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October 17, 1980

TO: LLNL Human Use Committee L-15
FROM: G. W. Campbell
SUBJECT: IAEA ^{92m}Nb Inhalation Experiment

Introduction

Calibration of x-ray counters for the assessment of plutonium in lungs is notoriously difficult, and the diverse approaches to the problem adopted by various laboratories have led to widely differing assessments of the sensitivity of essentially similar equipment.⁽¹⁾ The calibration of our own equipment is based on measurements made using the LLNL realistic chest phantom. However, one question that must be answered is how closely the phantom simulates plutonium in vivo.

Dr. Donald Newton of AERE Harwell, has proposed an IAEA-sponsored in vivo experiment in conjunction with LLNL, ANL and BNWL to verify the LLNL realistic phantom using volunteers that have inhaled a known amount of ^{92m}Nb . At the completion of the experiment we hope to show that the phantom is an acceptable substitute for in vivo experiments; that is, that it is indeed a realistic plutonium lung counter calibration phantom. The successful completion of this project will allow LLNL to take steps to establish the LLNL phantom as the Free World's standard phantom.



University of California

LAWRENCE LIVERMORE LABORATORY

REPOSITORY LLNL B361 Rm. B940A
COLLECTION Institutional Review Board
BOX No. IRB Protocol File
FOLDER George Campbell 5/12/83
81P-101-01 IAEA Inhalation
Experiment

1122158

Proposed Experiments

We propose that volunteers should inhale by mouth 5- μ polystyrene particles labeled with ^{92m}Nb (half-life 10 days). ^{92m}Nb decays by electron capture, with consequent emission of 15.8 keV Zr K x-rays. Since these x-rays are similar in energy to those associated with plutonium (17 keV), ^{92m}Nb is a practical plutonium simulant for in vivo studies. It also emits abundant 934-keV gamma rays which are readily detectable by whole-body counting. Thus, the activity retained in the lungs can be determined independently of x-ray counting, and the subjects can be used to calibrate our x-ray detectors for a 15.8 keV photon emitter; i.e., to indicate values of E_{Nb} (where E_{Nb} = counts per Zr K x-ray emitted in lungs).

^{92m}Nb can be made free of detectable radioactive impurities, with the variable-energy cyclotron at Harwell. Mr. R. Fleming of Harwell has developed a method of incorporating the activity into polystyrene and has successfully produced 5- μ monodisperse particles. He has also studied the rate at which activity may be leached from those particles in normal saline and in 0.1 M-HCl; in both cases only $\sim 0.1\%$ of the ^{92m}Nb was removed over a period of 30 days. We would not therefore expect appreciable systemic uptake of ^{92m}Nb , either from particles retained in the lungs, or from particles passing through the gut after early ciliary clearance.

It is proposed to employ up to seven subjects, if they are available. We would probably need to deposit typically $0.5 \mu\text{Ci } ^{92\text{m}}\text{Nb}$ in those regions of the lung from which clearance of $5\text{-}\mu\text{m}$ polystyrene particles is slow ($> \sim 100$ days half life). It is likely that in small subjects, for whom the x-ray attenuation would be relatively slight, a smaller quantity would suffice; conversely, for large individuals it might be necessary to increase the amount to $1 \mu\text{Ci}$. More reliable estimates of the amounts necessary will be obtained from a preliminary experiment with a small subject, employing $0.1 \mu\text{Ci}$.

Dose Commitment

The dose commitment to the lungs from $1 \mu\text{Ci } ^{92\text{m}}\text{Nb}$, declining only by radioactive decay, would be 42 mrem. Experience suggests that, to achieve an alveolar deposit of $1 \mu\text{Ci}$, it might be necessary to deposit as much as $3 \mu\text{Ci}$ (combined deposits in laryngeal, tracheo-bronchial and pulmonary regions) in the subject. The estimated dose to the lower large intestine, resulting from rapid clearance of the "excess" $2 \mu\text{Ci}$ via the GI tract, is 20 mrem.

Mass of Polystyrene to be Inhaled

Because of the low specific activity of the $^{92\text{m}}\text{Nb}$ available to us, the mass of polystyrene associated with $1 \mu\text{Ci}$ would be $\sim 300 \mu\text{g}$. This would be somewhat larger than in previous experiments with labeled polystyrene particles. The toxicity of polystyrene has been considered by Harwell's Tracer and Irradiation Studies Approval Committee (TISAC) and the

conclusion (TISAC (70) M1) was that there were no grounds for "concern about the effects of tens of microgramms of polystyrene used in the inhalation experiments at AERE." In their October 8, 1979 meeting they agreed that the use of polystyrene microspheres in lung burdens of up to 300 μg did not constitute a hazard to volunteer subjects.

