PHARMACOLOGY AND TOXICOLOGY OF URANIUM COMPOUNDS

With a Section on the Pharmacology and Toxicology of Fluorine and Hydrogen Fluoride

Vol. I

Edited by

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and

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FOREWORD

The United States program of development of atomic energy has been described by Major General L. R. Groves, who, as Commanding General of the War Department's Manhattan Project, directed the program from mid-1942 until December 31, 1946, as "a generation of scientific development compressed into three years." The tremendous scope of the Manhattan Project Technical Section of the National Nuclear Energy Series, which has been in preparation since 1944, is a tribute to the unprecedented accomplishments of science, industry, government, labor, and the Army and Navy working together as a team. These volumes can be a firm foundation for the United States atomic energy program which, in the words of the Atomic Energy Act of 1946, is " . . . directed toward improving the public welfare, increasing the standard of living, strengthening free competition in private enterprise, and promoting world peace."

David E. Lilienthal, Chairman
U. S. Atomic Energy Commission

ACKNOWLEDGMENT

The Manhattan Project Technical Section of the National Nuclear Energy Series embodies results of work done in the nation's wartime atomic energy program by numerous contractors, including Columbia University. The arrangements for publication of the series volumes were effected by Columbia University, under a contract with the United States Atomic Energy Commission. The Commission, for itself and for the other contractors who contributed to this series, wishes to record here its appreciation of this service of Columbia University in support of the national nuclear energy program.

PREFACE

This volume is one of a series which has been prepared as a record of the research work done under the Manhattan Project and the Atomic Energy Commission. The name Manhattan Project was assigned by the Corps of Engineers, War Department, to the far-flung scientific and engineering activities which had as their objective the utilization of atomic energy for military purposes. In the attainment of this objective, there were many developments in scientific and technical fields which are of general interest. The National Nuclear Energy Series (Manhattan Project Technical Section) is a record of these scientific and technical contributions, as well as of the developments in these fields which are being sponsored by the Atomic Energy Commission.

The declassified portion of the National Nuclear Energy Series, when completed, is expected to consist of some 60 volumes. These will be grouped into eight divisions, as follows:

Division I — Electromagnetic Separation Project
Division II — Gaseous Diffusion Project
Division III — Special Separations Project
Division IV — Plutonium Project
Division V — Los Alamos Project
Division VI — University of Rochester Project
Division VII — Materials Procurement Project
Division VIII — Manhattan Project

Soon after the close of the war the Manhattan Project was able to give its attention to the preparation of a complete record of the research work accomplished under Project contracts. Writing programs were authorized at all laboratories, with the object of obtaining complete coverage of Project results. Each major installation was requested to designate one or more representatives to make up a committee, which was first called the Manhattan Project Editorial Advisory Board, and later, after the sponsorship of the Series was assumed by the Atomic Energy Commission, the Project Editorial Advisory Board. This group made plans to coordinate the writing programs at all the installations, and acted as an advisory group in all matters affecting the Project-wide writing program. Its last meeting was held on Feb. 9, 1948, when it recommended the publisher for the Series.

The names of the Board members and of the installations which they represented are given below.

Atomic Energy Commission Public and Technical Information Service	Alberto F. Thompson
Technical Information Branch, Oak Ridge Extension	Brewer F. Boardman
Office of New York Operations	Charles Slesser, J. H. Hayner, W. M. Hearon *
Brookhaven National Laboratory	Richard W. Dodson
Carbide & Carbon Chemicals Corporation (K-25)	R. B. Korsmeyer, W. L. Harwell, D. E. Hull, Ezra Staple
Carbide & Carbon Chemicals Corporation (Y-12) †	Russell Baldock
Clinton Laboratories ‡	J. R. Coe
General Electric Company, Hanford	T. W. Hauff
General Electric Company, Knolls Atomic Power Laboratory	John P. Howe
Kellex Corporation	John F. Hogerton, Jerome Simson, M. Benedict
Los Alamos	R. R. Davis, David Hawkins
National Bureau of Standards	C. J. Rodden
Plutonium Project Argonne National Laboratory	R. S. Mulliken, H. D. Young
Iowa State College	F. H. Spedding
Medical Group	R. E. Zirkle
SAM Laboratories §	G. M. Murphy
Stone & Webster Engineering Corporation	B. W. Whitehurst
University of California	R. K. Wakerling, A. Guthrie
University of Rochester	D. R. Charles, M. J. Wantman

* Represented Madison Square Area of the Manhattan District.

