APR 28 1969

DML:LB:NB
(03-00046-13)

Department of the Army
Office of the Surgeon General
Washington, D. C. 20315

Attention: Col. James Andersen, MC
Preventive Medicine Division

Gentlemen:

Enclosed is Amendment No. 15 to License No. 03-00046-13.

Please note that the license provides for all uses specified in Groups I and II, Schedule A, Section 35.100, 10 CFR Part 35. All other isotopes and uses not included in Groups I and II have been specified separately. The license does not include the use of iodine 131 labeled human serum albumin for determination of cardiac output and iodine 131 and 125 labeled sodium iodipamide (cholegrafin) for determination of gallbladder and liver function. These uses are no longer considered routine uses. If the Hospital desires to perform these tests, a protocol as specified in the Medical Licensing Guide should be submitted.

Sincerely,

Nathan Bassin
Isotopes Branch
Division of Materials
Licensing

bcc: St. Br. Dist.
CO, Region I
DML

A/SD

OFFICE ▶	DML:LB					
SURNAME ▶	NBassin/lmf					
DATE ▶	4/24/69					

Form AEC-318 (Rev. 9-53) AECM 0240 U.S. GOVERNMENT PRINTING OFFICE : 1968 O—296-817

A Request for an Amendment is Submitted Pertaining to Use of C^{14}-Labeled Glucose in Tracer Amounts in Volunteer Human Experimental Research Subjects.

I. INTRODUCTION:

In the "Request for Approval for Human Use of Radioisotopes in Tracer Amounts in Volunteer Experimental Research Subjects" (copy inclosed), submitted 18 November 1966 by the U. S. Army Medical Research and Nutrition Laboratory, Denver, Colorado, for reconsideration and renewal of radioisotope license by the Atomic Energy Commission and the Office of The Surgeon General, detailed reference is made for use of C^{14}-labeled carbohydrates (page 19, inclosed copy of above "Request for Approval. . . .").

The general health physics for Carbon-14 was described on page 6 of the inclosed copy of the request.

With regard to the proposed usage of labeled carbohydrates, the following statement was made on page 19, paragraph 3, of the inclosed copy of the Request:

> "Studies on the interrelationship of various types of carbohydrates and other dietary components on serum triglycerides and cholesterol in the human have advanced to the state where tracer levels of common

"b. Request for use of Carbon-14 to label vitamin C and related compounds.

Therefore, because of demonstrated usefulness and necessity of using tracer techniques to study metabolic pathways, the proposal is being made that tracer amounts of Carbon-14, as glucose-6-C^{14}, glucuronolactone-6-C^{14}, glucuronic-6-C^{14} acid and ascorbic-1-C^{14} acid be administered by mouth to humans in further studies for the purpose of measuring the pool size and the rate of utilization of body ascorbic acid under varying conditions. The subjects to be used will be military personnel (volunteering for the specific study) or laboratoy personnel, both male and female, or Fitzsimons General Hospital personnel (as well as Fitzsimons General Hospital patients who volunteer). The possible hazards of the experiments will be explained in advance to all subjects. Although multiple experiments may be performed on individuals, in no case will the total body radiation dose from this experiment, other experiments, or from x-rays, exceed the maximum permissible limits for normals of 5 rem per year (lower tnlow age 25)."

II. SPECIFIC AMENDMENT REQUEST:

The following amendment of the inclosed Request is being sought:

That, in addition to what has been stated in the "Request for Approval for Human Use of Radioisotopes in Tracer Amounts in Volunteer Experimental Research Subjects", pertaining to C^{14}-

labeled carbohydrates, approval be granted for intravenous administration of a maximum of 50 microcuries of C^{14}-labeled glucose per adult for purpose of studying glucose metabolism in health and disease and under a variety of experimental conditions.

A sterile and pyrogen-free solution of C^{14}-labeled glucose will be injected intravenously in its pure form. All other safety standards will be followed as detailed in the inclosed 1968 request.

