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 REPOSITORY DOE-DAY  
 COLLECTION Environment + Safety Support Div.  
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 FOLDER 1300-3-B Human Subject  
Testing 1986-1987

October 2, 1987

Dr. Thomas R. Crites  
 Acting Head  
 Hazards Control Department  
 Lawrence Livermore National  
 Laboratory  
 University of California  
 Post Office Box 308  
 Livermore, CA 94550

SUBJECT: Whole Body Counting of Employee from AERE Harwell United Kingdom

Dear Dr. Crites:

We appreciate receiving your letter of September 10, 1987, advising us of the visit by Mr. George Harrison relative to the measurement of residual radioactivity in his body. Due to the sensitivity associated with any research which could be construed to involve human test subjects, it's important that we keep each other apprised of any new developments on this subject. Furthermore, we concur in the approval protocol being pursued. This matter is also being coordinated with the Office of Health & Environmental Research.

If you have any questions, please contact Jim Foster of my staff on FIS 536-7966.

Sincerely,

*Original signed by*

James T. Davis, Director  
 Environment, Safety and  
 Quality Assurance Division

bcc: R. Bredderman, DP  
 S. Ball, ER  
 J. Blasy, LSO

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# Lawrence Livermore National Laboratory

1987

September 10, 1987

DIVISION

Mr. James Davis  
U.S. Department of Energy  
DOE SAN  
1333 Broadway  
Oakland, CA 94612

SUBJECT: Visit Request and Whole Body Counting of Employee from AERE  
Harwell, U.K.

Dear Mr. Davis:

Enclosed for your information are documents submitted to the LLNL Human Subjects Committee regarding proposed Whole body counter measurements in mid-October 1987 for Mr. George Ernest Harrison, a radiobiologist employed by AERE Harwell. The purpose of Mr. Harrison's visit is to measure the residual radioactivity present in his body from Ba-133 and Sr-85 which were administered in the United Kingdom. Mr. Harrison came to the Laboratory for earlier measurements in March 1987 after receiving a planned administration of 76 kBq (2.05 uCi) of Ba-133 in an AERE experiment formally approved by their Tracer and Irradiation Studies Approval Committee. In June of 1987, Mr. Harrison received an additional administration of 106 kBq (2.86 uCi) Sr-85 in another program, which was also approved by the UK ethics committee.

Mr. Harrison was measured by several U.S. laboratories during his March visit to the United States and will be measured by at least three U.S. laboratories during his visit in October. These measurements are useful to LLNL and other DOE facilities as a means of calibrating radiation detectors used in various in vivo monitoring programs and have produced valuable data, enabling us to perform our work more accurately and with more confidence. If you have any questions regarding the above, please call Larry Anderson or Deborah Kruchten, of my staff on FTS 532-5158 or 532-5199 respectively.

Sincerely,

Thomas R. Crites, Acting Head  
Hazards Control Department

TC/pc  
Attachments

cc: Bart Gledhill  
w/o attachments

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**HARWELL**  
UK ATOMIC ENERGY AUTHORITY

**Environmental and Medical Sciences Division**  
B551 Harwell Laboratory  
United Kingdom Atomic Energy Authority  
Oxfordshire OX11 0RA

Telex: 83135  
Telephone: Abingdon (0235) 24141  
Extension **4157**

25th June 1987

Mr H E Palmer  
Personnel Dosimetry  
Battelle Pacific NW Laboratories  
P O Box 999  
Richland, WA 99352  
USA

Dear Earl

It seems from your recent letter (June 16) that we are still in with a chance as regards a second series of measurements on George Harrison. Will the enclosed material meet your requirement (and Larry's) for the "experimental protocol" of the  $^{85}\text{Sr}$  injection? It is in fact my submission to our Ethics Committee, and it's all I have ready at the moment, but I could of course supply whatever additional details you may request. The proposal was accepted and, as you know, the injection took place on June 1. We decided not to exploit the authorisation in full, and administered only 106 kBq, rather than the 150kBq sanctioned by the Committee, in the interests of not prejudicing the barium retention study for too long, so the dose estimates in Table 2 will come down accordingly.

Late September would suit George very well. As I indicated, he would not envisage as extensive (and intensive) a schedule as last time, but he would be prepared to consider going to one or two labs additional to PNL and LLNL if the scientific justification existed. Certainly you, and I presume Larry also, will want to set aside more than the day and a half allowed last time.

With best wishes,

Yours sincerely

D NEWTON.

cc Mr A L Anderson

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Interdepartmental letterhead

Mail Station L- 383

Ext: 25181

September 9, 1987

TO: Bart Gledhill, Chairman - LLNL Human Subjects Committee  
c/o Gerry Wyman

FROM: A. Larry Anderson *add*

SUBJECT: Whole Body Counting of Employee from AERE Harwell, U.K.

