717902

PROTECTION OF HUMAN SUBJECTS
LAWRENCE LIVERMORE NATIONAL LABORATORY

(TO BE COMPLETED BY P.I. AND SUBMITTED TO INSTITUTIONAL REVIEW BOARD PRIOR TO MEETING)

RECEIVED
JAN 27 1989
INSTITUTIONAL REVIEW BOARD

Project Title Lung Counter Calibration with Inhaled Nb-92 as a "Mock Plutonium"

Funding Source British Nuclear Fuels and the United Kingdom Central Electricity Generating Board

AGREEMENT OF COMPLIANCE STATEMENT

I agree to conduct my experiments according to this protocol and conform with the policies of Lawrence Livermore National Laboratory and Biomedical Sciences Division. Before any changes in this protocol can be implemented, a written notice of the proposed changes must be submitted to the Institutional Review Board as an amendment to the protocol.

Principal Investigator signature: Arthur L. Anderson

Date: January 27, 1989

A. NEW PROJECTS

1. What is the involvement of human subjects in this project and what human samples will be used?

2. What is the present or actual benefit to society in doing this project?

3. Outline Protocol.

REPOSITORY LLNL B361 Rm. B940A

COLLECTION Institutional Review Board

BOX No. IRB Protocol File

FOLDER Anderson IRB 88-101
Counting of Human Subjects Containing Nb-92m, Ba-133 and Sr-85 at the LLNL Whole Body Counter (title change at 3/8/89 mtg)

4. List source(s) of human samples

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5. How will confidentiality be insured?

6. Attach copy of filled-in consent form that subjects will be asked to sign ***(Use the attached copy of the Duke University checklist as a guide in completing the consent form.)***

7. List name(s) of collaborative institutions. **Approvals from those institutions must be on file with the LLNL Human Subjects Committee**

B. RENEWAL PROJECTS

1. Outline Protocol. The protocol is a continuation of radioactivity measurements on volunteers containing radioactivity-labeled particles in a planned experiment, using short half-life, low dose Nb-92m to simulate plutonium in the lungs. Data from these measurements will be used to determine in-vivo, the influence of spacial distribution on calibration factors for the internal measurement of real plutonium inhaled by people involved in accidental exposures.

Administration of one micron particles in England by the British are being compared with results of earlier work involving the uptake of five micron particles. LLNL is participating in a measurement capacity only. Data from the experiment is expected to improve measurement accuracies for plutonium lung counting equipment at LLNL and other DOE facilities, thereby improving the health management of exposure cases involving plutonium or other radionuclides.

2. Date of first Human Subjects Committee approval: _____
   Approval No. 88-101

3. Date of latest approval: ~~1/26/88~~ 1/27/89E

4. Will consent form need to be changed? If so, attach revised consent form.
   NO

5. Are there any changes in protocol for human subjects from most recent review?
   NO

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6. Since most recent review, have any additional potential hazards been identified?

NO

7. List any new collaborative institutions. **Approvals from those institutions must be on file with the LLNL Human Subjects Committee**

None

8. List any new sources of human samples

None

C. PROJECTS THAT INVOLVE SAMPLES COLLECTED ELSEWHERE

1. Has this project been reviewed and approved by the other institution's human subjects institutional review board?

Yes

2. Date of approval: 10/20/86

3. Does the consent form include a statement stating that some of the work will be done at LLNL?

No

4. Does the LLNL Human Subjects Committee have on file a copy of the form signed by subjects? Yes. Signed forms are attached with this application.

NOTE: Copies of these documents must be provided to the LLNL Human Subjects Committee

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FEB 10 1989
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FACSIMILE

UNITED KINGDOM ATOMIC ENERGY AUTHORITY
HARWELL LABORATORY
ENVIRONMENTAL AND MEDICAL SCIENCES DIVISION

FAX TEL NO. (BUILDING 364):
0235 43 2134 (DIRECT DIAL)
X 2134 (TIE LINE)

TO: LARRY ANDERSON 25181 7383

REPEAT:

FROM: DON NEWTON

DATE: 1 FEB 89

SUBJECT: Original proposal for ^{133}Ba work and endorsement by a respectable authority.

NO OF PAGES (INCL THIS): 8

REMARKS: My reaction to the assertion that the project has no "thought-through" experimental design.

1122018

ICRP International Commission on Radiological Protection

1985-02-05

Dr. D. Newton
Environmental and Medical Sciences Division
AERE Harwell
Oxon OX11 0RA

Dear Dr. Newton,

I am replying to your letter of 24 January concerning a proposed study for long term retention of barium in man.

