INTRA-LABORATORY CORRESPONDENCE MAR 26 1964

OAK RIDGE NATIONAL LABORATORY

March 20, 1964 COPY 707708

To : W. H. Jordan

From : W. S. Snyder

Subject : A Proposal for a Human Volunteer and/or Hospital Patient Study of the Metabolism of Injected and Ingested Ag^{111}

I am transmitting to you the subject proposal which was prepared by S. R. Bernard of our division. The experiment proposed here will enable us to obtain some human data which are needed to fill a recognized gap in the information we presently have as a basis for MPC's of isotopes of silver. While this is not the most pressing need for information relating to MPC's, such an experiment is one that is well within our capacity to carry out at the present time. We believe it is wise to begin with a problem involving minimum technical difficulties. However, you will note that there is a need for the experiment since the animal data available do not seem to be in line with estimates suggested by therapeutic uses or indirect estimates of these parameters obtained by the use of Tipton's data.

Please advise me soon on the procedure to follow to secure a review of the proposal and authorization to conduct the study.

Original Signed By

W. S. Snyder

Enclosure

cc: S. R. Bernard
K. Z. Morgan

WSS:ss

REPOSITORY OAK RIDGE/ENERGY SYSTEMS)

COLLECTION ORNL (Y-10)

BOX No. OFFICE OF RADIATION PROTECTION K. Z. MORGAN'S FILES (PAST DIV. DIR OF HEALTH PHYSICS)

FOLDER BLD. 4500 S, WING 4 ATTIC

A-00114

1026004

Human Subjects Project

UCN-430
(3 5-61)

March 18, 1964

To: S. R. Bernard

From: K. Z. Morgan

Thank you for your memorandum of March 18, 1964. Having approved the inhalation experiment with Ag^{111}, I certainly could not be consistent and refuse support for these injection experiments. It appears to me that the dose rates and integrated doses are reasonable though, again, of course, we would try to keep the doses as low as possible within the useful range of measurement. Also, in this case I would caution you that someone must be responsible to see that the injections are carried out properly and that the material injected is free from bacteria and viruses. It would be a minor calamity if some of these persons received hepatitis as the result of our supporting the use of unclean procedures.

Good luck!

Original Signed By
K. Z. MORGAN /y
Karl Z. Morgan

KZM:jc

cc: W. S. Snyder

INTRA-LABORATORY CORRESPONDENCE

OAK RIDGE NATIONAL LABORATORY

March 18, 1964

To : K. Z. Morgan

cc : W. S. Snyder

From : S. R. Bernard

Thank you for your memo of March 13, 1964, and for giving permission on the inhalation experiment with Ag^{111}.

I also sent you a memo sometime last year and a proposal for an injection experiment employing Ag^{111} (which is attached hereto). May we have your permission to carry out the injection experiment too? We feel that this experiment should be done before (or maybe concurrently with) the inhalation experiment.

I am asking Jeanne to give this to you to read on your trip. Please let us have your comments, suggestions, and approval by next Monday (March 23) so that we may take this proposal to Dr. Jordan for him to route on up the line of management and to AEC for their approval.

S.R.B

S. R. Bernard

Enclosure

SRB:ss

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UCN-430
-3 5-61)

INTRA-LABORATORY CORRESPONDENCE

OAK RIDGE NATIONAL LABORATORY

March 18, 1964

To : K. Z. Morgan

cc : W. S. Snyder

From : S. R. Bernard

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I also sent you a memo sometime last year and a proposal for an injection experiment employing Ag^{111} (which is attached hereto). May we have your permission to carry out the injection experiment too? We feel that this experiment should be done before (or maybe concurrently with) the inhalation experiment.

I am asking Jeanne to give this to you to read on your trip. Please let us have your comments, suggestions, and approval by next Monday (March 23) so that we may take this proposal to Dr. Jordan for him to route on up the line of management and to AEC for their approval.

S.R.B

S. R. Bernard

Enclosure

SRB:ss

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UCN-430
(3 5-61)

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9/17/63

A Proposal for a Human Volunteer and/or Hospital Patient Study of the Metabolism of Injected and Ingested Ag^{111}

by S. R. Bernard

INTRODUCTION

The purpose of this report is to outline a program for obtaining human data on the metabolism of very low tracer doses of Ag^{111} administered to human subjects. Data of this type are needed in the estimation and verification of maximum permissible concentration (MPC) values for ingestion by workers. (At present the ICRP and NCRP recommend an $(MPC)_w$ value of 4×10^{-4} μc/cc (168-hour week) based on the lower large intestine as the critical organ.)(1) Also, the data are needed in bioassay work and for use in estimation of maximum permissible concentrations in urinary and fecal excretions during or following exposure to radiosilver compounds. (At present the latest ICRP and NCRP reports do not list values for excretion, chiefly because of a lack of adequate data.)

The most recent report of ICRP cites the data obtained by Scott and Harrison(2) in experiments on rats. These data were employed by ICRP and NCRP to obtain the values of the biological parameters. These appear in Table I.

It has been noted that the whole body half-life of 5 days cited in the ICRP report is out of line with the biological half-lives of chemically similar elements. For example, Cu has a whole body T_b of 80 days, while Au has a whole body T_b of 120 days. Also, it is noted that when the data of Tipton et al.(3) on stable Ag metabolism by man are employed in the estimation of T_b for liver, an 81-day value

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Table I. ICRP-NCRP Biological Parameter Values Currently Employed for Ag^{111} Radionuclides

Organ	f_1[a]	f_2[b]	f'_2[c]	$f_w = f_1 f'_2$[d]	T_b(days)	T*(days)[e]
Whole body	0.01	1	1	0.01	5	3
Skeleton		0.1	0.05	5×10^{-4}	30	6
Liver		0.05	0.03	3×10^{-4}	15	5
Kidney		0.03	0.02	2×10^{-4}	10	4

[a]Fraction going from GI tract to blood

[b]Fraction of that in whole body present in the critical organ

[c]Fraction going from blood to critical organ

[d]Fraction going from GI tract to critical organ

[e]$T^* = T_r T_b / T_r + T_b$, the effective half-life where T_r is the radiological half-life of Ag^{111} (= 7.5 days).

is indicated. The handbook cites a 15-day T_b value for liver. In human experimental research on a patient with malignant carcinoid, Polachek et al.(4) found a T_b for liver of 48 days. This was estimated from measurements obtained by direct external counting of the patient's liver for a period of 20 days. It thus appears that the handbook value of 15 days is low by a factor of 3 or 5. This needs to be resolved.

In the study to be proposed, the data obtained would be used for the purpose of estimating or verifying the biological parameters shown in Table I. In the calculations which follow, the parameter values employed by ICRP and NCRP will be used in the estimation of organ and body burdens and dose rates and doses received by the subjects administered Ag^{111}. Also, since they were estimated from studies on rats the uncertainty in the doses will be discussed.

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Also, in this study the urinary and fecal excretion data will be used to estimate the retention in the whole body. This will be compared with the whole-body-counter-measured retention. The excretion data would indicate methods of interpreting data from employees accidentally exposed. Studies of disappearance of Ag^{111} from the blood would also be made, and these data are useful for interpretation of findings in cases of accidental exposure.

In the proposed study, human volunteers or hospital patients would receive administrations of Ag^{111}. The subsequent procedure is outlined below and would produce some human data to help resolve the above-mentioned problems, at least within the limits imposed by human biological variations.

PROCEDURE

There are four phases--single injection, multiple injection, single ingestion, and multiple ingestion--to be carried out in this experiment. The data obtained at the completion of the first phase would be used to determine the amount of Ag^{111} to be administered in the second phase, and that data obtained in the third phase would be used to decide upon the dose to be administered in the fourth phase. Phases 2 and 3 possibly could be interchanged, because the data from the single injection study should give sufficient guidance for the single ingestion study. The data obtained in phases 1 and 3 would be sufficient to provide estimates of all of the biological parameters used in the ICRP-NCRP model. The data obtained in phases 2 and 4

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would be used to verify the estimates of the parameter values obtained from the data in phases 1 and 3. Each phase of the study is discussed in detail.

Phase 1, Single Injection

The subject would be injected (by competent members of the ORNL Health Division if a volunteer is used) with a single dose of 1.0 μc of Ag^{111} (the compound to be injected will be discussed later in this report). All urine and feces voided after administration would be collected and analyzed for Ag^{111}. The period of excreta collection would continue for either as long as feasible or as long as significant data were obtained. Whole body counts and counts of liver and kidneys would be made on the average of several times per week and as long as significant data are obtained. Blood samples (taken by a medically competent member of the ORNL Health Division if a volunteer is used) would be collected on the average of once per week and for as long as significant data are obtained.