Approval is requested from the LLNL Human Subjects Committee for LLNL to participate in radioactivity measurements on Mr. George Ernest Harrison, a Radiobiologist employed by AERE Harwell.

Mr. Harrison received an administration of 76 kBq (2.05 uCi) of Ba-133 in March 1986 in a planned AERE experiment formally approved by their Tracer and Irradiation Studies Approval Committee. This committee is an ethics committee similar in human use oversight to our own (LLNL) Human Subjects Committee. In March 1987, Mr. Harrison visited the Whole Body Counter at LLNL in addition to several other United States facilities, where he was measured with LLNL's radiation detection equipment. In June of 1987, he received an additional administration of 106 kBq (2.86 uCi) Sr-85 in another program, also approved by their ethics committee.

The Ba-133 uptake (primarily now in bone) is known to within 5% and will provide useful additional data to that taken in March. The information is important to LLNL and other DOE laboratories, in that it provides valuable calibration data on radionuclides emitting higher energy photons than are observed from plutonium. The Sr-85 (a beta emitter also in bone), will provide additional information of value in establishing detector calibration factors for beta bone-seeking radionuclides.

Similar intercalibration programs have been conducted in the past with LLNL participation concerning subjects with Pd-103, Cr-51, Nb-92m, and various other radionuclides, including heavy elements such as Am-241 and Pu-239 that were taken up in the body as a result of accidental or occupational exposure. Usually, LLNL has been involved only in passive sense, that is in performing measurements only on the subjects; however, approval was received from the LLNL Human Subjects Committee in 1981 and 1982 to allow participation of two LLNL employees in a program involving the direct inhalation of Nb-92m labeled particles at AERE Harwell. Both employees, along with one other American and five British subjects were later counted at several British and American facilities, for the purpose of validating the LLNL plutonium lung counter calibration phantom which had been developed at this Laboratory. In further work, eleven women (all British), were employed in another Nb-92m intercalibration program to determine the suitability of the phantom as calibration medium for females. Both of these programs produced valuable data, enabling us to perform our work more accurately and with more confidence.

University of California

 Lawrence Livermore  
National Laboratory

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Pending approval by the LLNL Human Subjects Committee, we are proceeding to invite Mr. Harrison to return to LLNL during the week of October 12, 1987 for further measurements pertaining to his Ba-133 uptake and also to measure the residual radioactivity present from the second uptake of Sr-85. Representatives from DOE-SAN have been informed of LLNL's intended participation in these measurements and have stressed the need and importance of receiving LLNL Human Subjects Committee approval for the project and of having clear documentation that Mr. Harrison and Mr. Harrison's employer have agreed to the experimental protocol, via formal review. Attached for your information is the experimental proposal, including dose calculations by Dr. D. Newton (the AERE experimenter), regarding the Sr-85 administration as submitted to the AERE Tracer and Irradiation Studies Approval Committee, the committee minutes dated October 2, 1986 (Item 5) showing review and approval the experiment, and a letter from Dr. Newton to Mr. H.E. Palmer of Battelle Pacific Northwest Laboratory (co-ordinator of the U.S. program participation), indicating approval by the ethics committee for the experiment and that the Sr-85 was administered on June 1, 1987 in an amount lower than was originally authorized. Also attached is a copy of the AERE Code of Practice for use in biomedical research involving the irradiation of employees of the UKAEA.

Mr. Harrison will be counted at two other laboratories in the United States as part of an intercalibration program coordinated by Pacific Northwest Laboratory. These measurements are useful to LLNL and other DOE facilities as a means of calibrating radiation detectors used in various in vivo monitoring programs. If you have any questions regarding the above, please call Larry Anderson or Deborah Kruchten, on 2-5181 or 2-5199 respectively.

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Attachments

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PROPOSED ADMINISTRATION OF  $^{85}\text{Sr}$  BY INTRAVENOUS INJECTIONBackground

1 This proposed study is intended to supplement existing data on alkaline earth metabolism in a single, healthy male volunteer, Subject GH, and in particular to establish whether changes occur in the pattern of clearance of strontium from the skeleton during late adult life. On four previous occasions, Subject GH was injected with nuclides of calcium or strontium of sufficient half-life to allow their retention in the body to be studied for 300 - 400 days (Table 1).