† The Y-12 plant at Oak Ridge was operated by Tennessee Eastman Corporation until May 4, 1947, at which time operations were taken over by Carbide & Carbon Chemicals Corporation.

‡ Clinton Laboratories was the former name of the Oak Ridge National Laboratory.

§ SAM (Substitute Alloy Materials) was the code name for the laboratories operated by Columbia University in New York under the direction of Dr. H. C. Urey, where much of the experimental work on isotope separation was done. On Feb. 1, 1945, the administration of these laboratories became the responsibility of Carbide & Carbon Chemicals Corporation. Research in progress there was transferred to the K-25 plant at Oak Ridge in June, 1946, and the New York laboratories were then closed.

Many difficulties were encountered in preparing a unified account of Atomic Energy Project work. For example, the Project Editorial Advisory Board was the first committee ever organized with representatives from every major installation of the Atomic Energy Project. Compartmentation for security was so rigorous during the war that it had been considered necessary to allow a certain amount of duplication of effort rather than to permit unrestricted circulation of research information between certain installations. As a result, the writing programs of different installations inevitably overlap markedly in many scientific fields. The Editorial Advisory Board has exerted itself to reduce duplication in so far as possible and to eliminate discrepancies in factual data included in the volumes of the NNES. In particular, unified Project-wide volumes have been prepared on Uranium Chemistry and on the Analysis of Project Materials. Nevertheless, the reader will find many instances of differences in results or conclusions on similar subject matter prepared by different authors. This has not seemed wholly undesirable for several reasons. First of all, such divergencies are not unnatural and stimulate investigation. Second, promptness of publication has seemed more important than the removal of all discrepancies. Finally, many Project scientists completed their contributions some time ago and have become engrossed in other activities so that their time has not been available for a detailed review of their work in relation to similar work done at other installations.

The completion of the various individual volumes of the Series has also been beset with difficulties. Many of the key authors and editors have had important responsibilities in planning the future of atomic energy research. Under these circumstances, the completion of this technical series has been delayed longer than its editors wished. The volumes are being released in their present form in the interest of presenting the material as promptly as possible to those who can make use of it.

The Editorial Advisory Board

UNIVERSITY OF ROCHESTER PROJECT FOREWORD

The University of Rochester Manhattan Project had its inception on April 5, 1943, with the appointment of Dr. Stafford L. Warren,* Professor of Radiology and Chairman of the Department of Radiology at the University of Rochester School of Medicine and Dentistry, as Consultant to the Manhattan Engineer District (later as Chief of the Medical Section). Under his guidance and direction the local project was established and its operational policies formulated. On November 2, 1943, Dr. Warren was commissioned colonel in the Army Medical Corps, and the subsequent responsibility for the Project was assumed by the present Director on November 13, 1943.

In many respects the atmosphere of the work was in marked contrast to the academic freedom of a university environment. The research was frequently of applied rather than of fundamental nature, though the latter was by no means lacking. In addition to physical and spiritual isolation from our accustomed confreres, we found ourselves surrounded by a multitude of security, Army, governmental, and war-manpower regulations, but the majority of the personnel made the necessary mental adjustments without undue hardship and with commendable reasonableness and good grace. Not infrequently we found these apparent handicaps working to our mutual advantage.