An estimate of the peak organ and body burden, peak dose rates and total doses has been made, and these appear in Table II. (The details on the method of estimating these quantities appear in Appendix I.) As can be seen, the estimated peak burdens are less than 1/30 the permissible occupational burden. The estimated peak dose rates are less than 1/30 the occupational dose rates, and the estimated total doses are less than 1/390 the quarterly occupational exposure dose of 3.9 rem. It is necessary to consider the uncertainty in these

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Table II. Estimated Peak Organ Burdens, Dose Rates, and Total Doses to Organs and Whole Body of a Subject Injected with 10 μc of Ag^{111}

Organ	Peak Organ Burden (μc)	Permissible Organ Burden (μc)	Peak Dose Rate (rem/wk)	Total Dose (rem)
Whole Body	1.0	50	0.002	0.001
Skeleton	0.05	6	0.005	0.006
Liver	0.03	4	0.002	0.002
Kidney	0.02	0.6	0.010	0.010

estimates since the values of the biological parameters are estimated from studies on rats. The uncertainty is in f_2' and T_b for organs and tissues. These might be different in humans. We take the extreme case, i.e., all f_2''s = 1 and all T_b's $\rightarrow \infty$, i.e., one of the organs, but not all simultaneously, concentrates the Ag^{111} and the biological half-life is infinite. Since the radiological half-life is 7.5 days, the effective half-life would be 7.5 days. This is only, at most, 2.3 times the lowest T value appearing in Table I. This will only double the total dose. If the kidneys deposit the entire dose of 1 μc, the peak dose rate to kidneys would be 0.5 rem/wk and the total dose would be ~ 1 rem. This is still lower than the permissible quarterly occupational dose of 3.9 rem by a factor of 3.9. More than likely not all of the injection dose will deposit in kidneys, and if this is borne out in the experiment, a higher injection dose of 5 or 10 μc would improve the statistics. The dose of 10 μc if injected and if the biological

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parameters are correct, will correspond to dose rates and doses well below the permissible occupational doses.

Phase 2, Multiple Injection

The subjects will receive weekly injections of a dose of Ag^{111}, the quantity to be decided upon from the data obtained in phase 1, for a period of time such that equilibrium of the body burden can be established. If, for example, a subject was injected with 0.16 μc/wk for a period of 3 weeks, the equilibrium body burden of ~ 0.2 μc would be reached. Counts of the whole body and organs will be made during and after the intake has stopped. Urine, feces, and blood samples will be collected. The doses received by organs and tissues will be kept below the permissible occupational levels.

Phase 3, Single Ingestion

A single ingestion of a dose of Ag^{111} in an amount less than 80 μc, the permissible quarterly intake for occupational workers, will be given to the subject. A dose of 16 μc is suggested tentatively. The same sampling and counting frequency used in phase 1 would be employed. A dose of 16 μc would give a peak body burden of ~ 0.16 μc if f_1 is 10^{-2} as indicated in the rat studies.

Phase 4, Multiple Ingestion

The amount ingested per week and the number of weeks will be decided from the data obtained in phase 3. If the subject were to ingest 16 μc/wk for three weeks and if the rat data apply, then the

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body burden would equilibrate at ~ 0.2 μc. (See appendix for details of the calculations.) The total dose to the lower large intestine (LLI) would be 2.3 rem lower than the 3.9 rem permitted in occupational exposure.

Injection and Ingestion Solutions

The chemical compound of radiosilver to be injected and ingested probably will be the same as that employed by Scott and Hamilton. Here, carrier-free radiosilver was administered to rats as an isotonic solution of either sodium chloride or sodium sulfate. (We mention here that Polachek *et al*. administered to a carcinoid patient radiosilver complexed with blood. He obtained radiosilver from a supplier (not named) and transferred it to a silicone-coated bottle containing 10 ml acid citrate dextrose to which 45 ml of the patient's blood was added. He incubated this at room temperature for 30 minutes, during which time the solution was shaken gently. Then he intravenously injected 50 ml into the patient. We shall correspond with Polachek and ask about this or other methods he might suggest in our study.)

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REFERENCES

1. Health Phys. 3 (1960).

2. Scott, K. G., and J. G. Hamilton, J. Clin. Invest. 27, 555 (1948). Scott, K. G., and J. G. Hamilton, Univ. Calif. Publ. Pharmacol. (1950).

3. See ref. Ti-1 through Ti-7 in Health Phys. 3 (1960).

4. Polachek, A. A., C. B. Cope, R. F. Williard, and T. Enns, J. Lab. Clin. Med. 56, 4990505 (1960).

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APPENDIX I

In this section we estimate organ and body burdens for the specific phases of the study. It is to be kept in mind that these estimates are based on the small animal data and if different parameter values are observed in human studies, these calculations will be revised accordingly. It is also pointed out that the calculations, which follow, illustrate in detail how the human data are to be interpreted with the ICRP-NCRP model.

Organ and Body Burden Estimates

We employ the single exponential model of the ICRP and NCRP to estimate organ and body burdens for the case of a single intake and for repeated intakes. Let q denote the μc in the body, f_2 the fraction of that in the body which is in a critical organ, and f_2' the fraction of an injected dose I μc which goes from blood to the critical organ. The effective decay constant λ is the sum of the radiological decay constant λ_r and biological elimination constant λ_b. The body or organ burden at a time t after an injection is given by the equation

$$qf_2 = f_2' \, I \, e^{-\lambda t}. \qquad (1)$$

(The values of the parameters f_2' and λ appear in Table I.)

In the single injection phase of the program, a dose of 1 μc would be administered to the volunteer. The equation for the body burden is

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$$q = 1\, e^{-\frac{0.7}{3} t}\ \mu c, \quad t \text{ in days,}$$

while that for the skeleton is

$$qf_2 = 0.05\, e^{-\frac{0.7}{6} t}\ \mu c$$

and that for liver is

$$qf_2 = 0.03\, e^{-\frac{0.7}{5} t}\ \mu c$$

and that for kidney is

$$qf_2 = 0.02\, e^{-\frac{0.7}{4} t}\ \mu c.$$

According to these equations, the peak burdens occur at time zero, but there probably will be some time lag, and the peak will occur at a later time. We also mention here that the same equations apply for an ingestion of 100 μc of Ag^{111} since then only ~ 1% of the ingested dose is absorbed into the blood stream. However, an ingestion of 100 μc of Ag^{111} at a single time is greater than the maximum permissible single intake per quarter. The ICRP-NCRP recommends not more than 4×10^{-4} μc/cc $\times$ 2×10^5 cc/qtr = 80 μc per quarter be ingested by an occupational worker. Thus, we would have to take a lower single ingestion dose to stay within the limits imposed by ICRP-NCRP.

To estimate the organ and body burdens for the case of multiple injections or ingestions, we let t be an integral number of weeks and t' a fraction of a week ($0 \le t' \le 1$). In the general case let

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τ be the number of weeks after the last injection so that the total lapsed time is $t + t' + \tau$. A common formula can be used for the times before the end of the injection or for the times following that period. In case a time following the last injection is under consideration, $t' = 0$ and τ need not be an integer. Then

$$qf_2 = f_w I \sum_{i=0}^{t} e^{-\lambda(i+t'+\tau)} = f_w I e^{-\lambda(t'+\tau)}\left(\frac{1 - e^{-\lambda(t+1)}}{1 - e^{-\lambda}}\right) \quad (2)$$

which estimates the organ and body burden for the case of $t + 1$ ingestion of I μc/wk. Setting $I = 16$ μc/wk and considering a three-week period of intake such that the total intake is only 48 μc and inserting into (3) the values of the parameters in Table I, we obtain the equation for the burden in the total body,

$$q = 0.2\, e^{-\frac{0.7}{0.43}(t'+\tau)}\left(1 - e^{-\frac{0.7}{0.43}(t+1)}\right) \mu c$$

while that for bone is

$$qf_2 = 0.014\, e^{-\frac{0.7}{0.86}(t'+\tau)}\left(1 - e^{-\frac{0.7}{0.86}(t+1)}\right) \mu c$$

and that for liver is

$$qf_2 = 0.0077\, e^{-\frac{0.7}{0.71}(t'+\tau)}\left(1 - e^{-\frac{0.7}{0.71}(t+1)}\right) \mu c$$

and that for kidney is

$$qf_2 = 0.0045\, e^{-\frac{0.7}{0.57}(t'+\tau)}\left(1 - e^{-\frac{0.7}{0.57}(t+1)}\right) \mu c.$$

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These equations have been plotted and the graph appears in Fig. 1. From this figure the peak body and organ burdens can be estimated. These appear in Table I.A.