TABLE 1 DATA FROM PREVIOUS STUDIES WITH  $^{45}\text{Ca}$  OR  $^{85}\text{Sr}$  ADMINISTERED TO SUBJECT GH

Age	Nuclide	Duration of study (days)	C
53	$^{85}\text{Sr}$	336	$0.16 \pm 0.06$
57	$^{85}\text{Sr}$	399	$0.23 \pm 0.02$
60	$^{85}\text{Sr}$	388	$0.17 \pm 0.01$
66	$^{45}\text{Ca}$	388	$0.15 \pm 0.01$

2 In Table 1, the parameter C is the exponent in the power function

$$R = Bt^{-C}$$

where R represents the retention at time t after intake; the parameters B and C were derived by analysis of the retention data obtained after the early clearance of activity from labile pools was judged to be complete. C is presumed to reflect, empirically, the rate at which tracer in a series of pools associated with bone is depleted; more details of these analyses are given elsewhere\*.

3 Although C has no more specific metabolic significance, the trend of C with age may reasonably be used to indicate any age-related changes in the efficiency with which the tracer is removed from the skeleton. Unfortunately, the value (0.15) listed in Table 1 for age 66 does not bear legitimate comparison with the others, since it alone was derived following injection of radiocalcium, whereas the remainder emerged following intakes of strontium activity. Indications<sup>(1)</sup> are that the long-term treatment of the two elements by the skeleton is similar, but that calcium is less rapidly removed from the body because of the greater efficiency with which it is re-cycled into bone. Consequently, if the experiment at age 66 had involved strontium rather than calcium, it is likely that the value of C derived would have been  $> 0.15$ .

4 Overall therefore, the results in Table 1 suggest no important trend in the clearance pattern in this subject between ages 53 and 66, and this conclusion extends to the efficiency with which the tracer is initially deposited in the skeleton\*. The study now proposed would indicate what, if any, differences are to be found at age 82.

\* AERE-R 12227

## Proposal

5 The subject will receive an intravenous injection of 150 kBq  $^{85}\text{Sr}$  in isotonic saline. Assessments of whole body retention will be made at intervals for as long as feasible - probably 500 days. Complete collections of excreta are envisaged during the first 3 - 4 weeks with probably about 12 blood samples (20 ml) analysed during this period.

## Dosimetry

6 Weighted committed dose equivalents for each of the relevant organs listed in ICRP Publication 30 are given in Table 2, and are based on the metabolic model for strontium proposed in that document.

TABLE 2 WEIGHTED COMMITTED DOSE EQUIVALENTS ( $\mu\text{Sv}$ ) FOLLOWING INTRAVENOUS INJECTION OF 150 kBq  $^{85}\text{Sr}$

Organ	$\mu\text{Sv}$
Red marrow	32
G I tract	30
Gonads	27
Lungs	11
Adrenals	10
Bone surfaces	9
Pancreas	6
Total	125

## Summary

7 Approval is sought for the administration, by intravenous injection, of up to 150 kBq  $^{85}\text{Sr}$  to a single, healthy male volunteer aged 82, in an investigation of age-related trends in strontium metabolism.

D Newton  
EMSc Division  
Building 364

23 September 1986

## Reference

(1) J Reeve et al. Calcif. Tissue Int. 35, 9-15 (1983).

NOT FOR PUBLICATION

TISAC (86) M2

Tracer and Irradiation Studies Approval Committee

Minutes of the twentieth meeting held on Thursday, 2 October, 1986 in the Environmental and Medical Sciences Division, AERE Harwell.

Present:

Dr J Vennart (Chairman)	External member
Dr A C Chamberlain	External member
Dr J C Evans	Head of Medical Section, AERE
Dr A Morgan	Environmental & Medical Sciences Div
<del>Dr D Newton</del>	Environmental & Medical Sciences Div
Dr S Rae	External member
Mr J N Pritchard (Secretary)	Environmental & Medical Sciences Div

Mr R M Brown (Environmental & Medical Sciences Div) also attended.

Apologies for absence were received from Dr K Duncan and Dr R H Mole.

## 1. MINUTES OF THE NINETEENTH MEETING (TISAC (86) M1)

Dr Evans was erroneously omitted from the list of those present.

Minute 1. Subject to this alteration, the COMMITTEE accepted the minutes

## 2. MATTERS ARISING

## 2.1 Publication on working practices

Dr Morgan and Evans apologised for the slow progress on the publication dealing with the workings of the COMMITTEE. A combination of factors have impeded its progress and so a draft is unlikely to be available before the end of this year. Mr Pritchard drew the attention of the authors to a paper on a similar theme presented at the 10th Annual Conference of the Australian Radiation Protection Society (R Rosen, Radiation Protection in Australia, 3 (4), 156-159).