Inhalations

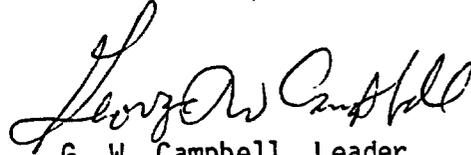
The first inhalation was carried out in August 1980. The results we obtained from this part of the study proved that we could see $^{92\text{m}}\text{Nb}$ in a larger individual (chest wall thickness = 3.1 cm) and that $^{92\text{m}}\text{Nb}$ can be used as a plutonium simulant to aid in the verification of the "realistic" phantom. The second subject who is from ANL will be at LLNL for counting on December 8, 9 and 10, 1980. The ANL Human Use Committee accepted the approval of the Harwell Committee for this study and therefore, they are allowing _____ to participate in the study.

Volunteers

We propose that _____ and _____ from LLNL Hazards Control Department be allowed to participate as volunteers in this experiment. These two individuals have a long-standing interest in plutonium lung counting and the benefit of having the phantom verified as a

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realistic calibration standard far outweighs any risk that may be involved. The volunteers would travel to AERE Harwell for the inhalation and then return to the United States to be counted by LLNL, ANL and BNWL.



G. W. Campbell, Leader
Dosimetry Group
Hazards Control Department

GWC:gw

Reference

1. D. Newton et al, "Interlaboratory comparison of Techniques for Measuring Lung Burdens of Low Energy Photon Emitters," Health Physics 34, 573 (1978).

TRACER AND IRRADIATION STUDIES APPROVAL COMMITTEE

Minutes of the twelfth meeting held on Monday, 8th October, 1979 in Environmental & Medical Sciences Division, AERE, Harwell.

PRESENT

Mr. N.G. Stewart (Chairman)	Environmental & Medical Sciences Division
Dr. R.H. Mole	Medical Research Council Radiobiology Unit
Dr. S. Rae	National Radiological Protection Board
Dr. J.C.A. Raison	" " " "
Dr. A.N.B. Stott	Environmental & Medical Sciences Division
Dr. A.C. Chamberlain	" " "
Mr. M. J. Heard	" " "
Mr. D. Newton	" " "
Mr. J.N. Pritchard(Acting Secretary)	" " "

1. LEGISLATION FOR THE ADMINISTRATION OF RADIOACTIVE SUBSTANCES TO HUMANS

In order to comply with a recent direction from the EEC on the use of ionising radiation (Article 5(a) of Directive 76/579/Euratom), the Government has introduced legislation to cover the administration of radioactive substances to humans for purposes of diagnosis, therapy or research. To assist in the implementation of this legislation, the Administration of Radioactive Substances Advisory Committee (ARSAC) has been appointed. The Chairman welcomed Dr. J.C.A. Raison, a member of ARSAC who had been invited to describe the new legislation and the manner in which it would affect proposals put before TISAC.

Dr. Raison began by explaining the definitions used in the regulations, pointing out that a "radioactive medicinal product" covered sealed sources (except nuclear-powered cardiac pacemakers), unsealed sources (including radioactive aerosols in this category) and irradiation induced activity, except where this is a by-product of treatment. However, naturally occurring radioactivity does not require authorisation. Such authorisation takes the form of a certificate issued by a Minister empowering the administration of a specified quantity of radioisotope or isotopes in a stated form to an indicated group of people. Such a certificate may be obtained by completing the attached application form and forwarding it to the Department of Health and Social Security, whence it is circulated to members of ARSAC who then make their recommendations to the Minister. Should a certificate be refused or revoked, a system of appeal exists to the Minister or to the Committee on Radiation from Radioactive Medicinal Products (CRMP). Certificates are only issued to a medical doctor or dentist, although he does not have to be personally involved, work may proceed under his direction. The certificate holder does not even have to be present although "in the case of long absences, or of the appointment being vacated", a new certificate holder must be arranged.

Dr. Raison indicated that ARSAC is not primarily concerned with the ethics of the experiment and that ultimate approval for the work still lies with the local ethical committee, even when a certificate has been granted (see paragraphs 53-55 of the attached "Notes for Guidance..."). However, ARSAC will normally expect the approval of the local committee before making a positive recommendation to the Minister. Guidelines for the performance of an ethical committee are laid down in "Supervision of the Ethics of Clinical Research Investigations and Foetal Research" D:SS, HSC(IS)153, although Dr. Raison was not clear how closely TISAC conformed to these regulations.

recommendations for an ethical committee and report to the COMMITTEE.