Table I.A. Peak Body and Organ Burdens of Ag^{111} for Ingestion of 16 μc/wk for 3 Weeks or Injection of 0.16 μc/wk for 3 Weeks

Organ	Peak Burden (μc)	Permissible Organ Burden (μc)
Whole Body	0.2	50
Bone	0.93	6
Liver	0.007	4
Kidney	0.0044	0.6

Also shown in this table are the permissible organ burdens for occupational workers. It can be noted that the peak organ burdens are very much less than the permissible organ burdens. The peak total body burden is only 1/250 the permissible body burden.

Next we estimate the peak dose rates and total radiation doses received by the subjects.

Estimated Dose Rate and Total Doses

The dose rate R in rem/wk from (qf_2) μc of a radionuclide uniformly distributed in m grams of tissue and whose effective energy per disintegration is ϵ Mev is given by the equation

$$R = \frac{357\,(qf_2)\epsilon}{m} \text{ rem/wk.} \qquad (3)$$

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The values of ϵ and m are obtained from the ICRP report. The peak organ burdens for single and multiple injections and ingestions are obtained from the above-mentioned considerations.

To obtain an estimate of peak dose rates to the various portions of the GI tract, we employ the ICRP model. We let I denote the μc ingested. This ingested amount is assumed to reside in a portion of mass m grams. Also, we assume only 1/2 of the effective energy is dissipated in tissue. The equation for estimating the dose rate to the GI tract is

$$R_{GI} = 26 \frac{I \epsilon}{m} \text{ rem/day.} \tag{4}$$

In the ICRP model, four regions of the GI tract are considered--stomach (S), small intestine (SI), upper large intestine (ULI), and lower large intestine (LLI). The residence times denoted by T in these regions are 1/24, 4/24, 8/24, and 18/24 days, respectively. Since I is also the μc ingested per week, then the weekly dose rate is

$$R_{GI}\, T = 26 \frac{I \epsilon}{m} T \text{ rem/wk.} \tag{5}$$

Table II.A. presents the estimated dose rates for intakes of Ag^{111} together with the values of ϵ and m used in equations (3), (4), and (5). The highest dose rate in the single injection study is received by the kidneys (10 mrem/wk). The kidney will receive the highest dose rate (19 mrem/wk) in the multiple injection studies. In the multiple

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Table II.A. Peak Dose Rates to Organs and Tissues from Intake of Ag^{111}

Organ	M (gms)	ϵ (Mev)	Peak Dose Rates (rem/wk) Single Injection of 1 μc	Multiple Injection of 0.16 μc/wk for 3 weeks	Multiple Ingestion of 16 μc/wk for 3 weeks
Total Body	70,000	0.4	0.002	0.004	0.004
Bone	7,000	1.8	0.005	0.012	0.012
Liver	1,700	0.38	0.002	0.006	0.006
Kidneys	300	0.37	0.010	0.019	0.019
S	250	0.38	~ 0	~ 0	0.026($\frac{.632}{rem/da}$)
SI	1,100	0.40	~ 0	~ 0	0.025($\frac{.151}{rem/da}$)
ULI	135	0.37	~ 0	~ 0	0.380($\frac{1.140}{rem/da}$)
LLI	150	0.37	~ 0	~ 0	0.770($\frac{1.026}{rem/da}$)

ingestion studies the ULI will receive a daily average dose rate of 1.140 rem/day (but only for 8 hours), while the highest weekly dose rate is received by the LLI (0.770 rem/wk). Even though these dose rates to the GI tract are in excess of the permissible weekly dose rates, they are nevertheless a factor of ~5 below the permissible single intake dose rates and thus should not constitute a serious hazard.

In order to estimate total rem doses D to organs and tissues from a single intake injection, we divide equation (3) by 7 days/wk, insert equation (1) for qf_2, and integrate over-all time to obtain

$$D = \int_0^{\infty} R\, dt = 51 \frac{f_2' I \epsilon}{\lambda m} \text{ rems.} \qquad (6)$$

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To estimate the total dose D in the case of multiple injection, we multiply (6) by 3 and obtain

$$D = 3\int_0^{\infty} R\,dt = 153\ \frac{f_2'\ I\ \epsilon}{\lambda\ \mathfrak{m}}\ \text{rems.} \qquad (7)$$

To estimate total dose to the GI tract, we multiply (5) by 3 and obtain

$$D_{GI} = 78\ \frac{I\ \epsilon\ T}{\mathfrak{m}}\ \text{rems.} \qquad (8)$$

After inserting appropriate values for the parameters into (6), (7), and (8) and calculating, we find the total doses, and these appear in Table III.A.

Table III.A. Total Rem Doses to Organs and Tissues from Injection and Ingestion of Ag^{111}

Organ	Total Dose (rem)		
	Single Injection of 1 μc	Multiple Injection of 0.16 μc/wk for 3 weeks	Multiple Ingestion of 16 μc/wk for 3 weeks
Total Body	0.001	0.0005	0.0005
Bone	0.006	0.003	0.003
Liver	0.002	0.001	0.001
Kidney	0.010	0.005	0.005
S	~ 0	~ 0	0.078
SI	~ 0	~ 0	0.075
ULI	~ 0	~ 0	1.140
LLI	~ 0	~ 0	2.310

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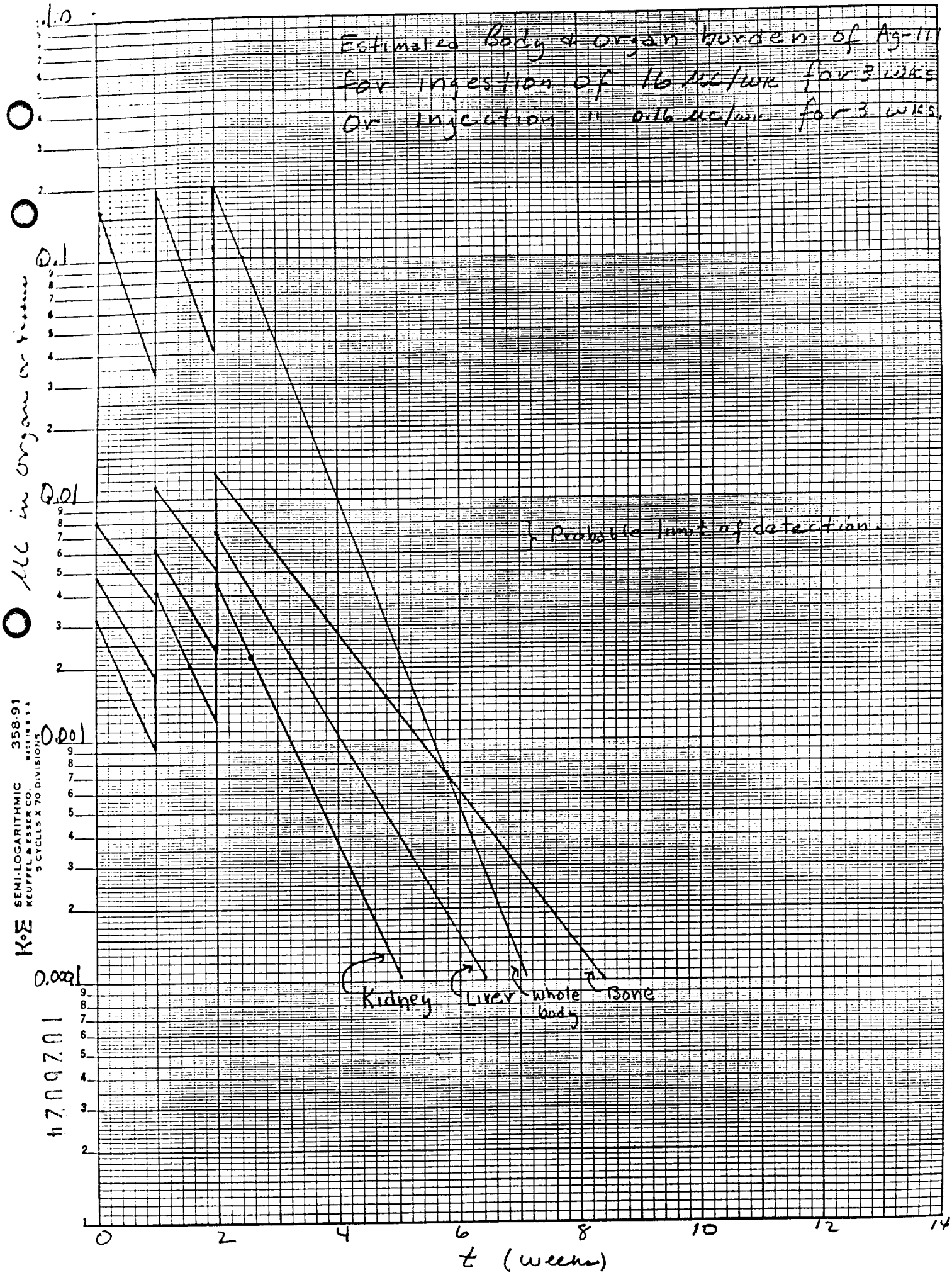
The dose of 10 mrem to kidneys is the largest dose received in the single injection study. The dose of 5 mrem to kidneys is the largest dose received in the multiple injection studies. The dose of 2.31 rem to the LLI in the multiple ingestion studies is the largest dose. This is lower by a factor of ~ 2 than the permissible quarterly dose to any section of the GI tract of an occupational worker.