Technically, your proposal seems well-considered, although I think you have underestimated the dose to be received, since you apparently forgot about the f_1 of 0.1. From ICRP Publication 30, Supplement to Part 2, page 396, I reckon that the effective dose equivalent from 1 Bq given orally is 4.35 10^{-10} Sv. (I have omitted the dose components from breast and gut).

With an injection of 1 Bq the dose is 10 times higher (1/0.1); so 75 kBq injected will give 75 10^3 x 4.35 10^{-4} x 10 = 330 µSv (not 50 µSv). I'm not sure how this will affect the deliberations of your ethical committee.

Yours sincerely,

FD Sowby

F.D. Sowby

NO — this approach includes also doses received by target organs from activity passing through the gut. My 230 µSv is corrected for injected activity. DN

Chairman: Prof. Bo Lindell, Statens strålskyddsinstitut, Fack, S—104 01 Stockholm, Sweden, Tel: 08—24 40 80, Telex: 11771 SAFERAD

Scientific Secretary: Dr. F.D.Sowby, ICRP, Clifton Avenue, Sutton, Surrey SM2 5PU England. Tel: 01—642 4880

1122019

PROPOSED ADMINISTRATION OF BARIUM-133 BY INTRAVENOUS INJECTION

Background

1. The ICRP's model of alkaline earth metabolism[1] provides the metabolic basis for the control of exposure to radionuclides of the elements calcium, strontium, barium and radium. Central to this model is a function intended to describe the whole-body retention of a single systemic input, up to times several decades later. Important parameters in this function relate (i) to the skeletal depletion of activity following diffusion through the calcified matrix, (ii) to the initial partition of long-term skeletal deposition between compact and trabecular bone and (iii) to the rates at which activity is lost from compact and trabecular bone through the process of skeletal resorption. Thus, the parameters determine not merely the whole-body retention, but also the retention in the two categories of bone individually. This is important in the dosimetry of radium[2], because an α-particle emitted by ^{226}Ra within trabecular bone is assumed to be four times more detrimental compared with one from ^{226}Ra deposited in compact bone. Moreover, an improved knowledge of the local retention functions would assist in the evaluation of data on the incidence of bone cancers in people who had acquired large burdens of radium.

2. To estimate the value of each parameter, the ICRP Task Group which developed the model reviewed evidence from the histological examination of bone and from human metabolic data, including data on the whole-body retention of radium in those relatively few instances where the intake was known. Those data (Fig 1) were scattered and fragmentary, and non-existent between 1 and 20 years after intake. The retention function, with the chosen values of its parameters, provides a visually acceptable fit (Fig 1), but the scatter is such that the data can offer only limited support either for that choice of values or for the postulates underlying the model. It would be more convincing if a systematic study of the retention could be undertaken, following a controlled administration of radium; the test would then be whether a function of the general form postulated in the model, embodying metabolically sensible values for its parameters, was found to provide a close fit to such data.

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3. In the case of radium, the radiation dose to volunteers in such an experiment would be prohibitive. However, in certain respects, barium appears to be a satisfactory tracer for radium. The excretory plasma clearance for both elements is high[1], so that ions released from bone have little chance of being re-incorporated; consequently, the extent of skeletal re-modelling will be reflected to the same degree in the pattern of whole-body retention of both elements. The losses through diffusion will differ for the two elements, and this will affect the retention pattern, but if the retention of a barium isotope is studied over a long enough period, the effects of diffusion, resorption of compact bone, and resorption of trabecular bone can in principle be separated.

4. Data exist to illustrate these possibilities. Fig 2 shows the percentage retention of an initial 2 μCi ^{133}Ba (half-life 10.7 years), over a 10-year period following its injection into a healthy 60-years-old male volunteer, Subject GH. The purpose of this experiment, which was in the first instance conducted jointly with the MRC Unit at Harwell, was primarily to compare the <u>short-term</u> metabolism of barium with that of other alkaline earth elements in the same subject[3]; Harwell contributed data from body radioactivity measurements. In fact, we continued to measure the ^{133}Ba for 19 years, making this by far the longest continuous survey of a known dose of a bone-seeker in man. The continuous curve in Fig 2 was derived by rigorous fitting of a function of the general form proposed in the model, and it provides a remarkably close fit over most of the 10-year period of the plotted data. The rate constants necessary to achieve this fit were 5.1 ± 0.8% yr^{-1} for resorption of compact bone and 21.9 ± 1.5% yr^{-1} for resorption of trabecular bone. These are somewhat larger than the values assumed by the Task Group (2.5 and 10% yr^{-1} respectively). The ratio of these two constants (4.3 ± 0.8) is, however, consistent with the ratio of 4 predicted from the relative surface area: volume ratios in the two categories of bone, which is a fundamental postulate in the model. Other evidence emerging from this study, and supporting both the basis of the model and the validity of ^{133}Ba as a tracer for radium, is given elsewhere[4].