## 2.2 Revised code of practice

The final draft of the revised code of practice was circulated by the COMMITTEE for information. However, prior to the meeting, Dr Mole had drawn the authors' attention to several points requiring clarification, including the omission of a discussion of the confidential nature of some projects. Thus, comments were invited from the remainder of the COMMITTEE. Dr Vennart suggested that doses should now be referred to as 'committed effective' dose equivalents, although Dr Newton pointed out the difficulty of quoting committed doses before the end of long-term metabolic studies. Dr Rae was assured that volunteer dose records are incorporated into medical records and will form part of the annual statement of dose issued to employees. Dr Evans indicated that a framework for compensation may be agreed along lines similar to the BNF plc scheme.

Dr Evans reported that the code of practice is currently being discussed by a sub committee of the Authority Joint Committee on Health and Safety before going to the Establishment's Directors Committee for final approval. In particular, the sub committee of the AJCHS is considering the role of the employees' representative in the newly constituted COMMITTEE. Dr Evans, who is a member of this sub committee, received a strong recommendation that such a representative should not belong to an organisation with a stated policy against volunteer

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experiments. It was pointed out that the mechanism for obtaining a deputy for this representative, should he be unable to attend a meeting, needs to be decided, else the COMMITTEE will be inquorate.

### 2.3 Dealings with ARSAC

JCE Dr Evans reported that he had been unable to contact Dr Williams by telephone despite numerous attempts. He agreed to write to ARSAC, questioning whether ethical approval was required prior to an application for a licence. However, the response time for research licence applications has improved markedly now that the applications for renewal of the 5-yearly licences for diagnosis and therapy have been processed.

The Chairman then requested an update on the proposal for investigating the effects of certain drugs taken on a prophylactic basis (TISAC (86) 3). Dr Evans replied that the results of an extensive literature search for relevant data were being assessed, prior to formulating a proposal to be put before a hospital Ethics Committee. Mr Pritchard added that preliminary results indicated that the lung could be dilated beyond the normal range in healthy subjects, even with prolonged treatment. This had been shown to affect deposition in the only published study found to date. Effects on mucociliary clearance appear to be drug specific with a range of responses.

## 3. PROGRESS REPORTS on APPROVED PROPOSALS

### 3.1 Retention of arsenic ingested in fish

Mr Brown reported that consultation is taking place with an Italian group who have published methods to synthesise inert and radioactive arsenobetaine and arsenocholine. It is hoped to be able to reproduce this synthesis by the end of this year.

### 3.2 Retention of ingested neptunium

Dr Newton stated that there had been no progress in achieving financial support for this proposal, nor was any expected. Dr Vennart drew his attention to a publication due shortly from David Taylor (KFK) on gut uptake, which has been accepted in principle by NRPB.

### 3.3 Pilot study of tar deposition during 'passive smoking'

Mr Pritchard reported that the findings of a very high vapour component in radiolabelled sidestream smoke have caused the sponsors to reconsider deposition studies until more is known about the physical and chemical changes which occur as the smoke undergoes dilution and ageing. Although a final decision is not yet known, it is anticipated that the volunteer programme will be suspended, pending studies of vapour-particle interactions, which it is hoped will also be conducted at Harwell.

### 3.4 Lead inhalation by car travellers

Sec. The Secretary reported that Mr Garland has still been unable to obtain funding for this study. He then suggested that, in future, it would save time if investigators notify the COMMITTEE only in the event of funding being obtained. However, the COMMITTEE felt it worth while for the Secretary to continue to monitor the progress of these proposals. The Chairman asked why proposals had been approved when their status was uncertain. Dr Newton replied that in

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contract negotiations it was often desirable, and sometimes essential, that ethical approval was obtained prior to signing contracts. The irregular frequency of COMMITTEE meetings sometimes results in a proposal being submitted before negotiations have been concluded successfully.

### 3.5 Clearance of cobaltous oxide from lung

Mr Pritchard reported the latest results from this study, presented at the second International Symposium on Aerosols in Medicine, Salzburg, 18-20 September. These showed both the solubility and mechanical transport of <sup>57</sup>Co to be species dependent, contradicting the postulate of species-independent solubility currently under consideration by ICRP. However, variations in solubility are less than those in mechanical transport. The data for the inter-species comparison will be completed this month, although long-term metabolism in humans will continue to be studied.

### 3.6 Metabolism of alkaline earths

Dr Newton reported that the first administration of <sup>133</sup>Ba had successfully taken place and that the next was anticipated in early November. The data arising from the first injection were presented under item 5.

### 3.7 Tar deposition in middle-tar smokers switching to low-tar cigarettes

Mr Pritchard referred to a memo circulated on 5.3.86 which cleared up a discrepancy in dose estimates between TISAC (86) 4 and TISAC (86) 5. In response to Dr Vennart, he said that the total doses from 15 experiments were correct, and those given on a per administration basis had been rounded to the nearest 0.1  $\mu$ Sv. The volunteer experiments were scheduled to start in mid-November and run for 6 months. The radio-label concentration in tar was currently being measured for the cigarette brand to be used in the study, and a pool of volunteers had been identified.

