	E. Number of animals upon which teaching, experiments, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic, analgesic, or tranquilizing drugs would have adversely affected the procedures, results, or interpretation of the teaching, research, experiments, surgery, or tests. *(An explanation of the procedures producing pain or distress on these animals and the reasons such drugs were not used must be attached to this report.)*	F. TOTAL NUMBER OF ANIMALS (Cols. C + D + E)
4. Dogs					
5. Cats					
6. Guinea Pigs					
7. Hamsters					
8. Rabbits					
9. Non-human Primates	4	8	0	11	19
10. Sheep					
11. Pigs	0	0	6	42	48
12. Other Farm Animals					
13. Other Animals					

ASSURANCE STATEMENTS

1.) Professionally acceptable standards governing the care, treatment, and use of animals, including appropriate use of anesthetic, analgesic, and tranquilizing drugs, prior to, during, and following actual research, teaching, testing, surgery, or experimentation were followed by this research facility.

2.) Each principal investigator has considered alternatives to painful procedures.

3.) This facility is adhering to the standards and regulations under the Act, and it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and approved by the Institutional Animal Care and Use Committee (IACUC). **A summary of all such exceptions is attached to this annual report.** In addition to identifying the IACUC approved exceptions, this summary includes a brief explanation of the exceptions, as well as the species and number of animals affected.

4.) The attending veterinarian for this research facility has appropriate authority to ensure the provisions of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use.

CERTIFICATION BY HEADQUARTERS RESEARCH FACILITY OFFICIAL
(Chief Executive Officer (C.E.O.) or Legally Responsible Institutional Official (I.O.))
I certify that the above is true, correct, and complete (7 U.S.C. Section 2143).

SIGN (b) (6), (b) (7)(C)