Dr. Raison finally drew attention to the "Notes for Guidance..." concerning research projects (paragraphs 48-52) with particular reference to the minimum volunteer age of 15 except under special circumstances, the consent of the subject and the dose commitment. Doses are categorised into <50mrem, <500 mrem and <5 rem equivalent total body dose, with the individual organ dose equivalents also stated. The Chairman stated that TISAC were empowered to grant approval of up to 50 mrem whole body dose equivalent, with single organ dose equivalent of up to 250 mrem (HMC 76(19)9, TISAC(76)M2). These figures were based on then current views (WHO/RHL/73.1, Br.Inst.Radiol. 1(2),4 (1975)) and are within the lowest dose category, equivalent to a level of risk within variations of natural background radiation.

MINUTE II - The COMMITTEE thanked Dr. Raison for his presentation.

2. MINUTES OF THE ELEVENTH MEETING OF THE TRACER AND IRRADIATION STUDIES APPROVAL COMMITTEE (TISAC(78)M1)

MINUTE III - The COMMITTEE accepted the minutes

3. MATTERS ARISING FROM THE ELEVENTH MEETING

Dr. Chamberlain informed the Committee that the letter to NATURE on the tetra ethyl and tetra methyl lead work was not considered of sufficient general interest and had instead, subsequently appeared in the Proceedings of "Heavy Metals in the Environment" (Imperial College, September 1979).

4. PROPOSALS FOR EXPERIMENTS ON THE UPTAKE OF RADIO-CADMIUM FROM THE GUT

The Working Party on the Monitoring of Foodstuffs for Heavy Metals have established that crabs, in particular brown crabmeat, tend to contain high levels of cadmium. Regular consumption of brown crab meat could lead to intakes well in excess of the FAO/WHO standards. The Ministry of Agriculture, Fisheries and Food (MAFF) are seeking to establish the risk to regular consumers and hence wish to ascertain the absorption and retention by humans. Dr. Chamberlain indicated that he had been approached by Dr. J.C. Sherlock of MAFF to perform such a study.

Dr. Chamberlain stated that there were two possible methods of approach to this problem (TISAC(79)2):-

- a) whole body gamma measurement at 5 days and longer after ingestion, measurements of ingested dose and urinary and faecal excretion enabling a balance to be struck
- b) Beta or Gamma measurement of ingested dose, urine and faeces to give retention by difference.

Dr. Chamberlain felt that although method (b) involved lower activity levels, it would require considerable manpower and would have large inherent errors if the retention were small. It was therefore proposed to use method (a) with Cadmium-115m (half-life 43d, 100% β , 1.9% γ). An initial administration to two subjects of 0.5 μ Ci would occur with a possible repeat at a dose of 2 μ Ci if the counting statistics were poor. Dr. Chamberlain pointed out that such an experiment would not only satisfy the requirements of MAFF, but would provide useful additional data on the blood:urinary excretion:faecal excretion ratios, an area where little information is currently available. Due to this, however, uncertainty exists as to the degree of uptake of cadmium in order to estimate the radiation dose to the volunteer. Dr. Newton assisted Dr. Chamberlain by presenting a table of equivalent whole-body doses for a range of uptakes, also indicating the experimental uncertainties.

Dr. Rae established that the specific activity of the cadmium would be approximately 100 $\mu\text{Ci}/\text{mg}$ resulting in an acceptable body intake of only a few microgrammes. Dr. Stott felt that the use of a radionuclide in such an experiment only demonstrated the short-term effect of uptake, whereas for MAFF to accurately estimate the risk a long-term balance was required. Mr. Pritchard indicated that more realistic results might be obtained by using volunteers who regularly consume crab meat rather than control subjects. Dr. Mole was concerned about the dose commitment and felt that an investigation of ways to improve the assessment of cadmium in excreta would be beneficial. Dr. Chamberlain felt that MAFF might not be prepared to provide the necessary funding for such an undertaking and indicated that conflicting evidence existed over the relationships between body burden and the relative differences between the excretion pathways. However, Dr. Mole felt that in view of the large number of factors involved, such a small experiment would not provide sufficient beneficial information when balanced against the possible dose commitment.