### 3.8 Factors affecting tar deposition

Mr Pritchard reported that this study was complete and that the COMMITTEE had been circulated with the draft of a paper presented to the 2nd International Aerosol Conference. This contains results from about half of the experiments. Three main conclusions could be drawn from this data. The effect of inhalation pattern on regional deposition was demonstrable although this was much less than that due to inter-subject variability. The shift in the regional deposition of hygroscopic materials agrees well with theoretical predictions. Not all of the behaviour of cigarette smoke can be explained by its hygroscopicity; following the discovery of the volatility of sidestream smoke, evaporation followed by diffusional deposition to the upper airways provide the most likely explanation. There followed a discussion of the factors affecting inter-subject variability, in particular the relative humidity in the different regions of the respiratory tract and its influence on particle growth.

## 4. STATUS OF ARSAC CERTIFICATES

The Secretary reported that applications to ARSAC have all been processed. Dr Evans informed the COMMITTEE that now that the back-log at ARSAC had been cleared, an application would be made for Dr J R Morgan to assume the existing certificates in line with the proposed new Code of Practice. The status of current certificates is:-

RPC 313-2 (1)	Inhalation of Nb by women	TISAC (82) 1	2 Dec 1987
	Passive smoking pilot study	TISAC (84) 5	
	Ingestion of As in fish	TISAC (84) 2	
	Inhalation of Tc by women	TISAC (84) 6	
	Ca kinetics in one subject	TISAC (84) 8	
RPC 313-2 (2)	Clearance of Co in man	TISAC (85) 6	2 Dec 1987
	Ingestion of Pb and Fe	TISAC (85) 3	
RPC 313-2 (7)	Breathing effects on tar deposition	TISAC (85) 9	20 Feb 1988
RPC 313-2 (8)	Retention of Ba	TISAC (85) 8	17 Feb 1988
RPC 313-2 (10)	Smokers switching to low-tar cigarettes	TISAC (86) 4	5 Jun 1988

5. PROPOSED ADMINISTRATION OF <sup>85</sup>Sr BY INTRAVENOUS INJECTION (TISAC (86) 7)

Dr Newton reported that the first subject to participate in the study of Ba metabolism (TISAC (85) 8), now aged 82, has taken part in a variety of studies of alkaline earth metabolism over the last 30 years. The Ba data suggest that renal clearance has reduced with age, with faecal clearance remaining similar, resulting in the proportion retained for long periods increasing from an estimated 6% twenty years ago to 8% in this experiment. Most of the early experiments had been conducted with Sr, so it is proposed to investigate whether the changes in Ba retention are mirrored by those in Sr.

In discussion, it was pointed out that the subject in question was a particularly active 82 year-old so that the data may not be typical for his age-group. However, this experiment would demonstrate differences in the behaviour of Sr and Ba, whilst the remaining subjects in the Ba experiment will give a range for inter-subject variability. If differences between Sr and Ba are observed, there is unlikely to be sufficient additional information to propose mechanisms for such a discrepancy; in particular, there is no baseline information on renal function for this subject. The Chairman asked about the total dose accrued by this volunteer. Dr Newton replied that the dose levels were low in comparison to that arising from a pre-existing <sup>226</sup>Ra burden. He added that there was no problem in obtaining informed consent; indeed, some of the impetus for this experiment came from the volunteer.

Minute II. The COMMITTEE approved the administration by intravenous injection of 150 kBq <sup>85</sup>Sr to a single volunteer, aged 82, with a total committed effective dose equivalent of 125 μSv

6. PROPOSED FURTHER STUDIES WITH <sup>92m</sup>Nb-LABELLED MICROSPHERES INHALED BY MEN (TISAC (86) 8)

Dr Newton began by summarising previous work that had taken place using 5 μm particles. Strictly speaking, the calibration derived from this work applies only for particles of this size, since it relies on the detection of particles within a few centimetres of the surface of the chest; it is conceivable that particles of smaller size could penetrate to this region to a greater extent, thereby altering the calibration factor. Existing evidence tends not to support this hypothesis, but such data are severely limited. Hence, it is proposed to repeat the original calibration exercise with 8 volunteers, using as many of the subjects from the original study as possible.

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In the discussion that followed, Dr Newton indicated that, if a particle-size effect is found, it may be possible to use particle size information from concurrent air samples to assist in deriving the correct calibration for in vivo measurements. The administration will take place in stages, so that the desired lung content may be approached gradually. Self-absorption effects within particles are unlikely to be significant at respirable particle sizes. Animal experiments have indicated a long-term clearance pathway to the pleural surface, which might affect detector response. However, no such effect has been observed in contaminees.