There is no need to estimate quarterly doses to the total body and organs because the estimated doses received by these tissues are well below the permissible occupational levels.


Estimated Body & organ burden of Ag-111
for ingestion of 16 μc/wk for 3 wks
or injection " 0.16 μc/wk for 3 wks.
Probable limit of detection
Kidney
Liver
whole body
Bone
μc in organ or tissue
t (weeks)
1.0
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9-10

March 13, 1964

To: S. R. Bernard

From: K. Z. Morgan

When I was having lunch today with Dr. Snyder, he happened to mention you were still awaiting my reply on your proposal for a human study of the deposition in and clearance from the lungs of inhaled Ag^{111} compounds by human volunteers and/or hospital patients. I was very much irritated with myself to hear that you were waiting for my reply to your proposal because I thought I had already indicated verbally that I approved this proposal and would like to see you go ahead with it. I am sorry for the delay and by copy of this memorandum I would like to indicate that this program has my full approval.

On page 5 of your proposal of January 8, 1964, you indicate that the total dose would only be approximately 0.2 rem and that the peak dose rate would be approximately 0.2 rem/wk on the first day in the first phase of the program and in the second phase the lung dose will be approximately 2 rem, corresponding to a dose rate of 1.5 rem/wk during the first day. These dose rates seem to be quite low but I hope it will be possible to use a maximum sensitivity in your measuring techniques in order to maintain these low doses or go even lower if possible. Recalling some criticism of the Laboratory human studies with iodine, I am suggesting that you and Dr. Snyder take whatever action you think is indicated in order to satisfy similar complaints regarding Ag^{111}. Since the health physicist believes that all ionizing radiation is potentially harmful, he agrees to radiation exposure only when it can be counterbalanced by benefits of an equal or greater magnitude. I am convinced that the benefits in this case far exceed the potential hazards and you have chosen a radionuclide with a hard gamma that is easy to measure and with an effective half life sufficiently short that the doses can be kept quite low. Nevertheless, I hope the doses and the dose rates you have indicated are a maximum and it might still be possible to get satisfactory data at even lower values.

Finally, by copy of this memorandum, I would like to assure you that I think this is a good experiment in that by the use of this relatively harmless radionuclide we can prove that our techniques are sound and that such experiments can be very rewarding.

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If I can be of further help in this matter, please let me know.

Original Signed By
K. Z. MORGAN

Karl Z. Morgan

KZM:jc

cc: W. S. Snyder

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J-11

January 21, 1964

To: W. S. Snyder

From: K. Z. Morgan

Subject: Human Inhalation Experiment

You are referred to Bernard's memorandum dated January 13, 1964, above subject. This experiment has my approval if it has yours.

Original Signed By
K. Z. Morgan

Karl Z. Morgan

KZM:jc

1026027

JAN 14 1964

INTRA-LABORATORY CORRESPONDENCE

OAK RIDGE NATIONAL LABORATORY

January 13, 1964

To : K. Z. Morgan
W. S. Snyder

cc : H. D. Landahl

From : S. R. Bernard

Subject: Human Inhalation Experiment

Attached hereto is a copy of "A Proposal for a Human Study of the Deposition in and Clearance from Lungs of Inhaled Ag^{111} Compounds by Human Volunteers and/or Hospital Patients."

May we have permission to carry out this experiment?

SRB.

S. R. Bernard

Attachment

SRB:ss

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UCN-430
(3 11-60)

1/8/64

A Proposal for a Human Study of the Deposition In and Clearance from Lungs of Inhaled Ag^{111} Compounds by Human Volunteers and/or Hospital Patients

By S. R. Bernard
Health Physics Division
Oak Ridge National Laboratory*
Oak Ridge, Tennessee

Introduction

The purpose in this report is to outline a program for a human inhalation experiment. There is almost an urgent need for human data by the committees on internal dose of the ICRP and NCRP. Currently they employ the lung model shown in Table 1 for estimations of maximum permissible concentrations in air, $(MPC)_a$. This model has been said to serve well as a guide for practical inhalation hazard control. It also has been said that some revision of this model should be made to account for the effect of particle size on deposition in the various regions of the respiratory tract.(1)

Some excellent studies on humans were carried out by Landahl(2) and his associates on this problem of deposition as a function of size and density of the inhaled particles using both soluble and insoluble compounds but with nonradioactive elements. Landahl also developed and tested a model for deposition in eleven regions of

*Operated by Union Carbide Corporation for the U. S. Atomic Energy Commission.

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the respiratory tract.[3] Thus, human data on deposition are available, but human data on clearance from lungs are almost nonexistent.

Numerous studies on animals to estimate lung clearance of various particles have been carried out.[4] Also, clearance studies of inhaled aerosols of not-too-well-known compounds and unknown particle sizes have been made with γ-ray scintillation counters on workers who have been exposed accidentally.[5] These data cannot be said to be adequate. Needed are human studies of clearance from lungs of known compounds and known particle sizes. It would seem very worthwhile to repeat Landahl's experiments on humans inhaling various particle sizes of known compounds and employing γ-ray scintillation counting techniques to check on the estimated deposition and to follow clearance of the various-sized particles from lungs. Also, complete excretion studies should be made on the subjects and efforts made to obtain a material balance.

In this proposal we review Landahl's experimental procedure that he used in studies of stable element compound inhalation and modify it for studies of radioactive element inhalation employing γ-ray scintillation counting of lungs and complete excretion studies. We propose to have humans inhale the insoluble compound $Ag^{111}O$ in low doses and of known particle-size distribution. The radiation dose to lungs from deposition of $Ag^{111}O$ is estimated with the lung model of ICRP and NCRP.

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Methods

Inhalation Apparatus

Fig. 1 shows the experimental apparatus used by Landahl in his inhalation studies. For dispersal of $Ag^{111}O$ particles, air would be passed through the flask containing the dry powder. The dust-laden air would be freed of the large particles by passing upwards through a vertical tube 5 feet long and 2 inches in diameter. Further removal of large particles would occur in passage through an impinger--the impinging surface being coated with a mixture of vaseline and lubricating oil to ensure retention of the impacted material. In some experiments several impingers would be connected in series, and orifice size would be varied to obtain different impinger efficiencies, thereby removing more or less of the large-sized particles from the cloud as desired. (Later on we would want to employ the spinning-disk system described by Whitby to go to submicronic-size particles.)

After removal of large particles, the cloud is passed into a chamber of at least 15 liters in volume. From there the cloud is drawn into a Y-tube and through the rest of the apparatus by a vacuum pump. On entering the central section of the Y-tube, it is stirred vigorously by two small stationary propellers of opposite pitch. The right arm of the Y-tube leads through a cascade impactor through which air is drawn by a vacuum pump. The left arm of the Y-tube is the exposure part. The subject places his mouth over the

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end of the left arm (No. 4) and inhales. He then exhales through his mouth into the tube No. 5 which leads through a cascade impactor and on into a vacuum pump.

Procedure

The subject is seated so that he can close his mouth over the left side arm of the Y-tube (No. 4 in Fig. 1) or the exhalation tube (No. 5 in Fig. 1). His hands are free to operate the valves (11C and 11L in Fig. 1). The respiratory cycle is fixed to reduce the variability and facilitate the interpretation of the data. On inspiration (which lasts 3/8 of the time for one complete cycle) the mouth is closed about the outlet of the Y-tube (No. 4 in Fig. 1) with the tongue depressed and the stopcock (C) for the control sampler opened. Thus, while a sample is being drawn into lungs, a sample also is being drawn into the control sampling instrument. During the next 1/8 of a cycle time, the control stopcock is closed and the mouth is moved over to and closed about the tube to the sampler for exhaled air, care being taken to avoid inhaling or exhaling at that time. Stopcock (L) for the exhaled air sampler is opened and air is exhaled for the next 3/8 of a cycle at a rate determined by a critical pressure orifice. The manometer (No. 6 in Fig. 1) is kept near zero by the subject. At the end of this interval, stopcock L is closed. Then during the last 1/8 of the cylce time, the mouth is moved back to the starting position ready to repeat the cycle.