DATE SIGNED 26 NOV 2018

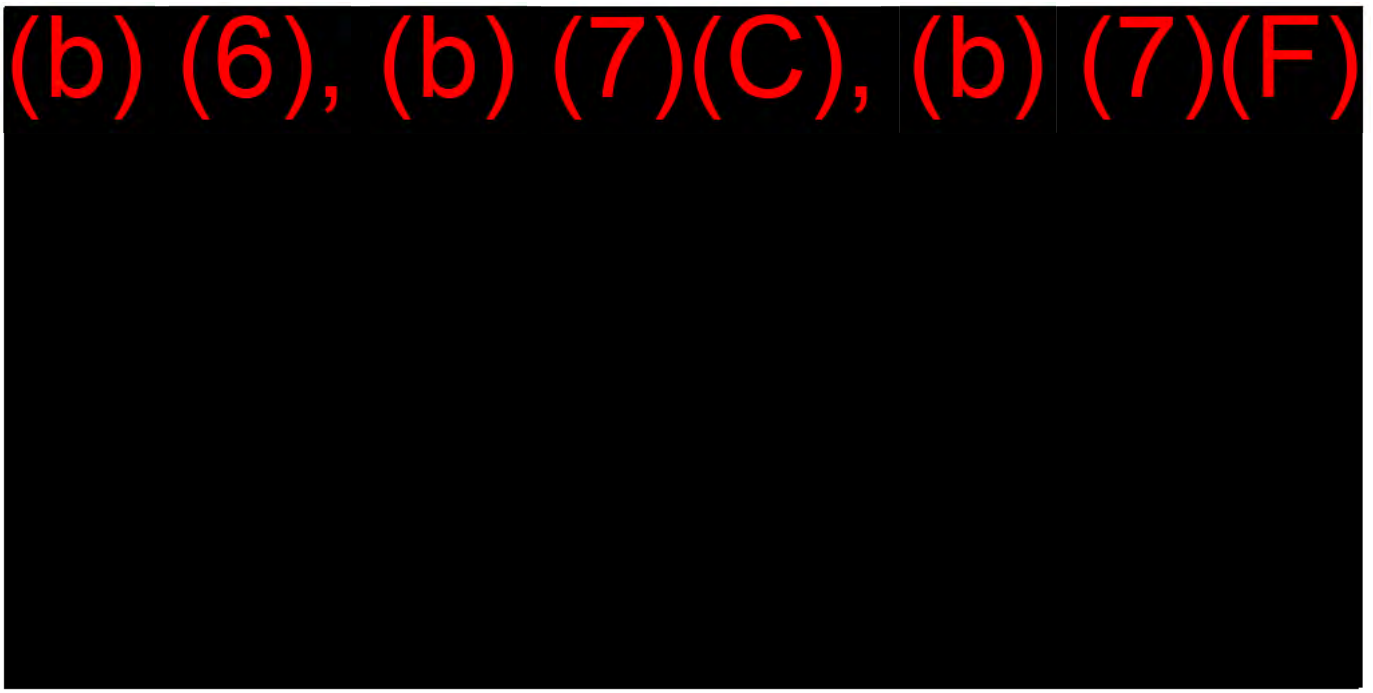
APHIS FORM 7023
JUL 2013

19-04161_000005

29 NOV 2018

CURRENT PERSONNEL LIST

USDA Registration #51-F-0003
4555 South Palmer Road
Bethesda, MD 20889-5648



29 NOV 2018

OMB APPROVED
0579-0036

This report is required by law (7 U.S.C. 2143). Failure to report according to the regulations can result in an order to cease and desist and to be subject to penalties as provided for in Section 2150.

Interagency Report Control No. 0180-DOA-AN

Fiscal Year: 2017

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

ANNUAL REPORT OF RESEARCH FACILITY

(TYPE OR PRINT)

REGISTRATION NUMBER: 51-F-0003

Customer Number:

2. HEADQUARTERS RESEARCH FACILITY *(Name and Address, as registered with USDA, include ZIP Code)*

ARMED FORCES RADIOBIOLOGY RESEARCH INSTITUTE
AFRRI/VSD
8901 WISCONSIN AVENUE, BLDG 43 BETHESDA, MD 20889

Telephone: 301-295-1365

3. REPORTING FACILITY *(List all locations where animals were housed or used in actual research, testing, teaching, or experimentation, or held for these purposes. Attach additional sheets if necessary.)*

FACILITY LOCATIONS *(Sites)* *See Attached Listing*

REPORT OF ANIMALS USED BY OR UNDER CONTROL OF RESEARCH FACILITY *(Attach additional sheets if necessary or use APHIS FORM 7023A.)*

A. Animals Covered By The Animal Welfare Regulations	B. Number of animals being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not yet used for such purposes.	C. Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use of pain-relieving drugs.	D. Number of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic, or tranquilizing drugs were used.	E. Number of animals upon which teaching, experiments, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic, analgesic, or tranquilizing drugs would have adversely affected the procedures, results, or interpretation of the teaching, research, experiments, surgery, or tests. *(An explanation of the procedures producing pain or distress on these animals and the reasons such drugs were not used must be attached to this report.)*	F. TOTAL NUMBER OF ANIMALS (Cols. C + D + E)
4. Dogs					
5. Cats					
6. Guinea Pigs					
7. Hamsters					
8. Rabbits					
9. Non-human Primates		4	29	129	162
10. Sheep					
11. Pigs				74	74
12. Other Farm Animals					
13. Other Animals					

ASSURANCE STATEMENTS

1.) Professionally acceptable standards governing the care, treatment, and use of animals, including appropriate use of anesthetic, analgesic, and tranquilizing drugs, prior to, during, and following actual research, teaching, testing, surgery, or experimentation were followed by this research facility.

2.) Each principal investigator has considered alternatives to painful procedures.

3.) This facility is adhering to the standards and regulations under the Act, and it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and approved by the Institutional Animal Care and Use Committee (IACUC). **A summary of all such exceptions is attached to this annual report.** In addition to identifying the IACUC approved exceptions, this summary includes a brief explanation of the exceptions, as well as the species and number of animals affected.

4.) The attending veterinarian for this research facility has appropriate authority to ensure the provisions of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use.

CERTIFICATION BY HEADQUARTERS RESEARCH FACILITY OFFICIAL
(Chief Executive Officer (C.E.O.) or Legally Responsible Institutional Official (I.O.))
I certify that the above is true, correct, and complete (7 U.S.C. Section 2143).

SIGNATURE OF [redacted] (b) (6), (b) (7)(C)

DATE SIGNED: 4 Dec 2017

APHIS FORM 7023
JUL 2013

05 DEC 2017

NP 1/8/18

19-04161_000001

Column E Explanation

1. Registration Number: Armed Forces Radiobiology Research Institute, Certificate #51-F-0003

2. Number of animals used in this study: 129

3. Species (common name) of animals used in the study: Nonhuman primates; Rhesus macaques (*Macaca mulatta*)

4. Explain the procedure producing pain and/or distress.

Pain is not expected from the irradiation procedure itself, but the sequelae of radiation exposure at the levels used in this study can cause pain and distress. Animals were sedated with anesthetic agent (Ketamine) throughout the irradiation procedure to reduce stress. Seven to ten days post-irradiation, various changes occur in the body (e.g. compromised immune system leading to immunosuppression, bone marrow suppression, gastrointestinal upset, etc.). These changes can potentially lead to bacterial infections, fever, anorexia, bleeding, nausea, vomiting, constipation, and diarrhea which can cause pain and distress in the animal. If pain or distress was observed, the principal investigator and attending veterinarian were notified to evaluate and determine the appropriate treatment.