The organization of the Project was likewise unusual and, to a certain extent, experimental. To accomplish the task in the specified time and to utilize effectively experienced personnel made scarce by previous demands of the war, individuals were placed in positions where their capabilities could produce maximum benefit to the Project as a whole. To this end, ten autonomous but mutually interdependent divisions were established,† whose coordination was effected through the Director's Office so that priorities on material, manpower, and concentration of effort could be channeled in the proper direction with the shifting phases of the various problems. Experiments were discussed and organized on a cooperative basis through a system of

*Now Dean of the Medical School, University of California at Los Angeles.
†See Appendix for organization chart.

"planning sessions" in such a manner that the expert opinion of participating members of specialized divisions could make major contributions to the structure of many of the experiments. This procedure also enabled the divisions of Pathology, Hematology, and Statistics to coordinate their activities with other divisions so that they could analyze properly the mass of experimental data which must, of necessity, pass through their respective laboratories.

It would be misleading to aver that this system of research procedure presented here was without fault and not beset by difficulties. It is not an easy matter for an investigator to reconcile his ideas and personal ambitions with those of a group for a common objective, especially when frequently his entire training and previous progress have been based upon individual achievement. Particularly is this true when he has not had the privilege of participating in the selection of his associates. The system, however, worked surprisingly well under somewhat unfavorable circumstances and is worthy of further exploration under peacetime conditions.

It is impossible to pay proper tribute to the many individuals—scientific, technical, and nontechnical—who participated in this endeavor. Neither can one, by reading the following pages, appreciate fully the mental and physical labor that went into the enterprise. Approximately two million man-hours were required to produce the research from which these volumes are derived.

The Administrative Office wishes to express its appreciation to the Project personnel for their confidence and loyalty; to the University as a whole for its support and cooperation; to the many Rochester industries and businesses for the materials supplied and the services rendered; to the Area Engineer's Office for its aid in facilitating the conduct of the program; to Dr. Ellice McDonald, Director of The Biochemical Research Foundation of the Franklin Institute, at Newark, Del., for his cooperation in coordinating the research under his contract with that of Rochester.

Andrew H. Dowdy, M.D.
Professor of Radiology and
Director of the University of
Rochester Project

April, 1949
Rochester, N. Y.

VOLUME EDITOR'S PREFACE

This volume reports the comprehensive experimental studies carried out by the Division of Pharmacology of the Manhattan Department of the University of Rochester under a contract with the Manhattan District.

The material is divided into two parts. Part I deals with the Pharmacology and Toxicology of Uranium Compounds, a subject that received the major attention. The work on the exposure of animals for periods of one year to the inhalation of air containing certain uranium compounds is nearing completion and will be published at a later date.

Part II is concerned with some observations on the toxic action of fluorine and hydrogen fluoride.

The preparation of this volume was authorized early in January 1946 with the request that the manuscripts be completed by July 1, 1946. The fact that the manuscript was completed on the specified date is a credit to all those who took part in this work. Many of the wartime personnel had already left the project. Hence, the writing of the reports had to be done by the remaining personnel. These handicaps account for some imperfections in form of presentation, but do not detract from the value of the scientific contribution.

It is fair to say that the study of the toxicology of uranium compounds herein described represents the most comprehensive experimental investigation of an industrial poison ever carried out by any group of scientific workers in such a short time.

From the standpoint of industrial toxicology, the present investigation has emphasized the great need of new methods for the study of the relationship between particle size of toxic atmospheric dust and the rate and degree of absorption of the toxic material from the respiratory tract. A promising beginning has been made in this field.

The observations on the mechanism of action of uranium on the kidney may be regarded as fundamental contributions (1) to renal pathology and (2) to the understanding of acquired tolerance to a toxic chemical agent.

Carl Voegtlin

April, 1949
Rochester, N.Y.