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The timing of the respiration cycle is controlled by a metronome. Also, timers operated by a Hg control switch (which respond to a reduced pressure in the line between the critical pressure orifice and the valve) are used to determine how long the valves are open. Furthermore, the total flow (flow rate times reading on timer) is checked against a calibrated flow meter.

Inhalation Doses and Estimated Radiation Doses

Currently the ICRP and NCRP recommend an $(MPC)_a$ of 8×10^{-8} μc/cc (168-hour week) for insoluble compounds of Ag^{111} based on the GI tract as the critical organ. (On the basis of lung, $(MPC)_a$ is 9×10^{-8} μc/cc, only slightly different.) For a single intake in a quarter, 146 μc can be inhaled. We propose a two-phase study. The first phase is a single inhalation study. The second phase is a repeated inhalation study. In the first phase we propose to have the subject inhale ~ 8 μc of Ag^{111} as the oxide. Using the ICRP-NCRP model, this means that only - 1 μc will be retained in the lower respiratory passages with a half-life of 120 days. The total dose to lungs will only be ~ 0.2 rem from this deposit. The peak dose rate will be ~ 0.2 rem/wk on the first day.

In the second phase of the program, the inhaled dose will be decided upon from the data obtained in the first phase of the study. Tentatively, we propose one dose per week of 4 μc for a period of ten weeks. From the ICRP model the lung burden can be expected to equilibrate at ~ 1 μc. The total dose to lungs will be ~ 2 rem--

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less than the permissible dose of 3.9 rem in a quarter by a factor of 2. Also, the peak dose rate to lungs will not exceed ~ 0.2 rem/wk from intake of 4 μc/wk for ten weeks.

The dose to the GI tract will be a little greater than the dose to lungs. In the single intake case, the permissible daily intake is 1.6 μc to give 0.3 rem/wk to the lower large intestine. Since 8 μc will be taken in, the GI tract dose will correspond to an average dose of $8/1.6 \times 0.3 = 1.5$ rem/wk but only for a period of 1 day. In the multiple intake case the dose of 4 μc once each week will correspond to an average dose of ~ 0.11 rem/wk but only for 1 day of each week for a period of ten weeks. The total dose received by the GI tract will be 1.1 rem. This is lower by a factor of 3.5 than the 3.9 rem permitted in 1 quarter for occupational workers.

References

1. "Effects of Inhaled Radioactive Particles," NAS-NRC Publ. 848, Washington, D. C. (1961).

2. H. D. Landahl and R. G. Herrmann, "On the retention of airborne particulates in the human lung," J. Ind. Hyg. Toxicol. 30(31), 181-188 (1947).

3. H. D. Landahl, "On the removal of airborne droplets by the human respiratory tract: I. The Lung," Bull. Math. Biophys. 12, 43-56 (1950).

4. P. E. Morrow, F. R. Gibb, and L. Johnson, "Clearance of insoluble dust from the lower respiratory tract," Submitted to Health Phys. (1963).

5. B. R. Fish, "Inhalation of uranium aerosols by mouse, rat, dog, and man," Inhaled Particles and Vapours (Pergamon Press, Oxford, 1961), pp. 151-165.

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Table 10. Particulates in respiratory tract of the standard man

Retention of particulate matter in the lungs depends on many factors, such as the size, shape and density of the particles, the chemical form and whether or not the person is a mouth breather; however, when specific data are lacking it is assumed the distribution is as shown below.

Distribution	Readily soluble compounds (%)	Other compounds (%)
Exhaled	25	25
Deposited in upper respiratory passages and subsequently swallowed	50	50
Deposited in the lungs (lower respiratory passages)	25 (this is taken up into the body)	25*

* Of this, half is eliminated from the lungs and swallowed in the first 24 hrs, making a total of 62½ per cent swallowed. The remaining 12½ per cent is retained in the lungs with a half-life of 120 days, it being assumed that this portion is taken up into body fluids.

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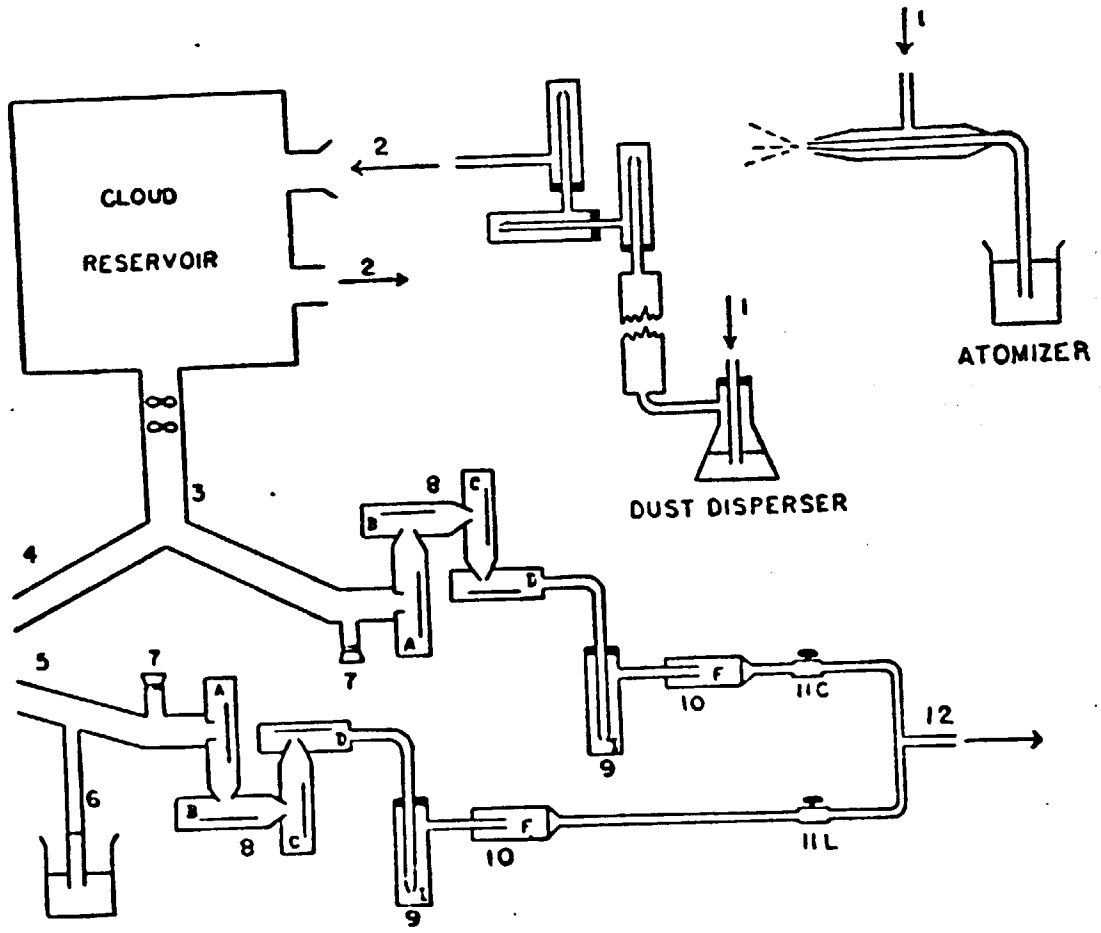

Direction of flow of compressed air. 2. Direction of flow of air through cloud reservoir. This flow was maintained only in experiments where great dilution of the cloud was desired. 3. Y-tube, with stationary propellers of opposite pitch. 4. Side-arm of Y-tube for inspiration. 5. Tube for collecting exhaled air. 6. Manometer and safety valve. 7. Port in line for withdrawing or injecting air from stream entering the cascade impactor. 8. Cascade impactor. 9. Impinger. 10. Filter. 11. Stopcock. C control, L lung. 12. Vacuum pump connection.

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3-10

December 20, 1963

To: S. R. Bernard

From: K. Z. Morgan

Re: Comments on the Information Meeting with Dr. John Hursh

I think you did a very good job in describing your programs to Dr. Hursh. There are a few questions I would like to ask, some of which refer to your program. They are as follows:

18000 μμc/l — x20 — 900 μμc/l

(1) What were the values of $(MPC)_w$ for Rn^{222} for adults and for children?

(2) What value of f_w should we use for I^{131} in the revised ICRP handbook of Committee 2?

(3) Is information being accumulated for the forthcoming handbook revisions for several specific compounds of uranium, some of which are soluble and others are insoluble?