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Proposal and justification

5. The data for ^{133}Ba are confined to those for Subject GH, and they need to be supplemented by studies in other subjects, to indicate the variability between subjects of values for the important parameters. We propose to inject five additional male volunteers with 75 kBq (2 μCi) ^{133}Ba, and also to re-inject subject GH with the same quantity, in order to compare his retention pattern with that (Fig 2) found 20 years ago. Measurements of whole-body retention would be supplemented in the early stages by assessment of ^{133}Ba in samples of blood and excreta.

6. If the data from these studies, like those already obtained from Subject GH, were found to follow functions of the form predicted by the model, these data would provide valuable additional support for the basis of dosimetry for an important group of radionuclides. If they failed to show such behaviour, implying that the consistency found in our studies with GH was perhaps fortuitous, then this would be an equally important outcome, demonstrating deficiencies in the model. In that case the data, together with those at present available for Subject GH, would provide information, unique in its detail and reliability, on the long-term behaviour of an alkaline earth element in man, which would be invaluable in the formulation of any revised model.

Dose estimates

7. The weighted committed dose equivalents for the organs listed in ICRP Publication 30[8], over a period of 50 years following injection of 75 kBq ^{133}Ba, are as follows:

Organ	WCDE (μSv)
Red marrow	120
Bone surfaces	42
Gonads	38
Lungs	19
Adrenals	13
TOTAL	233

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References

1. ICRP Publication 20 (1973). Alkaline earth metabolism in adult man.

2. ICRP Publication 30, Part 1 Supplement, p 286 (1979).

3. Harrison et al, Int J Radiat Biol, 13, 235-247 (1967).

4. Newton et al, AERE-R 11407, (1985).

5. ICRP Publication 30, Part 2 Supplement, p 394 (1981).

D Newton

EMSc Division
Bldg 364
AERE, Harwell

1st July 1985

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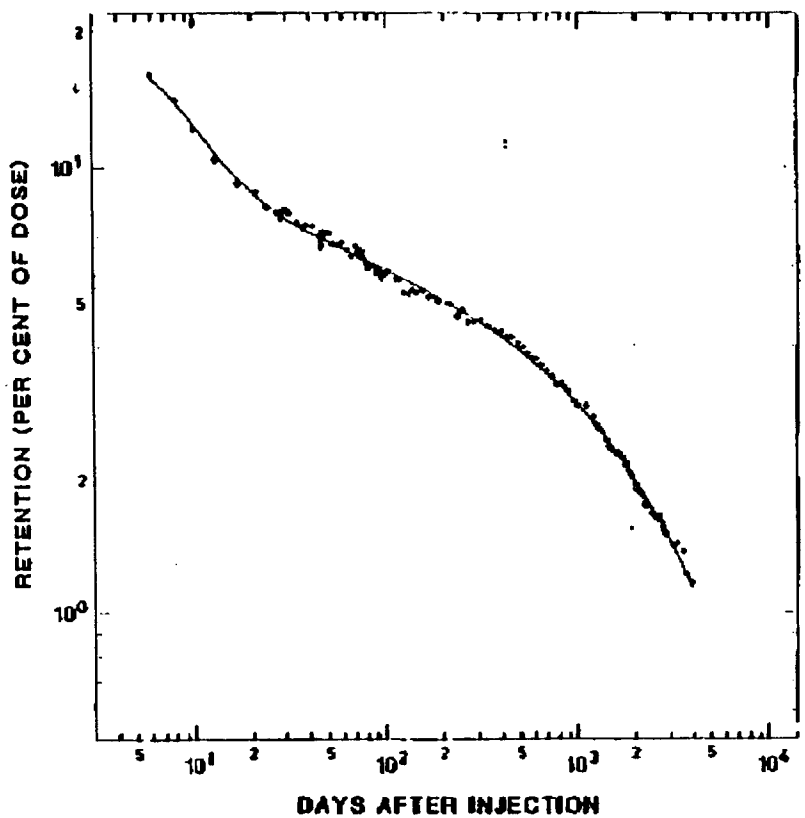

