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January 29, 1981

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.

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

University of California
LAWRENCE LIVERMORE LABORATORY

112211b

Proposed Experiments

We propose that volunteers should inhale by mouth 5-μm 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-μm 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 ~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 μCi ^{92m}Nb in those regions of the lung from which clearance of 5-μm polystyrene particles is slow (>~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 μCi. More reliable estimates of the amounts necessary will be obtained from a preliminary experiment with a small subject, employing ~0.1 μCi. Since the inhalations are carried out in stages, we will count the subject at each stage to insure that the total quantity inhaled has not exceeded 1 μCi. The inhalations will be stopped when it is determined that the subject has inhaled 1 μCi.

Dose Commitment

The dose commitment to the lungs from 1 μCi ^{92m}Nb, declining only by radioactive decay, would be 42 mrem. Experience suggests that, to achieve an alveolar deposit of 1 μCi, it might be necessary to deposit as much as 3 μCi (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 μCi via the GI tract, is 20 mrem. An independent calculation by Bill King of the dose committment based on ICRP 26 gives a lung dose of 123 mrem and a GI dose of 12.6 mrem.

Mass of Polystyrene to be Inhaled

Because of the low specific activity of the ^{92m}Nb available to us, the mass of polystyrene associated with 1 μCi would be ~300 μg. 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 second inhalation was carried out in August 1980. The results we obtained from this part of the study proved that we could see ^{92m}Nb in a larger individual (chest wall thickness = 3.1 cm) and that ^{92m}Nb can be used as a plutonium simulant to aid in the verification of the "realistic" phantom. The third subject who is from ANL was 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 Dr. Richard Toohey to participate in the study. Dr. Toohey's trip report states that he feels there is a need for each Laboratory to have a person to count on a regular basis until the ^{92m}Nb has decayed to the background level. The necessity for this will be discussed in the section on Need for Further Inhalation Experiments.

As requested, we have attached the data analysis for the subjects we have already counted. (See Figure 1.).

Volunteers

We propose that [redacted] and [redacted] 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 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.

Need for Further Inhalation Experiments

We feel that three points do not provide us with enough data to draw a statistically significant comparison between the phantom data and the human inhalation data. The variation in the ^{103}Pd data as shown in Figure 2b tends to support this concept. This figure shows large differences in efficiency for subjects PK and KFB for similar chest-wall thicknesses. Somasundaram[2] goes on to suggest that this is not due to differences in particle size or exposure technique, but to inter-subject variables other than chest-wall thickness.

The scatter of 16-17 keV subject efficiencies about predicted efficiencies from the phantom is potentially greater than the scatter that is shown for 20 keV in Figure 2, because any variable affecting the attenuation of the 20-23 keV X-rays from ^{103}Pd must have a far greater affect on the attenuation of low energy X-rays such as those from ^{92m}Nb or plutonium.[2] We consider it important to assess the above, and this requires more than three subjects.

The scatter of the data shown in Figure 1 appears to be small; however it should be noted that in Figure 2b the 4th and 5th subjects are the ones furthest from the cruve. This again supports the need for further inhalations.

Another major reason for having LLNL subjects participate in this study is that we would be able to count them on a routine schedule until the ^{92m}Nb has decayed into the background. This will allow us to compare our calculated minimum detectable activity (MDA) with actual counting data and thus verify our MDA. The verification of our phantom, measurement techniques and MDA will give us verified data to give the press and the public should we need to count members of the public after an off-site release. We are sure you will agree that this last item is of extreme importance to the Laboratory's Health & Safety Program.

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).

2. S. Somasundaram et al, and D. Newton, "X-Ray Detection Efficiencies for Palladium-103 in Lungs: Synthesis of Data from Two Laboratories," submitted to Health Physics (1981).