Minute III. The COMMITTEE approved the administration by inhalation of approximately 80 kBq <sup>92m</sup>Nb, with an estimated committed effective dose equivalent of 53 µSv from lung, 11 µSv from gut and 6 µSv from thymus to a total of 8 volunteers

## 7. ANY OTHER BUSINESS

Mr Brown presented an extra item, proposing the administration of trace quantities of stable Sr to two volunteers (hereafter referred to as TISAC (86) 9). The purpose of the study is to validate techniques for the analysis of biological samples using Inductively Coupled Plasma-Mass Spectrometry (ICP-MS). To date, blood and urine samples spiked with <sup>86</sup>Sr have been successfully analysed, so it is proposed to investigate whether biological incorporation will alter the results. This will also enable the sampling schedule to be optimised. In the future, it is hoped to apply these techniques to study neonates and pregnant women and also to estimate gut uptake factors of actinides using stable lanthanides to model their behaviour. It is proposed to administer 1 mg of Sr as carbonate in milk over and above the normal dietary intake (also approximately 1 mg). There may be sub-populations who routinely ingest considerably higher quantities of Sr, one example being people using "Sensodyne" toothpaste, whose active ingredient is strontium chloride (10% by weight).

In view of the very low risk associated with the administration, Dr Rae queried the level of risk associated with the intravenous intrusion involved in the collection of blood samples, giving hepatitis and AIDS as potential hazards. Dr Evans replied that such risks are considered, citing an example where γ-globulin treatment has been discontinued because of the relative risks of AIDS versus hepatitis. He added that the "medical laboratory at Harwell conforms with the HOWIE recommendations". Notwithstanding, explaining the risks associated with blood sampling forms part of the process of obtaining informed consent. Dr Morgan suggested that the information obtained using stable isotopes and ICP-MS could be contrasted with that from radio-tracer studies, which Mr Brown agreed to consider.

Minute IV. The COMMITTEE approved the administration by ingestion of 1 mg of <sup>86</sup>Sr as strontium carbonate to two volunteers

The Secretary added that he has been unable to effect his resignation to date and has agreed to stay in post until the new Code of Practice becomes operational. There being no further business, the Chairman closed the meeting.

J N Pritchard  
20 October 1986

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A CODE OF PRACTICE FOR USE IN BIOMEDICAL RESEARCH  
INVOLVING THE IRRADIATION OF EMPLOYEES OF THE UKAEA

by

A. Morgan and N. Foord

ABSTRACT

Volunteers have been used in biomedical studies at Harwell since 1964. The procedures to be followed by investigators and the responsibilities of the Head of Environmental and Medical Sciences Division and the Chief of Medical Services were described in the minutes of the inaugural meeting of the Inhalation Studies and Approval Committee. Recently, these procedures have been reviewed and to make them readily available are summarised in this Code of Practice.

Environmental and Medical Sciences Division  
UKAEA Research Group  
Atomic Energy Research Establishment  
HARWELL

August 1976  
HL76/2374

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## INTRODUCTION

Volunteers have been used in biomedical research at Harwell since 1964. The purpose of the early experiments involving volunteers was to provide basic information on the fate of inhaled radioactive particles and vapours to enable more precise estimates of radiological dose to be made. Since that time, however, experiments in which radionuclides have been administered to volunteers have been conducted in order to investigate problems in the fields of medicine and of occupational and environmental health.

Experiments involving the use of volunteers at Harwell, were regulated initially by the Inhalation Studies Approval Committee (ISAC, later modified to INSAC). In 1970 INSAC was renamed the Tracer and Irradiation Studies Approval Committee (TISAC) to cover experiments involving the ingestion of radionuclides and the external irradiation of volunteers. This Committee includes medically qualified members with expert knowledge of radiation effects drawn both from the United Kingdom Atomic Energy Authority and other organisations.

The principles governing the use of volunteers were codified in 1964 by the Inhalation Studies Approval Committee in the minutes of the inaugural meeting (ISAC-2). In view of the important ethical considerations inherent in the use of volunteers and the fact that investigators may not be familiar with the procedures evolved at Harwell, it was felt desirable to review procedures and to prepare a code of practice covering the irradiation of volunteers, who are employees of the UKAEA, in which the principles to be followed are stated clearly.

### OBTAINING APPROVAL FOR AN INVESTIGATION

#### INVOLVING THE USE OF VOLUNTEERS

##### Responsibilities of the investigator

- (1) An investigator must obtain the approval of the Tracer and Irradiation Studies Approval Committee before undertaking any investigation involving the use of volunteers.

