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BERKELEY: DONNER LABORATORY AND DONNER PAVILION

March 10, 1975

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To the PAC Committee

Gentlemen and scholars,

Pursuant to a conversation with Dr. Budinger (which he will agree was acrimonious) I am submitting the first, and I hope last, revision of my 1976-77 189 form. I have tried, within the bounds of what I judge reasonable and useful, to meet the comments (suggestions for improvement? requests for information? demands for program changes? it was not clear what was wanted) relayed to me.

1. All of the material has been reorganized into a single package.
2. p. 2, I try to meet the request for more specifics on the inadequacy of biological parameters for the actinides.

3. p. 4, I address the question -- why use Pu citrate? The present monkey studies have two specific purposes, which are now defined in the text. First, to duplicate the citrate injection studies in the large experiment with dogs at Utah and in the hospital patients just after WWII. These two sets of studies provide most of the information from which the current ICRP and NCRP Pu standards are derived. If monkeys are to be useful in large-scale studies of Pu metabolism and toxicity of "real-world" compounds, the metabolic similarities or differences between monkeys, dogs, and people must be well defined for the simplest case. Second, I view my role as a single practitioner (rather than a member of a large program effort) as that of a pathfinder and instigator rather than a gatherer of mountains of data. Elucidation of metabolic pathways and mechanisms can best be done by studying the fate of single Pu atoms -- which they most often are after crossing cell barriers. It has been shown in the dog (BALLOU et al., 1972) and rat (SCOTT et al., 1944) that the distribution of the absorbed body burden of Pu is the same for injected Pu citrate as it is for soluble Pu compounds fed or inhaled or instilled intratracheally. The intravenous route permits study of Pu transport and complexing with serum proteins, and the intramuscular route permits study of Pu introduced directly into extracellular fluid (as it is after absorption from GI or lung). Furthermore, absorption from a wound site has not been studied in large animals (except for insoluble PuO₂), and it appears from our initial results with both Pu and Am that such absorption (even of Pu citrate) is much more rapid in monkeys than in small animals like rats and mice. The implications for management of industrial workers with wounds contaminated by soluble Pu compounds is obvious.

Plutonium chemistry is about as complicated as one can imagine, and I am no Pu chemist. The LBL Chemistry Dept. has very nearly gone out of the Pu chemistry business. Isotopes and compounds must be begged or bought from others. The time lag between preparation of a Pu compound and its use in an animal study is often great (of the order of months), and I need to have a known, stable, and reproducible material. Other investigators expend much effort in the preparation of Pu sources, and most of the time the products of those efforts are poorly characterized. Thus, the use of Pu citrate is a compromise between stability, ease of handling and "real life" compounds.

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4. Some of the above argument applies also to the preliminary studies of in vivo measurement of ²⁴¹Am. These studies are designed to test techniques at first, and should be as clean-cut as possible. We already have a base of data from similarly-injected monkeys with which to compare the new results.

5. p. 13, The question is addressed -- why do Pu studies in rabbits? First, the studies involving Pu behavior in hypoxic and plethoric animals seems, on the advice of colleagues, to be best carried out in rabbits. Some preliminary investigations by others indicate a normally low Pu uptake in skeleton in adult rabbits, thus any changes should be more readily apparent in rabbits than in rats which normally have a high Pu uptake in skeleton. The Interagency Working Group on Health and Environmental Effects of Energy Use report calls repeatedly for cheap quick-fix test systems. Some of the data obtained in the studies on rabbits with manipulated erythropoietic systems (that from the normal controls) can be used as a starting point for some other simple studies. Why not make a few more measurements to provide data that will help others decide about what species to use in a quick test system. In addition, I have been interested for a long time in the comparative metabolism of these exotic minerals in different species. The available rabbit data are almost useless, but there are indications (KOSHURNIKOVA, 1971) that rabbits may be more sensitive to chronic Pu action (bone tumor formation) than small rodents or dogs.

6. p. 9, para 9. Dr. Schmidt and I DO intend in vivo studies of actinides and lanthanides introduced into the lungs of both dogs and monkeys. Inhalation experiments are discussed in general below. It is enough to say here that of course inhalation is the most likely route of actinide acquisition either industrially or from the environment. That has been recognized since the very earliest experiments of Hamilton et al. at Berkeley and Abrams et al. at Argonne. There are those who quarrel vigorously with intratracheal intubation or insufflation as proper means of exposing the lungs, because the deposition of inhaled airborne particles is not reproduced. However, for reasons given below LBL is not now and probably will not ever be equipped to perform real inhalation exposures. We plan, when the kinks have been worked out of the in vivo measuring systems (animal positioning and repeated use of long-acting tranquilizers are serious problems) to examine the absorption of intubated materials from the lungs of monkeys. Meanwhile we will also try to arrange for one of the established inhalation laboratories (Battelle Northwest or Lovelace Inhalation Toxicology Research Institute) to expose some animals for us. The earliest phases of absorption and clearance would be lost, however. At the moment neither laboratory is interested in performing service inhalation exposures for others, but perhaps that could change later on.