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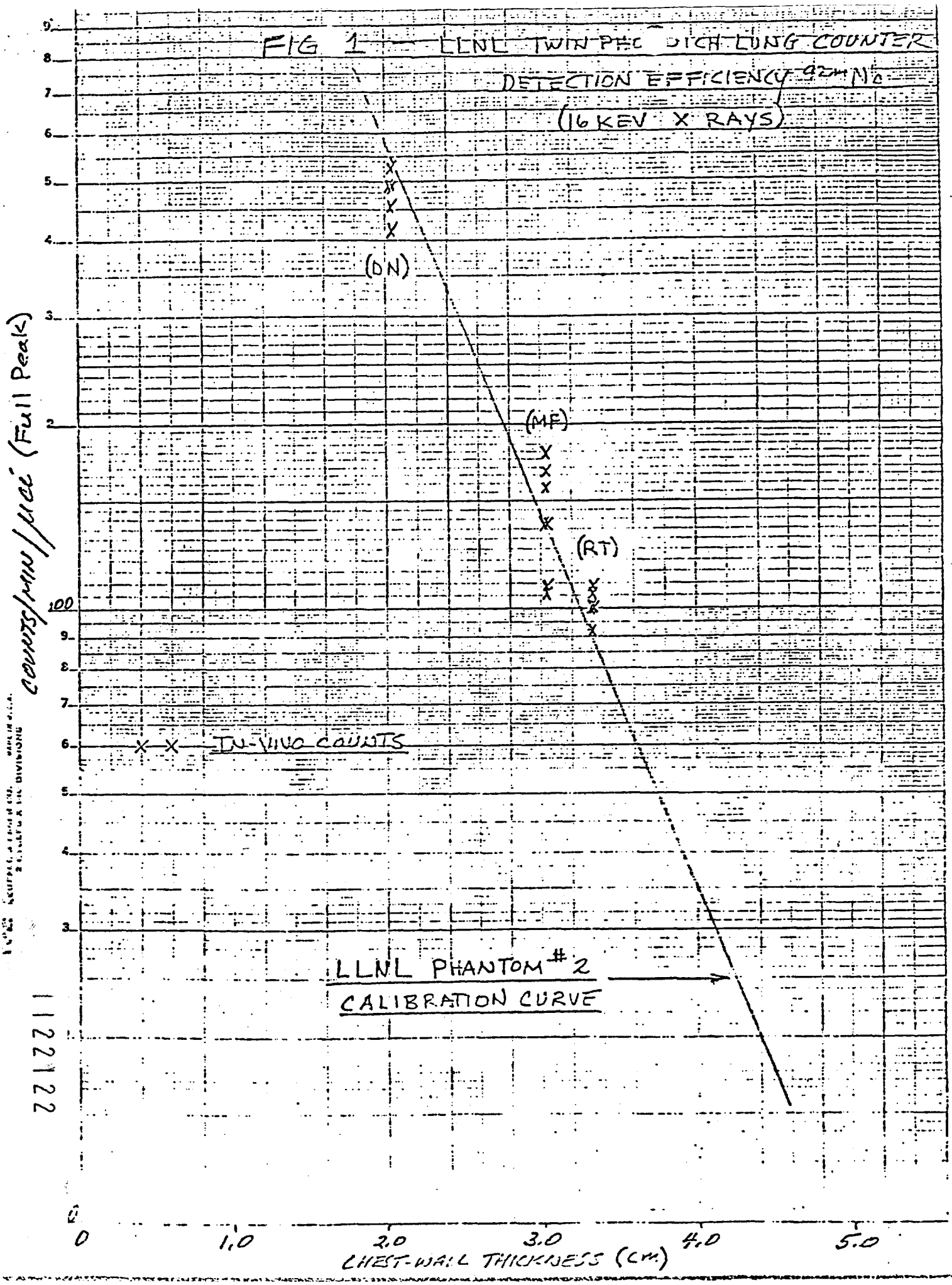
FIG 1 — LLNL TWIN PHC DICH LUNG COUNTER
DETECTION EFFICIENCY 92mMo
(16 KEV X RAYS)
(DN)
(MF)
(RT)
IN-VIVO COUNTS
LLNL PHANTOM #2
CALIBRATION CURVE
COUNTS/MIN/μCi (Full Peak)
CHEST-WALL THICKNESS (CM)
0
1.0
2.0
3.0
4.0
5.0
100