(2) Submissions to IIRAC must provide information on the following points:-

- a) Justification for the proposed experiments including details of relevant animal studies.
- b) A summary of experimental procedures.
- c) Estimates of the likely radiological dose either to the whole body, or to the single organ which it is anticipated will receive the greatest dose, with information on how this was derived.
- d) Estimates of the number of subjects involved and whether single or multiple administrations will be used.

Terms of reference of the Tracer and Irradiation Studies Approval Committee

These are as follows:-

- a) To advise the Head of the Environmental and Medical Sciences Division on the suitability and safety of radioactive tracer experiments using human volunteers.
- b) To discuss and approve proposals for experiments.
- c) To review and comment on the results of the experiments.

RADIOLOGICAL DOSE

Responsibilities of the investigator

- (1) The investigator must ensure that the radiological doses incurred by volunteers are as low as possible, commensurate with obtaining the desired experimental information.
- (2) The investigator is responsible for calculating the radiological dose received. An independent assessment of radiological dose may be obtained from the Dosimetry Research Section of the Radiation Physics Group.

Limitations on radiological dose

In the minutes of the inaugural meeting, it was stated that the total dose to any volunteer should not exceed 1.5 rem per year (or the equivalent maximum

permissible organ dose appropriate to non-radiation workers) as a result of such (volunteer) experiments. Although the Medical Research Council have kept the question of dose limits for volunteer experiments under review, they do not publish specific dose limits on the grounds that these have the effect of removing responsibility from the investigator to ensure that the doses used are as low as possible.

In 1972 the World Health Organisation and the International Atomic Energy Agency assembled a group of consultants from several countries which considered the question of dose limits when ionizing radiation is used on human beings for medical research and training. The report of this Committee (1972) has been circulated as a consultative document, but not as a formal publication. The recommendations, therefore, have no legal standing. A summary of this document has been published by the British Institute of Radiology (1975). Among the proposals are that research projects be categorised, corresponding to the level of dose equivalent involved according to the following scheme:-

Category of project	Limits of dose equivalent (rem)	
	Total body	Single organs
I	<0.05	<0.25
II	0.05 - <0.5	0.25 - <2.5
III	0.5 - <5	2.5 - <25
IV	5 - 10	25 - 50

In Category I, the total body radiation permitted would be within the variations of natural background radiation received by the subject annually (i.e.  $\sim 10^{-2}$  rem). In Category II, the total body radiation permitted would be of the same order as that received annually from natural sources (i.e.  $\sim 10^{-1}$  rem). In Category III the total body radiation permitted to a subject is of the same order of magnitude as the annual limits of radiation permitted by the ICRP for

occupationally exposed persons.

The dose limits proposed by the WHO/IARC for projects will be taken as annual limits for volunteers resulting from all investigations at Harwell. The Head of the EMS Division has formal delegated authority to approve investigations in Category I, subject to minuted decisions of TISAC. Investigations in Category II must also be approved by TISAC and in addition, the Head of the EMS Division must consult the Director of the Atomic Energy Research Establishment, Harwell.

#### OBTAINING VOLUNTEERS

##### Responsibilities of the investigator

- (1) An investigator must not ask people directly to participate in experiments.
- (2) Volunteers may be obtained by advertising.
- (3) Pregnant women or people below the age of 18 years must not be used as volunteers.
- (4) No financial inducement shall be offered to volunteers except to ensure that there shall be no loss of earnings as a result of taking part in an investigation.

By advertising in the Harwell Bulletin, the Inhalation Toxicology Group of the EMS Division has obtained a panel of people who, in principle, are willing to participate in investigations. Members of this panel are circulated with details of specific experiments and asked if they will volunteer. At the same time, it is made quite clear that they may withdraw from the experiment at any time if they change their mind. One advantage of this system is that, as many of the volunteers are not members of the EMS Division, the problem of special relationships between investigator and volunteers is reduced.

In the event of a query by a volunteer's superior officer or manager, the Head of the EMS Division will send the relevant Division Head the letter shown in Appendix I, with a copy to the volunteer's superior officer or manager.

CLEARANCE OF VOLUNTEERS

Responsibilities of the Chief of Medical Services (or Medical Officer nominated by him)

- (1) The Chief of Medical Services is responsible for ensuring that volunteers are medically fit to participate in the proposed investigation. A note to this effect will be made on the volunteer's medical record.
- (2) The Chief of Medical Services is responsible for obtaining informed consent from volunteers and must also satisfy himself that such consent has been given freely.
- (3) The Chief of Medical Services is responsible for completing the Volunteer Consent Form shown in Appendix II and for ensuring that it is signed both by the volunteer and by himself.

Responsibilities of the investigator

- (1) The investigator is responsible for preparing the necessary volunteer consent forms (see Appendix II) and filling out the details of the investigation which must include (a) the purpose (b) the appropriate TISAC paper reference (c) the method of administration (d) the radionuclide(s) involved (e) the approximate total activity administered (f) the estimated total dose to the relevant critical organ(s) and (g) whether single or multiple administrations are involved.