7. Inhalation studies; general comments. The earliest fission product and actinide inhalation studies were simple. Rats were placed in a reactor stack to breathe the effluent or were made to breathe ether sprays or smokes containing Pu compounds through glass tubes sealed to their noses (SCOTT et al., 1949). Rodents and larger animals were also placed in dust chambers in which they breathed compounds of U and Th of low specific activity (VOEGTLIN and HODGE, 1949-1953). Particle sizes were not measured. The fur was contaminated. Lung burdens were uncontrolled and variable.

Deposition of particles in the deep lung depends on particle size.

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To be worthy of note modern studies must provide for particle sizes that are well characterized and small enough to be deposited. Exposures for toxicological studies must be controlled such that lung burdens are known and reproducible.

There are several requirements for achieving those conditions. Skilled chemists and particle physicists are needed to prepare particles and expose animals. Expensive specialized equipment is needed with which to make and characterize particles and expose animals.

The AEC spent several million dollars, and ERDA will spend more to install and maintain large groups of people and high quality inhalation facilities at Battelle and ITRI in Albuquerque. There is a smaller group doing low activity and pilot-study projects at U. Rochester. Both major inhalation facilities are located on large tracts of flat land in isolated spots with a high degree of security (because of the large amounts of radioactivity on the premises). When the ITRI group (originally called the Fission Product Inhalation Laboratory) was being planned, most of the world's small supply of particle and inhalation experts were located at the U. Rochester. Instead of enlarging the Rochester Project, people were moved across the country and a new facility was constructed. It is my understanding that several Labs (perhaps LBL was one) bid for or showed interest in having the inhalation facility on their premises (including U. Rochester), but it was decided to locate in an isolated spot on free land rather than on a University campus in a crowded urban setting where land was expensive and expansion opportunities limited.

At both Battelle and ITRI it has been necessary to develop techniques and train personnel on the job. Those efforts have taken a long time, and there are still no extra trained people who can be spared to go elsewhere.

The above remarks serve as an introduction to why I have not proposed genuine inhalation studies at LBL. Although I have been interested in and have followed and tried to understand the results of inhalation experiments conducted elsewhere, I do not have the technical competence myself to initiate such studies on my own. To do them properly, with known, controlled, and reproducible experimental conditions, takes a small army of specialists ranging from particle chemists and physicists to specially trained animal caretakers. The costs of equipment and space are enormous, even for a modest effort. The amounts of radioactivity needed to feed the inefficient aerosol generators are in the multicurie range which means special enclosures, shielding and monitors. Special facilities are needed to house the "hot" animals shortly after exposure and to dispose of "hot" wastes.

For all of those reasons I do not foresee ERDA establishing and supporting inhalation studies of actinides at LBL. We have no trained people; equipment or facilities; Construction costs are high; The laboratories are insecure insofar as they are crowded and close to other non-radioactive projects, so that the large amounts of radioactivity might pose hazards to students, visitors, and other workers in the buildings. It is my belief that if we were to propose any such effort, we would be considered foolish -- either presumptuous or ill informed.

Rather than make rash and foolish promises that probably cannot be kept, it seemed most honest to set forth what might reasonably be accomplished by two or three people in 5 years (assuming no major changes in levels of animal space, technical assistance, and equipment). Management of each monkey and the processing of the alpha activity from each takes a great deal of time, and only a few animals can be studied each year. As it is proposed now the actinide program provides for a continuous output

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of small amounts of information that is useable immediately. That seems to be the goal of ERDA-DBER at the present time. For example, the metabolic model used to calculate biological effects in the Liquid Metal Fast Breeder Reactor (LMFBR) environmental impact statement assumes (in the absence of any real data) very conservative values for Pu and Am content and residence times in gonads. The result is that the model predicts genetic defects as the limiting factor for breeder reactor effluents -- not bone or lung tumors. Further, the ultraconservative values chosen for GI absorption and soil-to-plant transfer of actinides lead to the conclusion that the main hazards from those elements will be by way of diet rather than inhalation.

I have spent much of my working and leisure time in the last 4 years reviewing the accumulated information on the metabolism and toxicity of the actinides and their chemical analogues (DURBIN, 1972, 1973, 1974, materials prepared for hearings on siting Beaver Valley reactors, 1973). I have tried to identify information gaps (see preceding paragraph) and design my program to meet some of them given the restrictions of program size and location. For example, much better values for gonadal content of actinides should be forthcoming in the next year or two, which will hopefully lead to more rational solutions of the environmental models.

Sincerely,

Patricia W. Durbin
Patricia W. Durbin

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