MINUTE IV - The COMMITTEE recommended that, after consultation with the Harwell Bioassay Group, Dr. Chamberlain should approach MAFF to discuss the possibility of a full-scale project involving the analysis of excreta and blood

5. PROPOSALS FOR THE INHALATION OF Nb-92m LABELLED PARTICLES

Dr. Newton began by stressing the difficulties encountered in the assessment of plutonium in the lung due to the low energy of the emitted X-rays and consequent attenuation in the body. At present Harwell's equipment is calibrated from measurements of known quantities of ^{103}Pd in volunteers (TISAC(72)M2). However, the difference in X-ray energy between ^{103}Pd (average 20 keV) and plutonium (average 17 keV) means that mathematical corrections for the differing attenuations by the chest wall must be made. Work with phantoms has shown that the corrected calibrations are reasonably accurate under these conditions, but that there is a need to be re-assured such calibrations are as accurate in the human case. It was therefore proposed to use $^{92\text{m}}\text{Nb}$ (half-life 10 d, E.C., 15.8 keV) labelled polystyrene microspheres of 5 μm diameter to produce a relationship between count rate and chest wall thickness (CWT). This would be analogous to that obtained in the work with ^{103}Pd . Thus a comparison of the ratio of the two, again as a function of CWT, with that expected from the mathematical model, could be made (TISAC(79)1).

Up to seven subjects would be used, with an initial alveolar burden of approximately 0.5 μCi , this quantity being smaller for subjects with a thin chest wall and larger, up to 1 μCi , for large subjects. To achieve this alveolar burden it might be necessary to deposit up to 3 μCi in total, resulting in a dose commitment to the lungs of 42mrem, and that to the lower large intestine of 20mrem.

Dr. Mole was re-assured by Dr. Newton that there was no more satisfactory isotope for these purposes.

MINUTE V - The COMMITTEE approved the proposed experiments in which up to seven volunteers would receive a maximum burden of 3 μCi of $^{92\text{m}}\text{Nb}$ -labelled polystyrene microspheres with a resulting maximum dose commitment to the lung of 42mrem and the lower large intestine of 20mrem

Although the estimated lung burden of polystyrene of 300 μg , was larger than that used in previous experiments, Dr. Newton felt that the basis for the decision of the committee on the toxicity of polystyrene was still valid; TISAC(70)M1 states that there were no grounds for "concern about the effects of tens of microgrammes of polystyrene used in inhalation experiments..."

MINUTE VI - The COMMITTEE agreed that the use of polystyrene microspheres in lung burdens of up to 300 μg did not constitute a hazard to volunteer subjects

6. PROPOSALS FOR THE EXTENSION OF STUDIES ON THE UPTAKE OF LEAD BY BONE

Mr. Heard began by describing the aims of the study and the results achieved to date. Within 48 hours of intake, 55% of inorganic lead may be found attached to red blood cells, but the fate of the remainder is difficult to ascertain. Some concentration of non-blood lead occurs in the liver, but bone is considered the major long-term store. The purpose of this study is to ascertain if bone is an early store as well and if so, the speed of uptake.

Calcium was also used in this study for cross-calibration checks. However, whereas lead showed a steady increase when expressed as the corrected fraction in the foot, and hence the skeleton, of the whole body content, calcium showed a decline. Further evidence that calcium behaves differently is that the calcium measurements tended to follow smooth curves where the scatter on lead measurements was greatly in excess of counting errors. Longitudinal scans of the body indicated that the liver was also a significant storage site but changes with time have not yet been established (IISAC(79)3).

To confirm the trends demonstrated and elucidate the relative importance of the liver and bone as storage organs, it was proposed to take measurements extending over a period of three weeks, resulting in a dose increase of a factor of 10. This would then give a whole body equivalent dose of 9 mrem of which 7 mrem would be accounted for by the liver and kidney (21 mrem and 76 mrem maximum organ doses respectively). It was therefore proposed to inject intravenously 15 μCi of $^{203}\text{PbCl}_2$ to not more than two subjects.

During the discussion that followed, the committee agreed that the benefits to be obtained from the experiment outweighed the dose commitment.

MINUTE VII - The COMMITTEE approved the intravenous injection of 15 μCi of $^{203}\text{PbCl}_2$ to not more than two subjects with a resulting maximum dose commitment of

Kidney	76 mrem
Liver	21 mrem
Whole body equivalent	9 mrem

7. PROPOSALS TO STUDY THE UPTAKE OF LEAD BY INGESTION UNDER A VARIETY OF CONDITIONS

Mr. Heard pointed out that although a lot of work has been done on the uptake of lead via inhalation, injection and ingestion, the large number of factors influencing the way people cook and eat has left large gaps in the understanding of the metabolism of lead by ingestion. Recent work has shown the tendency of lead to adsorb onto vegetables during the cooking process and studies at Harwell indicate that this could be equivalent to a daily intake in the range of 20-170 μg . Work at the Water Research Centre has uncovered new routes by which lead may become dissolved in tapwater.

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