The general ethical principles involved in investigations on human subjects have been discussed in a statement by the Medical Research Council (1964). The distinction between procedures contributing to the benefit of the individual and those which have no direct benefit is carefully drawn. Investigations of the type carried out at Harwell generally fall into the latter category. The MRC, which had in mind the wide range of new treatments and investigations in present day medical research, pointed out that "the possibility or probability that a particular investigation will be of benefit to humanity or to posterity would offer no defence

in the case of legal proceedings. It is always necessary, therefore, to ensure that the true consent of the subject is obtained explicitly. By true consent is meant consent freely given, with proper understanding of the nature and consequences of what is proposed. Assumed consent, or consent obtained by undue influence, is valueless and in this latter respect, particular care is necessary when the volunteer stands in special relationship to the investigator. Written consent unaccompanied by other evidence that an explanation has been given, understood and accepted is also of little value."

### RECORD KEEPING

#### Responsibilities of the investigator

- (1) The investigator must inform the Head of Medical Records of every experiment involving the use of a volunteer by completing the appropriate form (see Appendix III) and returning it within one week of the experiment.
- (2) The investigator must ensure that the subject's cumulative dose from all investigations in the current calendar year shall not exceed 50 mrem to the whole body, or 250 mrem to any single organ.

#### Responsibilities of the Head of Medical Records

- (1) The Head of Medical Records shall keep a register of all experiments involving the use of volunteers. The register will include (a) the name of the investigator and volunteer (b) the reference number of the appropriate TISAC paper (c) the radionuclide and activity retained and (d) the radiological dose to the critical organ.
- (2) The Head of Medical Records will also record the cumulative dose to the volunteer in the current calendar year and, if this exceeds 50 mrem to the total body, or 250 mrem to any single organ, he will notify the Chief of Medical Services.
- (3) The Head of Medical Records will enter details of dose incurred in

each volunteer's medical record at the end of the calendar year or, if a volunteer leaves the employment of the UNRISA, at the time of leaving.

The purpose of a central register of all investigations using volunteers is to ensure that, in cases where a volunteer is being used by more than one investigator, an accurate record of cumulative dose is maintained.

#### References

Report of a WHO/IAEA consultation on the use of ionizing radiation on human beings for medical research and training including the use of radioactive materials (1972) WHO/PHL 73.1. (This is an unpublished WHO document copies of which may be seen on request).

Irradiation of human subjects for medical research (1975) British Institute of Radiology Bulletin 1/2 p.4.

Responsibility in investigations on human subjects. Statement by the Medical Research Council (1964) Report of the Medical Research Council for the year 1962-1963, HMSO.

Appendix I

STAFF IN CONFIDENCE

Letter notifying a volunteer's Division Head and superior officer/manager that he wishes to participate in an experiment

A member of your Division Dr/hr ....., has volunteered to take part in an investigation involving the administration of a radionuclide. This investigation has been approved by the Tracer and Irradiation Studies Approval Committee (the AERE Ethical Committee). Management at Harwell has sanctioned the use of volunteers in biomedical research, provided that prior approval of the Ethical Committee is obtained.

Each volunteer is fully acquainted with the nature of the procedures involved and the associated risks and is given a thorough medical examination to ensure that he is fit to participate. A volunteer may withdraw his consent at any time if he so wishes.

I trust that you will agree to this volunteer's participation. Provision can be made for the time spent by a volunteer to be booked against the appropriate project number.

(17)

Appendix II

STAFF IN CONFIDENCE

Purpose of investigation

Authorisation

TISAC paper reference .....

Minute reference .....

Details of investigation

Radionuclide(s) administered .....

Likely number of administrations .....

Total activity administered .....

Anticipated total dose(s) to critical organ(s) .....

Name of investigator .....

Signed .....

Date .....

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VOLUNTARY CONSENT

The nature of the study and its possible hazards have been fully explained to me by Dr ..... I hereby consent to take part and to carry out the procedures outlined above. It is understood that I may withdraw at any time from participation in the study.

Name .....

Signed ..... (Volunteer)

Date .....

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I confirm that I have explained the nature of the investigation described above to this volunteer.

Name .....

Signed ..... (Medical Officer)

Date .....

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Appendix III

STATE IN CONFIDENCE

To Head of Medical Records

Dose record for volunteer experiment

Name of Volunteer .....

TJSAC approval reference .....

Date of experiment .....

Radionuclide(s) .....

Activity retained .....

Critical organ(s) .....

Calculated dose to critical organ(s) .....

Name of investigator .....

Signed .....

Date .....

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