Fig 2 Plotted points : observed whole-body retention in Subject GH, up to 10 years after injection of ^{133}Ba

Curve : function of the form postulated in the ICRP model, fitted to the data for Subject GH

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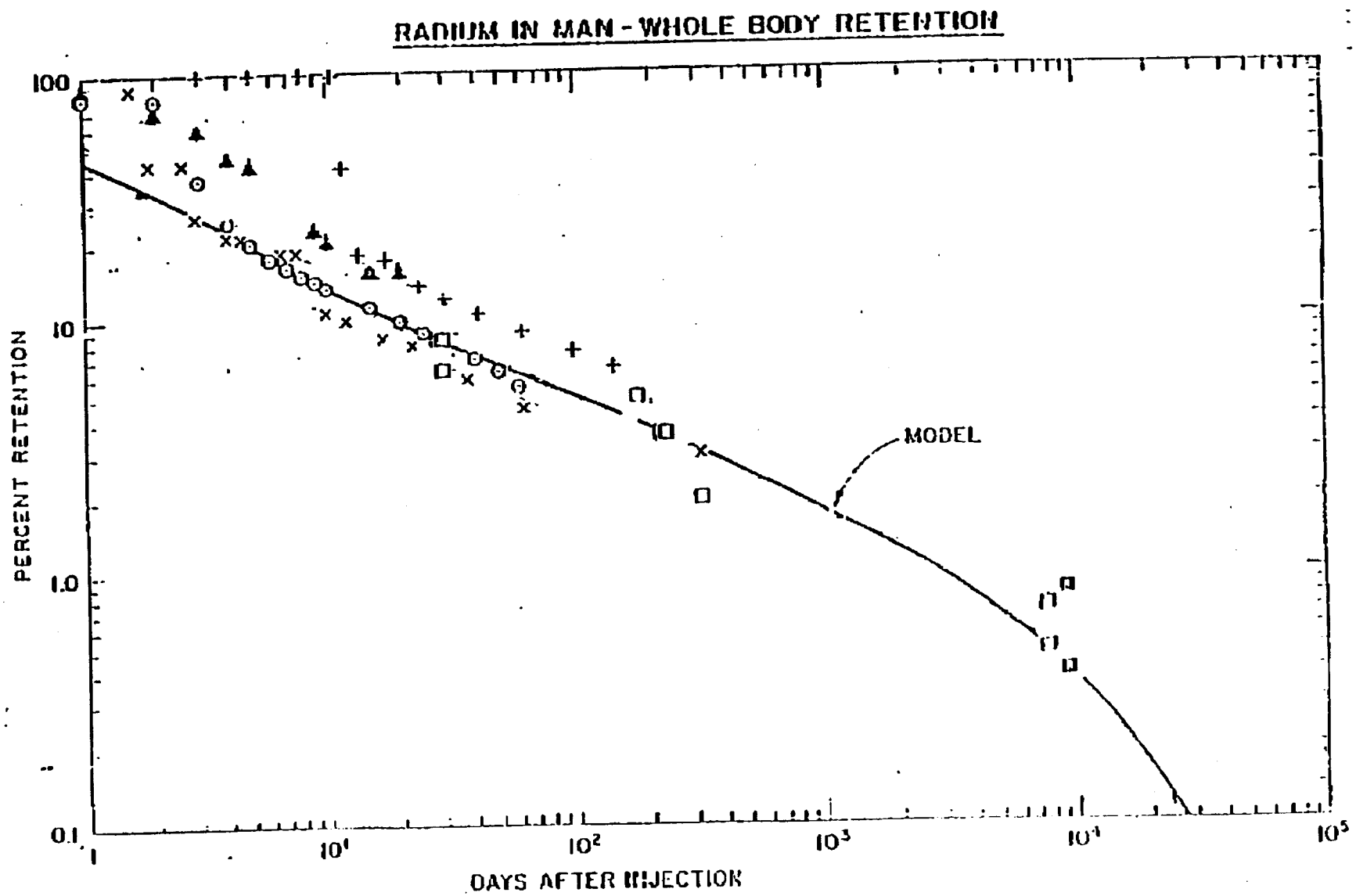

Fig 1 Data on the whole body retention of radium in man, reviewed by the ICRP Task Group in formulating the model of alkaline earth metabolism