(4) I understand you plan to get studies under way with Ag^{111}. Part of the argument for these studies is the uncertainty of the value of T_b for man. Since the value of T_r is 7.5 days, what change in the present value of T is expected as the result of these experiments?

(5) Why are we interested in obtaining data on Ag^{111}. Is this isotope commonly used in the treatment of patients? I believe you indicated a relatively small amount is shipped by the Isotopes Division. Are there other sources of Ag^{111}; for example, is it an important constituent in any reactor waste?

These are the sort of questions we may have to answer when outsiders hear of this program.

(6) We are in the process of obtaining data for blood. What correction, if any, will we have to make to our q and MPC values when we assume the blood is contained in the organs?

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(7) Mary Rose Ford was talking about some paper; I did not understand what paper she kept referring to. Perhaps, by copy of this memo, she will inform me.

Original Signed By
K. Z. MORGAN

Karl Z. Morgan

KZM:jc

cc: Mary Rose Ford
W. S. Snyder

Bernard

Dec 19, '63

1- What were values of (MPC)w for Ra^{222} for adults and for children?

2- What value of fw should we use for I^{131} in revised ICRP-Handbook of Comm II?

3- What about data on several specific compounds of U — soluble + insoluble?

4- What correction is applied in value of T for Ag^{111}? (T_b = 15-80 d but T_r = 7 d)

5- What correction if any for blood in organs? W/S

6- What paper is NRF talking about?

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9-10

SEP 23 1963

INTRA-LABORATORY CORRESPONDENCE

OAK RIDGE NATIONAL LABORATORY

September 17, 1963

To : K. Z. Morgan
W. S. Snyder
E. G. Struxness

cc : M. J. Cook
B. R. Fish

Subject: A Proposal for a Human Volunteer and/or Hospital Patient Study of the Metabolism of Injected and Ingested Ag^{111}

Attached hereto is an outline of a procedure for obtaining human data on the metabolism of Ag^{111}. If this meets with your approval and if we have your permission to carry out this study, please take the necessary steps to obtain AEC approval. Also, if there are any comments or suggestions for improving this proposal so that we can be more sure of AEC approval, let's include it too.

S. R. Bernard

S. R. Bernard

Attachment

SRB:ss

1 - Why [illegible] Ag^{111} [illegible]
2 - Where [illegible] Ag^{111} [illegible] in human [illegible]
3 - [illegible] Ag^{111} [illegible]
4 - [illegible]
5 - [illegible]

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9/17/63

A Proposal for a Human Volunteer and/or Hospital Patient Study of the Metabolism of Injected and Ingested Ag^{111}

by S. R. Bernard

INTRODUCTION

The purpose of this report is to outline a program for obtaining human data on the metabolism of very low tracer doses of Ag^{111} administered to human subjects. Data of this type are needed in the estimation and verification of maximum permissible concentration (MPC) values for ingestion by workers. (At present the ICRP and NCRP recommend an $(MPC)_w$ value of 4×10^{-4} μc/cc (168-hour week) based on the lower large intestine as the critical organ.)[1] Also, the data are needed in bioassay work and for use in estimation of maximum permissible concentrations in urinary and fecal excretions during or following exposure to radiosilver compounds. (At present the latest ICRP and NCRP reports do not list values for excretion, chiefly because of a lack of adequate data.)

The most recent report of ICRP cites the data obtained by Scott and Harrison[2] in experiments on rats. These data were employed by ICRP and NCRP to obtain the values of the biological parameters. These appear in Table I.

It has been noted that the whole body half-life of 5 days cited in the ICRP report is out of line with the biological half-lives of chemically similar elements. For example, Cu has a whole body T_b of 80 days, while Au has a whole body T_b of 120 days. Also, it is noted that when the data of Tipton et al.[3] on stable Ag metabolism by man are employed in the estimation of T_b for liver, an 81-day value

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Table I. ICRP-NCRP Biological Parameter Values Currently Employed for Ag^{111} Radionuclides

Organ	f_1[a]	f_2[b]	f'_2[c]	$f_w = f_1 f'_2$[d]	T_b(days)	T*(days)[e]
Whole body	0.01	1	1	0.01	5	3
Skeleton		0.1	0.05	5×10^{-4}	30	6
Liver		0.05	0.03	3×10^{-4}	15	5
Kidney		0.03	0.02	2×10^{-4}	10	4

[a]Fraction going from GI tract to blood

[b]Fraction of that in whole body present in the critical organ

[c]Fraction going from blood to critical organ

[d]Fraction going from GI tract to critical organ

[e]$T^* = T_r T_b / T_r + T_b$, the effective half-life where T_r is the radiological half-life of Ag^{111} (= 7.5 days).

is indicated. The handbook cites a 15-day T_b value for liver. In human experimental research on a patient with malignant carcinoid, Polachek et al.[4] found a T_b for liver of 48 days. This was estimated from measurements obtained by direct external counting of the patient's liver for a period of 20 days. It thus appears that the handbook value of 15 days is low by a factor of 3 or 5. This needs to be resolved.

In the study to be proposed, the data obtained would be used for the purpose of estimating or verifying the biological parameters shown in Table I. In the calculations which follow, the parameter values employed by ICRP and NCRP will be used in the estimation of organ and body burdens and dose rates and doses received by the subjects administered Ag^{111}. Also, since they were estimated from studies on rats the uncertainty in the doses will be discussed.

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Also, in this study the urinary and fecal excretion data will be used to estimate the retention in the whole body. This will be compared with the whole-body-counter-measured retention. The excretion data would indicate methods of interpreting data from employees accidentally exposed. Studies of disappearance of Ag^{111} from the blood would also be made, and these data are useful for interpretation of findings in cases of accidental exposure.

In the proposed study, human volunteers or hospital patients would receive administrations of Ag^{111}. The subsequent procedure is outlined below and would produce some human data to help resolve the above-mentioned problems, at least within the limits imposed by human biological variations.

PROCEDURE

There are four phases--single injection, multiple injection, single ingestion, and multiple ingestion--to be carried out in this experiment. The data obtained at the completion of the first phase would be used to determine the amount of Ag^{111} to be administered in the second phase, and that data obtained in the third phase would be used to decide upon the dose to be administered in the fourth phase. Phases 2 and 3 possibly could be interchanged, because the data from the single injection study should give sufficient guidance for the single ingestion study. The data obtained in phases 1 and 3 would be sufficient to provide <u>estimates</u> of all of the biological parameters used in the ICRP-NCRP model. The data obtained in phases 2 and 4

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would be used to verify the estimates of the parameter values obtained from the data in phases 1 and 3. Each phase of the study is discussed in detail.

Phase 1, Single Injection

The subject would be injected (by competent members of the ORNL Health Division if a volunteer is used) with a single dose of 1.0 μc of Ag^{111} (the compound to be injected will be discussed later in this report). All urine and feces voided after administration would be collected and analyzed for Ag^{111}. The period of excreta collection would continue for either as long as feasible or as long as significant data were obtained. Whole body counts and counts of liver and kidneys would be made on the average of several times per week and as long as significant data are obtained. Blood samples (taken by a medically competent member of the ORNL Health Division if a volunteer is used) would be collected on the average of once per week and for as long as significant data are obtained.

An estimate of the peak organ and body burden, peak dose rates and total doses has been made, and these appear in Table II. (The details on the method of estimating these quantities appear in Appendix I.) As can be seen, the estimated peak burdens are less than 1/30 the permissible occupational burden. The estimated peak dose rates are less than 1/30 the occupational dose rates, and the estimated total doses are less than 1/390 the quarterly occupational exposure dose of 3.9 rem. It is necessary to consider the uncertainty in these

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f_2' assumed T_b

$\frac{.3}{50} = .06$

Table II. Estimated Peak Organ Burdens, Dose Rates, and Total Doses to Organs and Whole Body of a Subject Injected with 10 μc of Ag^{111}

Organ	Peak Organ Burden (μc)	Permissible Organ Burden (μc)	Peak Dose Rate (rem/wk)	Total Dose (rem)
Whole Body	1.0	50	0.002	0.001
Skeleton	0.05	6	0.005	0.006
Liver	0.03	4	0.002	0.002
Kidney	0.02	0.6	0.010	0.010

estimates since the values of the biological parameters are estimated from studies on rats. The uncertainty is in f_2' and T_b for organs and tissues. These might be different in humans. We take the extreme case, i.e., all f_2''s = 1 and all T_b's $\rightarrow \infty$, i.e., one of the organs, but not all simultaneously, concentrates the Ag^{111} and the biological half-life is infinite. Since the radiological half-life is 7.5 days, the effective half-life would be 7.5 days. This is only, at most, 2.3 times the lowest T value appearing in Table I. This will only double the total dose. If the kidneys deposit the entire dose of 1 μc, the peak dose rate to kidneys would be 0.5 rem/wk and the total dose would be ~ 1 rem. This is still lower than the permissible quarterly occupational dose of 3.9 rem by a factor of 3.9. More than likely not all of the injection dose will deposit in kidneys, and if this is borne out in the experiment, a higher injection dose of 5 or 10 μc would improve the statistics. The dose of 10 μc if injected and if the biological

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parameters are correct, will correspond to dose rates and doses well below the permissible occupational doses.

