EPA 680/0-74-002
July 1974

PULMONARY CARCINOGENIC EFFECTS OF PLUTONIUM-238 PARTICLES IMPLANTED IN THE LUNGS OF HAMSTERS

by

A. A. Mullen
Monitoring Systems Research and Development Laboratory
National Environmental Research Center
Las Vegas, Nevada

Program Element 1FA082

NATIONAL ENVIRONMENTAL RESEARCH CENTER
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
LAS VEGAS, NEVADA 89114

PULMONARY CARCINOGENIC EFFECTS OF PLUTONIUM-238 PARTICLES IMPLANTED IN THE LUNGS OF HAMSTERS

July 1974

ROAP: 21RAL
Plumonary Carcinogenic Effects of Radioactive Particles

Task 003: INTERIM REPORT

Periodic serial sacrifice, histological examination of selected tissues, dosimetry

I. CONCLUSIONS

Inference of conclusions for this study is premature because of the limited number of observations to date.

Ten months after implantation of single microspheres containing plutonium-238 in the lungs of 900 Syrian hamsters, 400 animals have been necropsied and the remaining 500 are still alive. Aproximately 11,000 slides representing 268 of the animals have been prepared for histopathological examination. Half of these have been reserved as duplicates for later study, if required. To date, the lungs of 31 animals have been examined for histopathology by the pathologist.

No gross lung lesions were observed in any animals necropsied during the first eight months. However, at nine months, lung lesions were observed in animals from all experimental groups (I-IV), but not in the controls (V-VI).

II. RECOMMENDATION

Completion of the project with additional assistance for histological slide preparation is recommended.

III. INTRODUCTION

This ROAP was developed to meet Agency needs in evaluating the environmental impact of nuclear power programs, principally in the areas of fast breeder reactors for the production of plutonium fuel, in nuclear fuel reprocessing plants, in nuclear fuel fabrication facilities, and in localities where plutonium has been released to the environment during past activities (e.g., Nevada Test Site and Rocky Flats). Plutonium is discharged in liquid and gaseous wastes from fuel reprocessing and has been measured in off-site air samples (Need 02ADK, 15 Oct 72). Of concern are the inhalation of particles from the discharge plume as well as inhalation of resuspended particles previously deposited. Present standards for plutonium are based on the assumption that inhaled plutonium is uniformly distributed throughout the

lung; however, it is well-known that inhaled particles will not be uniformly distributed, and that the resulting localized areas of intense radiation may present a greater hazard. This study will aid in determining whether current standards are adequate for this type of exposure and to determine a realistic definition of the non-uniformity factor for alpha radiation from particles deposited in the lung.

IV. OBJECTIVES AND APPROACH

The objectives of this study were as follows:

1. Determine in animals the carcinogenic potential of radioactive particles deposited in the lung, with special attention to dose/response, latent period for cancer induction, and sequential precancerous changes.

2. Evaluate the role of non-uniform distribution of dose on the carcinogenic response.

3. After the introduction of plutonium, determine the RBE for plutonium alpha as compared to fission product inventory betas for the production of primary lung tumors in animals.

The animal selected for this initial study was the Syrian hamster, an animal which is relatively free from the chronic respiratory diseases of other rodents and is reported to have a dose-response similar to man with respect to cancer types induced following inhalation of known carcinogens.

A simple, relatively atraumatic technique for implanting a single radioactive particle in the lung of rodents was developed for this project by Stanley and Lloyd (1972). A small polyethylene cannula introduced into the trachea of an anesthetized rodent provided the passageway for the insertion into the deep lung of a fine catheter containing a radioactive particle.

The particles used in this study were silicate glass microspheres produced by the Monsanto Research Corporation, Mound Laboratory, Miamisburg, Ohio. The microspheres (100 $\pm$ 20 um, CMD) contain specified amounts of plutonium oxide along with 1 nCi of a gamma emitting tracer (^{22}Na). The technique used to manufacture the microspheres is fully described in the paper by Jones *et al.* (1964).

Six groups of 150 Syrian hamsters (*Mesocricetus auratus*) each were used for this study. Animal groupings and measured particle activities are described in the following table.

Immediately following sacrifice or death, each animal is necropsied and a detailed description of all gross observations is recorded. Although several other tissues are routinely collected, the lung is the tissue of principal interest. The lobe containing the particle, as ascertained by visual identification of necrotic lesions or by gamma counting, is immediately fixed in formalin.