The Manhattan Project Technical Section of the National Nuclear Energy Series is intended to be a comprehensive account of the scientific and technical achievements of the United States program for the development of atomic energy. It is not intended to be a detailed documentary record of the making of any inventions that happen to be mentioned in it. Therefore, the dates used in the Series should be regarded as a general temporal frame of reference, rather than as establishing dates of conception of inventions, of their reduction to practice, or of occasions of first use. While a reasonable effort has been made to assign credit fairly in the NNES volumes, this may, in many cases, be given to a group identified by the name of its leader rather than to an individual who was an actual inventor.

HISTORICAL FOREWORD

By Harold C. Hodge

The first days of the Medical Section of the Manhattan Project brought out the immediate need of a toxicological guide for the safety of those handling uranium in laboratories and in plants. How much uranium could be taken into the lungs daily without serious sequelae? What if dirty hands put milligrams of a uranium salt into an incautious mouth at lunch hour? Would there be trouble, and where? Would drops of a uranium solution splashed onto bare hands and arms cause poisoning by skin absorption? Of the numerous uranium compounds, which were more dangerous and exactly how poisonous was each? The questions were many and the answers few.

There was no time to wait for months, or even for weeks, while the accepted laboratory tests established the toxicological facts. Production had to proceed with no delays. Some working rule had to be adopted pro tem. The toxic heavy metal, lead, had been carefully studied both in animals which had been experimentally exposed and in workers who had been incidentally exposed to its compounds. A maximum daily exposure to 1,500 μg of lead had been proposed and widely accepted as a workable compromise between safety and engineering practice. The average man doing physical labor breathes about 10 cu m of air daily; therefore the maximum allowable concentration of lead permitted in factory air was 150 μg/cu m. The ventilation engineers were able to keep air contamination below this amount, and few persons are made ill by such a minute intake.

No such voluminous literature was available on the toxicity of uranium. A number of papers about the turn of the century had reported unsuccessful attempts to treat human diabetes by uranium salts; unfortunately, the studies of the patients' responses were not carefully done. A specific injury to kidney had been repeatedly and minutely described in various animal experiments. Since milligram doses produced detectable kidney damage in rabbits and dogs, uranium compounds seemed fraught with danger to industrial workers who must

handle pounds. Uranium is radioactive; this hazard was also considered but seemed less important for acute exposures than the chemical toxicity. In factory operations the inhalation hazard is considered the most insidious and the most important. No data at all were available on the inhalation toxicity of uranium compounds.

It was imperative that some figure be selected as a tentative maximum allowable concentration for uranium in factory air. The Medical Section selected (wisely as will be seen) the same amount, namely, 150 μg/cu m, which had proved feasible in the case of lead. There was no thought that lead and uranium were alike in their toxic effects or in the way they were handled by the body. The air concentration chosen could be achieved in the lead industry. It should be possible to achieve it in the uranium industry. As far as injury was concerned, a thorough program of health examinations and checkups was started to detect evidences of dangerous exposures.

About this time the first studies in uranium toxicology were initiated.

1., INHALATION HAZARD

It is generally conceded that a major industrial hazard in the handling of inorganic chemicals is the inhalation hazard. The processes of manufacturing are usually designed to obviate high-grade exposures via either the skin or gastrointestinal canal. The dust hazard, however, is serious. In the first place, it is frequently insidious, i.e., the exposed individual takes in a surprisingly large amount without being aware of a high-grade exposure; in the second place, absorption of very soluble materials through the respiratory tract has a unique rapidity which may even approach that of intravenous injection. Consequently, when the problem of determining the toxicities of the various uranium and fluorine compounds was presented in May 1943, the dust hazard was given the highest priority, and the major program was built around the study of animals exposed to atmospheres containing controlled concentrations of the toxic materials.

2. TOXICOLOGY PROGRAM

2.1 Basic Problems. With a working basis established (150 μg of uranium element per cubic meter), the industrial aspects of the project could go forward while biological studies characterized uranium poisoning and determined the relative toxicities of the various compounds. Four basic problems were outlined:

(a) Safety Standards. Development of safety standards for the control of health hazards due to contamination of factory air with uranium, fluorine, and other toxic materials requires:

1. Acute and chronic exposure of various animal species to air containing different concentrations of the toxic materials in order to correlate concentration and toxicity.