III. DOSAGE CONSIDERATIONS AND CALCULATIONS:

a. The maximum dose of 50 microcuries of C^{14}-labeled glucose to be administered per adult is well within the officially approved dosage (maximum permitted is 300 microcuries) for study of metabolic processes in man as noted in:

1. Proc. of the Second International Conference for Peaceful Uses of Atomic Energy. Geneva, Sept 1 - 13, 1958, Vol. 25.

2. U. S. Department of Commerce, National Bureau of Standards, Handbook 69, June 5, 1959.

b. Since 1954, C^{14}-labeled glucose has been used in human subjects to study glucose metabolism, and the following references are only 3 of a voluminous and well-known literature on this subject:

1. Baker, N., et al.: C^{14} studies in carbohydrate metabolism. I. The oxidation of glucose in normal human subjects. J. Biol. Chem. 211: 575, 1954.

2. Bolinger, R. E., et al.: Effect of prolonged fasting on the expired $C^{14}O_2$ from palmitate and glucose in obese subjects. Metabolism 15: 394, 1966.

3. Forbath, N. and Hetenyi, G.: Glucose dynamics in normal subjects and diabetic patients before and after a glucose load. Diabetes 15: 778, 1966.

b. According to Baker, et al (1954) and Bolinger, et al (1966), about 60 percent of C^{14}-labeled glucose, injected intravenously, was expired in the first 24 hours as $C^{14}O_2$. About 90 percent of the label will appear in $C^{14}O_2$ in expired air within 72 hours after injection. Thus, the majority of injected glucose is oxidized to CO_2 and H_2O, mostly via breakdown to active acetate and entry into the Krebs cycle. In that regard, following the intravenous administration in man of 100 μc of acetate-1-C^{14}, Gould, et al. (J. Lab. Clin. Med. 46: 373, 1955) reported that approximately 56 percent of radiocarbon was eliminated during the first 24 hours. On this basis, they assumed that less than 25 μc of C^{14} is "retained" in the "fat compartments" of the body following a single 100 μc dose. Inasmuch as the maximum permissible dose of C^{14} compounds retained in the body is estimated to be 250 μc (Handbook 52 of the National Bureau of Standards), Gould and his coworkers felt justified in administering, over a period of several months, a maximum of five 100 μc doses of C^{14}-acetate to human subjects without regard to their life expectancy. Radioautograph studies by Hellman and coworkers (J. Clin. Invest. 33: 142, 1954) of tissues obtained at postmortem

examination from patients who had received 200 uc of C^{14}-acetate also failed to disclose areas of concentration of the isotope.

c. The dose of radiation from 50 microcuries of C^{14}-glucose is calculated, based on above information in the literature and using the formulae described in:

1. Quimby, E. H. and Feitelberg, S.: Radioactive isotopes in medicine and biology. 2nd Edition, Lea & Febiger, Philadelphia, 1963, page 113.

If one assumes that all 50 microcuries of C^{14}-glucose are retained in the body indefinitely (which of course is not the case), then

$$d\beta = 51.2 \times C \times \bar{E}\beta \text{ rads (per day)}$$

where,

C = microcuries per gram body weight

= 50 uc/70,000 g for an average-size adult

$E\beta$ = average beta ray energy per disintigration in Mev

= 0.050 Mev. for C^{14}

thus,

$$d\beta = 51.2 \times \frac{50 \times 0.05}{70,000} = 1.83 \times 10^{-3} \text{ r/day}$$

(or 0.013 r/week)

Therefore, even if one assumes all 50 uc of C^{14}-glucose are retained in the body, the radiation received from them will be within the permissible dose of 0.1 rem per week, as noted in:

Report of Committee II on Permissible Dose Internal Radiation. Pergamon Press, New York, 1959, page xxi.

It must be emphasized, however, that the majority of the injected dose is excreted as $C^{14}O_2$ in expired air, as referenced earlier. Thus, each subject will receive a considerably less radiation dose from the 50 μc of C^{14}-glucose than 1.83×10^{-3} r/day.

Assuming that 90 percent (45 μc) of C^{14} is excreted from the body and 10 percent (5 μc) retained indefinitely, each subject will receive a total life time dose of 2.35×10^{-3} rad from the 45 μc, and 1.83×10^{-4} r/day from the 5 μc retained in the body.

IV. USE OF GLUCOSE C^{14}:

Intravenous administration of C^{14}-labeled glucose will be used to study:

a. Intermixing glucose mass

b. Apparent distribution space of glucose, and

c. Rates of appearance (mostly hepatic output) and disappearance (tissue uptake) of glucose

in human subjects exposed to altitude and various dietary and drug regimens, and in patients with metabolic disorders.

Each volunteer will sign a Voluntary Consent Statement (see attached copy at the end).