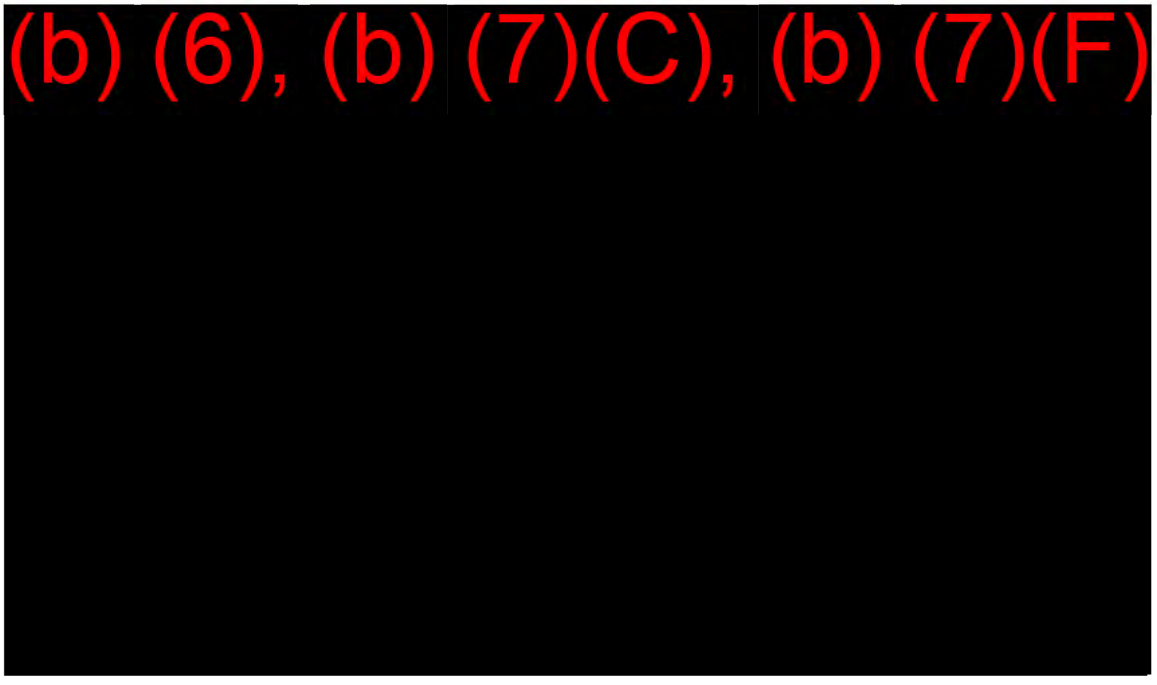
Antibiotics, analgesics, antipyretic agents, nutritional supplements, and oral electrolyte supplements were used to provide relief from any discomfort or pain. Blood transfusion, intravenous fluids, anti-diarrheal, anti-ulcer, and anti-emetics were provided to some animals. These medical interventions provided relief from any discomfort or pain the animals may have experienced. Around 30 days post-irradiation, the animal's immune system, bone marrow, and gastrointestinal system typically start recovering. Animals were closely monitored post-irradiation and multiple times a day until they completely recovered from acute radiation syndrome (ARS).

5. Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results.

Nonhuman primates are necessary for the pre-clinical development of radiation countermeasures intended for use in humans because drug metabolism and physiology in nonhuman primates are similar to humans. There is a greater than 95% DNA sequence similarity between nonhuman primates and humans. This animal model is considered as the gold standard by the US Food and Drug Administration (FDA) for drug development. Testing a drug with potential for human application in nonhuman primates ensures safety and specificity prior to the drug entering into the clinic for human trials. Rhesus macaques are the model of choice for investigations of radiation injury and countermeasures because of the large database available from the existing literature that allows for robust comparison. The FDA has accepted rhesus macaques as the appropriate animal model for pilot and pivotal efficacy testing of radiation countermeasures under the Animal Efficacy Rule, where drug efficacy cannot be performed in humans.

UPDATED PERSONNEL LIST

USDA Certificate #51-F-0003



05 DEC 2017