2. Construction of exposure chambers and engineering control of the concentration of noxious agents in the chamber air.

3. Elaboration of suitable analytical methods for the quantitative estimation of the various toxic materials, use of such methods in experiments on animals and in the quantitative estimation of toxic material in factory air and in urine samples of workers.

4. Ingestion experiments on animals to determine what part gastro-intestinal absorption may play in the toxicity following exposure of animals to contaminated air; intratracheal administration to determine the toxicity by applying the materials directly to the lower respiratory tract.

5. Special studies to determine the local and systemic toxic effects following the application of toxic materials to the skin and eyes of animals.

6. Experiments on the relation between rate of excretion and rate of storage of uranium in the tissues of the body, using the fluorophotometric method, such data to serve as a basis for the interpretation of results of analyses of spot samples of workers' urine.

(b) Protective Devices. Testing of masks and respirators for the emergency use of plant personnel.

(c) Approximate Toxicity Determinations. Tests on new special materials of unknown toxicity (for the guidance of plant personnel).

(d) Provision of Methods for the Recognition and Control of Poisoning. Mechanism Studies. Three principal topics were as follows: kidney function as influenced by uranium compounds; search for a non-toxic complex that will promote urinary excretion and prevent storage of uranium in the body; determination of the degree of acquired tolerance following repeated small doses of uranium.

Field Work. To provide techniques and personnel for collaborative tests assisting plant medical supervisors.

2.2 Preparation. The aim of all this work was to secure information that would eliminate, in so far as possible, hazards to the health of workers handling the toxic materials in plants.

Initially, such studies were to be relatively short (30 days) exposures to find the acute poisonous effects and to determine, if possible, dust concentrations that would not produce toxic effects. On the basis of such information chronic (1 year or longer) exposures were to be undertaken to determine (1) the effects of chronic poisoning, (2) the amounts that could be tolerated by inhalation for a long period with no evidence of damage, (3) the amounts in the atmosphere that would pro-

duce some evidences of toxic effect in some animals, i.e., the border zone between "safe" concentrations and toxic concentrations.

Inhalation toxicity studies required intricate machines and apparatus for the production, measurement, and control of dust concentrations. Following visits to the industrial hygiene laboratories of the Dow Chemical Company of Midland, Mich.; the Kettering Laboratories of the University of Cincinnati, Cincinnati, Ohio; the Bureau of Mines in Pittsburgh, Pa.; and the National Institute of Health in Bethesda, Md.,* plans were made and materials were ordered for the construction of the first exposure chamber. A search for technical personnel began. Problems of priorities and lack of materials for construction appeared.

2.3 Relation of Inhalation to Oral Toxicity. Under the conditions selected, it was impossible to distinguish a "pure" lung exposure. Most of the animals were put into exposure chambers unprotected so that there was a possibility of percutaneous exposures and a more important probable exposure, the oral one. The animals licked their fur more or less and ingested a certain amount of toxic material in this way. Furthermore, any particulate material that is taken into the lung may be deposited in those parts of the respiratory tract lined by ciliated epithelium. The cilia have the function of bearing up through the trachea any particulate material that falls thereon. Thus a sizeable fraction of that material deposited in the lung may ultimately arrive in the gastrointestinal tract. This tract also may be the route by which a part of other particulate material caught in the upper respiratory and nasal passages is removed. Of course, the solubility of the particulate material influences this picture to a marked degree. Highly soluble substances would probably be absorbed through the mucose of the upper respiratory tract and the epithelium of the lung. It is apparent that some knowledge of the oral toxicity of the various substances is necessary for the interpretation of the lung-exposure data.

Preliminary information on oral toxicity can be acquired very rapidly by using colonies of rats. Such a program was promptly set up, and by the end of the summer of 1943 a listing had been made of a number of uranium compounds grouped roughly according to their oral toxicities.