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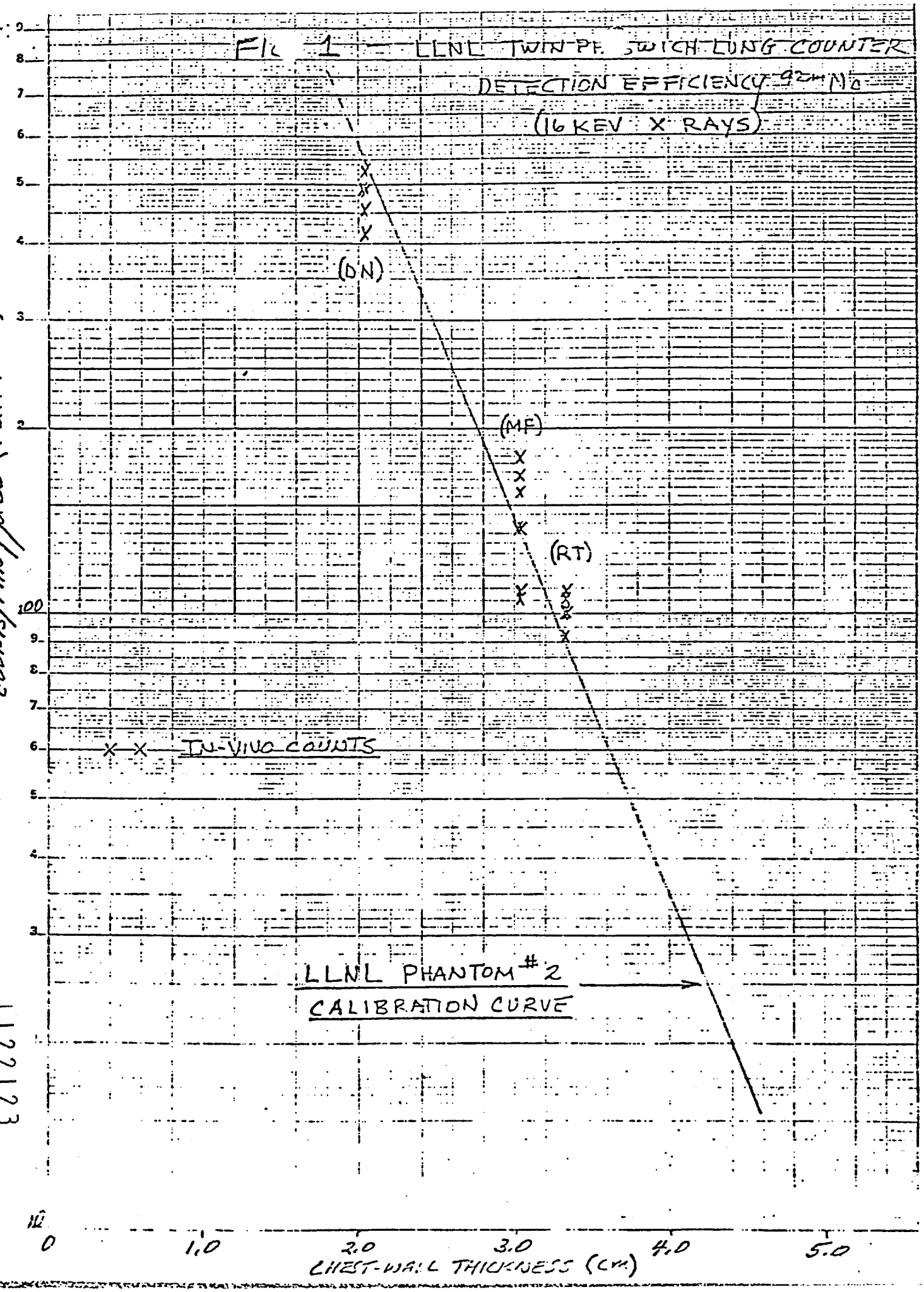
FIG 1 — LLNL TWIN PH. SWITCH LUNG COUNTER
DETECTION EFFICIENCY ^{92m}Nb
(16 KEV X RAYS)
(DN)
(MF)
(RT)
IN-VIVO COUNTS
LLNL PHANTOM # 2
CALIBRATION CURVE
counts/min//μCi (Full Peak)
CHEST-WALL THICKNESS (CM)
0
1.0
2.0
3.0
4.0
5.0
100