Phase 2, Multiple Injection

The subjects will receive weekly injections of a dose of Ag^{111}, the quantity to be decided upon from the data obtained in phase 1, for a period of time such that equilibrium of the body burden can be established. If, for example, a subject was injected with 0.16 μc/wk for a period of 3 weeks, the equilibrium body burden of ~ 0.2 μc would be reached. Counts of the whole body and organs will be made during and after the intake has stopped. Urine, feces, and blood samples will be collected. The doses received by organs and tissues will be kept below the permissible occupational levels.

Phase 3, Single Ingestion

A single ingestion of a dose of Ag^{111} in an amount less than 80 μc, the permissible quarterly intake for occupational workers, will be given to the subject. A dose of 16 μc is suggested tentatively. The same sampling and counting frequency used in phase 1 would be employed. A dose of 16 μc would give a peak body burden of ~ 0.16 μc if f_1 is 10^{-2} as indicated in the rat studies.

Phase 4, Multiple Ingestion

The amount ingested per week and the number of weeks will be decided from the data obtained in phase 3. If the subject were to ingest 16 μc/wk for three weeks and if the rat data apply, then the

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body burden would equilibrate at ~ 0.2 μc. (See appendix for details of the calculations.) The total dose to the lower large intestine (LLI) would be 2.3 rem lower than the 3.9 rem permitted in occupational exposure.

Injection and Ingestion Solutions

The chemical compound of radiosilver to be injected and ingested probably will be the same as that employed by Scott and Hamilton. Here, carrier-free radiosilver was administered to rats as an isotonic solution of either sodium chloride or sodium sulfate. (We mention here that Polachek *et al*. administered to a carcinoid patient radiosilver complexed with blood. He obtained radiosilver from a supplier (not named) and transferred it to a silicone-coated bottle containing 10 ml acid citrate dextrose to which 45 ml of the patient's blood was added. He incubated this at room temperature for 30 minutes, during which time the solution was shaken gently. Then he intravenously injected 50 ml into the patient. We shall correspond with Polachek and ask about this or other methods he might suggest in our study.)

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REFERENCES

1. Health Phys. 3 (1960).

2. Scott, K. G., and J. G. Hamilton, J. Clin. Invest. 27, 555 (1948).
Scott, K. G., and J. G. Hamilton, Univ. Calif. Publ. Pharmacol. (1950).

3. See ref. Ti-1 through Ti-7 in Health Phys. 3 (1960).

4. Polachek, A. A., C. B. Cope, R. F. Williard, and T. Enns, J. Lab. Clin. Med. 56, 4990505 (1960).

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APPENDIX I

In this section we estimate organ and body burdens for the specific phases of the study. It is to be kept in mind that these estimates are based on the small animal data and if different parameter values are observed in human studies, these calculations will be revised accordingly. It is also pointed out that the calculations, which follow, illustrate in detail how the human data are to be interpreted with the ICRP-NCRP model.

Organ and Body Burden Estimates

We employ the single exponential model of the ICRP and NCRP to estimate organ and body burdens for the case of a single intake and for repeated intakes. Let q denote the μc in the body, f_2 the fraction of that in the body which is in a critical organ, and f_2' the fraction of an injected dose I μc which goes from blood to the critical organ. The effective decay constant λ is the sum of the radiological decay constant λ_r and biological elimination constant λ_b. The body or organ burden at a time t after an injection is given by the equation

$$qf_2 = f_2' \, I \, e^{-\lambda t}. \qquad (1)$$

(The values of the parameters f_2' and λ appear in Table I.)

In the single injection phase of the program, a dose of 1 μc would be administered to the volunteer. The equation for the body burden is

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$$q = 1\, e^{-\frac{0.7}{3} t}\ \mu c, \quad t \text{ in days,}$$

while that for the skeleton is

$$qf_2 = 0.05\, e^{-\frac{0.7}{6} t}\ \mu c$$

and that for liver is

$$qf_2 = 0.03\, e^{-\frac{0.7}{5} t}\ \mu c$$

and that for kidney is

$$qf_2 = 0.02\, e^{-\frac{0.7}{4} t}\ \mu c.$$

According to these equations, the peak burdens occur at time zero, but there probably will be some time lag, and the peak will occur at a later time. We also mention here that the same equations apply for an ingestion of 100 μc of Ag^{111} since then only ~ 1% of the ingested dose is absorbed into the blood stream. However, an ingestion of 100 μc of Ag^{111} at a single time is greater than the maximum permissible single intake per quarter. The ICRP-NCRP recommends not more than 4×10^{-4} μc/cc x 2×10^{5} cc/qtr = 80 μc per quarter be ingested by an occupational worker. Thus, we would have to take a lower single ingestion dose to stay within the limits imposed by ICRP-NCRP.

To estimate the organ and body burdens for the case of multiple injections or ingestions, we let t be an integral number of weeks and t' a fraction of a week ($0 \le t' \le 1$). In the general case let

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τ be the number of weeks after the last injection so that the total lapsed time is $t + t' + \tau$. A common formula can be used for the times before the end of the injection or for the times following that period. In case a time following the last injection is under consideration, $t' = 0$ and τ need not be an integer. Then

$$qf_2 = f_w I \sum_{i=0}^{t} e^{-\lambda(i+t'+\tau)} = f_w I e^{-\lambda(t'+\tau)}\left(\frac{1 - e^{-\lambda(t+1)}}{1 - e^{-\lambda}}\right) \quad (2)$$

which estimates the organ and body burden for the case of $t + 1$ ingestion of I μc/wk. Setting $I = 16$ μc/wk and considering a three-week period of intake such that the total intake is only 48 μc and inserting into (3) the values of the parameters in Table I, we obtain the equation for the burden in the total body,

$$q = 0.2\, e^{-\frac{0.7}{0.43}(t'+\tau)}\left(1 - e^{-\frac{0.7}{0.43}(t+1)}\right) \mu c$$

while that for bone is

$$qf_2 = 0.014\, e^{-\frac{0.7}{0.86}(t'+\tau)}\left(1 - e^{-\frac{0.7}{0.86}(t+1)}\right) \mu c$$

and that for liver is

$$qf_2 = 0.0077\, e^{-\frac{0.7}{0.71}(t'+\tau)}\left(1 - e^{-\frac{0.7}{0.71}(t+1)}\right) \mu c$$

and that for kidney is

$$qf_2 = 0.0045\, e^{-\frac{0.7}{0.57}(t'+\tau)}\left(1 - e^{-\frac{0.7}{0.57}(t+1)}\right) \mu c.$$

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These equations have been plotted and the graph appears in Fig. 1. From this figure the peak body and organ burdens can be estimated. These appear in Table I.A.

Table I.A. Peak Body and Organ Burdens of Ag^{111} for Ingestion of 16 μc/wk for 3 Weeks or Injection of 0.16 μc/wk for 3 Weeks

Organ	Peak Burden (μc)	Permissible Organ Burden (μc)
Whole Body	0.2	50
Bone	0.93	6
Liver	0.007	4
Kidney	0.0044	0.6

Also shown in this table are the permissible organ burdens for occupational workers. It can be noted that the peak organ burdens are very much less than the permissible organ burdens. The peak total body burden is only 1/250 the permissible body burden.

Next we estimate the peak dose rates and total radiation doses received by the subjects.

Estimated Dose Rate and Total Doses

The dose rate R in rem/wk from (qf_2) μc of a radionuclide uniformly distributed in m grams of tissue and whose effective energy per disintegration is ϵ Mev is given by the equation

$$R = \frac{357\,(qf_2)\epsilon}{m} \text{ rem/wk.} \qquad (3)$$

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The values of ϵ and m are obtained from the ICRP report. The peak organ burdens for single and multiple injections and ingestions are obtained from the above-mentioned considerations.