Each lung lobe containing a particle is dehydrated and imbedded in paraffin so that the convex surface will be tangential to the microtome knife when sectioning begins. Each lobe is completely sectioned at five micrometers and at each 100 micrometer interval, two adjacent pairs of sections are mounted on two slides. One of these is stained with Hematoxylin and Eosin for examination by the contract pathologist and the other is reserved for later study, if needed.

V. PRELIMINARY RESULTS

Nine months after particle implantation, 500 of the original 900 animals are still alive. Four hundred animals have been necropsied and the lungs of 268 of these have been sent to the pathologist (or a total of approximately 5,500 slides). Results from 31 of these animals have been returned. In general, the gross pathology may be summarized as follows: No gross lesions were observed in the lungs of any animals examined during the first eight months after particle implantation. At nine months necrotic areas less than 1 mm in diameter were observed in lungs from animals in the first four experimental groups. No gross differences were observed between dose groups. No lesions were observed in the control groups. In a previous study, using implanted beta emitting particles, necrotic areas from 1 mm to 3 mm in diameter were seen two weeks after particle implantation.

Histologically, of the 31 animals examined, all animals except nine exhibited focal pleuritis, a characteristic reaction to the radioactive implant. This lesion was characteristically the same in each animal and varied significantly only in degree. The morphologic appearance consisted of a cavity (most likely the exact site of particle placement) approximately 100 micrometers in diameter surrounded by an area of inflammatory reaction. This cavity was surrounded by chronic reactive cells, most of which were plasma cells and lymphocytes, and mild connective tissue proliferation. In cases where the lesion closely approximated the pleural surface, excess fibrous tissue extending from the pleural membrane was found. Free hemosiderin and phagocytized hemosiderin particles in large macrophages were seen in most cases. Mild proliferation of alveolar epithelium adjacent to the lesion was frequently observed but no adenomatoid responses like those in the previous "hot" particle study, using beta emitters, was observed.

VI. DISCUSSION

No firm conclusions can be drawn at this time because of the limited number of observations.

TABLE SHOWING ANIMAL GROUPS AND PHYSICAL PARAMETERS OF IMPLANTED PARTICLES

Group	Treatment	Radioactivity	
		^{22}Na Tracer (nCi)	^{238}Pu Alpha Radiation at Particle Surface (nCi)
I	Single radioactive Particle	1	47 ± 7
II	Single radioactive Particle	1	90 ± 13
III	Single radioactive Particle	1	348 ± 26
IV	Single radioactive Particle	1	649 ± 54
V	Inert particle with gamma tracer	1	---
VI	Environmental control	0	---

VII. REFERENCES

Cember, H., J. A. Watson, and A. S. Spritzer. (1955) "Bronchogenic Radioactive Cerium Fluoride." A. M. A. Archives of Industrial Health 19, 14-23.

Chevalier, H. H., et al. (1971) "Sur Formalen Genese der Pseudoadenomatose der Lunge bein Syrschen Goldhamster." Z. Versuchstierk 13, 38-50.

Feron, V. (1972) "Respiratory Tumors in Hamsters After Intratracheal Instillation of Benzopyrene Alone and With Furfural." Canc. Res. 32, 28-36.

Gross, P., et al. (1965) "Experimental Lung Cancer in Hamsters." Arch. Environ. Health 11, 59.

Homburger, F. (1969) "Chemical Carcinogenesis in the Golden Syrian Hamster, A Review." Cancer 23, 313.

Jones, L. V., et al. (1964) "Plutonium-Bearing Glass for Nuclear Applications." Am. Ceramic Society Bull. 43, 131-135.

Kotrappa, P. (1974) "Hazards of Airborne Particulates." Scavenger 4, 3-6. (Published in Bombay, India).

Mikhail, S. Z. (1970) Tissue Beta Radiation Doses From Particulate Fission Product Sources, Environmental Science Associates, ESA-TR-70-01.

Spencer, L. V. (1960) National Bureau of Standards Monograph One.

Stanley, R. E. and S. R. Lloyd. (1972) "A Technic for Implanting a Radioactive Particle in a Rodent Lung." Lab. Animal Sci., 22, 424-427.

Ulverg, J. C. and D. B. Kochendorfer. (1966) Models for Estimating Beta Dose to Tissue From Particle Debris in Aerospace Nuclear Applications, U.S.N.R.D.L.-TR-1107.