1122123

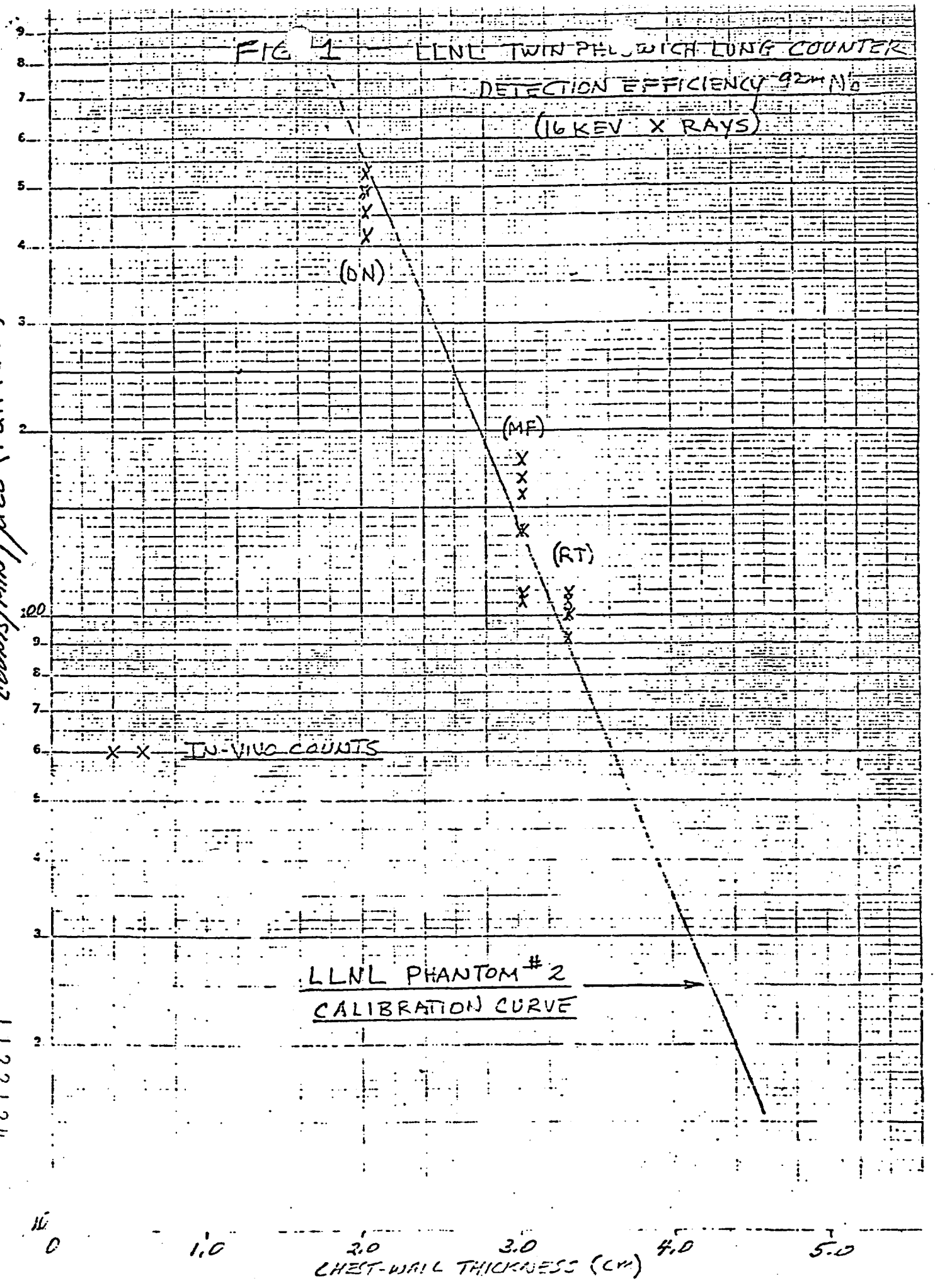
FIG 1 — LLNL TWIN PHLOWICH LUNG COUNTER
DETECTION EFFICIENCY 92m Nb
(16 KEV X RAYS)
(DN)
(MF)
(RT)
IN-VIVO COUNTS
LLNL PHANTOM # 2
CALIBRATION CURVE
counts/min/μrad (Full Peak)
CHEST-WALL THICKNESS (CM)
0
1.0
2.0
3.0
4.0
5.0
100

1122124

Dr. Rae established that the specific activity of the cadmium would be approximately 100 μCi/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 ^{92m}Nb(half-life 10 d, E.C., 15.8 keV γ) 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 ^{92m}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 (TISAC(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 9mrem of which 7mrem 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 $^{203}PbCl_2$ 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 $^{203}PbCl_2$ 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.