To obtain an estimate of peak dose rates to the various portions of the GI tract, we employ the ICRP model. We let I denote the μc ingested. This ingested amount is assumed to reside in a portion of mass m grams. Also, we assume only 1/2 of the effective energy is dissipated in tissue. The equation for estimating the dose rate to the GI tract is

$$R_{GI} = 26 \frac{I \epsilon}{m} \text{ rem/day.} \tag{4}$$

In the ICRP model, four regions of the GI tract are considered--stomach (S), small intestine (SI), upper large intestine (ULI), and lower large intestine (LLI). The residence times denoted by T in these regions are 1/24, 4/24, 8/24, and 18/24 days, respectively. Since I is also the μc ingested per week, then the weekly dose rate is

$$R_{GI}\, T = 26 \frac{I \epsilon}{m} T \text{ rem/wk.} \tag{5}$$

Table II.A. presents the estimated dose rates for intakes of Ag^{111} together with the values of ϵ and m used in equations (3), (4), and (5). The highest dose rate in the single injection study is received by the kidneys (10 mrem/wk). The kidney will receive the highest dose rate (19 mrem/wk) in the multiple injection studies. In the multiple

Table II.A. Peak Dose Rates to Organs and Tissues from Intake of Ag^{111}

Organ	M (gms)	ϵ (Mev)	Peak Dose Rates (rem/wk)		
				Multiple	
			Single Injection of 1 μc	Injection of 0.16 μc/wk for 3 weeks	Ingestion of 16 μc/wk for 3 weeks
Total Body	70,000	0.4	0.002	0.004	0.004
Bone	7,000	1.8	0.005	0.012	0.012
Liver	1,700	0.38	0.002	0.006	0.006
Kidneys	300	0.37	0.010	0.019	0.019
S	250	0.38	~ 0	~ 0	0.026($\frac{.632}{rem/da}$)
SI	1,100	0.40	~ 0	~ 0	0.025($\frac{.151}{rem/da}$)
ULI	135	0.37	~ 0	~ 0	0.380($\frac{1.140}{rem/da}$)
LLI	150	0.37	~ 0	~ 0	0.770($\frac{1.026}{rem/da}$)

ingestion studies the ULI will receive a daily average dose rate of 1.140 rem/day (but only for 8 hours), while the highest weekly dose rate is received by the LLI (0.770 rem/wk). Even though these dose rates to the GI tract are in excess of the permissible weekly dose rates, they are nevertheless a factor of ~5 below the permissible single intake dose rates and thus should not constitute a serious hazard.

In order to estimate total rem doses D to organs and tissues from a single intake injection, we divide equation (3) by 7 days/wk, insert equation (1) for qf_2, and integrate over-all time to obtain

$$D = \int_0^\infty R\,dt = 51\,\frac{f_2'\,I\epsilon}{\lambda\,m}\ \text{rems.} \qquad (6)$$

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To estimate the total dose D in the case of multiple injection, we multiply (6) by 3 and obtain

$$D = 3\int_0^{\infty} R\,dt = 153\ \frac{f_2'\ I\ \epsilon}{\lambda\ m}\ \text{rems.} \qquad (7)$$

To estimate total dose to the GI tract, we multiply (5) by 3 and obtain

$$D_{GI} = 78\ \frac{I\ \epsilon\ T}{m}\ \text{rems.} \qquad (8)$$

After inserting appropriate values for the parameters into (6), (7), and (8) and calculating, we find the total doses, and these appear in Table III.A.

Table III.A. Total Rem Doses to Organs and Tissues from Injection and Ingestion of Ag^{111}

Organ	Total Dose (rem)		
	Single Injection of 1 μc	Multiple Injection of 0.16 μc/wk for 3 weeks	Multiple Ingestion of 16 μc/wk for 3 weeks
Total Body	0.001	0.0005	0.0005 0.05
Bone	0.006	0.003	0.003 0.3
Liver	0.002	0.001	0.001 0.1
Kidney	0.010	0.005	~~0.005~~ 0.5
S	~ 0	~ 0	0.078
SI	~ 0	~ 0	0.075
ULI	~ 0	~ 0	1.140
LLI	~ 0	~ 0	2.310

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The dose of 10 mrem to kidneys is the largest dose received in the single injection study. The dose of 5 mrem to kidneys is the largest dose received in the multiple injection studies. The dose of 2.31 rem to the LLI in the multiple ingestion studies is the largest dose. This is lower by a factor of ~ 2 than the permissible quarterly dose to any section of the GI tract of an occupational worker.

There is no need to estimate quarterly doses to the total body and organs because the estimated doses received by these tissues are well below the permissible occupational levels.

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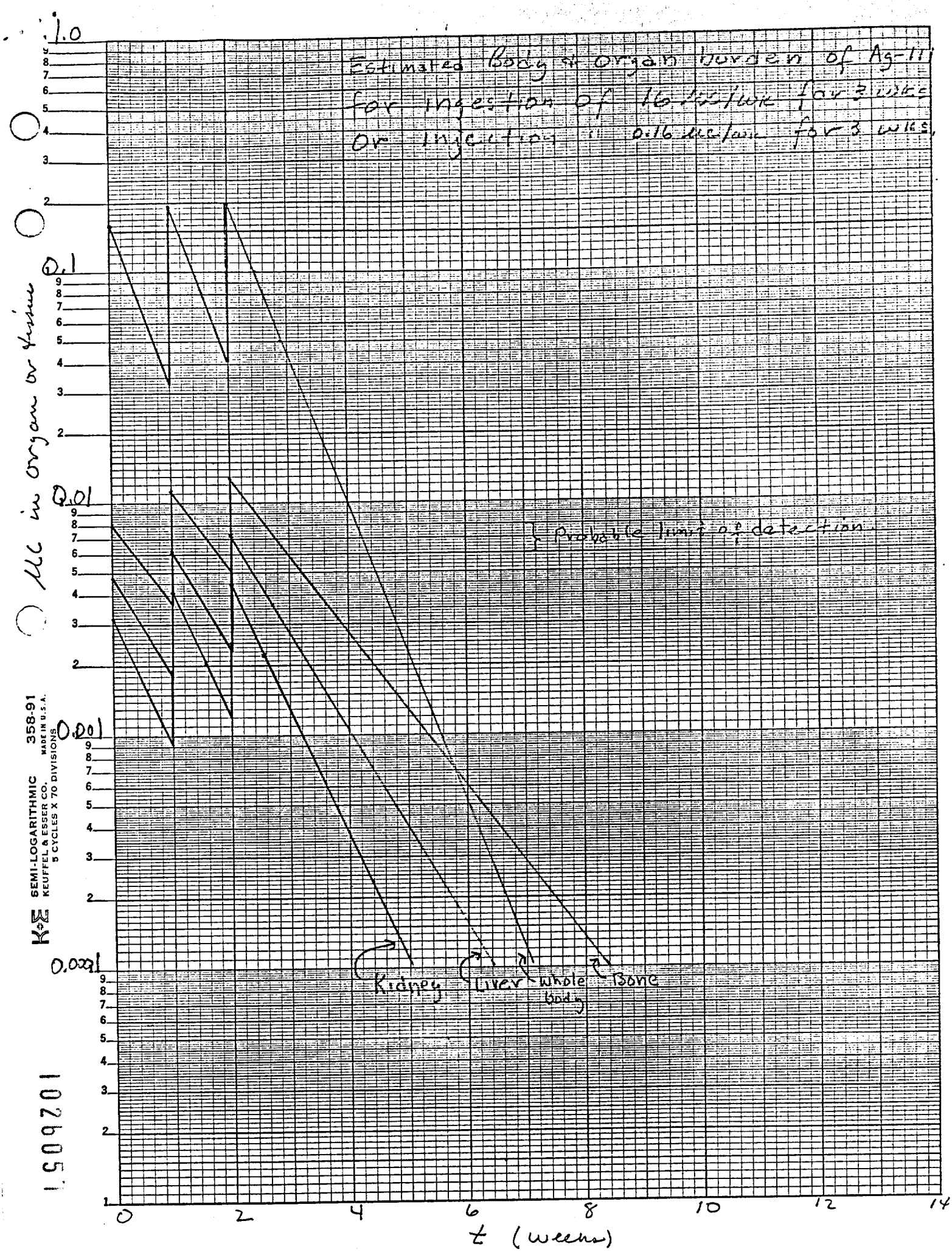
Estimated Body & Organ Burden of Ag-111
for ingestion of 16 μc/wk for 3 wks
or injection " 0.16 μc/wk for 3 wks.
μc in organ or tissue
1.0
0.1
0.01
0.001
0.0001
Probable limit of detection
Kidney
Liver
Whole body
Bone
0
2
4
6
8
10
12
14
t (weeks)
K+E SEMI-LOGARITHMIC 358-91
KEUFFEL & ESSER CO. MADE IN U.S.A.
5 CYCLES X 70 DIVISIONS