*It is a pleasure to acknowledge the courtesies of Don D. Irish and staff of the Dow Chemical Company; F. F. Treon, R. A. Kehoe, and Edward Largent of the Kettering Laboratories; A. N. Sayre, H. H. Schrenk, and coworkers at the Bureau of Mines; and Lawrence T. Fairhall and associates at the National Institute of Health.

2.4 Toxicological Priorities. Based on this information, with the additional data furnished by Albert Tannenbaum from comparable studies on mice, a listing of the approximate toxicities of these compounds was made in September 1943 and amended in March 1944. In the choice of toxicological priorities, two factors were considered: (1) the toxicity and (2) the number of persons who had real or potential exposures to each compound. When these two ratings were combined the toxicological priorities were ordered as shown in Table 1. This list of priorities was to serve as a guide in planning the program of inhalation exposures.

Table 1—Toxicological Priorities

Compounds	Rating from number of persons exposed	Rating from relative toxicity
Uranium:		
1. $UO_2F_2(UF_6)$	1	1
2. $UO_2(NO_3)_2$	2	2
3. Uranium fumes	2	3
4. UCl_4	4	2
$UOCl_2$	4	2
5. UO_3	3	
6. UO_4	4	
7. UF_4	3	4
8. U_3O_8	2	5
9. UO_2	3	5
10. $Na_2U_2O_7$	4	
11. $(NH_4)_2U_2O_7$	4	
Non-uranium:		
1. F_2		2
2. HF_2		

3. PERSONNEL

A large number of people have been associated with the project and have given wholeheartedly of their ideas and energies. It seems impossible to give individual mention to each of those who contributed in an outstanding fashion to the success of this project. Some notion of the degree of responsibility that various people have assumed may be gained from the designations in the list of personnel given in Appendix

III, following Part II. The term of service is indicated by the dates placed immediately after each name.

The Pharmacology Division. Here is included Carl Voegtlin, who served as Consultant and as Chief Toxicologist, and whose guidance was obtained at every step. It is not too much to say that, without his mature knowledge of pharmacology and his experience as an administrator, the work reported in this volume would have gone haltingly indeed. His was a major contribution.

Here also are listed consultants whose expert advice was obtained in the special fields indicated. J. F. Treon, with his experience in similar laboratory studies involving exposure chambers, gave especially helpful advice. H. H. Schrenk and S. J. Pearce guided, both technically and strategically, the experiments that were carried out on respiratory protective devices. H. S. Gardner assisted with the chemical engineering problems. D. R. Goddard advised on certain metabolic problems and critically reviewed certain studies.

(a) Toxicology. This section, under the leadership of Herbert E. Stokinger, was responsible for the inhalation studies of toxicology.

(b) Pharmacology. This section, under Frances Haven, was responsible for oral toxicological studies, skin and eye toxicity studies, distribution and excretion studies, and a number of biochemical problems.

(c) Mechanism. Under the leadership of Alexander Dounce, this section undertook the study of the effect of uranium on enzymes and protein, the physicochemical behavior of uranium in solution, and the role of the kidney in uranium poisoning.

(d) Engineering. Under Capt. Geoffrey Goring and Sgt. Neil Murphy, the engineering section designed and built the multiplicity of devices used in connection with the exposure chambers.

(e) Analytical. Under the direction of John Flagg, the analytical section had the responsibility of conducting research activities on analytical methods. All routine biochemical determinations and the routine fluoride determinations were carried out in this program.

(f) Collaborating Divisions from the Manhattan Project of the University of Rochester. A number of persons are listed under collaborating divisions. Most of these divisions performed functions and services beyond their contacts with the Pharmacology Division. A few persons are mentioned in each of the collaborating divisions in an effort to give at least a small acknowledgment of the important role played by their work (see Appendix III).

4. THE VALUE OF ANIMAL EXPERIMENTATION

One of the most discussed questions when toxicologists gather is: