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International Radiobiology Archives of Long-Term Animal Studies

Vol. 1 Descriptions of Participating Institutions and Studies

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International Radiobiology Archives of Long-Term Animal Studies

I. Descriptions of Participating Institutions and Studies

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Under the Auspices of the

European Commission
Nuclear Fission Safety Programme
Radiological Impact on Man and the Environment
and the
European Late Effect Project Group (EULEP)

U.S. Department of Energy
Office of Health and Environmental Research

Japanese Late Effects Group (JLEG)

July, 1996

International Radiobiology Archives of Long-Term Animal Studies
I. Descriptions of Participating Institutions and Studies

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Preface

This document, "Long-Term Animal Studies in Radiobiology, I. Descriptions of Participating Institutions and Studies," describes archived radiobiology studies. Companion documents are: "Long-Term Animal Studies in Radiobiology, II. The Databases and Their Use," which outlines the structure of the archive database, and "Long-Term Animal Studies in Radiobiology, III Bibliography," which summarizes published research results. The latter documents are expected to appear in 1997. Together, these documents provide a comprehensive guide to the International Radiobiology Archives (IRA), which is composed of the European Radiobiology Archives (ERA), the U.S. National Radiobiology Archives (NRA), and the Japanese Radiobiology Archives (JRA).

Document Outline

The document has three major divisions, introductory material, and four indexes. The bulk (>400 pages) of the document is devoted to descriptions of individual studies. The study descriptions are presented in a stylized format in which the following topics are presented:

Study Identification (number and title)

Institution:	The institution name
Scientists:	List of principal scientists and their working status
Purpose:	Brief statement of the problem to be solved by the study
Status:	State of completion of the study and/or availability of archival material
Treatment:	Brief summary of treatment(s) applied to animals
Dosimetry:	Short description of the dosimetric techniques used
Endpoints:	Description of biological changes observed
Animal:	Number and species/strain of animal employed
Results:	Brief summary of significant findings
References:	Bibliographic citations of significant publications
Experimental Groups:	Tabulation of the experimental design, with archival group identification numbers.

Identification Scheme

For purposes of database organization, the participating institutions and studies have been assigned unique identification numbers which appear throughout this document and are also used in the computerized database. The ERA was given institution numbers between 1 and 99, and presently includes 18 laboratories. The NRA was given institution numbers between 101 and 199; 11 of these are described in this document. The JRA was given institution numbers between 201 and 299, and, so far, has assigned 14. Within each institution, studies are numbered sequentially (usually in chronological order).

Typesetting Style

The text of this document (excluding the tables) is stored as "memo" fields in the database as well as being printed here. Due to software limitations, subscripts, superscripts and nontraditional characters (i.e., ♂ or ♀) cannot be stored in such database fields. Therefore, the writing style may appear somewhat ponderous, with explicit spelling out of chemical symbols, etc. rather than reader-friendly typesetting (e.g., plutonium-239 dioxide rather than $^{239}PuO_2$, and female rather than ♀). We did use sub- and superscripts and nontraditional characters in the tables since they cannot be placed directly in the database.

July, 1996

Foreword

ERA

Radiation protection research on the scale of the European Community was initiated as a consequence of the EURATOM Treaty concluded between the six Member States in 1957. This Treaty gave the Commission of the European Communities the responsibility not only for "... establishing uniform safety standards to protect the health of workers and of the general public and ensure that they are applied ..." but also for "... studying the harmful effects of radiation on living organisms ...," thereby closely linking the activities regulation and research in radiation protection. During its more than 35 years of existence, the Radiation Protection Research Programme of the Commission of the European Communities—now the "Nuclear Fission Safety Programme; Radiological Impact on Man and the Environment" of the European Commission—has supported and coordinated a substantial part of ongoing research activities in Member States, thereby developing a common approach to topical problems of radiation protection.

Research in animal radiation carcinogenesis in the Community was never able to match the long-term studies on large animals undertaken in the United States because of the lack of facilities and funds. Instead, such research in the Community concentrated on selected problems with emphasis on rodents as experimental animals, although a certain number of studies on monkeys, dogs, and pigs were also carried out. Because of limited means it became crucial to develop an optimal approach to late-effect studies; in particular, those which needed careful planning and standardization, which has been greatly facilitated by cooperative groups, particularly by the European Late Effect Project Group (EULEP).

EULEP was formed in 1970 as an association of scientists from various European countries and has since received consistent support from the European Commission's Radiation Protection Research Action Program. EULEP had been instrumental in standardizing the dosimetry of animal studies, pathology diagnosis; and in carrying out several cooperative pilot projects. Most important, however, EULEP generated a climate of confidence among scientists in the Community, encouraging collaboration in larger cooperative projects under the auspices of the European Commission. The archives of long-term animal experiments in radiobiology are an excellent example of what can be achieved by cooperation. Therefore, it has been a welcome development that this undertaking did not remain restricted to the European Union. The global problems encountered in radiation protection and the increasingly limited means available in manpower and funds make a global approach imperative not only to recommendations and regulations in radiation protection but also to research. We very much hope that from this beginning further common enterprises will arise.

The development of the European section of this Archive and the collation of all the European animal radiobiological data in the archive is due, almost solely, to the work and dedication of George Gerber, and it is a pleasure to acknowledge the deep gratitude that we owe him. We would also like to express our thanks to the many European scientists who have willingly provided all the original and detailed information about their animal experiments to make the Archive possible.

It is our hope that the details presented in this archive will be used in reanalyses to test and validate new approaches to radiation effects and to derive deeper insight into the way in which external irradiation and internally deposited radioactivity induce cancer.

Dr Jaak Sinnaeve
Head of Unit Nuclear Fission Safety Programme; Radiological Impact on Man and the Environment

Dr. John Hopewell
Chairman of the European Late Effect Project Group (EULEP)

NRA

The U.S. Department of Energy (DOE), and its predecessor agencies, has long recognized the need for scientific information about the health effects of radiation and radionuclides. Over the past 50 years, many DOE-funded long-term studies, involving thousands of animals, were conducted in several laboratories. Those studies are either complete, or are nearing completion. Much has been learned; thousands of scientific papers have been written; countless committees have pondered the results and formulated recommendations that safeguard the health of nuclear industry workers and the general public. It is safe to say that current regulatory limits on radiation exposure, especially those associated with internally deposited radionuclides, are, in large part, based on these landmark radiobiology studies.

This document is intended to provide future researchers with descriptions of this rich legacy of radiobiology information and materials from animals. The Department has recognized its obligation to preserve these archived materials and make them available to future researchers. For the past 5 years, the National Radiobiology Archives (NRA) project has been conducted at Pacific Northwest National Laboratory. The mission of the NRA was to gather, organize, and catalog data, original documents, and tissues related to DOE radiobiology life-span studies. The NRA had three tasks: (1) operate an interlaboratory computerized information system containing a dose-and-effects database to summarize data on individual animals, and to compile an inventory database and a bibliographic database; (2) establish a document archive of original (or "record copy") research materials such as logbooks, clinical notes, radiographic films, and pathologists' observations; and (3) assemble a specimen archive of histopathology blocks, slides, and tissue samples.

A somewhat parallel effort has been underway with regard to specimens and information about human contamination with radionuclides. The U.S. Transuranium and Uranium Registries (USTUR), located at Washington State University—Tri Cities, is charged with understanding the biokinetics, dosimetry, and potential health effects of transuranic elements and those of the uranium series based on actual human experience. In July, 1992, the USTUR was expanded through creation of the National Human Radiobiology Tissue Repository (NHRTR) for radiological specimens. In addition to extracts of tissues in solution, histopathology slides and blocks and tissues from USTUR cases that have not been analyzed, the NHRTR contains tissues collected by Argonne National Laboratory for their comprehensive Radium Dial Painter Study.

The NRA project will be merged with the USTUR in the near future. The collected records, histopathology slides, and paraffin blocks have already been transferred to the NHRTR. The database will be transferred to the USTUR early in 1997. This unique collection of human and animal tissues and dose-effects information will be made available to the scientific community through the USTUR.

This document, *International Radiobiology Archives of Long-Term Animal Studies, I. Descriptions of Participating Institutions and Studies*, is the result of the efforts of a number of dedicated scientists, among them, the late Roy C. Thompson, Robert G. Thomas, and the current project director, Charles R. Watson. Roy Thompson's book: *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, published in 1989, established the framework for combining and comparing the studies, and has become the guide to the beagle portion of the NRA database. Bob Thomas served for many years as OHER technical monitor with responsibility for the life-span beagle studies. It was his encouragement and perseverance which resulted in establishment of the NRA as a follow-on to Thompson's work. Chuck Watson has been NRA project director since its inception. He is to be commended for his dogged determination to gather this information into a cohesive archive and for his efforts to standardize the international archival database.

This document and, eventually, an updated version on CD-ROM, are a guide to the archival resources of the NRA and its companion efforts, the ERA and JRA. It has been a privilege to provide technical guidance and project support for this effort.

Marvin Frazier
U.S. Department of Energy, Office of Health and Environmental Research OHER

JRA

It has been well recognized that long-term animal experiments are a very important factor for understanding the biological effects of ionizing radiations but, because of limited funds available in Japan, such experiments have been carried out only in a limited number of institutions. To encourage such studies and interinstitutional collaboration, the Japanese Late Effects Group (JLEG) was organized in 1972, as described in detail in the Chapter on the history of the Japanese Radiobiology Archives.

Recent progress in molecular biology and statistical analysis, on the one hand, and recent criticism against animal experiments that make animal experimentation increasingly difficult, on the other hand, make it very important to preserve as much data and materials of past experiments for future analysis and to avoid duplication of similar experiments. Unfortunately, however, we had no system to promote this kind of activity in Japan. When we received an invitation to join the Radiobiology Archives, we agreed to the proposal in principle but had no organization to be responsible for this effort. Fortunately, JLEG, a voluntary group which has a long experience of scientific activities, accepted the proposal to organize the Japanese Radiobiology Archives and actively participated in compiling the requested data. Since all activities have been done voluntarily; some details are still missing from the data.

The Japanese Radiobiology Archives is a completely new activity of JLEG which should be extended and continued further. We hope that the Archives will contribute greatly to understanding the biological late effects of ionizing radiation. We would also appreciate not only the further support of scientists in this field but also that of the governmental as well as nongovernmental funding agencies for further development.

Takashi Aoyama
Japanese Late Effects Group
Shigefumi Okada
Japanese Late Effects Group
Tsutomu Sugahara
Japanese Late Effects Group

Purpose and Status of Radiobiology Archives

Information on risks from ionizing radiation and radioactivity, particularly on risks of cancer and hereditary damage, originates from four approaches:

- epidemiological observations, including molecular epidemiology;
- experimental studies on animals (survival, genetics, pathology, histopathology, molecular pathology);
- *in vitro* experiments on cells and biological molecules (clonal death, mutations, transformation; molecular biology of DNA);
- biophysical and biological models.

Each approach, *per se*, is incapable of providing a complete answer to the following question: what are the risks of developing cancer or engendering offspring with hereditary damage after a given radiation exposure. Epidemiological data, such as those obtained from the survivors of the atomic bombs in Hiroshima/Nagasaki and from medical exposures, are most pertinent for human risk assessment. However, they are not useful for the most common exposure situations, i.e., exposure to a low dose delivered at low dose rates, for high-LET radiation, and for many important radionuclides such as actinides. Risk estimates for such exposures depend very much on the extrapolation of data from long-term animal studies.

The many long-term animal studies that have been carried out in the past have given invaluable information. At present, however, such studies are scarce, and many institutions and scientists formerly active in this area have turned to other problems. Moreover, experiments on animals have become controversial so that very few, if any, large-scale animal radiation experiments are likely to be carried out in the future. In order not to lose information from experiments that will not be replicated, it is imperative to safeguard existing data and material from animal experiments in a way which will allow their later evaluation and study. Indeed, newly developed approaches and methods allow one to exploit more fully the information gathered in past animal experiments. New statistical tools have become available, better standardization of animal pathology has been achieved, and techniques of molecular biology make it possible to investigate, in tissue preparations, changes in the cells and their genome. Moreover, meta-analysis of data from different experiments seems a promising approach for a more accurate assessment of the incidence of certain diseases and for a better understanding of the factors involved in extrapolating risks between species. The use of such data is not limited to radiation biology: studies on aging, toxicology, general carcinogenesis, etc. can use the information on life spans, disease spectra, and histopathological material.

These needs were recognized during the middle 1980s by both European and U.S. scientists and their sponsoring agencies. Therefore, the Office of Health and Environmental Research of the U.S. Department of Energy and the Radiation Protection Programme of the European Commission embarked on the collection of all available information on long-term animal studies with the aim of archiving them in a form suitable for permanent conservation and further scientific exploitation. More recently, the Japanese have joined this endeavor, and it is hoped that institutes and countries not currently engaged in the archiving efforts will also participate in these activities. From the beginning, the U.S. and European archives were destined to become integrated in order to allow direct comparison of data. This task turned out to be more difficult than originally anticipated because of the different nature of the studies and types of data, e.g., on rodents and dogs, and the problems involved in agreeing on common definitions of pathological diagnoses in different strains and species. However, satisfactory homogenization has now been achieved, so that results can soon be made available to the scientific community.

The combined International Radiobiology Archives (IRA) consist of several parts:

- a detailed description of the experiments carried out, i.e., this publication, listing all long-term animal studies for which information on exposure, dosimetry, animal, experimental groups, and references could so far be obtained. It should be emphasized that the authors are aware that this list is not yet complete and that errors may have crept in. We urge all readers to bring to our attention experiments which were not included and make suggestions to improve the presentation.
- detailed information on pathology and, where pertinent and available, the clinical chemistry and radioactivity of individual animals. This information is being incorporated into the structure of a PARADOX data base and will

be made available in the US National Radiobiology Archives (NRA), the European Archives (ERAD) and Japanese Centers. Studies for which all or most data have already been incorporated into the PARADOX data base are indicated in this publication.

- an extensive database on references pertinent to long-term animal studies. These are stored in the PAPYRUS data base and are expected to be completed in about a year. The data base will include key words and abstracts and can be made available to interested scientists. Reprints of most of these references, as well as other pertinent documents, are also being stored.
- a collection of histopathological material from the experiments described. This is located either in the NRA at the Pacific Northwest National Laboratory (PNNL), Richland WA, USA, or in the laboratories in Europe and Japan where they were collected.

Persons interested in access to the material and information in the database are encouraged to contact those responsible for the respective domain (ERA, NRA, JRA). Addresses to which such request can be made are given below. Typically, such demands will be initiated by telephone or personal conversation which will help to refine the initial query and lead to a formal written response. The information can either be handled at the respective centers where the data base is stored, or subsets of the data base can be sent to users in a format appropriate to their computer hardware/software. However, it must be emphasized that the data remain the intellectual property of the scientists who carried out the studies and of the institutions which sponsored and funded them. Any use of the material in the archives for further evaluation and publication will require the written consent of these institutes/scientists. This consent must be secured by the person making the application for use.

This venture would have been impossible without the consistent support and encouragement of the funding agencies:

- European Commission, Nuclear Fission Safety Programme, Radiological Impact on Man
- Environment European Late Effect Project Group (EULEP)
- U.S. Department of Energy, Office of Health and Environmental Research
- Japanese Late Effects Project Group (JLEG)

G.B. Gerber, European Radiobiology Archives (ERA)
C.R. Watson, National Radiobiology Archives (NRA)
T. Sugahara and S. Okada, Japanese Radiobiology Archives (JRA)

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The European Radiobiology Archives (ERA)

Since the beginning of the era of ionizing radiation and radioactivity, an increasing number of observations on radiotherapy patients and radiologists have drawn attention to the risk of cancer and other late effects. However, before World War II, radiobiological research was essentially confined to university departments, which did not have the means for carrying out long-term studies on a large number of animals. Thus, it was only after World War II that radiobiological research became intensive, and it took about another decade until such research turned away from the investigation of acute radiation effects toward studies on late effects.

World War II annihilated much of the scientific infrastructure in Europe. Some countries, however, especially France and the United Kingdom, developed special research institutions to deal with the challenge of nuclear energy in the 1940s, and were soon followed by Denmark, Germany, Greece, Italy, Spain and Sweden, all of which created research institutions specifically devoted to research and development of atomic power and, implicitly, of radiation protection.

The Treaty establishing the European Atomic Community (EURATOM), signed in 1957, stipulated that a Research Programme on Radiation Protection (RPRP) would be developed by the Commission of the European Communities (now European Commission, EC). This program has supported, by means of cost-shared contracts, a substantial percentage of all research relevant to the area of radiation protection in the European Community (now European Union, EU), including long-term animal studies. This program has also been instrumental in promoting the cooperation of scientists working on problems related to radiation protection within the Community and in other national and international organizations. These include the International Commission on Radiological Protection (ICRP), the International Commission on Radiation Units and Measurements (ICRU), the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), the World Health Organization (WHO), and the U.S. Department of Energy (DOE).

The European Late Effect Project Group (EULEP) was initiated in 1970 by scientists from different European research institutes under the sponsorship and with the support of the RPRP, with the aim of developing cooperation among European research institutes studying the late effects of radiation. The goal was to standardize approaches and methods of dosimetry, pathology, and molecular biology, to facilitate the exchange of information, to train scientists in topics related to their research, as well as in general problems of radiation protection, and to initiate cooperative research projects.

Thanks to the Community Radiation Protection Programme and the cooperative groups supported by it, such as EULEP, the European Dosimetry Group (EURADOS), the International Union of Radioecologists (IUR), as well as to the efforts of Member States governments, research in radiation protection has become efficient, up-to-date, and closely integrated in a European network. However, during the 1980s and thereafter, despite the burning questions raised by the Chernobyl accident, funding of radiobiological research at universities, national and international institutions, and the EU has diminished progressively. Several institutes gave up or reduced markedly research in radiation protection; an older generation of scientists retired and was not fully replaced; and, unless concerted efforts were undertaken, data and histopathological material from long-term animal studies risked being lost. In order to preserve this unique information, the RPRP created an *ad hoc* group in its Management and Coordination Advisory Committee (CGC) and carried out a preliminary evaluation of the situation. Subsequently, the RPRP asked EULEP to develop a European Radiobiological Archive of Animal Experiments (ERA). For this purpose, EULEP has set up an advisory committee consisting of:

Prof. Wolfgang Gössner, Neuherberg, Germany (Chairman)
Prof. Johan Broerse, Rijswijk, The Netherlands
Prof. Vincentio Covelli, Rome, Italy
Dr. Ken Chadwick, CEU Brussels, Belgium
Prof. Georg B. Gerber, Mol, Belgium
Dr Eric Humphrey, Chilton, UK
Prof. Arne Luz, Neuherberg, Germany
Prof. Roland Masse, Fontenay-aux-Roses, France, now at OPRI le Vésinet
Dr Chris Zurcher, Rijswijk, The Netherlands

Collection of information and data was started in 1992. To date, the archives have obtained data from about 90,000 individual animals. Some experiments are still under way, representing about 10,000 animals, but data on individual animals from some older studies, even those mentioned in this book, may be irretrievably lost because original data have been discarded, scientists have left, or the organizations cannot provide the data. So far, the ERAD database has been used mainly for compiling statistics for scientists terminating ongoing studies.

The U.S. National Radiobiology Archives (NRA)

The United States government, through the U.S. Atomic Energy Commission (AEC), now the Department of Energy (DOE), actively supported intense scientific efforts in the 1940s to understand acute effects of external irradiation and internally deposited fission-product radionuclides. Initially, these studies were concentrated in a few universities (Rochester, Chicago, California at Berkeley), and results were reported through government documents, with limited open-literature summarization. When these effects had been adequately characterized, attention shifted to effects of lower doses and lower dose rates. The special requirements for handling contaminated biological waste and animal carcasses prompted a concentration of research efforts in a group of DOE laboratories, some on university campuses and other at National Laboratories. The primary information dissemination mechanism in the 1950s consisted of project reports in the form of limited-distribution government documents. The most comprehensive description of these studies is given by J. Newell Stannard, in *Radioactivity and Health, A History*, 1988 (DE88013791) Office of Scientific and Technical Information, Springfield, Virginia.

In these studies, particular attention was given to the problem of determining the effects of internally deposited by-products of atomic energy production, namely, the transuranic (i.e., uranium, plutonium) and metabolically interesting fission products (i.e., strontium, iodine, cesium). The most likely route of exposure to these materials is ingestion or inhalation. From the chronic ingestion of radium by dial painters it was known that bone-seeking radionuclides required special attention because of the very long latent period between ingestion and tumor development. Consequently, in the decades of the 1950s and 1960s, several life-span studies were initiated using beagle dogs, which have a median life span of about 14 years. These studies, conducted at the University of Utah (U of Utah), the University of California at Davis (UC Davis), Argonne National Laboratory (ANL), Pacific Northwest National Laboratory (PNNL), and the Inhalation Toxicology Research Institute (ITRI), were summarized by Roy C. Thompson in *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, (PNL-6822), PNNL, Richland, Washington.

As the beagle studies were being completed, the DOE instigated an archival project to assure that detailed research records would be available for future analysis. This activity commenced in 1989 in conjunction with the decommissioning of the radiobiology laboratory at UC Davis. The NRA, operated by PNNL for the DOE, is a repository for information about tens of thousands of individual rodents and other animals which were used in long-term radiobiology studies conducted by the US government over the last 50 years. The mission of the NRA is to gather, organize, and catalog data, original documents, and tissues related to DOE radiobiology life-span studies. The NRA has three tasks:

- operate an interlaboratory computerized information system containing a dose-and-effects database to summarize data on individual animals, an inventory database, and a bibliographic database;
- establish a document archive of original (or "record copy") research materials, such as logbooks, clinical notes, radiographic films, and pathologists' observations;
- operate a specimen archive of histopathology blocks, slides, and tissue samples.

The NRA concentrated initially on studies of beagle dogs exposed to ionizing radiation at five DOE laboratories; results for each of more than 6000 life-span-observation dogs have been transferred and are available. Details of major studies comparing strains of mice were transferred from Oak Ridge National Laboratory and Brookhaven National Laboratory; results for nearly 30,000 mice are available. Additionally, the NRA recently acquired records and specimens from a life-span study of almost 4000 rats that inhaled plutonium at PNNL. Life-span biokinetics data on over 300 nonhuman primates are also available.

At its inception, in 1989, it appeared that the primary task of the NRA was to gather electronic information related to radiobiology studies and combine it into a master database system. The studies, conducted over a long time span in many different laboratories, each used a different approach to data management, ranging from handwritten laboratory notebooks to elaborate computerized database management systems. The DOE wanted to be able to combine results from studies in a unified electronic format accessible from a microcomputer. At that time the NRA task was to design and populate a unified database structure.

As experience was gained with users of the combined data base, it became very evident that the NRA is much more than a combined, unified data base. The NRA is a living, value-added organization which strives to preserve original material yet, at the same time, makes it readily available to new users. The users need access to original data files and documentation to supplement their use of the unified data base, and we must carefully distinguish between the original information and the value-added standardization provided by the archival service.

The NRA is selective in scope. The goal is to characterize and preserve the key radiobiological experiments, especially those that are large and costly, which will never be repeated. New studies are added at the concurrence of the advisory committee. When a study is nominated for inclusion, we consider the availability of materials. The optimal approach is to be able to collect electronic data, written documents, histopathology slides and paraffin blocks, tissues, radiographs, and other materials—in order to provide the entire spectrum of materials for interpretation by new analytical or statistical techniques. In other words, a slide collection is useless without extensive supporting documentation, preferably in the form of a computer data base. On the other hand, a data base without a slide collection can provide a valuable addition to our collection because it can be combined with other data bases in cross-cutting analyses.

NRA Advisory Committee

The NRA Advisory Committee meets annually. Its members are:

Steven A. Benjamin, Colorado State University
J. A. Louis Dubeau, University of Southern California
Elizabeth Sandager, Peabody Museum
Kenneth L. Jackson, University of Washington
Philip R. Watson, Oregon State University
Bruce B. Boecker, ITRI
Ronald E. Filipy, U.S. Transuranic and Uranium Registries (USTUR), Washington State University
Bruce Carnes, ANL
Scott C. Miller, University of Utah
Richard E. Weller, PNNL
Otto G. Raabe, University of California, Davis
David Thomassen, U.S. DOE

NRA Usage and Plans

There have been several retrieval activities from the NRA specimen collection. Two groups of investigators have retrieved brain tissue from aged dogs for studies of Alzheimer's disease. This is an excellent illustration of an unforeseen use of archived materials (the harvested tissues were preserved in formalin in the early 1970s). An investigator is working with paraffin blocks of plutonium-induced lung tumors, using advanced molecular biology techniques to compare them with spontaneously occurring lung tumors. His aim is to determine whether the plutonium-induced tumors have the same pattern of genetic mutations as the spontaneous tumors.

The formation phase of the NRA is essentially complete; no significant studies are expected to be added. The project is phasing into a maintenance/user service mode. It is anticipated that these activities will be merged with those of the United States Transuranium Registries (USTUR) under the direction of Dr. Ronald L. Kathren.

The Japanese Radiobiology Archives (JRA)

History of Radiation Research in Japan

In the late 1930s and early 1940s, Dr Y. Nishina built a cyclotron at the Institute of Physical and Chemical Research, Tokyo. His group explored the frontiers of nuclear physics and related sciences in Japan. One of the first radiobiological experiments performed was a study of the effects of neutrons and gamma rays on silkworms. The second world war interrupted the further development of radiation research in Japan.

In 1947, the U.S. National Academy of Sciences, under the Atomic Energy Commission, established the Atomic Bomb Casualty Commission (ABCC) at Hiroshima and Nagasaki to study the biomedical effects of atomic bomb survivors in cooperation with the National Institute of Health of the Ministry of Health and Welfare of Japan. In 1975, the Radiation Effects Research Foundation (RERF) succeeded the ABCC to continue the studies on the survivors. The Foundation, still at Hiroshima, has been jointly operated by the Japanese Ministry of Health and Welfare and the U.S. National Academy of Sciences.

In 1954, fishermen of the Lucky-Dragon (Fukuryu-Maru) boat were exposed to radioactive fallout from a hydrogen bomb test conducted by the U.S. at the Bikini Atoll in the Pacific Ocean, and, at about that time, one began to detect radioactive fallout all over Japan. These incidents motivated the Science Council of Japan (Japanese Academy of Sciences) to initiate scientific research on atomic radiation in Japan. The Japanese government decided to explore atomic energy research and radiation sciences and took the following actions: it started with the establishment of the Japan Atomic Energy Research Institute (JAERI) in 1956 with the aim to explore applications of atomic energy, and followed this up by creating the National Institute of Radiological Sciences (NIRS) in 1957 for studying radiological sciences (radiation physics, radiobiology, radioecology, radiation medicine, etc.).

In order to promote education and research on radiation sciences, the Ministry of Education, Science, Sport and Culture of the Government built four research institutes and centers, and established 18 departments in national universities by 1976. All these institutions were devoted to the study of various aspects of radiobiology, health physics, radiation physics, radiation protection, nuclear medicine, radioecology, and radiotherapy.

The Japan Radiation Research Society was organized in 1959 and played a central role in the promotion of radiation research in Japan. The Japan Health Physics Society was initiated in 1961 and contributed to the development of radiation protection in Japan. At an international scale, the International Association for Radiation Research (IARR) was founded in 1958 and organized the first International Congress of Radiation Research in 1958 (Japan was one of the founders of this Association). Since this time, the International Congress has been held continuously nearly every 4 years with the 6th Congress having been organized in Tokyo in 1969.

The Japanese Late Effects Group (JLEG)

In 1970, a proposal was made to the Japan Radiation Research Society to create the Japanese Late Effects Group (JLEG) in order to encourage late-effects studies in Japan. The Society approved organization of the JLEG as an independent voluntary group of the Society. The JLEG started to function in 1972. Its activities concentrated mostly on the exchange of information on late effects studies nationally as well as internationally. The JLEG has organized a symposium every year and publishes a newsletter. With respect to international activities, the JLEG has been a member of the International Late Effects Group (ILEG) and has sent a speaker(s) to the ILEG symposium at each International Congress of Radiation Research since the 4th ICRR (1972).

Late-Effect Animal Studies in Japan

Experimental studies of radiation-induced late effects were initiated in the 1960s. Animals used were mice, rats, and medaka fishe. In most experiments, exposure was from external, low-LET radiation. Biological effects studied were mainly life-shortening and cancer induction. Their main aim was to develop extrapolation to human risks from low-dose radiation on the basis of experimental studies of dose-effect relationship, age-dependency, RBE, dose-rate effects, and modifying factors (diet, hormones, etc.). Internal exposure was studied mostly with tritium and plutonium. Studies on high-LET radiation were also performed with neutrons and heavy ions. Some of the results have often been cited in the reports of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), the proceedings of the International Commission on Radiological Protection (ICRP), and in international radiation research journals.

Japanese Radiobiology Archives (JRA)

In March, 1995, Dr. G.B. Gerber of the European Radiobiology Archives invited Japanese radiobiologists to join the International Radiobiology Archives (IRA). In response to this invitation, a small tentative group, the Japanese Late Effects Project Group (JLEPG), was organized to prepare actions on the Japanese Radiobiology Archives in time for the 10th ICRR in October, 1995. During this preparation it was considered that

- international collaboration would be the most important matter to start at this stage,
- the 10th ICRR would be a suitable occasion to start the International Radiobiology Archives,
- Japanese participation should not be made by the small voluntary group, JLEPG, but rather through JLEG and with its support and approval.

Since this was a completely new activity for JLEG, the proposal for the Archives should be discussed thoroughly within JLEG to obtain the active participation of all members.

The aim of the Japanese Radiobiology Archives is to gather systematically all data and materials of all late-effects studies of animals in Japan. Because of the limited funds available and the need to achieve a consensus, the JRA intended, at this stage, to participate in the publication of the book-style database (including animal experiment information so far available, collection of original papers, names of scientists and their institutions), and to undertake efforts to develop a computerized information system containing a dose-effects database.

At its annual general assembly in November 1995, JLEG accepted the proposal by JLEPG and decided to act as the organizer of JRA. The JRA would prepare the database, which appears in this book, and the JLEG will participate in the IRA activity. The JRA expects to collaborate closely with the European Radiobiology Archives and the U.S. National Radiobiology Archives in this venture.

Acknowledgments

We greatfully acknowledge the help of Dr. Shin Saigusa for taking over the responsibility as Scientific Secretary for the Japanese Radiobiology Archives and for his continuous efforts in compiling the Archives. We thank Professor Takashi Aoyama, who, as the chairperson of the JLEG, made valuable suggestions in editing the archives We appreciate the collaboration of the members of the JLEG and of the Japanese Radiation Research Society for providing their own data to the Archives.

Institutes Participating in the Archives

Institutes Participating in the European Radiobiology Archives[1]

1 AEA Environment & Energy, Biomedical Research Department, Harwell Laboratory GB-OX11 ORA Harwell, UK, Tel. 44-1235-821111, Fax 44-1235-434695

Contact Person: Dr. Clare Collier

AEA technology, the trading name of the UK Atomic Energy Authority (UKAEA), was set up as a government-funded, mission-led organization in 1954 to develop the UK nuclear program . The Health Physics and Medical Division was responsible for radiological safety at the Harwell site and carried out research in several fields. Examples are: the fate of fallout from nuclear weapons testing, the incorporation and transmission of fission products through food chains, the effect of particle size and breathing pattern on deposition in the human respiratory tract and the uptake of radioactive vapors.

From 1965, UKAEA progressively widened its field of application and, in 1986, was set up as a trading fund, which required it to operate on a more commercial basis. Today AEA is a fundamentally changed organization which has developed to a world-class service business, using its scientific and engineering skills for the benefit of a wide range of customers.

Interest in radiobiology started in 1982 when the Biomedical Research Department of the UKAEA (head, Dr. A. Morgan) initiated a collaborative project with the Department of Radiobiology at St. Bartholomew's Medical College, dealing with late effects of actinides. At Harwell, a facility for exposing mice to aerosols of actinide oxides was built, and early effects on lung cells and radiation-induced fibrosis were studied. Dr. Morgan retired as Head of the Biomedical Research Department in 1982 and was replaced by Dr. N.D. Priest. Current research deals with three main areas:

- The study of **radiation effects,** the largest field of research in the department, aims to improve the understanding of radiation risks and to reduce the uncertainties in extrapolating observations at high doses and high dose rates to the levels of practical concern in radiological protection. These studies also aim to clarify the partitioning of risks between different organs and to establish in more detail the relative biological efficiency of different types of radiation.
- Studies on the **radiobiology of the cell** range from the identification of individual genes affecting cellular reproduction to the gross behavior of cell colonies exposed to particular insults. Of particular interest are the investigations on the mutagenicity of Auger emitters, and the variability of radiosensitivity among individuals.
- The ***in vivo* studies** are concerned with effects in lung, where the biological effects of radon and other inhaled radionuclides are being investigated. Other studies are comparing the relative biological effects of inhaled or injected alpha- and beta-emitting particles in the lung and bone marrow. Important efforts are devoted to epidemiological studies of radiation workers in the nuclear industry.
- Research in **radiation dosimetry** concentrates on bone dosimetry and the modeling of plutonium metabolism. Human volunteer studies are making notable contributions in this area. A significant program is continuing in the area of external dosimetry. Refining dose estimates in response to reduced regulatory limits has required further consideration of the energy spectra of both photons and neutrons.
- Research in **environmental radioactivity** includes studies on mechanisms of radionuclide migration, the properties of hot particles, the radiological assessment of tide-washed pastures, and the influence of processing on radionuclides in foodstuffs.

[1]This list of laboratories includes only those which have supplied information and is, by no means, a complete list of all institutions working in the field of radiation biology.

2 **CEN-FAR,** Centre d'Études Nucléaires de Fontenay-aux-Roses, Departement de Pathologie et Toxicologie Expérimentales (DTPE), BP No 6, Fontenay-aux-Roses, F-92265, France, Tel. 33-1-46547080/8585 Fax 33-1-46548189

Contact Person: Dr. Michele Morin

The Commissariat à l'Energie Atomique (CEA) was created in 1946 and was endowed with the responsibilities needed to develop civilian and military nuclear energy on a national level. Consequently, the CEA also took charge of the different aspects of radiological protection and, in particular, of research into the biological effects of ionizing radiation. At this time, accidental external and internal exposure was the topic of main concern. Health protection was placed under the directorship of Dr. H.P. Jammet, who also directed the Service de Radiopathologie at the Hôpital Curie. At the end of 1960, experimental research was reoriented toward late effects and, especially, the induction of cancer.

Three laboratories of the CEA under three different directions were involved in these studies. One, at Bruyères-le-Châtel, concentrated on the radiopathology of plutonium; another, at Razés, studied the risks at uranium mines; and the third, at Fontenay-aux-Roses, was occupied with the health aspects of retreatment of radioactivé material. All three laboratories were subsequently placed under the directorship of Dr. Jammet, although they kept a certain independence in their work. Integration of work from Razés and Fontenay-aux-Roses became almost complete, especially with respect to the computerized storage of the experimental results. At Bruyères-le-Châtel, the data were not computerized and are now available only in publications, not as original data.

Since its establishment, the laboratory at Razés has been directed by Dr J. Chameaud. The laboratories of Bruyères-le-Châtel and Fontenay-aux-Roses were directed successively by Drs. Jammet, J. Lafuma, R. Masse, H. Métivier, and M. Morin..

During the 1960s, the research pursued two goals: (1) to understand the risks of radon in particular also its possible synergy with silicium in causing lung fibrosis and silicosis in miners; (2) to define the risks of alpha-emitting actinides to workers in the nuclear industry, especially by way of inhalation..

When, in the 1970s, it became clear that one could obtain lung cancers in rats similar to those in miners, an important program to determine dependency on dose and dose rate was inaugurated. Thus, the actinide and radon programs followed similar lines in attempting to determine risks to man on the basis of data in rats. The experiments with beta-emitting cerium isotopes supplemented these studies. Since certain actinides also diffuse in the body and cause other types of cancer, it was of interest to also study the effect of dose and dose-rate from high-LET radiation (neutrons), and compare them with the effects of gamma rays. Several studies were also undertaken related to the effect of age and sex as well as the influence of chemical pollutants and therapeutic drugs with respect to the processes of initiation-promotion of cancer, either *per se* or in combination with radon and other radiation exposures.

3 **ENEA** (Ente per le Nuove Tecnologie, l'Energia e l'Ambiente), Department of Health Effects (AMB-BIO), CRE-Casaccia, P.O. Box 2400, I-00100 Rome, Italy, Tel 39-6-30483401, Fax 39-6-30483644

Contact Person: Dr. Vincenzio Covelli

The Radiation Biology Laboratory was organized in 1962 with Dr. G. Silini as head of the department. Dr. V. Covelli has been head of the Laboratory of Pathology since 1990.

The laboratory aims to study the mechanisms of radiation and chemicals, with particular attention to:

- individual factors (age, sex , etc.) affecting the dose-effect relationships for radiation-induced leukemia/lymphomas and solid tumors *in vivo*,
- malignant transformation of epithelial and nonepithelial immortalized cell lines *in vitro*,
- genetic predisposition and control of spontaneous, or radiation-, or chemical-induced leukemia/lymphomas and solid tumors.

4 **Deutsches Krebsforschungszentrum,** Institut für Radiologie und Pathophysiologie, Abteilung für Onkologische Diagnostik und Therapie, Im Neuenheimer Feld 280, FRG, D- 69120 Heidelberg, Tel.49-6221-422577, Fax 49-6221-422572

Contact Person: Prof. Dr. Horst Wesch

The Department of Radiology (formerly Department of Nuclear Medicine) of the German Cancer Research Center was founded in 1964 under the leadership of the late Prof. K.E. Scheer. The goal of the department was to investigate the use of radioactive substances for the diagnosis and treatment of cancer and related diseases. Three divisions were created: Nuclear Medicine; Biophysics and Medical Radiation Physics; Radiation Chemistry and Radiopharmacology.

In 1984, the Nuclear Medicine Division was integrated in the Division of Oncological Diagnostics and Therapy which was formed in 1978 (Head, Prof. G. Van Kaick). The main objective of this division is the development and clinical testing of new radiological methods for oncological diagnosis and therapy. The German Thorotrast study was, from the beginning, an important component of the division. The goal of this long-term epidemiological study was to determine, in patients, late effects of chronic radiation from Thorotrast. 2326 patients who received Thorotrast and 1890 control patients have been followed since 1967. Of these, 899 Thorotrast patients and 662 control patients have been examined by clinical and biophysical methods every two years.

In the context of the patient study, four extensive animal studies regarding radiation- and nonradiation-effects have been performed by the Division of Biophysics and Medical Radiation Physics (Head, Prof. W.J. Lorenz). The German Thorotrast study was supported by the Federal Ministry for Research and Technology, and later by the Ministry for the Environment; in addition, by the Radiation Protection Research Programme of the European Union.

Two years ago, a new research activity was begun dealing with risk evaluation of working in uranium mines of former East Germany.

5 **GSF,** Forschungszentrum für Umwelt und Gesundheit, Institut für Pathologie, Ingolstädter Landstr.1, FRG, D-85758 Neuherberg, Tel. 49-89-3187-2636 or (3425), Fax 49-89-3176/3360

Contact Person: Prof. Dr. Arne Luz

The GSF is a National Research Center, supported by the Federal Government and the State of Bavaria. Research is focused on activities related to the protection of man and his environment from harmful effects of resulting from radiation and chemicals.

The GSF was established in 1964 under the name Gesellschaft für Strahlenforschung. Its scientific directors were Prof. Dr. R. Wittenzellner from 1964-1981, Prof. Dr. H.W. Levi from 1981-1990, Prof. Dr. J. Klein from 1990-1995 and Prof. Dr. E-G Afting since 1995.

In 1964, experimental studies on the pathogenesis of late somatic effects of radiation started in the Institute of Biology (Prof. Dr. O. Hug) under an association contract linking EURATOM and the Gesellschaft für Strahlenforschung.

Radiopathological research has continued since 1966 in the Department of General and Experimental Radiopathology, which in 1985 was renamed the Institute of Pathology (Prof. Dr. W. Gössner; since 1989 Prof. D. H. Höfler). Joint studies were performed with the research group Molecular Cell Biology in 1991 reconstructed as the Institute of Molecular Virology (Prof. Dr. V. Erfle).

The main topics of interest studied at the institute were:

- late effects of internal irradiation with short-lived bone-seeking radionuclides,
- mechanisms of bone tumor production,
- the dependence of the risk of radiation-induced osteosarcoma on dose, time (protraction) and quality of radiation,
- the role of various endogenous. (age, strain) and exogenous factors, including retroviruses, with regard to radiation-induced late effects.

Today, the principal interests of the institute are studies of the molecular mechanisms involved in radiation carcinogenesis, in particular osteosarcomagenesis.

6 **KFK,** Kernforschungszentrum Karlsruhe, Institut für Genetik und Toxikologie von Spaltstoffen, Postfach 3640, D-76344 Karlsruhe-Leopoldshafen, FRG, Tel. 49-7247-823209, Fax 49-7247-825070

Contact Person: Prof. Dr. H. Dertinger

The institute was created in 1958, at the same time as the Kernforschungszentrum. The first directors were Prof. G. Zimmer, whose principal interests were basic and molecular aspects of the effects of radiation on organisms, and Prof. A. Catch, who concentrated on the toxicology and metabolism of fission products and means to decorporate them from the human body. After the retirement of Prof. Zimmer and the death of Prof. Catch, Prof. D. Taylor took over the institute in 1979 and continued the work on the toxicology of radionuclides, particularly in bone, including physicochemical aspects . Prof. V. Volf continued Prof. Catch's work on metabolism and decorporation of radionuclides. The genetics department was continued by Prof. P. Herrlich, who now works on more basic aspects of molecular genetics. Following the retirement of Prof. Taylor and Prof. Volf, Prof. H. Dertinger took over the department in 1992, continuing work on the toxicology of radiation and radionuclides.

7 **MRC,** Medical Research Council, Radiobiological Unit, Chilton, Didcot GB- OX11 ORD, UK, Tel. 44-1235-834393, Fax 44-1235-834918

Contact Person: Dr. Dudley Goodhead

The Radiobiological Laboratory was established in 1947 to define the risks from radioactive substances. Its director were Dr. J.F. Loutit from 1947, Dr. R.H. Mole from 1971, Dr. J. Vennaert from 1979, Dr. G.E. Adams since 1983. In addition, the department has investigated microdosimetric methods and models; DNA damage and repair; chromosomal damage and genetic instability; molecular, cellular and animal genetics; risks of myeloid leukemia; radiosensitizers and biokinetics; and effects of radionuclides, particularly in bone and lung.

8 **NRPB,** National Radiological Protection Board, Chilton, Didcot Gb- OX11 ORQ, UK, Tel. 44-1235-831600, Fax 44-1235-833891

Contact person: Dr. Roger Cox

The National Radiological Protection Board (NRPB) is an independent body set up by the Radiological Protection Act 1970. This Act gave the board the responsibility to advance acquisition of knowledge about the protection of mankind from radiation hazards and give advice.

The headquarters of NRPB are at Chilton in Oxfordshire; there are also centers at Glasgow and Leeds. The current director of NRPB is Professor Roger H. Clarke; previous directors were Dr. A.S. MacLena (1971-1981) and Mr. H.J. Dunster (1981-1987). Biological research is undertaken largely in the Biomedical Effects department headed by Dr. R. Cox and consisting of 28 scientists divided into four research groups: Cytogenetics, Molecular Biology, Inhalation Studies, and Radionuclide Biokinetics. The main areas of work are studies of the biokinetics, dosimetry and effects of incorporated radionuclides, and studies of the cytogenetic and molecular mechanisms involved in radiation carcinogenesis.

9 **SCK/CEN,** Studiecenter voor Kernenergie/Centre d'Étude de l'Energie Nucléaire, Mol, Belgium, B-2400 Mol Tel.32-14-312111, Fax 32-14-320372

Contact Person: Dr. Lucile Baugnet-Mahieu

The Belgian Atomic Study Center was constituted in 1954 and given a radiobiological department in 1960, Head of the department was Prof. J.R. Maisin until 1987; Prof. A. Léonard from 1987 to 1988; from 1989 to 1995 Dr. P. Govaerts; and since 1995, Dr. M. Loos. In 1989, VITO (the Flemish Institute for Technological Studies) was split from SCK-CEN and with it went a substantial part of the manpower and funding of the department. VITO is now working on topics unrelated to radiation.

During the sixties and early seventies, the department concentrated on studies related to radioprotectors and the morphological and biological mechanisms of acute radiation consequences as well as on the genetic damage. Later, interest shifted toward long-term studies on animals, late effects of radiation (especially in lung and brain),and molecular mechanisms of radiation-induced leukemia. Toward the end of eighties, and especially after the splitting of the department, research had to concentrate on fewer topics and now emphasizes effects on the developing organism with respect to induction of malformations from irradiation of mothers, early divisions of the embryos, and damage to the developing central nervous system.

10 Medical College of St Bartholomew's Hospital, Department of Radiation Biology, University of London, Charterhouse Square, GB- EC1 6BQ, London, UK, Tel. 44-171-9826106, Fax 44-171-9826107

Contact person: Prof. Dr. John E. Coggle

The Department of Radiation Biology at the Medical College of St Bartholemew's Hospital London was created as a group of the Department of Physics in the late 1950s. It then became an independent department under the directorship of Dr. P. Lindop in 1960. Its work concentrated on late effects of radiation, especially on carcinogenesis in lung and skin, on plutonium-induced life-shortening, on the role of macrophages, on pion radiobiology, and on late effects in bone marrow, kidneys, heart and GI tract. After the departure of Dr. Lindop in 1981, Dr. J. Coggle was interim director until 1986, when Dr. K.R. Trott took over the directorship. Today the principal interests of the department are: role of growth factors in skin carcinogenesis, *in utero* leukemogenesis, accelerated stem cell repopulation in human keratinocyte cultures and delayed cell death.

11 TNO Organisatie Natuurwetenschappelijk Onderzoek Medical Biological Laboratory, NL-2280 Rijswijk, Lange Kleiweg 151, The Netherlands, Tel 31-15-842842, Fax 31-15-8438191

Contact person: Prof. Dr. Johan J. Broerse, Deptartment of Clinical Oncology, University Hospital Leyden, P.O.Box 9600, NL 2300 RC

The Radiobiological Institute of the TNO at Rijswijk was created in 1956 with Prof. Dr. D. van Bekkum as director and was given the mission to conduct research in the area of radiobiology and related fields in the service of public health. Main topics of interest of the institute were hemopoietic damage from radiation with emphasis on treatment by bone-marrow transplantation and hemopoietic growth factors, including dose assessments from medical procedures, LET-RBE relationship for different radiations with emphasis on mammary tumors, mechanisms of radiation-induced carcinogenesis, carcinogenic effects of radon, dosimetry with emphasis on optimization of diagnostic radiology. In 1990, the Radiobiological Institute merged with the Primate Center TNO. In an avalanche of events due to management and financial perils, the research activities on deterministic and stochastic effects in experimental animals have been appreciably reduced and part of the staff were incorporated in the TNO Center for Radiological Protection and Dosimetry, whereas other staff joined the Department of Clinical Oncology at the University Hospital in Leyden. The histological material remains under the responsibility of Dr. C. Zurcher, Leyden; the analysis of late effects is performed by Prof Dr J.J. Broerse at the same hospital; and studies on lung tumor induction and molecular biological aspects are continued at Rijswijk by Dr. R.W. Bartstra and Dr. P Bentvelzen, respectively. Leyden can be contacted for details on the research projects.

12 Universität Freiburg, Institut für Biophysik und Strahlenbiologie, Albertstr.23, D-79104 Freiburg, FRG, Tel. 49-761-2032535

Contact person: Prof. Dr. G. Konermann

The Radiologisches Institut was created in 1914 under the directorship of W. Friedrich in order to give support to medical applications of radiation with respect to questions of dosimetry and the biological basis for modalities of delivering tumor treatment. Later directors were: Prof. Hammer from 1926-1929, Prof. O. Risse from 1929-1936, Prof. H. Langendorf from 1936-1972, and Prof. W Kreutz since 1971. The institute was destroyed by an air raid in 1944 and reconstructed after the war. During the latter years, work concentrated on the radiosensitivity of tissues, radioprotecting substances, combined effects of radiation and other agents, effects of neutrons, and biochemical alterations after irradiation. The institute was renamed Institut für Biophysik und Strahlenbiologie in 1975 in line with changes in interest. Today, radiobiological work concentrates on developmental effects of *in utero* irradiation.

13 National Defence Research Institute, Division of Radiobiology, Sundbyberg, Swedish University of Agricultural Sciences, Faculty of Veterinary Medicine, Department of Pathology, Box 7028, S-75007 Uppsala, Sweden, Tel. 46-18-671216 Fax 46-18-673532

Contact person: Dr. Pär N. Bierke

The Swedish National Defence Research Institute was founded in 1945. Its Department of Radiobiology at Sundbyberg was organized in the mid-fifties with the principal mission of developing methods for the assessment of risks associated with exposure to ionizing radiation. Research at the department dealt, in particular, with the carcinogenic and genetic effects of Sr-90, Pu-239, X-rays and neutrons, and with radioprotective substances.

The first head of the department was Prof. Karl Johan Clemedsson, followed by professors Arne Nelson, Agnar Nilsson, and Gunnar Walinder. The department concentrated on research dealing with the carcinogenic and genetic effects of Sr-90, Pu-239, X-rays and neutrons as well as on studies on radioprotectors. In 1979, the department was split into two divisions, one of which was located in Umea. The study of late effects remained in Sundbyberg until 1981 when this research temporarily became an integrated part of Stockholm University before it was ultimately transferred to the Department of Pathology at the Swedish University of Agricultural Sciences in Uppsala.

14 URCRM, Ural Research Center of Radiation Medicine, Medgorodok Chelyabinsk, 454076, Russia, Tel. 7-3512-344-331, Fax 7-3512- 344-321

Contact person: Prof. Dr. V.L. Shvedov

Branch N4 of the Institute of Biophysics, USSR Ministry of Health, Moscow, was organized in 1958 as a governmental institute. Its principal missions were epidemiological, clinical and hygienic investigations of the population of the Ural region and an experimental assessment of the influence of radiation pollution. The experimental laboratory aimed principally to study the effects of Sr-90 in rats and chronic external gamma irradiation.

The head of the experimental laboratory from 1962 to 1990 was Prof. V.L. Shvedov, M.D. In 1990, Branch N4 of the Institute of Biophysics was renamed the Ural Research Center for Radiation Medicine (URCRM) (Director: A.V. Kleyev, M.D.). Since 1990, Dr. V.S. Korytny has headed the URCRM Experimental Department.

At the present time, the principal topics of interest are the mechanisms of chronic radiation disease, radiation carcinogenesis, and tumor prophylaxis.

15 EULEP, European Late Effect Project Group

Contact person: Prof Dr. John W. Hopewell, University of Oxford, CRC, Normal Tissue Radiobiology Group, The Churchill Hospital, GB Oxford OX3 7LJ, UK, Tel. 44-1865-225848, Fax 44-1865-225847

The European Late Effect Group (EULEP) was created in 1970 as a formally constituted research network comprising at the present time 23 institutions and university laboratories as voting laboratories plus a substantial number of corresponding members. The objectives of EULEP are to coordinate research relevant to understanding the late biological effects of ionizing radiation in the mammalian organism, including man; to promote exchange of scientific information between the member institutions; and to offer expert advice to administrations and governmental agencies concerning the risks and the safe use of ionizing radiation. The first chairman of EULEP, Dr. K. Hollander was followed by Dr. J.M. Duplan and Dr. J.R. Maisin and, since 1995, by Dr. J.W. Hopewell. EULEP receives its principal support from the Radiation Protection Research Program of the European Commission (EC) and is now being coordinated by EC in a larger cooperative network with the European Radiation Dosimetry Group (EURADOS) and the International Union of Radioecologists (IUR).

16 University of Oxford, CRC Normal Tissue Radiobiology Research Group, The Churchill Hospital, GB Oxford, OX3 7LJ, UK, Tel. 44-1865-225848, Fax 44-1865-225847

Contact Person: Prof. Dr. John W. Hopewell

The Churchill Hospital Research Institute was set up in 1970 as a University Institute with the principal mission to examine the effects of radiation on normal healthy tissues from the viewpoint of radiation therapy and radiobiological protection. The Institute is presently working on the following general topics:

- cellular and molecular mechanisms of radiation damage to normal tissue,
- treatment methods for the modulation of normal tissue radiation damage,
- radiological protection aspects of the effects of "hot" particles on the skin,
- effects of modified dose fractionation schedules and low dose-rate irradiation on normal tissue responses,
- radiological aspects in normal tissues related to the clinical application of boron neutron capture therapy for the treatment of glioblastoma.

The founder and Director of the Institute (1970-1980) was Dr. G. Wiernik. Dr. W. Hopewell has been Director of the Institute from 1980 until the present time.

17 Universität Ulm, Institut für Arbeits und Sozialmedizin, Albert Einstein Allee 11 D-89081 Ulm, FRG, Tel. 49-731-5023400, Fax 49-731-5023415, e-mail fliedner@faw.uni-ulm.de

Contact person: Prof. Dr. Theodor M. Fliedner

The Department of Clinical Physiology, Occupational and Social Medicine of the University of Ulm was founded on Feburary 25, 1967. It was on this particular day that the University of Ulm was created, and Prof. T.M. Fliedner, the Director of the Department, has been one of the eight founding full professors of the University of Ulm. At that time, the department was part of the clinical research center whose main function was research and teaching. The research was devoted to the study of the physiology and pathophysiology of cell renewal systems, especially of hemopoiesis, using, at that time, autoradiographic and cell culture techniques. In addition and, due to the support of the European Communities (EURATOM), the Department of Clinical Physiology devoted many of its resources to the study of radiation-induced early and late effects of hematopoiesis. It was in this context that the diagnostic and therapeutic procedures to treat the acute radiation syndrome were further developed and improved. Special attention was paid to the development of the experimental basis for the use of blood stem cells for the restoration of radiation-induced bone-marrow failure.

Between 1967 and 1995, the research work of the department developed to include studies on the use of cytokinines to influence bone-marrow regeneration after total-body irradiation, to study the development of biomathematical models for understanding the pathophysiology and clinical development of the acute radiation syndrome. In addition, studies were launched, and continue, on the molecular biology of the regulation of hematopoiesis under normal circumstances and after total body irradiation. Further studies were devoted to biological monitoring and to environmental medicine.

As far as academic teaching is concerned, the department is involved in the teaching of radiation biology and occupational medicine. The department also has responsibilities in occupational medicine and takes care of occupational medicine for more than 10,000 employees. The department is recognized as a WHO Collaborating Center for Radiation Accident Management.

18 Dr. Daniel den Hoed Cancer Center (DDHCC), Department of Radiation Oncology, subdivision of Clinical Radiobiology, Groene Hilledijk 301, PO Box 5201. NL 3075, EA Rotterdam, The Netherlands, Tel. 31-10-4301658, Fax 31-10-4864596, Email aardweg@rtrh.azr.nl

Contact person: Dr. Gerard J.M.J. van den Aardweg

In 1914, the Rotterdam Radiotherapeutic Institute was founded. In 1964, it moved to its current location and was renamed Dr. Daniel den Hoed Cancer Center (DDHCC) after its former director. Clinical research at the department of Radiation Oncology (Head, Dr. P.C. Levendag) is currently focused on brachytherapy (HDR/PDR/LDR) and conformal therapy. In the subdivision of Clinical Radiobiology, research is concentrated around three topics:

- improvement of acute and late normal tissue responses in a brachytherapy setting with emphasis on
  - the kinetics of SLD-repair using skin as a model,
  - age-related changes in the gut after irradiation, in collaboration with the Institute of Pathology, EUR (Head, Prof. W.J. Mooi);
- tumor response after brachytherapy;
- molecular mechanisms of DNA-repair after ionizing radiation. This is a collaborative project with the Department of Cell Biology and Genetics, Erasmus University, Rotterdam (Head, Prof. D. Bootsma).

Institutes Participating in the U.S. National Radiobiology Archives

101 UTAH Radiobiology Laboratory, University of Utah, Department of Radiobiology, Building 586, University of Utah, Salt Lake City, Utah 84112, USA, Tel. 801-581-7117, Fax 801-581-7008

Contact Person: Dr. Scott Miller

The Radiobiology Laboratory at the University of Utah conducted experiments on a variety of radionuclides starting in 1950. The origins of the Utah program were described by T. Dougherty et.al. in "Studies of the biological effects of ^{226}Ra, ^{239}Pu, ^{228}Ra (MsTh), ^{228}Th (RdTh) and ^{90}Sr in adult beagles" *Radiation Research* **17**:625-681,1962, and B.J. Stover and C.N. Stover, Jr., "The laboratory for Radiobiology at the University of Utah," in *Radiobiology of Plutonium*, JW Press, Salt Lake City, 1972, pp. 29-46. The kennels were demolished to allow for campus expansion, and remaining life-span animals were transferred to the Inhalation Toxicology Research Institute (ITRI) in 1987. Department of Energy support of the laboratory was phased out by 1995. Formalin- or alcohol-fixed tissues, histopathological slides, microdosimetry preparations of bone specimens and radiographs have been discarded. Paraffin blocks and clinical records are available at the University of Utah. Electronic copies of the database are available at the National Radiobiology Archives.

The Beagle studies at Utah were initiated by the Atomic Energy Commission to predict the risk from ^{239}Pu in people, based on the observed effects in the U.S. radium dial painters and the relative toxicity of ^{239}Pu vs. ^{226}Ra, to be established in young adult beagles. For simplicity and reproducibility, most of the dogs received a single intravenous injection of radionuclide, usually in citrate solution, at about 17 months of age when their skeletal maturity corresponded to that of an 18-year-old radium dial painter or plutonium worker. Additional radionuclides were also studied in young adult beagles. Some dogs were injected with ^{239}Pu or ^{226}Ra at either 3 months of age (to represent children) or 5 years of age (to represent middle-aged persons).

Drs. Austin Brues, Robley Evans, and Wright Langham provided the impetus and guiding direction for the Utah studies. The laboratory directors have been: John Z. Bowers (1950–1952), Thomas F. Dougherty (1952–1974), W. "Web" S.S. Jee(1974–1979) McDonald E. Wrenn (1979–1987), and Scott C. Miller (1987–1995). Other investigators associated with the Utah studies were (in alphabetic order): J.S. Arnold, D.R. Atherton, D.L. Berliner, F.W. Bruenger, J.H. Dougherty, R.D. Lloyd, C.W. Mays, C.E. Rehfeld, N.P. Singh, W. Stevens, B.J. Stover, G.N. Taylor, M.A. Van Dilla and L.A. Woodbury. In addition, Erich Polig of the Kernforschungszentrum, Karlsruhe, Germany, has had a long association with the Utah studies.

102 Institute of Toxicology and Institute of Toxicology and Environmental Health (ITEH), University of California at Davis (Davis), Old Davis Road, Davis, California 95616, USA, Tel: 916-752-7754, Fax 916-752-5300

Contact Person: Dr. Otto Raabe

The DOE-sponsored laboratory at the University of California at Davis has been known by several names including: AEC Project Four or Six, the Laboratory for Energy-Related Health Research (LEHR), and, most recently, Institute of Toxicology and Institute of Toxicology and Environmental Health (ITEH). The Davis laboratory conducted X ray, strontium-90, and radium-226 life-span dog experiments. The X-ray study focused on tumor induction and life-span shortening after acute exposure. The strontium studies were used to evaluate the health risk from fallout strontium-90. The radium-226 study was designed to simulate the exposure pattern of the human dial painters. Department of Energy support of the laboratory phased out by 1992; biological specimens and research records were transferred to the NRA in 1990.

Laboratory directors at Davis have been: A.C. "Bud" Andersen (1951–1965), Leo K. Busted (1965–1973), Marvin Goldman (1973–1985), Leon S. Rosenblatt (1985–1990), and Otto G. Raabe (1990–1992). Other investigators associated with the Davis studies were (in alphabetic order): S.A. Book, G.R. Cain, M.R. Culbertson, R.J. Della Rosa, T.G. Kawakami, A.K. Klein, D.H. McKelvie, M.H. Momeni, J.P. Morgan, N.J. Parks, R.R. Pool, W.L. Spangler, and F.D. Wilson.

103 Argonne National Laboratory (ANL), Center for Mechanistic Biology and Biotechnology, 9700 South Cass Avenue, Argonne, IL 60439, USA, Tel: 708-252-3824, Fax: 708-252-3387

Contact Person: Dr. Bruce Carnes

Argonne National Laboratory and its predecessor the University of Chicago (Metallurgical Laboratory) were very active in radiobiological research from the 1940s through the 1990s. The early studies conducted by Brues and Sacher at the University of Chicago and by Lorenz at NCI (funded by the Metallurgical Laboratory) focused primarily on estimating a maximum permissible dose for X-rays and gamma-rays using a variety of mouse strains. Once the Division of Biological and Medical Research was established at Argonne National Laboratory in the 1950s, research shifted to issues of long-term injury, dose response, and interspecies comparisons. When the JANUS biomedical reactor became operational in 1970, a 22-year effort was begun to investigate the acute and chronic effects of neutron and gamma-ray exposure using the B6CF1 mouse. A documentation of the ANL mouse studies conducted between 1953 and 1992 has been described by D. Grahn in two ANL technical documents published in 1994 and 1995 and available through the NRA.

ANL began beagle experiments in 1956 with studies of strontium-90 conducted by Miriam Finkel. These were followed in 1960 by life-span studies of injected cerium-144, cesium-137, conducted by Thomas E. Fritz and William P. Norris. A large study of life-span effects of continuous exposure to Co-60 gamma-ray studies was initiated by Dr. Norris; this study was terminated in 1992, when remaining animals were transferred to ITRI. Study materials from the beagles are stored at ANL. Most tissue specimens have been discarded. Paraffin blocks and histopathology slides are available.

The Internal Emitter Program at Argonne was, for 25 years, the focal point of medical and dosimetric studies of the U.S. radium dial painters. Argonne's study is the largest ever undertaken of the effects on humans of an internally deposited radioelement. One may argue that such a human epidemiology study is not, strictly speaking, a radiobiology study, and thus is inappropraite for inclusion in this document. However, we have elected to include it because so many radiobiology investigations were based on the premise that effects in animals could be extrapolated to humans by comparision of the effects of radium. A comprehensive review of the dial painter study, by R.E. Rowland, was published as a book by ANL in 1994. Research materials from the Internal Emitter Program are available at the United States Transuranium Registries.

Investigators associated with the ANL radiobiology studies were (in alphabetic order): J.S. Arnold, E.J. Ainsworth, A.M. Brues, B. A. Carnes, A. J. Finkle, M.P. Finkel, T.E. Fritz, R.J.M. Fry, S.A. Fry, D.J. Grdina, D. Grahn, L.V. Kaspar, A.T. Keane, S. Lesher, L.S. Lombard, W.B. Looney, W.P. Norris, R.E. Rowland, J. Rundo, G.A. Sacher, T.M. Seed, S.P. Stearner, R.G. Thomas, J.F. Thomson, R.E. Toohey, D.V. Tolle, and F.S. Williamson

104 Pacific Northwest National Laboratory (PNL), Health Division, Biology and Chemistry Department, 331 Building, PO Box 999, Richland, WA 99352, USA, Tel. 509 372 4838

Contact Person: Dr. Dick Weller

PNL, formerly known as Hanford Works, HW, Hanford Engineering Works, was active in large-animal radiobiology studies (sheep, pigs, dogs) in addition to conventional rodent studies. The name of the laboratory was changed to Pacific Northwest National Laboratory (PNNL) in 1995, but it will be refered to as PNL in this document.

PNL started its life-span dog plutonium experiments in 1959. The studies, which include inhalation of plutonium oxide and plutonium nitrate, were initiated by W.J. "Bill" Bair and continued under J.F. Park. Significant long-term studies involving rodents include the radon studies conducted by F.T. Cross and the low-level plutonium studies of C.L. Sanders. Paraffin blocks, histopathology slides, radiographs, and clinical records are available at the National Radiobiology Archives at PNL. Tissue specimens have been discarded.

Investigators associated with the PNL radiobiology studies were (in alphabetic order): W.J. Bair, L.K. Bustad, W.J. Clarke, D.K. Craig, F.T. Cross, G.E. Dagle, R.E. Filipy, M.E. Frazier, E.B. Howard, F.P. Hungate, H. Kornberg, J.E. Lund, R.O. McClellan, K.E. McDonald, W.D. Norwood, R.F. Palmer, J.F. Park, H.A. Ragan, C.L. Sanders, M.R. Sikov, V.H. Smith, B.O. Stuart, M.F. Sullivan, C.R. Watson, and R.E. Weller.

105 Inhalation Toxicology Research Institute (ITRI), Lovelace Biomedical and Environmental Research, PO Box 5890, Albuquerque, NM 87185-5890, USA, Tel. 505-845-1090, Fax: 505-845-1198

Contact Person: Dr. Bruce Boecker

The Inhalation Toxicology Research Institute (ITRI) is operated by the Lovelace Biomedical and Environmental Research Institute; early publications cite Lovelace as the institution at which the research was performed. ITRI is the largest DOE-supported laboratory dedicated to the study of basic inhalation toxicology. Studies cover the entire range of biological systems, including macromolecules, cells, tissues, laboratory animals, and humans.

ITRI has conducted dog life-span experiments on a variety of fission products including yttrium-90, strontium-90, yttrium-91, cesium-137, and cerium-144, radionuclides that predominate in a reactor inventory after a period of sustained operation. Subsequently, investigations were extended to include plutonium-238 and 239 dioxide. The dosimetry and pathogenesis of disease for inhaled radionuclides were studied for a broad range of α-, β-, and γ-emitting radionuclides in different physical and chemical forms. Long-term rodent studies at ITRI include repeated inhalation exposures of plutonium-239or cerium-144 oxide , combined exposures of plutonium-239 oxide and 1) X-rays, 2) inhaled beryllium metal aerosols, 3) inhaled cigarette smoke, or 4) injected chemical carcinogens. Additional long-term studies have involved inhaled curium-244 oxide, injected Thorotrast and plutonium-239 citrate.

Materials from these studies are available at ITRI; electronic copies of database files are available throuth the National Radiobiology Archives at PNL.

Investigators associated with the ITRI long-term radiobiology studies were (in alphabetic order): S.A. Benjamin, M.A. Berry, B.B. Boecker, A.L. Brooks, T.L. Chiffelle, R.G. Cuddihy, J.H. Diel, G.L. Finch, N.A. Gillett, W.C. Griffith, R.A. Guilmette, F.F. Hahn, C.H. Hobbs, R.K. Jones, S.E. Jones, G. Kanapilly, D.L. Lundgren, J.L. Mauderly, R.O. McClellan, T.T. Mercer, J.A. Mewhinney, B.A. Muggenburg, G.J. Newton, K.J. Nikula, J.A. Pickrell, O.G. Raabe, H.C. Redman, B.R. Scott, D.O. Slauson, M.B. Snipes, and R.G. Thomas.

106 Ernst O. Lawrence Berkeley Laboratory (LBL), University of California at Berkeley, 1 Cyclotron Road, Berkeley, CA 94720, USA, Tel: 510-486-6055, Fax: 510-486-6746

Contact Person: Dr. Patricia Durbin

Lawrence Berkeley Laboratory has a long history of biomedical research. Initial efforts were conducted using a 36-inch cyclotron in the Lawrence Radiation Laboratory. Other biomedical functions were associated with the medical research facility, the Donner Laboratory. Much of the early research was associated with the Crocker Laboratory until the dismantling of the 60-inch medical cyclotron in 1960 caused merging of all radiobiology programs under the aegis of LBL.

J. G. Hamilton and P.W. Durbin conducted numerous metabolism studies characterizing each newly available artifically produced radionuclide. Durbin's work with primates using neptumium-237, plutonium-237, plutonium-238, amiricium-241, and strontium-90 is unique. Paraffin blocks, histopathology slides, and dosimetric preperations are available at LBL. Detailed summary information from these studies is stored as a sequestered collection at NRA, pending release by Dr. Durbin.

107 Oak Ridge National Laboratory (ORNL), Biology Division, PO Box 2009, Oak Ridge, TN 37831-8077, USA, Tel. 615-574-1251, Fax 615-576-4149

Contact Person: Dr. R.J. Michael Fry

ORNL conducted many studies using external irradiation of rodents. Details of many of the early "megamouse" studies are no longer available. Two recent studies, focused on the influence of gamma-irradiation on the development of cancer and the susceptibility for radiogenic cancer related to natural incidence, are available through the NRA. ORNL became the leading institution in the field of internal radionuclide dosimetry, through the efforts of W.S. Snyder and K.Z. Morgan. Electronic records are available at the NRA. Laboratory records, slides, and paraffin blocks are at ORNL.

Investigators associated with the ORNL radiobiology studies were (in alphabetic order): R.J.M. Fry, A. Hollaender, C.R. Richmond, L.B. Russell, W.L. Russell, J.B. Storer, R.L. Ullrich, and A.C. Upton

108 CETT/CRHL Colorado State University (CSU), Foothills Campus, Fort Collins, CO 80523, USA, Tel. 303-491-8285, Fax 303-491-8304

Contact Person: Dr. Stephen Benjamin

In 1962, a beagle colony was established at CSU as a joint effort of Colorado State University, the U.S. Public Health Service Radiological Health Division, and the National Institutes of Health. After completion of the facilities, funding was primarily through the U.S. Food and Drug Administration's Center for Devices and Radiological Health (formerly Bureau of Radiological Health), which sponsored a large life-span beagle dog study to determine the lifetime hazards associated with prenatal and early postnatal exposure to Co-60 gamma irradiation. Other experiments with simulated plutonium-contaminated wounds were conducted for the DOE, but no animals were kept for life-span observation. In 1992, the laboratory became the Center for Environmental Toxicology, and, in 1995, the Center was renamed the Center for Environmental Toxicology and Technology (CETT).

Formalin-fixed tissues, paraffin blocks, histopathology slides, serial radiographs, and extensive clinical records are available at Colorado State University. Copies of the computer databases are available through the NRA.

Laboratory Directors were: William D. Carlson; 1962-64, R. John Garner, 1964-71; Max R. Zelle, Acting (1972); Robert D. Phemister, 1973-76; and Stephen A. Benjamin, 1977-91.

Investigators associated with the CSU radiobiology studies were (in alphabetic order): G.M. Angleton, M.M. Benjamin, S.A. Benjamin, J.L. Bishop, R.D. Brewster, R.K.Brooks, W.D. Carlson, R.J. Garner, B.F. Hamilton, A.M. Hargis, R.S. Jaenke, D.N. Kitchen, A.C. Lee, C.W. Miller, G.K. Miller, D.L. Montgomery, A.C. Nicholson, K.J. Nikula, R. W. Norrdin, R.D. Phemister, W.A. Sansing, W.J. Saunders, J.N. Shively, L.C. Stephens, R.W. Thomassen, W.J. Tietz, and J.S. Williams.

109 Brookhaven National Laboratory (BNL), Brookhaven Associated Universities, Building 409, Upton, NY 11973, USA, Tel. (516) 282-7538, Fax (516) 282-5311

Contact Person: Dr. Eugene Cronkite

The Brookhaven National Laboratory has always had a strong biomedical division, with a focus on human exposures and therapy, environmental contamination and dosimetry. Some large studies of rodents and weapons testing fallout were conducted in the late 1950s. The detailed results of these have been discarded. Two significant studies were started in the 1980s. These are sequestered donations to the National Radiobiology Archives. The experiments are ongoing, and results will be published by BNL personnel.

Investigators associated with the BNL radiobiology studies were (in alphabetic order): V.P. Bond, A.L. Carsten, R. Conrad, E.P. Cronkite, L. Farr, H.A. Johnson, and J.A. Shellabarger.

110 University of Rochester (UR), Strong Memorial Hospital (formerly Atomic Energy Project), Crittenden Blvd, Rochester NY14618, USA

Contact Person: Dr. J. Newell Stannard, 17446 Plaza Dolores, San Diego, CA 92128

The U.S. Atomic Energy Commission supported research at the University of Rochester from 1943 to 1965. Responsibility for the project resided in two academic departments, the Division of Radiobiology and Biophysics, and the Division of Pharmacology and Toxicology in the School of Medicine and Dentistry. Organized as part of the Manhattan Project, under the leadership of Andrew Dowdey and Harold C. Hodge, over 300 people worked round-the-clock to characterize the biological properties of the newly produced radioactive materials. The University of Rochester is primarily associated with studies of uranium, polonium, plutonium, and radium, and development of inhalation toxicology techniques. Eventually, rats, dogs, and monkeys were exposed in a chamber containing uranium ore dust on a 6-hour/day, 5-day/week schedule for several years. Materials, including laboratory record books, from the UR studies have been discarded.

Investigators associated with the UR radiobiology studies were (in alphabetic order): W.F. Bale, G. Boyd, G. Casarett, D.R. Charles, A.L. Dounce, R. Fink, J.W. Howland, H.C. Hodge, R. Metcalf, W.F. Neuman, A. Rothstein, H. Silberstein, H. Stokinger, and G. Suter.

111 Chalk River Laboratories, Atomic Energy of Canada, Limited (AECL), Chalk River, Ontario, K0J 1J0, Canada, Tel. (613)584-3311 Ext. 4728, Fax (613)584-4024

Contact Person: Richard V. Osborne

AECL was established in 1952 with a mandate to conduct R&D and to commercially exploit technologies related to nuclear energy. AECL's major achievement, in collaboration with Canadian utilities and private sector companies, is the development of the CANDU nuclear power system, which is a key component of Canada's energy sector. Research at Chalk River spans four key areas:

- reactor scientists and engineers provide the underlying knowledge that ensures the continuing superior performance of the CANDU power reactor;
- environmental researchers examine environmental processes to protect against undesirable impacts of nuclear energy;
- **the research of biologists and other health scientists ensures that nuclear technologies do not impact on Canadians health and well-being;**
- physicists and other researchers investigate the fundamental properties of matter and materials using accelerators and neutron scattering techniques.

Materials, including laboratory record books, from the AECL studies are available at the laboratory.

Investigators associated with the AECL radiobiology studies were (in alphabetic order): H.C. Bernbom, N. Gentner, N.J. Gragtmans, J.R. Johnson, A.R. Jones, A.M. Marko, R.E.J. Mitchel, D.P. Morrison, D.K. Myers, H. Newcombe, and M. Paterson.

Institutes participating in the Japanese Radiobiology Archive[2]

201 National Institute of Radiological Sciences (NIRS), 4-9-1 Anagawa, Inage-ku, Chiba-shi, Chiba 263, Japan, Tel. 81-43-251-2111, Fax 81-43-256-9616

Contact person: Dr. Toshiaki Ogiu

NIRS was established on July 1, 1957 as a special research institute under the auspices of the Science and Technology Agency of the Japanese government. The aim of the NIRS is to investigate radiation injury and related fields; in particular, the mechanisms, prevention, diagnosis and treatment, as well as the medical application of radiation and radioactive isotopes. The research projects conducted by several research divisions are based on two major objectives:

- the medical use of radiation and radioisotopes. This includes radiation therapy of malignant tumors with neutron and proton beams. The heavy ion beam delivered by the HIMAC (Heavy Ion Medical Accelerator in Chiba) has been in operation since 1993.
- radiation health sciences which covers two areas:
  - environmental research; i.e., radioecology, radiotoxicology, radiation measurements, protection and risk analysis;
  - biomedical research; i.e., radiation biology, clinical treatment of exposed subjects, late effects of radiation, and mechanisms of hematological and immunological disorders.

202 Institute of Environmental Science (IES), Department of Radiobiology, 1-7 Ienomae, Obuchi, Rokkasho-Mura, Aomori 039-32, Japan, Tel. 81-175-71-1246, Fax 81-175-72-3690

Contact Person: Dr. Sumiko Sasagawa

The IES was established under the auspices of the Science and Technology Agency (STA) of the Japanese government in December, 1990 at Rokkasho-Mura in the Aomori Prefecture, where large-scale commercial nuclear fuel cycle facilities are being installed.

The objective of research projects conducted by three research departments in the IES is as follows:

- to study experimentally the effects of low dose ionizing radiation on animal and the biological responses to ionizing radiation within the LERF (Low-Dose Radiation Effects Research Facilities);
- to develop site-specific transfer parameters and more realistic transfer models for radioactive nuclides through radioecological studies in the local environment;
- to construct the Closed Ecology Experiment Facility (CEEF) and to study circulation mechanisms of materials in the environment using the strictly controlled CEEF.

The IES is also contributing to local communities through the transfer of technologies and information obtained by research activities.

203 Hokkaido University, Graduate School of Veterinary Medicine, Department of Environmental Veterinary Medicine, Laboratory of Radiation Biology, Sapporo 060, Japan, Tel. 81-11-706-5235, Fax 81-11-717-7569

Contact Person: Dr. Fumiaki Sato

Hokkaido University was established in 1876, and now has 12 faculties and 13 graduate schools. The school of Veterinary Medicine has 17 laboratories and an animal hospital. The Laboratory of Radiation Biology is interested in the effects of ionizing radiation on DNA, tissues, and whole bodies.

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[2] All the data, including institute description and experimental data, were provided by the courtesy of scientists themselves and by no means represent a decision or policy of the institute. Since communication with some institutions may be difficult, it is recommended either to write a letter or send a facsimile to the contact person or to Dr. Shin Saigusa, Scientific Secretary of JRA.

204 Tohoku University, School of Medicine, Department of Radiation Research, Seiryo-machi 2-1, Aoba-ku, Sendai-shi, 980-77, Japan, Tel. 81-22-274-1111, Fax 81-22-272-7273

Contact Person: Dr. Tetsuya Ono

The Department of Radiation Research was established in 1962 to perform research in radiation biology and related subjects. The chairpersons were Dr. Masatoshi Sakka from 1963, Dr. Kiyohiko Sakamoto from 1981, and Dr. Tetsuya Ono since 1988. Current studies are on molecular mechanisms of aging and late effects of radiation, DNA methylation, DNA damage and repair, mutational effects of radiation, radiation sensitivities, and low-dose effects.

205 The University of Tokyo, Faculty of Medicine, Department of Radiation Biophysics, Hongo 7-3-1 Bunkyo-ku, Tokyo 113, Japan, Tel 81-3-3812-2111

Contact Person: Dr. Tetsuya Ono, Department of Radiation Research, Tohoku University

The Department of Radiation Biophysics was established in 1967 for research and education on radiation effects. The first chairman was Dr. Shigefumi Okada. The second is Dr. Norio Suzuki, since 1986. Current research is on tumor radiobiology, metastasis, molecular biology of radiation effects, protein kinesis, and cell death.

206 The University of Tokyo, Faculty of Medicine, Department of Radiological Health, Hongo 7-3-1 Bunkyo-ku, Tokyo 113, Japan, Tel 81-3-3812-2111, Fax 81-3-5684-5274

Contact Person: Dr. Tomoko Kusama

The department was established in 1960 to carry out research on fundamental radiation protection. The first and second Directors of Department were H. Katsunuma and Y. Yoshizawa. Current Director is Y. Aoki.Basic research deals with radiation protection and risk estimation of carcinogenesis in the medical and nuclear energy field, with radiation carcinogenesis studies in mice, especially with embryonic / fetal effects and with radiation effects on the molecular level.

207 Research Institute of Environmental Medicine, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-01, Japan,Tel. 81-52-789-3874, Fax 81-52-789-3887

Contact Person: Dr. Yoshiro Kameyama

The Research Institute was established at the Nagoya University in 1946. The institute consistis of six departments: Neurology and Sensory Functions, Metabolism and Endocrinology, Circulation and Respiration, Pathology and Embryology, Aerospace Physiology, Aerospace Psychology. The primary purpose of the institute is to investigate human adaptation to environments and its medical application. Environmental medicine is a multidisciplinary biomedical science to study how to maintain good health and how to prevent diseases caused by the disruption of adaptation in rapidly changing living environments and in newly explored environments, such as outer space and high altitude.

Since 1958, the Department of Pathology and Embryology has conducted experimental studies on developmental effects of physical environmental agents (e.g., ionizing radiation, microwaves, radiation hypoxia) and of chemical environmental agents.

208 Shiga University of Medical Science, Department of Experimental Radiology, Otsu, Shiga 520-21, Japan, Tel. 81-775-48-2207, Fax 81-775-43-5709

Contact Person: Dr. Hiroshi Kimura

The Department of Experimental Radiology was established in 1976. The chairperson is Prof. Takashi Aoyama (since 1976), who will retire at the end of March, 1996. Current research subjects are molecular mechanisms of radiation, sensitivity of cultured cells, recovery processes in radiation-induced damage, radiation mutagenesis, and radiation effects on bone. Epidemiological study on Japanese radiological technologists and measurements of environmental radon concentrations have also been carried out.

209 Nara Medical University, Department of Biology, 840 Shijo-cho, Kashihara, Nara, 634, Japan, Tel. 81-7442-2-3051, Fax 81-7442-5-3345

Contact Person: Dr. Takeo Ohnishi

The Department of Biology was established in 1958 for education and research in biology and its related fields. The directors were Dr. T. Hara from 1958, followed by Dr. K. Nozu from 1974 and Dr. T. Ohnishi since 1989.The current research subjects are biological responses to and molecular mechanism of environmental stresses, including ionizing radiation, UV and the space environment.The relationship between carcinogenesis and gene expression has been emphasized, as well as the mechanisms of development/differentiation in space environment.

210 Osaka University, Faculty of Medicine, Department of Radiation Biology, Yamada-Oka, Suita, Osaka 565, Japan, Tel. 81-6-879-3819, Fax 81-6-879-3810

Contact Person: Dr. Taisei Nomura

Radiobiological studies started in 1967 in Osaka University to define the mechanism of cell death, mutagenesis, teratogenesis and carcinogenesis in man and animals and to estimate the risk of radiation to human beings. Director and principal investigator of this project was Dr. T. Nomura at the first Department of Surgery from 1967 to 1975, at the Institute for Cancer Research from 1973 to 1984, at the Department of Radiation Biology and Institute of Experimental Animal Sciences from 1978 to the present time, and also at the Radioisotope Center from 1995. In addition, studies on mutagenesis and carcinogenesis as well as basic studies on morphology and function have been carried out with human organs and tissues maintained in severe combined immunodeficient mice.

211 Osaka Prefecture University, Research Institute for Advanced Science and Technology, Department of Applied Biological Sciences, 1-2 Gakuen-cho, Sakai-shi, Osaka 593, Japan, Tel. 81-722-52-1161, Fax 81-722 52-1163

Contact Person: Dr. Masaaki Okumoto

Osaka Prefecture University was founded in 1949 and now has five colleges, five graduate school divisions, and a research institute. The Research Institute for Advanced Science and Technology was established from the Radiation Center of Osaka Prefecture in 1990 for interdisciplinary studies on advanced science and technology, across the framework of various departments and colleges.

The Department of Applied Bioscience was set up in order to fulfill its responsibility for rapidly progressing areas of life science. The current subjects of research are molecular mechanisms of radiation carcinogenesis and some hereditary diseases.

212 Hiroshima University, Research Institute for Radiation Biology and Medicine, Kasumi 1-2-3, Minami-ku, Hiroshima, 734, Japan, Tel. 81-82-257-5555, Fax 81-82-255-8339

Contact Person: Dr. Hiromitsu Watanabe

The Institute was established under the name Research Institute for Nuclear Medicine and Biology in 1961 to investigate radiation biology and medicine and reorganized as the Research Institute for Radiation Biology and Medicine in 1995. Its director were Dr. Susumu Watanabe from 1961, Dr. Kiyoshi Shimizu from 1967, Dr. Naomasa Okamoto from 1970, Dr. Takeshi Ohkita from 1977, Dr. Kenjiro Yokoro from 1981, Dr. Minoru Kurihara from 1985, Dr. Takao Hattori from 1987, Dr. Atsushi Kuramoto from 1989, and Dr. Yukio Satoh since 1995. The institute has four research divisions: the Division of Environmental Biology (Department of Radiation Biology, Environment and Mutation, Cancer Research, Regulatory Radiobiology), Molecular Biology (Department of Molecular Pathology, Cancer Cytogenetics, Biochemistry and Biophysics, Developmental Biology and Oncology), Social Medicine (Department of Epidemiology, Envirometrics and Biometrics) and Clinical Research (Department of Hematology and Oncology, Surgical Oncology), and three attached facilities; the International Radiation Information Center, Radiation Facilities and Animal Facilities. Moreover, the two clinical departments, Internal Medicine and Surgery, provide accommodations with 90 beds in the University Hospital, and have been operating clinics for atomic bomb survivors since 1962.

The following institutions while not directly involved in late-effect studies on experimental animals, play a crucial role in the promotion of radiation protection research and practice in Japan:

213 Nuclear Safety Research Association (NSRA), Hibiya-daibiru, 1-2-2 Uchisaiwai-cho, Chiyoda-ku, Tokyo 100, Japan, Tel. 81-3-3503-5785, Fax 81-3-3508-9093

Contact person: Dr. Kazuo Tanaka (Technology Research Department, Section 4)

NSRA was established on June 1, 1964, as a nonprofit research organization on nuclear safety under the auspices of the Prime Minister and the Minister of International Trade and Industry. The objective of NSRA is to practice various activities on nuclear safety, including surveys and researches, international cooperation, and management and dissemination of information on the fields related to nuclear fuel cycle, such as nuclear power plants, nuclear fuel, radioactive waste disposal, and off-site emergency plans and preparedness. The association is also conducting research programs for cellular and animal studies on the effects of radiation and their relationship to effects in man with the participation of scientists from universities. The programs include: safety assessment of low level radiation exposure, epidemiological collaborative study on high-background areas in China, and mechanisms of cancer from low-dose radiation exposure.

214 Health Research Foundation (HRF), 130-5, Tanaka-Monzen-cho, Sakyo-ky, Kyoto 606, Japan Tel. 81-75-702-1141, Fax 81-75-702-2141

Contact Person: Prof. Dr. Tsutomu Sugahara (Chairman)

The Health Research Foundation (HRF) was established by the Ministry of Education, Science and Culture in 1942 as a nonprofit organization for the health research and utilisation of its outcome by the public and was based on a donation from Prof. emeritus Kanji Tsuji. The activities of the foundation are concerned with two major objectives:

- health topics, including: health promotion, cancer prevention and treatment, health risks, and analytical methods in biology and medicine;
- public activities, including: operation of a blood bank, bimonthly publication of the periodical " Environment and Health" since 1988, and financial support to scientific societies and organizations.

A current research project, epidemiological studies of high-background radiation, is pursued in cooperation with Chinese and Indian scientists.

Scientists Responsible for, or Participating in, the Animal Investigations

(in alphabetical order with the institution where the experiments were carried out, their present address when known, and their personal status, when known)

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Prepared under the Auspices of

European Commission
Nuclear Fission Safety Programme
Radiological Impact on Man and the Environment

and the

European Late Effect Project Group (EULEP)

by

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01 AEA Environment & Technology Harwell Laboratory

01.01 Combined Effects of Pu-239 Dioxide and Cigarette Smoke on the Production of Lung Tumors in the Mouse

Institution: Biomedical Research Department, AEA Technology, Harwell Laboratory, Harwell, UK

Scientists: N.D. Priest; active
T.M. Eldred; active
P.N. Brooks; active
J.P. Kellington; active

Purpose: To determine whether cigarette smoke and Pu-239 dioxide act synergistically with respect to the production of lung tumors in CBA/Ca mice.

Status: 1987 - 1991, terminated

Treatment: Actinide exposure: single nose-only inhalation of Pu-239 (1.5 μm AMAD, 1.2-1.3 σg) prepared by calcination of the oxalate at 550°C for 3 hours.
Smoke exposure: Nose-only inhalation of mainstream smoke generated from high-tar un-tipped cigarettes diluted 40-fold with clean air (tar particulate =1.4 mg/l, CO concentration =1000 ppm). Twice-daily 30 minute exposures, 5 days a week for 12 months.
A Dose effect relationship
B Effect of smoking

Dosimetry: Radiochemical analysis to determine Pu239 content of lungs from mice killed at 1, 7, 28, 84, 196 and 364 days post actinide exposure. Trapezoidal method to calculate average radiation dose to lungs.

Endpoints: Terminal sacrifice 18 months after actinide exposuree, plus sporadic deaths. Necropsy observation and histopathology of all macroscopically obvious abnormalities. Lungs cleared to determine the absolute number of lung lesions.

Animal: Female CBA/Ca mice 10 weeks of age (approximately 20 g) at time of actinide exposure.

Results: The study failed to demonstrate a synergistic effect on the production of lung tumors following the exposure of CBA/Ca mice to the combined insult of Pu-239 and cigarette smoke. The results did, however, indicate an apparent effect of stress on the tumor frequency, as animals that were sham-smoked also had a lower incidence of lung tumors compared to cage-controls given the same dose of plutonium.

References:

Talbot, R.J., A. Morgan, S.R. Moores and D.H. Matulionis. Preliminary studies of the interaction betwen $^{239}Pu\ O_2$ and cigarette smoke in the mouse lung. *Int. J. Radiat. Biol.* **51**:1101-1110, 1987.

Priest, N.D., S.R. Moores, A. Black, R. Talbot and A. Morgan. The combined effects of plutonium and cigarette smoke on the production of lung tumors, pp. 433-436. *In* E.P. Goldfinch [ed.], *Radiation Protection- Theory and Practice. Institute of Physics*, Bristol, 4th Inter. Sympos. Malvern, 1989.

Priest, N.D., P.N. Brooks, T.M. Eldred, W. Purbrick and J.P. Kellington. The combined effects of plutonium and cigarette smoke on the production of lung tumors in the CBA mouse. in preparation, 1994.

Experimental Groups:

Study 01.01
Combined Effects of Pu-239 Dioxide and Cigarette Smoke on the Production of Lung Tumors in the Mouse

A. Dose effect relationship

Dose Gy	0	28	73	110	144	169	221
Group Id	1	2	3	4	5	6	7
Number mice	100	100	100	100	100	100	100

B. Effect of smoking

	Cage Control			Sham Exposure			Tobacco smoke		
Bq IAD	Group Id	No mice	Gy	Group Id	No mice	Gy	Group Id	No mice	Gy
0	8	59 (36)	0	11	38	0	13	47	0
24±3	9	53 (36)	1.1		-	-	14	42 (24)	1.9
60±4	10	58 (36)	2.6	12	59 (24)	2.4	15	44 (24)	3.8

No mice = Number of animals used for histopathology, values in parenthesis animals used for radiochemistry

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01.02 Life-span Study of the Induction of Lung Tumors in CBA/Ca Mice by Pu-239 Dioxide

Institution: Biomedical Research Department, AEA Technology, Harwell Laboratory, Harwell, UK

Scientists: N.D. Priest; activ
A. Morgan; retired
J.P. Kellington; active
P.N. Brooks; active
T.M. Eldred; active

Purpose: To investigate the processes preceding and accompanying Pu-induction of lung tumors in mice and to compare histological and site characteristics of mouse tumors with those in man with a view of evaluating the validity of the mouse lung tumor model.

Status: 1990 - 1993

Treatment: Inhalation Pu -239 dioxide (AMAD 1.5 μ) to give a mean IAD of about 100 Bq (corresponding to the maximal lung tumor incidence). Serial sacrifices of 50 Pu-exposed and 50 sham-exposed mice (including intercurrent deaths) at 8, 12, 16, 20, 24, and 28 months. Remainder killed when moribund. Groups of 4 Pu-exposed mice killed for the assessment of residual Pu in lung.

Dosimetry: Cumulative calculated dose to lung at 24 months is 4.5 Gy.

Endpoints: Macroscopic/microscopic pathology of the lung, and all macroscopically obvious abnormalities.

Animal: Female CBA/Ca mice aged 63 ± 5 days.

Results: Spontaneous incidence of lung tumors in control mice was below 10% up to an age of 20 months and increased with age after this time. Pu-239 exposed mice showed a significant and progressive increase in lung tumor incidence with the difference between control and exposed mice increasing with age. The lung tumors observed in exposed mice were mostly of the bronchiolo-alveolar type; no small cell tumors

and, in contrast to rats, no squamous tumors were seen. Studies carried out in paralell in the same strain followed the long-term behavior of Pu-239 and U-235 dioxide particles in lung.

References: Morgan A., P.N. Brooks, T.M. Eldred and K.A. Ambrose. Lifespan study of tumor induction in CBA mice following inhalation exposure to $^{239}Pu\ O_2$. . *In* Poster at 24th ESRB Meeting; Erfurt., 1992.

Kellington R.P., T.M. Eldred, K. Ambrose and P.N. Brooks. Lifespan study of CBA mice exposed to $^{239}Pu\ O_2$ by inhalation., 1995. In press

Experimental Groups:

Study 01.02
Life-span Study of the Induction of Lung Tumors in CBA/Ca Mice by Pu-239 Dioxide

Month of sacrifice	0 Bq		100 Bq	
	Group Id	No of mice	Group Id	No of mice
8	1	54	7	53
12	2	51	8	53
16	3	51	9	51
20	4	47	10	49
24	5	47	11	55
28	6	30	12	31

In addition, 2 mice/group were used to assess Pu content in lung

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01.03 Effects of Alpha and Beta Emitters in Lung

Institution: Biomedical Research Department, AEA Technology, Harwell Laboratory, Harwell, UK

Scientists: J.P. Kellington; active
T.M. Eldred; active

Purpose: To determine the relative biological effectiveness (RBE) of inhaled, insoluble alpha- and beta-emitting radionuclides with respect to late carcinogenic effects.

Status: 1990 - 1994

Treatment: Single nose-only exposure to fused aluminosilicate particles (FAP) labeled with Cm-242 (alpha-emitter) or Ca-45 (beta-emitter), AMAD about 1,6 µm, 1.2-1.3 sigma g.

Dosimetry: Initial alveolar deposit (IAD and radiochemical analysis to determine Cm-242 or Ca-45 content of lungs from mice killed at 1, 7, 28, 84, 196, 308, 504, and 672 days post exposure. Trapezoidal method used to calculate average radiation dose to lungs.

Endpoints: Life-span study with sacrifice of moribund animals. Necropsy observation and histopathology of all macroscopically obvious abnormalities. Lungs cleared to determine the absolute number of lung lesions.

Animal: Female CBA/Ca mice 10 weeks of age at time of exposure

Results: The survival studies do not indicate differences between the treated and non-treated groups. Macroscopic studies on the lung suggest, however, that lung tumors in controls begin to appear at an age of about 700 days and increase steadily to about 30% towards the end of the life. Following exposure to Cm-242 or Ca-45 labelled FAPs the latency period appeared reduced and the incidence increased. There was, as yet, no indication that the RBE could be 20 for alpha particles. The histopathological evaluation is now under way to confirm the these data.

References:

Experimental Groups:

Study 01.03
Effects of Alpha and Beta Emitters in Lung

IAD Bq ^{242}Cm	Group Id	No mice*	IAD Bq ^{45}Ca	Group Id	No mice*
0 Controls	1	124 (0)			
0 Inhaled Nonrad.FAP	2	372 (40)			
17	3	111 (50)	919	7	113 (50)
49	4	118 (45)	3000	8	109 (50)
81	5	101 (50)	6000	9	113 (50)
142	6	112 (50)	8900	10	109 (44)

* Mice used for histopathology; values in parenthesis: number of additional mice used for radiochemistry

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01.04 Effects of Radiation Quality on the Induction of Leukemia in CBA/CA Mice

Institution: Biomedical Research Department, AEA Technology, Harwell Laboratory, Harwell, UK

Scientists: J.P. Kellington; active
T.M. Eldred; active

Purpose: To study the induction of myeloid leukemia in mice following the administration of fused aluminosilicate particles (FAP) incorporating aloha- and beta-emitting radionuclides. This information will be used to estimate the most appropriate value for the quality factor of high LET radiations with respect to radiation-induced haemopoietic malignancies.

Status: 1991 - 1995

Treatment: Single intravenous administration of fused aluminosilicate particles (FAP) labeled with Cm -242(alpha-emitter) or Ca-45 (beta-emitter). Actual diameter of FAP =1.90±0.85 μm.

Dosimetry: Radiochemical analysis to determine Cm -242 or Ca-45 content of tissues from mice killed at 1, 7, 14, 30, 76, 150, 300 and 601 days post injection. Trapezoidal method used to calculate average radiation dose to tissues. Also autoradiographic analysis of liver, spleen and bone marrow to determine microdistribution of FAP.

Endpoints: Life-span study with sacrifice of moribund animals. Necropsy observation and histopathology of all macroscopically obvious abnormalities. Also full haematology for all animals killed *in extremis*

Animal: Female CBA/Ca mice 10 weeks of age (approximately 20 g) at time of exposure

Results: Following injection with the highest levels of Cm-242 or Ca-45 FAPs, survival was reduced by about 4 and 3 months respectively from the 900 days lifespan of controls . Liver tumors were observed in about 10% of the controls but in about 20% of Cm242-injected mice. Subcutaenous masses thought to arise from benign enlargement of subcutaneous lymphnodes were the most common (30%) abnormality in controls and contributed to morbity and mortality of the animals. However, the incidence of these masses was reduced in animals injected with the highest levels of Cm-242 or Ca-45 FAPs. On the contrary the incidence of animals with enlargement of multiple lymphnodes, splenomegaly and accumulation of fluid in abdomen and thoracic cavity, signs characteristic of leukemia, increased from low levels in controls to 11% following injection of radiolabelled FAPs. The histopathological evaluation is now under way.

References:

Experimental Groups:

Study 01.04
Effects of Radiation Quality on the Induction of Leukemia in CBA/CA Mice

kBq ^{242}Cm initial body burden	Group Id	No mice*	kBq ^{45}Ca initial body burden	Group Id	No mice*
0 Control	1	71 (0)			
0 administr. nonrad.FAP	2	588 (10)			
0.6	3	395 (5)	48	6	395 (5)
1.1	4	393 (5)	88	7	388 (5)
1.6	5	384 (5)	129.6	8	366 (5)

* Mice used for histopathology; values in parenthesis: number of additional mice used for radiochemistry

01.05 Effect of Paternal Exposure to Pu-239 on the Incidence of Cancer

Institution: Biomedical Research Department, AEA Technology, Harwell Laboratory, Harwell, UK

Scientists: J.P. Kellington; active

Purpose: To determine whether internal contamination with Pu-239 increases the incidence of cancer, in particular leukemia, in the F1 generation of CBA mice.

Status: 1993 - ongoing

Treatment: Intravenous injection with Pu-239 citrate or trisodium citrate of male mice. After 54 days, each male was mated with 2 females for up to 2 weeks and the offspring was followed for a life-time

Dosimetry: Amount injected, determination of Pu-239 in tissues of the injected males including liver, testis and accessory sex organs.

Endpoints: Necropsy observation and histopathology of all macroscopically obvious abnormalities in injected males and F1 offspring.

Animal: Male CBA/Ca mice 10 weeks of age.

Results: The data on Pu-239 content in testes and the corresponding dose have been obtained from the mice used for radiochemistry (see table below). Histopathological analysis showed no abnormalities in the testes of treated animals. No statistical difference between groups was observed with respect to the number of dams becoming pregnant, the number of double-failed matings (both females in the cage), the gestation period or the sex ratio. However, the control group faired worse than the exposed one with respect to pre-weaning mortality, litter size and pup weight. However, since the experiment was started with the controls that improvmemt of conditions with time could be a confounding factor. The lifespan study of the offspring which is still under way shows some sex differences in mortality, mainly as a result of the high incidence of liver tumors in the male.

References:

Experimental Groups:

Study 01.05
Effect of Paternal Exposure to Pu-239 on the Incidence of Cancer

Group Id	Pu injected Bq/g	Dose (mGy)* (No mice for radiochemistry)	No ♂ mice injected	No ♂ pups	No ♀ pups
1, 2, 3	Control (trisodium citrate)	0 (56)	50	315	235
4, 5, 6	5.9 Bq/g	2.8 ± 0.4 (47)	50	330	278
7, 8, 9	59.5 Bq/g	36.5 ± 20.5 (51)	50	344	305

* Estimated cumulative absorbed dose to testis at 54 days post injecion mGy ± SD

01.06 Lung Cancer in Rats Exposed to Radon/Radon Daughters

Institution: Biomedical Research Department, AEA Technology, Harwell Laboratory, Harwell, UK

Scientists: C.G. Collier; active

Purpose: To determine the risk of radon at low levels and to determine the effects of confounding factors which act in exposure to radon in mines vs that in homes.

Status: 1992- ongoing

Treatment: Radon exposure is carried out in a specially designed exposure chamber allowing continuous exposure (up to 3 months) under well defined conditions (recirculating air and removal of carbon dioxide, ammonia, humidity and replenishment of oxygen. The dose rate in the first study was kept constant at 1000WL

Dosimetry: Determination of radon/radon daughters in inhaled air, deposition of Bi-214 and Pb-214

Endpoints: Life-span study with necropsy observation and histopathology of all macroscopically obvious abnormalities. Lungs cleared to determine the absolute number of lung lesions. In addition, to the lifespan study and the determination of deposition, nuclear aberrations in alveolar macrophages and cell proliferation of bronchial and alveolar epithelial cells was investigated 14 days after cessation of exposure. To this end, bromodeoxyuridine was injected i.p 4 hours before sacrifice.

Animal: Male Sprague-Dawley rats age 12 weeks .

Results: An intercomparison of the exposure facilities at the CEA (see 02.01 to 02.16) and TNO (see 11.04) showed reasonable agreement between exposure conditions.A preliminary study on cell proliferation in male rats of different age exposed to 440 WLM demonstrated that it is not appropriate to use animals younger than 12 weeks. Deposition checked by measuring Bi-214 and Pb-214 showed a good correlation with exposure. The incidence of abnormal (micronucleated, binucleated, fragmented nuclei) cells increased with exposure with micro- and bin-nucleated cells decreasing at higher doses. The studies on lifespan and p53 gene expression are still under way.

Plans are being made to supplement the above studies with exposure rates of 250, 500 and 1000 WL as well as with discontinuous (6h/d) exposure.

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Experimental Groups:

Study 01.06
Lung Cancer in Rats Exposed to Radon/Radon Daughters

Group Id	Exposure WLM Nominal (individual*)	Number of Rats		
		lifespan	deposition	short-term
1	0 (sham exposed)	68	0	4
2	0 (cage controls)	72	0	2
3	200 (174,195,250,254)	156	8	6
4	400 (382,383,390)	114	4	4
5	800 (758,795,801)	102	4	6
6	1600 (1577,1586,1594)	102	8	6
7	3200 (3095)	34	8	2

* actual exposure levels for the different exposure groups

02 Commissariat à l'Énergie Atomique, Centre d'Études Nucléaires de Fontenay-aux-Roses

02.01 Combined Controls From Sprague-Dawley and Wistar Rats

Institution: CEA, DSV-DPTE (IPSN) Fontenay-aux Roses, France

Scientists: M. Morin; active
R. Masse; active
J. Chameaud; active
J. Lafuma; retired

Purpose: Combined controls from all the different groups carried out over a period of 20 years.

Status: 1970 - ongoing, data in ERAD

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology.

Animal: Sprague-Dawley or Wistar rats

Results: These groups represent the combined controls all untreated rats for the experiments 02. 02 to 02.16, including those receiving wine etc, but not those receiving chemicals.

References: See 02.06

Experimental Groups:

Study 02.01
Combined Controls From Sprague-Dawley and Wistar Rats

Group Id	Strain	Sex	No Animals	Remarks
1	Sprague-Dawley	♂	1135	before 12.31.81
2	Sprague-Dawley	♂	688	after 1.1.82
3	Sprague-Dawley	♀	240	
4	Wistar	♂	313	
5	Wistar	♀	262	

02.02 Lung Tumors in Rats After Inhalation of Radon

Institution: CEA, DSV-DPTE (IPSN) Fontenay-aux Roses and COGEMA, France

Scientists: M. Morin; active
R. Masse; active
J. Chameaud; active
J. Lafuma; retired
J.P. Morlier; active
G. Monchaux; active

Purpose: To determine the risks of lung tumors after radon inhalation.

Status: 1968-1982, terminated except for group 1 (1989); data in ERAD except for groups indicated in italics.

Treatment: Inhalation of radon (0.1-0.3 μm AMAD, 6.2% unattached)

Dosimetry: Activity inhaled (dose from daughter products deposited 2-3 mGy/WLM)

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology unless otherwise stated below.

Animal: Sprague-Dawley SPF rats of different ages as indicated , controls see under 02.01

Results: The studies on dose-effect relationships of radon can be classified into 4 groups:
Very high doses and dose rates with doses varying from 2000 to 10,000 WLM at concentrations from 2500 to 5000 WL. At doses of more than 4000 WLM, rats do not live long enough to develop cancer and, at the very high concentrations, damage to lung is too severe to allow tumor development.
High doses at high dose rates. In a first study in 1972, the rat received doses from 800 to 4400 WLM at a dose rate of 2500 WL, resulting in a dose-dependent increase in lung cancer incidence from 23 to 67%. In a new study started in 1977, concentration was 1500 WL, and the dose of 3000 WLM was either given over 2 months (23% cancers) or 6 months (80% cancers). In 1985, different doses were delivered at a concentration of 1200 WL resulting in cancer incidences of 14% (200 WLM), 14% (500 WLM), 35% (1000 WLM), 40% (3000 WLM) and 16% (6000 WLM), ie again a reduction of cancer incidence at very high doses.
Low doses at average dose rates. From 1975, the experiments were carried out at dose levels comparable to those uranium miners are exposed. When 300 rats were exposed to 50 WLM radon at 150 WL (1975), 11 lung cancers were found; an exposure to 25 WLM at 150 WL (1978) caused 14 cancers in 500 rats. In 1980, two series of 500 rats received 25 and 50 WLM yielding respectively 11 and 19 lung cancers.
Low doses and low dose rates: In 1989, a study was started with a the very low concentration of 2 WL and a dose of 25 WLM. Only 3 lung cancers (0.6%) ,ie slightly less than in controls, were observed.
In conclusion, the three parameters most important for the causation of lung cancer from radon are: total dose, concentration in the atmosphere and the fractionation of the dose.

References: See 02.06

Experimental Groups:

Study 2.02
Lung Tumors in Rats After Inhalation of Radon

Group Id	Expos. WLM (Conc. WL)	Age months (Exp. months)	Remarks	No rats
1	25 (2)	2.5 (3.5)	comparison dose rate	500 ♂
2	25 (100)	2.5 (3.5)	comparison dose rate	501 ♂
3	25 (150)	2.5 (6)	comparison dose rate	500 ♂
4	40 (120)	2.5 (1)		28 ♂
5	50 (15)	2.5 (1)		24 ♂
6	50 (100)	2.5 (6)	comparison dose rate	500 ♂
7	50 (114)	2.5 (1.5)		294 ♂
8	87 (800)	2.5 (0.5		15 ♂
9	145 (60)	3 (2)		10 ♂
10	160 (600)	3 (2)		5 ♂
11	200 (800)	2.5 (0.5		28 ♂
12	225 (3000)	2.5 (0.1)		43 ♂
13	290 (60)	3 (2)	65 Serial sacrifice + 21 spont.death	86 ♂
14	500 (1500)	2.5 (0.75)		10 ♂
15	800 (2500)	3 (2)	10 Serial sacrifice + 20 spont.death	30 ♂
16	1000 (1000)	2.5 (1.5)		16 ♂
17	1012 (1350)	2.5 (0.75)		25 ♂
18	1050 (1050)	2.5 (0.75)		25 ♂
19	1200 (1200)	2.5 (1)		20 ♂
20	1470 (2500)	3 (2)	10 Serial sacrifice + 20 spont.death	30 ♂
21	1500 (1500)	2.5 (1)		8 ♂
22	1600 (1200)	9(1)		50 ♂
23	1600 (3000)	2.5 (4)		60 ♂
24	1600 (3000)	2.5 (4)		190 ♂
25	1600 (3000)	2.5 (2)	Saline +82d 4*30d	61 ♂
26	1665 (1350)	2.5 (1.25)		25 ♂
27	1800 (1384)	2.5 (2)		50 ♂
28	1800 (1350)	2.5 (1.5)		30 ♂
29	1900 (1500)	7 (1.5)		20 ♂
30	1960 (1050)	2.5 (2)		16 ♂
31	2000 (1500)	2.5 (1.5)		25 ♂
32	2100 (1050)	5 (2)		93 ♂
33	2100 (1050	2.5 (1.5)		46 ♂
34	2100 (1050)	8 (2)		25 ♂
35	2100 (1050)	12 (2)		25 ♂

Group Id	Expos. WLM (Conc. WL)	Age months (Exp. months)	Remarks	No rats
36	2100 (1050)	5 (2)	Sacrifice after one year	42 ♂
37	2100 (3600)	2.5 (1)		33 ♂
38	2100 (3600)	2.5 (1.5)		51 ♀
39	2100 (3600)	10 (1)		5 ♂
40	2200 (2500	3 (2)	Serial sacrifice	9 ♂
41	2240 (1200)	2.5 (2.5)		8 ♂
42	2430 (1350)	2.5 (1.5)		25 ♂
43	2800 (1050)	2.5 (3)		180 ♂
44	2800 (4800)	2.5 (1)		58 ♂
45	2970 (2500)	3 (2)	10 Serial sacrifice +40 spont.death	50 ♂
46	3000 (1500)	2.5 (1.5)		35 ♂
47	3000 (1500)	2.5 (7)		40 ♂
48	3000 (1500)	6 (0.5)		40 ♂
49	3100 (1350)	2.5 (2)		26 ♂
50	3150 (5400)	2.5 (1.5)		97 ♂
51	4000	2.5 (2)	Saline IN + 30d	18 ♂
52	4500 (2500)	3 (2)	9 Serial sacrifice + 40 spont.death	49 ♂
53	5600 (4800)	2.5 (3)		79 ♂
54	6900 (2500)	3 (2)	Serial sacrifice	12 ♂
55	7650 (2500)	3 (2)	Serial sacrifice	9 ♂
56	8400 (4800)	2.5 (4.5)		48 ♂
57	9250 (2500)	3 (2)		20 ♂
58	11200 (4800)	2.5 (6)		89 ♂

02.03 Lung Tumors in Rats After Inhalation of Radon and Mine Pollutants or Tobacco

Institution: CEA, DSV-DPTE (IPSN) Fontenay-aux Roses and COGEMA, France

Scientists: M. Morin; active
R. Masse; active
J. Chameaud; active
J. Lafuma; retired

Purpose: To determine the risks of lung tumors after radon inhalation together with tobacco, soot or gases

Status: 1972 - 1982, terminated; data in ERAD except for groups indicated in italics

Treatment: Inhalation of radon (0.1-0.3 μm AMAD 6.2% unattached), inhalation of tobacco smoke usually 2-3 h for 5 days per week. For further details see individual experiments below.

Dosimetry: Activity inhaled (dose from daughter products deposited 2-3 mGy/WLM)

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology unless otherwise stated below

Animal: Sprague-Dawley SPF rats of different ages as indicated in the tables, controls see under 02.01

Results: Several polluants occurr ing in mines were tested with respect to their capacity to act in synergism with radon. No synergism was found between radon and uranium mineral or between radon and diesel exhaust fumes. Rats given intratracheally (IT) soot from engines used in mines together with radon had a two times greater lung cancer rate than those exposed only to radon or to radon and IT saline solution. No synergism was seen between radon and sulfur dioxide (experiment 1976). On the contrary, a clear synergism could be demonstrated for tobacco fumes. An experiment in 1975 with rats exposed to 1800 WL of radon alone or together with 350 hours of passive smoking yielded twice the lung cancer rate in the rats exposed additionally to smoking. A study of the influence of timing between radon exposure and smoking in 50 rats exposed to 1600 WLM of radon (in 1979) showed that radon alone produced 18% lung cancers, smoking prior radon exposure produced 16% cancers and radon followed by smoking produced as many as 80%.

References: See 02.06

Experimental Groups:

Study 02.03
Lung Tumors in Rats After Inhalation of Radon and Mine Polluants or Tobacco

Group Id	Expos. WLM (Conc.WL)	Age months (Exp.mo)	Remarks	No rats
1	40 (120)	2.5 (1)	Tobacco +1d for 350 h	30 ♂
2	145 (500)	3 (2)	Tobacco (300 h) serial sacrifice	14 ♂
3	200 (800)	2.5 (0.5)	Tobacco +1d for 350 h	30 ♂
4	225 (3000)	2.5 (0.1)	Tobacco inh. +8 d 3h/d 5d/w for 200 d	45 ♂
5	1600 (1200)	9 (1)	Tobacco IN -180 d for 300h 6m	50 ♂
6	1600 (1200)	9 (1)	Tobacco IN +43 d for 300 h 6 m	50 ♂
7	1600 (3000)	2.5 (4)	Non-filt tobacco 12.5 d	50 ♂
8	1600 (3000)	2.5 (4)	Filt.tobacco 12.5 d	50 ♂
9	1800 (1350)	2.5 (1.5)	Tobacco 2.5h/d 30h total	35 ♂
10	1800 (1350)	2.5 (1.5)	Tobacco 2.5h/d 100h total	35 ♂
11	1800 (1384)	2.5 (2)	Tobacco (350 h after)	50 ♂
12	2100 (1050)	2.5 (1.5)	Tobac.+150d, retin. 25 mg/kg +240d 24x7d	50 ♂
13	2240 (1200)	2.5 (2.5)	Tobacco +280d for 3.5 m	10 ♂
14	2240 (1200)	2.5 (2.5)	Tobacco +280d +25mg BNF	10 ♂
15	4000 (4800)	2.5 (2)	Tobacco (350 h)	50 ♂
16	1050 (1050)	2.5 (0.75)	Soot IT +80 d	25 ♂
17	1600 (3000)	2.5 (2)	Soot IT 10 mg + 82 d 4* 30 d	56 ♂
18	2100 (1050)	2.5 (1.5)	Soot IT 50 mg at +171d & +200d	90 ♂
19	2240 (1200)	2.5 (2.5)	Soot IT 1x30 d	10 ♂
20	3000 (1500)	2.5 (2)	Soot from Diesel IT +80 d	15 ♂
21	2100 (1050)	5 (2)	SO_2-100 d	40 ♂
22	2100 (1050)	5 (2)	SO_2+150 d	40 ♂
23	0	7 (1.5)	Trichloreth. INH 100 ppm -90 d for 90d	20 ♂
24	0	7 (1.5)	Trichloret h. INH 500 ppm -90 d for 90d	20 ♂
25	1900 (1500)	7 (1.5)	Trichlorethylene INH 100 ppm -90 d for 90d	20 ♂
26	1900 (1500)	7 (1.5)	Trichlorethylene INH 500 ppm -90 d for 90d	20 ♂

Abbreviations: +### d: application ### days after (-### d before) radon exposure;
*x# d #: * applications over # days.
IM intramuscular, IP intraperitoneal, IT intratracheal, IN inhaled, OR oral, IPI intrapleural

02.04 Lung Tumors in Rats After Inhalation of Radon and Cocarcinogenic Factors

Institution: CEA, DSV-DPTE (IPSN) Fontenay-aux Roses and COGEMA, France

Scientists: M. Morin; active
R. Masse; active
J. Chameaud; active
J. Lafuma; retired
J.P. Morlier; active

Purpose: To determine the risks of lung tumors after inhalation of radon together with co-carcinogens

Status: 1976 - 1982, data in ERAD except for groups indicated in italics

Treatment: Inhalation of radon (0.1-0.3 µm AMAD 6.2% unattached), injection of different co-carcinogenic factors. Controls injected at different ages (+ d from an age of 2.5 months). For further details see individual experiments below.

Dosimetry: Activity inhaled (dose from daughter products deposited 2-3 mGy/WLM)

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology unless otherwise stated below

Animal: Sprague-Dawley SPF rats of different ages as indicated below; controls see 02.01

Results: Beta-naphtoflavone (BNF) is a specific promoter of epidermoid lung cancer; therefore, the study of the influence of BNF on radon initiation or promotion of lung cancer seemed of particular interest for the understanding of the carcinogenic action of radon. If radon was given prior to BNF, lung cancer developed after 3 months; radon thus behaved as an initiator with BNF promoting the appearance of cancer. Different application forms, intramuscular or intraperitoneal injection, gave similar results. An intratracheal application of BNF resulted in 9 lung cancers in 10 rats, all of which were adenocarcinomas whereas BNF-induced carcinomas are usually of the epidermoid type. Further studies were carried out varying concentrations of radon and/or BNF.

References: See 02.06

Experimental Groups:

Study 02.04
Lung Tumors in Rats After Inhalation of Radon and Cocarcinogenic Factors

Abbreviations: +### d: application ### days after (-### d before) radon exposure;
*x# d #: * applications over # days.
IM intramuscular, IP intraperitoneal, IT intratracheal, IN inhaled, OR oral, IPI intrapleural
BNF= β-naphthoflavone, αBNF= α-naphthoflavone, BP= benzo-α-pyren,

Group Id	Expos.WLM (Conc.WL)	Age Months (Exp.Mo)	Cofactor Treatment	No Rats
1	0	2.5	BNF IM 25 mg/kg +0 d	14 ♂
2	0	2.5	BNF IP 12*25 mg/kg +0 d +500 d	18 ♂
3	0	5	BNF IM 16*25 mg/kg + 210 d	24 ♂
4	0	2.5	BNF IM 8*25 mg/kg +130 d	12 ♂
5	0	2.5	BNF IM 25 mg/kg +144 d	14 ♂
6	0	5	BNF IM 12*25 mg/kg +150 d	37 ♂
7	0	2.5	BNF IM 25 mg/kg +170 d	14 ♂
8	40 (120)	2.5 (1)	BNF IP 3 mg/kg +144 d 12x7 d	16 ♂
9	40 (120)	2.5 (1)	BNF IP 25 mg/kg +144 d 12x7 d	16 ♂

Group Id	Expos.WLM (Conc.WL)	Age Months (Exp.Mo)	Cofactor Treatment	No Rats
10	50 (150)	2.5 (1)	BNF IM 25 mg/kg +265 d 8x	16 ♂
11	100 (150)	2.5 (2)	BNF IM 25 mg/kg +265 d 10x	16 ♂
12	200 (800)	2.5 (0.5)	BNF IP 9 mg/kg +137 d 12x7 d	16 ♂
13	200 (800)	2.5 (0.5)	BNF IP 25 mg/kg +137 d 12x7 d	16 ♂
14	225 (1500)	2.5 (0.07)	BNF IM 25 mg/kg +112d 7x15 d	4 ♂
15	225 (1500)	2.5 (0.07)	BNF IM 25 mg/kg +232d 8x15 d	8 ♂
16	225 (1500)	2.5 (0.07)	BNF IM 25 mg/kg +232d 12x15 d	8 ♂
17	450 (1350)	2.5 (0.33)	BNF IM 25 mg/kg +112d 4x30 d	8 ♂
18	450 (1350)	2.5 (0.33)	BNF IM 25 mg/kg +232d 4x15 d	8 ♂
19	450 (1350)	2.5 (0.33)	BNF IM 25 mg/kg +232d 12x15 d	8 ♂
20	500 (1500)	2.5 (0.75)	BNF IM 25 mg/kg +3d 4x7 d	10 ♂
21	500 (1500)	2.5 (0.75)	BNF IM 25 mg/kg +250d 4x15 d	10 ♂
22	500 (1500)	2.5 (0.75)	BNF IM 25 mg/kg +360d 4x15 d	10 ♂
23	1000 (1000)	2.5 (1.5)	BNF IP 3 mg /kg + 170 d 12 x7 d	16 ♂
24	1000 (1000)	2.5 (1.5)	BNF IP 9 mg /kg + 170 d 12 x7 d	16 ♂
25	1000 (1500)	2.5 (0.75)	BNF IM 25 mg/kg +112d 4x30 d	4 ♂
26	1000 (1500)	2.5 (0.75)	BNF IM 25 mg/kg +232d 3x15 d	8 ♂
27	1000 (1500)	2.5 (0.75)	BNF IM 25 mg/kg +232d 6x15 d	8 ♂
28	1200 (1200)	2.5 (1)	BNF IM 25 mg/kg +3d 4x7 d	10 ♂
29	1200 (1200)	2.5 (1)	BNF IM 25 mg/kg +100d 4x15 d	10 ♂
30	1200 (1200)	2.5 (1)	BNF IM 25 mg/kg +360d 2x15d	10 ♂
31	1200 (1200)	2.5 (1)	BNF IM 6.25 mg/kg +3d 4x 7 d and +120 d 12x7 d	10 ♂
32	1200 (1200)	2.5 (1)	BNF IM 25 mg/kg +360d 2x15 d	10 ♂
33	1200 (1200)	2.5 (1)	BNF IM 6.25 mg/kg +100d 4x15d & 25 mg/kg + 250d 3x15d	10 ♂
34	1500 (1500)	2.5 (1)	BNF IM 25 mg/kg +112d 4x30 d	4 ♂
35	1500 (1500)	2.5 (1)	BNF IM 25 mg/kg +232d 2x15 d	8 ♂
36	1500 (1500)	2.5 (1)	BNF IM 25 mg/kg +232d 4x15 d	8 ♂
37	1500 (1500)	2.5 (1)	BNF IM 25 mg/kg +232d 2x15d and +423d 2x15 d	8 ♂
38	1500 (1500)	2.5 (1)	BNF IM 25 mg/kg +423d 2x15 d	8 ♂
39	1500 (1500)	2.5 (1)	BNF IM 25 mg/kg +423d 4x15 d	8 ♂
40	1600 (3000)	2.5 (2)	BNF 4*25mg/kg +300 d	4 ♂
41	1960 (1050)	2.5 (2)	BNF IP 3 mg/kg +112 d 12x7 d	16 ♂
42	1960 (1050)	2.5 (2)	BNF IP 9 mg/kg +112 d 12x7 d	16 ♂
43	1960 (1050)	2.5 (2)	BNF IP 25 mg/kg +112 d 2x7 d	8 ♂
44	1960 (1050)	2.5 (2)	BNF IP 25 mg/kg +112 d 4x7 d	8 ♂
45	1960 (1050)	2.5 (2)	BNF IP 25 mg/kg +112 d 12x7 d	16 ♂
46	1960 (1050)	2.5 (2)	BNF IT 3 mg/kg +112 d 4x7 d	10 ♂
47	1960 (1050)	2.5 (2)	BNF IM 25 mg/kg +112 d 12x7 d	10 ♂
48	1960 (1050)	2.5 (2)	BNF OR 25 mg/kg +112 d 12x7 d	10 ♂

Group Id	Expos.WLM (Conc.WL)	Age Months (Exp.Mo)	Cofactor Treatment	No Rats
49	2000 (1500)	12 (1.5)	BNF IM 6.25 mg/kg +60 d 4x 7 d	4 ♂
50	2000 (1500)	2.5 (1.5)	BNF IM 6.25 mg/kg +60 d 16x 7 d	5 ♂
51	2000 (1500)	2.5 (1.5)	BNF IM 6 mg/kg +63d 4x7d and 25mg/kg +107 d 4 x15d	16 ♂
52	2100 (1050)	2.5 (3)	BNF IM 25 mg/kg +3 d 6-12x7 d	10 ♂
53	2100 (1050)	5 (2)	BNF IP 25 mg/kg +85 d (12x15 d)	5 ♂
54	2100 (1050)	2.5 (3)	BNF IM 25 mg/kg +100 d 1x7 d	5 ♂
55	2100 (1050)	2.5 (3)	BNF IM 25 mg/kg +100 d 2x7 d	5 ♂
56	2100 (1050)	5 (2)	BNF IP 25 mg/kg x3 +140 d	20 ♂
57	2100 (1050)	5 (2)	BNF IM 25 mg/kg x1 (2)+140 d	17 ♂
58	2100 (1050)	2.5 (3)	BNF IM 9 mg/kg +217 d 3x30 d	4 ♂
59	2100 (1050)	2.5 (3)	BNF IM 9 mg/kg +217 d 5x30 d	4 ♂
60	2100 (1050)	5 (2)	BNF IP 25 mg/kg x6 +280 d	8 ♂
61	2100 (1050)	5 (2)	BNF IP 25 mg/kg x13 +500 d	8 ♂
62	2240 (1200)	2.5 (2.5)	BNF IM 25 mg/kg +95 d 12x7 d	10 ♂
63	2240 (1200)	2.5 (2.5)	BNF IM 25 mg/kg +176 d 3x30 d	4 ♂
64	2240 (1200)	2.5 (2.5)	BNF IM 25 mg/kg +280 d 5x7 d	10 ♂
65	4200 (2255)	2.5 (2)	BNF IP 25 mg/kg -82 d 12x7 d	10 ♂
66	1000 (1000)	2.5 (1.5)	α BNF IP 25 mg/kg +170 d 12x 7 d	8 ♂
67	2240 (1200)	2.5 (2.5)	α BNF 25 mg/kg +190 d 12x7 d	16 ♂
68	1500 (1500)	2.5 (1)	Bromoflavone +245d	6 ♂
69	0	5	BP 5 mg	16 ♂
70	225 (1500)	5	BP IP 5 mg/kg +229 d	16 ♂
71	1000 (1000)	5	BP IT 10 mg	10 ♂
72	1000 (1000)	5	BP IP 2.5 mg/kg +170 d 12x 7 d	8 ♂
73	1600 (3000)	5	BP IM 15mg/kg -8 d mothers post fert.	45 ♂
74	1600 (3000)	5	BP IM 15mg/kg -8 d mothers post fert.	51 ♀
75	1600 (3000)	5	BP IM 15mg/kg +10d mothers post fert.	75 ♂
76	1600 (3000)	5	BP IM 15 mg/kg mothers during pregnancy	25 ♀
77	2100 (1050)	5	BP IM +365 d	6 ♂
78	2240 (1200)	5	BP IP 25 mg/kg +155 d 12x7 d	16 ♂

02.05 Lung Tumors in Rats After Inhalation of Radon and Application of Different Minerals

Institution: CEA, DSV-DPTE (IPSN) Fontenay-aux Roses and COGEMA, France

Scientists: M. Morin; active
R. Masse; active
J. Chameaud; active
J. Lafuma; retired
G. Monchaux; active
J.P. Morlier; active

Purpose: To determine the risks of lung tumors after radon inhalation together with various minerals

Status: 1968- 1984, terminated; data in ERAD except for groups indicated in italics

Treatment: Inhalation of radon (0.1-0.3 μm AMAD 6.2% unattached), inhalation, or intrapleural or intratracheal injection different minerals, for further details see individual experiments below.

Dosimetry: Activity inhaled (dose from daughter products deposited 2-3 mGy/WLM)

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology unless otherwise stated below

Animal: Sprague-Dawley SPF rats of different ages as indicated below; controls see 02.01

Results: The influence of different fibrous minerals, given either directly or in a lixified state, on the carcinogenic effect of radon was studied because some of these minerals are known to cause pleural mesotheliomas in man. In first series of experiments, no synergism was found between radon and different fibrous minerals (chrysotile, crocydolite, amosite which had been lixified). but these minerals caused pleural mesotheliomas. In another experimental series, attapulquite, mucipulguite gastropulquite showed no synergistic effect and did not cause any mesothelioma. The same experimental design applied to hematite, quartz DQ12 or beryllium also did not indicate any synergism.

References: See 02.06

Experimental Groups:

Study 02.05

Lung Tumors in Rats After Inhalation of Radon and Application of Different Minerals

Abbreviations: +### d: application ### days after (-### d before) radon exposure;
*x# d #: * applications over # days.
IT intratracheal, IN inhaled, IPI intrapleural, SC subcutaneous

Group Id	Expos. WLM (Conc. WL)	Age months (Exp.mo)	Cofactor	No rats
1	0	2.5 (0)	Chrysotile SC 20 mg +0 d for 1 m	105 ♂
2	1000 (1000)	2.5 (1.5)	Chrysotil IPI 2 mg +71 d contin.	8 ♂
3	1600 (3000)	2.5 (4)	Chrysotile SC 20 mg +0 d for 1 m	109 ♂
4	1600 (3000)	2.5 (2)	Chrysotile sonified 10 mg IN +300 d	18 ♂
5	2240 (1200)	2.5 (2.5)	Chrysotile IPI 1x2mg +88d	10 ♂
6	2240 (1200)	2.5 (2.5)	Chrysotile lix.AD IPI 1x2mg +88d	10 ♂
7	2240 (1200)	2.5 (2.5)	Chrysotile lix.AO IPI 1x2mg +88d	10 ♂
8	2100 (1050)	2.5 (3)	Attapulgite IPI 1x 2 mg +130 d	20 ♂
9	2100 (1050)	2.5 (3)	AttapulgiteAC IPI 1x 2 mg +130 d	10 ♂
10	2100 (1050)	2.5 (3)	Mucipulgite IPI 1x 2 mg +130 d	10 ♂
11	2100 (1050)	2.5 (3)	Gastropulgite IPI 1x 2mg +130 d	10 ♂
12	1600 (3000)	2.5 (2)	Crocidolite 10 mg IN +300 d	18 ♂
13	2240 (1200)	2.5 (2.5)	Crocidolite IPI 1x 2mg +88d	10 ♂
14	2240 (1200)	2.5 (2.5)	Crocid.lix. AD IPI 1x 2mg +88d	10 ♂
15	1600 (3000)	2.5 (2)	Amosite 10 mg IN +300 d	18 ♂
16	2240 (1200)	2.5 (2.5)	Amosite IPI 1x 2 mg +88d	10 ♂
17	2240 (1200)	2.5 (2.5)	Amosite lix. AO IPI 1x 2 mg +88d	10 ♂
18	1600 (3000)	2.5 (2)	Hematite 20 mg IN +300 d	18 ♂
19	1050 (1050)	2.5(0.75)	Mineral dust (Salsigne) IT +52 d	25 ♂
20	1050 (1050)	2.5(0.75)	Mineral dust Fe IT +52 d	25 ♂
21	3000 (1500)	2.5 (2)	Mineral dust Fe IT +52 d	4 ♂
22	0	3	U mineral IN	10 ♂
23	9250 (2500)	3 (6)	U mineral IN	20 ♂
24	1600 (3000)	2.5 (2)	Beryllium 0.6 mg IN +300 d	18 ♂
25	7800 (2500)	3	stable Ce IN 1 mg	12 ♂
26	1600 (3000)	2.5 (2)	Glas fibers 20 mg IN +300 d	19 ♂
27	2240 (1200)	2.5 (2.5)	Glas fiber IPI 1x 2 mg +88d	10 ♂
28	1600 (3000)	2.5 (2)	Quartz DQ 10 mg IN +300 d	18 ♂
29	2240 (1200)	2.5 (2.5)	Quartz DQ 12 IPI 1 x2 mg +88 d	10 ♂
30	2240 (1200)	2.5 (2.5)	Quartz BRGM IPI 1 x2 mg +88 d	10 ♂

02.06 Lung Tumors in Rats After Inhalation of Radon and Treatment with Different Cofactors

Institution: CEA, DSV-DPTE (IPSN) Fontenay-aux Roses and COGEMA, France

Scientists: M. Morin; active
R. Masse; active
J. Chameaud; active
J. Lafuma; retired

Purpose: To determine the risks of lung tumors after inhalation of radon in combination with treatment with various cofactors.

Status: 1973- ongoing; data in ERAD

Treatment: Inhalation of radon (0.1-0.3 µm AMAD 6.2% unattached), treatment with radiation, radionuclides or different cofactors, for details see individual experiments below.

Dosimetry: Activity inhaled (dose from daughter products deposited 2-3 mGy/WLM), for Triton see 02.14

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology unless otherwise stated below

Animal: Sprague-Dawley SPF rats of different ages as indicated below

Results: Several pharmaceutical active agents were given together with radon exposure to test whether, on the one hand, certain of these substances (eg cyclophosphamide, bleomycine, methotrexate) would reduce the incidence of cancer, or , on the other hand, whether such substances when used for different therapeutic purposes (eg rifampicine, BCG, isoniazide, endoxan, largactil, phenobarbitol) could act as cofactors for radon-induced cancer. None of the substances had any positive or negative effect on the rate of incidence of radon-induced lung cancer. Alcohol also had no effect whatsoever.

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Experimental Groups:

Study 02.06

Lung Tumors in Rats After Inhalation of Radon and Treatment with Different Cofactors

Group Id	Expos. WLM (Conc.WL)	Age months (Exp.mo)	Treatment	No rats
1	5600 (4800)	2.5 (3)	Fe-59 IT	10 ♂
2	5600 (4800)	2.5 (3)	^{144}Ce IM	10 ♂
3	40 (120)	2.5 (1)	Neutrons Triton 3.05 Gy +250 d	16 ♂
4	200 (800)	2.5 (0.5)	Neutrons Triton 2.14 Gy +245 d	16 ♂
5	2240 (1200)	2.5 (2.5)	Butter yellow OR +190 d cont.	16 ♂
6	0	5 (3)	Methylcholanthrene once/w IP 25mg/kg +365 (465) d	12 ♂
7	2100 (1050)	12 (3)	Methylcholanthrene once/w IP 25mg/kg +365 d	6 ♂
8	2100 (3600)	2.5 (1)	5-Fluorouracil once/w +1d*	30 ♂
9	2100 (3600)	2.5 (1)	Endoxan 50 mg/kg once/w +1d*	30 ♂
10	2100 (1050	5 (2)	Endoxan 50 mg/kg once/w +1d*	30 ♂
11	2100 (3600)	2.5 (1)	Bleomycine 10 µg once/w +450d*	30 ♂
12	1960 (1050)	2.5 (2)	Largactil oral 400 mg/l +113 d for 84 d	16 ♂
13	1960 (1050)	2.5 (2)	Phenothiazine IM 40 mg/kg +112d 12x7 d	16 ♂
14	2240 (1200)	2.5 (2.5)	Promethazin OR +190 d	16 ♂
15	2100 (1050)	2.5 (2)	Phenobarbital IP +365 d	6 ♂
16	2240 (1200)	2.5 (2.5)	Phenobarbital IP+OR 80mg/kg +190d 12x7d (2)+ cont.	16 ♂
17	1000 (1000)	2.5 (1.5)	INH IP 35 mg/kg+169 d 12x7 d	8 ♂
18	1960 (1050)	2.5 (2)	INH IP 35 mg/kg +118 d 12x7 d (x2)	16 ♂
19	1000 (1000)	2.5 (1.5)	Rifampicine IP 50 mg/kg +1 d 2x /w	8 ♂
20	2240 (1200)	2.5 (2.5)	Rifampicine IP 50 mg/kg +190d 12x7d(2)	16 ♂
21	1000 (1000)	2.5 (1.5)	0.6 mg/kg acetylaminofluorene 12 w +170d	8 ♂
22	1000 (1000)	2.5 (1.5)	Pentamethylquercetin +171d	8 ♂
23	2800 (1050)	2.5 (3)	BCG +1 d {therapeutic human dose scaled to rat}	20 ♂
24	2100 (1050)	5 (2)	BCG +450 d {therapeutic human dose scaled to rat}	30 ♂
25	1000 (1000)	2.5 (1.5)	Wine ad lib. +67 d cont.	8 ♂

*Three doses following the European standard treatment protocol scaled for rats

Abbreviations: +### d: application ### days after (-### d before) radon exposure;
*x# d #: * applications over # days. IM intramuscular, IP intraperitoneal, IT intratracheal, OR oral
INH Isonicotine acid hydrazide, BCG extract Bac. Calmette-Guerin

02.07 Lung and Sinus Tumors in Rats After Inhalation or Topical Injection of Ce-44 and Treatment with Different Cofactors

Institution: CEA, DSV-DTPE (IPSN) Fontenay-aux Roses, France

Scientists: M. Morin; active
J. Jasmin; active
W. Skupinski; retired

Purpose: To determine the cancer risks from beta-emitters after inhalation or, to simulate uptake from wounds, after injection of radioactive particles into the leg, the sinus or the maxillary bone and to compare the results with those obtained from alpha-emitters, in some experiments, also in the presence of cofactors.

Status: 1975 - 1978 terminated; data in ERAD

Treatment: Inhalation in a single session, intramuscular injection or injection into the maxillary, the sinus or the tooth of Ce-144 trichloride (or Ce-141 oxide or trichloride adjusted to pH 5 for inhalation).

Dosimetry: Mean initial activity inhaled or injected, measurement of lung burden 3 days after exposure, determination of organ activities at autopsies; dose calculated from these data

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology.

Animal: Male Sprague-Dawley SPF rats aged 3 months (one group 5 days); controls see 02.01

Results: **Inhalation of Ce-144 chloride** at doses from 3 to 62 Gy caused a dose-dependent reduction in survival and an increase in lung cancers. When stable Ce was added to retard the dissolving of the Ce hydroxyde in the alveoli, the number of lung cancers increased significantly after doses from 15-54 Gy. The cancers observed were mainly of the epidermoid type, but 1 osteosarcoma and 6 angiosarcoma were also observed.

Inhalation of the oxide Ce-141 (a β-emitter of much lower energy than Ce-144 and the oxide of which is very insoluble in lung) caused lung cancers and sarcoma in the dose range of 0.1-22 Gy. One third of the lung cancers were of the epidermoid type or adenocarcinomas, two third were bronchiolo-alveolar carcinomas. These experiments demonstrated the (possibly synergistic) relation between radioactivity and masse and, especially, the influence of the spatio-temporal distribution of the exposure on the histological type of lung cancers.

Local administration was performed to study the induction of osteosarcomas, the time of appearance of tumors and the efficiency of therapeutic methods used in man. The method used allowed to determine exactly the begin of the tumor development because the site of injection of the insoluble radioactive solution was known. It was found that the incidence of metastasis, occurring mainly in lung, was comparable to that seen in man.

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Experimental Groups:

Study 02.07
Lung and Sinus Tumors in Rats After Inhalation or Topical Injection of Ce-144 and Treatment with Different Cofactors

Group Id	Compound Activity kBq (Gy)	Application	No rats
1	$^{144}Ce\ Cl_3$ 11 (3)	Inhalation	3
2	$^{144}Ce\ Cl_3$ 40 (11)	Inhalation	10
3	$^{144}Ce\ Cl_3$ 59 (16)	Inhalation	12
4	$^{144}Ce\ Cl_3$ 83 (22.5)	Inhalation	23
5	$^{144}Ce\ Cl_3$ 127 (33.5)	Inhalation	18
6	$^{144}Ce\ Cl_3$ 163 (42)	Inhalation	11
7	$^{144}Ce\ Cl_3$ 290 (62)	Inhalation	22
8	$^{144}Ce\ Cl_3$ 55 (15)	Inhalation +50 mg Ce stable	24
9	$^{144}Ce\ Cl_3$ 30 (22)	Inhalation +50 mg Ce stable	12
10	$^{144}Ce\ Cl_3$ 82 (54)	Inhalation +50 mg Ce stable	12
11	^{141}Ce oxide 2 (0.1)	Inhalation	3
12	^{141}Ce oxide 9 (0.3)	Inhalation	29
13	^{141}Ce oxide 42 (1.5)	Inhalation	10
14	^{141}Ce oxide 84 (3)	Inhalation	12
15	^{141}Ce oxide 165 (6)	Inhalation	12
16	^{141}Ce oxide 418 (15)	Inhalation	24
17	^{141}Ce oxide 608 (22)	Inhalation	12
18	$^{141}Ce\ Cl_3$ 42 (1.2)	Inhalation	36
19	$^{141}Ce\ Cl_3$ 57 (1.8)	Inhalation	12
20	$^{90}Y\ Cl^3$ 129 (30)	Inhalation	12
21	$^{144}Ce\ Cl_3$ 110	IM Injection (Wistar)	11
22	$^{144}Ce\ Cl_3$ 155	IM Injection (Wistar)	50
23	$^{144}Ce\ Cl_3$ 155	IM Injection	40
24	$^{144}Ce\ Cl_3$ 215	IM Injection	75
25	$^{144}Ce\ Cl_3$ 315	IM Injection	12
26	$^{144}Ce\ Cl_3$ 1600	IM Injection	8
27	$^{144}Ce\ Cl_3$ 2.6	IM Injection (5 day old)	20

Group Id	Compound Activity kBq (Gy)	Application	No rats
28	$^{144}Ce\ Cl_3$ 185	IM Inj.+ saline	40
29	$^{144}Ce\ Cl_3$ 1600	IM Inj.+ 15mg/kg Endoxan 2*/month	8
30	$^{144}Ce\ Cl_3$ 1600	IM Inj.+ 1mg/kg Imuran 2*/month	8
31	$^{144}Ce\ Cl_3$ 1600	IM Inj.+ 1U/rat Calcitar 2*/month	9
32	$^{144}Ce\ Cl_3$ 1600	IM Inj.+ 9.25 kBq ^{241}Am	8
33	$^{144}Ce\ Cl_3$ 1660	IM Inj. + Amput.+Interferon	40
34	$^{144}Ce\ Cl_3$ 1.85	Intramaxill.	21
35	$^{144}Ce\ Cl_3$ 1.85	Intramaxill. (5 day old)	61
36	$^{141}Ce\ Cl_3$ 185	Intramaxill.+ 296 kBq ^{144}Ce	61
37	$^{141}Ce\ Cl_3$ 185	Intramaxill. + 13 kBq ^{241}Am	20
38	$^{141}Ce\ Cl_3$ 0.74	Intrasinusal	13
39	$^{141}Ce\ Cl_3$ 4.44	Intrasinusal	12
40	$^{141}Ce\ Cl_3$ 18.5	Intrasinusal	12
41	$^{141}Ce\ Cl_3$ 166	Intrasinusal	12
42	$^{141}Ce\ Cl_3$ 18.5	Intradental	13

02.08 Lung Tumors in Rats After Inhalation of Actinides

Institution: CEA, DSV-DTPE (IPSN) Fontenay-aux Roses, France

Scientists: M. Morin; active
J.C. Nénot; active

Purpose: To assess the risks of lung tumors after inhalation of different alpha-emitting actinides and help to understand the problem of "hot spots"

Status: 1965 - 1975, terminated; data in ERAD.

Treatment: Inhalation, intramuscular (IM) or intravenous (IV) injection of Th-227 (chloride) Pu-238 (oxide and nitrate), Pu-239 (oxide and nitrate) , Am-241, (oxide and nitrate), Cm-244 (nitrate) with or without cofactor.

Dosimetry: Activity inhaled, activity retained, calculated average lung doses for a group.

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology

Animal: Male Sprague-Dawley SPF rats aged 3 months; for controls see 02.01

Results: The data demonstrate very clearly that the more a dose was homogeneously distributed the more it was efficient in causing cancer and that the opinion that a heterogeneous distribution of exposure in hot spots represents a greater cancer risk is intenable. The degree of homogeneity of dose was varied by inhalation different physicochemical forms of various actinides. Inhalation of oxides caused a heterogeneous distribution of dose whereas that of salt solution which formed hydroxydes at higher pH resulted in a nearly homogeneous solution . Other experiments were carried out to study the role of dose rate which depended on the speed of dissolution of the aerosols deposited in lung, the possible synergy with smoking tobacco, the therapy with DTPA and the influence of im or iv injection on the induction of osteosarcoma and leukemia.

When actinides were inhaled in a soluble physico-chemical form not only excess lung cancers but also extra-pulmonary cancers were observed. In order to analyse the the dose-effect relation-ships from these studies correctly, a study on exposure to fission neutrons delivered at various doses and dose rates was carried out (02.12).

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Experimental Groups:

Study 02.08
Lung Tumors in Rats After Inhalation of Actinides

Group Id	Radionuclide	KBq initial activity (Gy calculated)	No rats
Inhalation			
1	$^{244}Cm\ (NO_3)_3$	2.33 (1.5)	12 ♂
2	$^{244}Cm\ (NO_3)_3$	7.77 (5)	11 ♂
3	$^{244}Cm\ (NO_3)_3$	9.76 (6.3)	11 ♂
4	$^{244}Cm\ (NO_3)_3$	13.6 (8.8)	22 ♂
5	$^{244}Cm\ (NO_3)_3$	23.7 (15.3)	9 ♂
6	$^{244}Cm\ (NO_3)_3$	32.1 (20.7)	15 ♂
7	$^{244}Cm\ (NO_3)_3$	38.7 (25)	11 ♂
8	$^{244}Cm\ (NO_3)_3$	48 (31)	11 ♂
9	$^{244}Cm\ (NO_3)_3$	6.51 (4.2) +50mg/kg DTPA 1 d	11 ♂
10	$^{244}Cm\ (NO_3)_3$	9.61 (6.2) +50mg/kg DTPA 1 d	11 ♂
11	$^{244}Cm\ (NO_3)_3$	21.4 (13.8) +50mg/kg DTPA 1 d	7 ♂
12	$^{244}Cm\ (NO_3)_3$	30 (19.4) +50mg/kg DTPA 1 d	4 ♂
13	$^{244}Cm\ (NO_3)_3$	59 (38.2)+50mg/kg DTPA immed	11 ♂
14	$^{227}Th\ Cl_2$	8 (3.1)	24 ♂
15	$^{227}Th\ Cl_2$	17.8 (9.2)	12 ♂
16	$^{241}Am\ (NO_3)_3$	0.67 (0.52)	24 ♂
17	$^{241}Am\ (NO_3)_3$	0.81 (0.65)	36 ♂
18	$^{241}Am\ (NO_3)_3$	1.0 (0.8)	24 ♂
19	$^{241}Am\ (NO_3)_3$	1.11 (0.9)	24 ♂
20	$^{241}Am\ (NO_3)_3$	1.26 (1.05)	48 ♂
21	$^{241}Am\ (NO_3)_3$	1.52 (1.21)	48 ♂
22	$^{241}Am\ (NO_3)_3$	1.66 (1.37)	24 ♂
23	$^{241}Am\ (NO_3)_3$	1.81 (1.5)	12 ♂
24	$^{241}Am\ (NO_3)_3$	2.22 (1.78)	36 ♂
25	$^{241}Am\ (NO_3)_3$	2.44 (2)	36 ♂
26	$^{241}Am\ (NO_3)_3$	2.77 (2.3)	35 ♂
27	$^{241}Am\ (NO_3)_3$	3.7 (3)	34 ♂
28	$^{241}Am\ (NO_3)_3$	4.81 (4)	12 ♂
29	$^{241}Am\ (NO_3)_3$	7.4 (6.4)	36 ♂
30	$^{241}Am\ (NO_3)_3$	11.8 (9.7)	24 ♂
31	$^{241}Am\ (NO_3)_3$	18.1 (14.7)	35 ♂
32	$^{241}Am\ (NO_3)_3$	22.2 (18.8)	24 ♂
33	$^{241}Am\ (NO_3)_3$	31.1 (25)	12 ♂
34	$^{241}Am\ (NO_3)_3$	51.8 (39)	25 ♂
35	$^{241}Am\ (NO_3)_3$	104 (58)	29 ♂

Group Id	Radionuclide	KBq initial activity (Gy calculated)	No rats
36	$^{241}Am\ (NO_3)_3$ +DTPA 1d	25.1 (19)	24 ♂
37	$^{241}Am\ (NO_3)_3$ +DTPA 1d	59.2 (40)	12 ♂
38	$^{241}Am\ (NO_3)_3$ +DTPA 11d	74 (41)	12 ♂
39	$^{241}Am\ (NO_3)_3$ +DTPA 19d	51.8 (36)	12 ♂
40	$^{241}Am\ (NO_3)_3$ +DTPA 1d	113 (42)	12 ♂
41	$^{241}Am\ (NO_3)_3$ +DTPA 1d	190 (67)	12 ♂
42	Tobacco alone	0	30 ♂
43	$^{241}Am\ (NO_3)_3$ +Tobacco	10.7 (8.9)	11 ♂
44	$^{241}Am\ (NO_3)_3$ +Tobacco	15.5 (12.5)	10 ♂
45	$^{241}Am\ (NO_3)_3$ +Tobacco	18.5 (15)	10 ♂
46	$^{241}Am\ O_2$	1.66 (1.2)	24 ♂
47	$^{241}Am\ O_2$ (9 months)	10 (5.3)	24 ♂
48	$^{241}Am\ O_2$	8.62 (6.7)	11 ♂
49	$^{241}Am\ O_2$	10 (9.3)	34 ♂
50	$^{241}Am\ O_2$	18.5 (15.6)	23 ♂
51	$^{241}Am\ O_2$ (200g)	24.4 (28)	24 ♂
52	$^{241}Am\ O_2$ (200g)	55.5 (53)	24 ♂
53	$^{241}Am\ O_2$	851 (241)	6 ♂
54	$^{241}Am\ O_2$ +DTPA	51 (14.8)	12 ♂
55	$^{238}Pu\ (NO_3)_4$	8.51 (12.3)	20 ♂
56	$^{238}Pu\ (NO_3)_4$	15.9 (17.8)	24 ♂
57	$^{238}Pu\ (NO_3)_4$	30.3 (24.8)	12 ♂
58	$^{238}Pu\ O_2$	1.22 (2.6)	34 ♂
59	$^{238}Pu\ O_2$	6.66 (13.4)	11 ♂
60	$^{239}Pu\ (NO_3)_4$	0.59 (2.3)	10 ♂
61	$^{239}Pu\ (NO_3)_4$	8.81 (27.1)	20 ♂
62	$^{239}Pu\ (NO_3)_4$	37 (84.7	12 ♂
63	$^{239}Pu\ (NO_3)_4$	78 (132)	8 ♂
64	$^{239}Pu\ O_2$	1.63 (9.3)	31 ♂
65	$^{239}Pu\ O_2$	3.51 (17.6)	36 ♂
66	$^{239}Pu\ O_2$	5.55 (29)	34 ♂
67	$^{239}Pu\ O_2$	12.6 (70)	42 ♂
68	$^{239}Pu\ O_2$	29.4 (94)	10 ♂
69	$^{239}Pu\ O_2$	124 (196)	13 ♂
Injection			
70	^{244}Cm IV	37	28 ♂
71	^{244}Cm IM	37	33 ♂
72	^{241}Am IV	78	28 ♂
73	^{241}Am IM	78	33 ♂

Group Id	Radionuclide	KBq initial activity (Gy calculated)	No rats
74	^{241}Am IM	0.111	50 ♂
75	^{241}Am IM	0.37	50 ♂
76	^{241}Am IM	1.11	10 ♂
77	^{241}Am IM	6.66	184 ♂

02.09 Lung Tumors in Monkeys After Inhalation of Actinides

Institution: CEA, DSV-DTPE (IPSN) Fontenay-aux Roses, France

Scientists: H. Métivier; active
R. Masse; active

Purpose: To determine the risks of lung tumors after inhalation of different actinides.

Status: 1972 - ongoing

Treatment: Inhalation of Pu-239 dioxide (2.3μ AMAD, 0.6μ CMAD) prepared at 1000C

Dosimetry: Activity inhaled, activity retained, calculated average lung doses

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology, sacrificed at terminal stage, radiographs of the thorax

Animal: 59 male and female baboons (Papio papio) 2-4 years (2-10 kg)

Results: A comparison of the early mortality (less than 1000 days) showed that the immature baboons had a similar sensitivity than the adult dogs studied at Batelle. Death at this time was mainly due to fibrosis, interstitial peumonia and some lung tumors. Fibrosis and lung tumors were also the principal causes of death during the long-term observation period. A plot of log survival time against the log of Pu concentration in lung yielded a linear dependency which paralelled the curves obtained for dogs and did not significantly differ between these species. Plutonium was cleared from lung at an excretion rate (half life 600 - 3900 days) which decreased with time. Pu content of thoracic lymphnodes reached a maximum of 10-40% of initial lung burden about 1000 days after contamination.

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Experimental Groups:

Study 02.09
Lung Tumors in Monkeys After Inhalation of Actinides

Group Id	Range of initial deposition kBq	No of animals
1	1 - 6	1 ♀ 5 ♂
2	6 - 12	2 ♀ 2 ♂
3	13 - 21	4 ♀ 3 ♂
4	22 - 32	1 ♀ 3 ♂
5	33 - 50	3 ♀ 1 ♂
6	51 - 68	3 ♀ 4 ♂
7	70 - 92	3 ♀ 8 ♂
8	110 - 144	1 ♀ 9 ♂
9	145 - 200	2 ♀ 2 ♂
10	220 - 450	2 ♀ 4 ♂
11	>1000	1 ♀

02.10 Tumors and Lifespan in Rats After High and Low Dose Rate Gamma Irradiation

Institution: CEA, DSV-DTPE (IPSN) Fontenay-aux Roses, France
Scientists: M. Morin; active
Purpose: To determine the dose rate reduction factor for gamma irradiation
Status: 1979 - 1985, data in ERAD
Treatment: Exposure to a Co-60 gamma source
Dosimetry: Ionization chamber
Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology
Animal: Male Sprague-Dawley SPF rats aged 3 months, controls see 02.01
Results: See 02.11
References: See 02.11

Experimental Groups:

Study 02.10
Tumors and Lifespan in Rats After High and Low Dose Rate Gamma Irradiation

Group Id	Dose Gy	Dose Rate Gy/hr	No animals
1	6	0.025-0.12	77
2	10	0.12	20
3	12	0.12	40
4	13	0.12	20
5	16.5	0.12	36
6	18.5	0.12	40
7	20	0.12	20
8	26	0.12	20
9	28	0.12	30
10	31	0.12	20
11	39	0.12	20
12	8	15	15
13	9	15	13
14	9.5	10	24
15	12	10	20
16	19	10	20
17	24	5	20
18	28.5	10	20
19	12 split 6+6 62d	0.25	20
20	16 split 10+6 67d	0.25	19
21	22 split 12+6+6 70d	0.25	29

02.11 Tumors and Lifespan in Rats After Gamma Irradiation At Different Ages

Institution: CEA, DSV-DTPE(IPSN) Fontenay-aux Roses, France

Scientists: M. Morin; active

Purpose: To determine the effects of age and the dose rate reduction factor for external gamma irradiation.

Status: 1982-1990, terminated, data in ERAD

Treatment: Exposure to a low dose rate Co-60 gamma source at different ages and dose rates

Dosimetry: Ionization chamber

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology

Animal: Sprague-Dawley SPF rats

Results: Epidemiological studies so far did not reveal an increase in cancer incidence among people occupationally exposed to small doses of radiation at low dose rates with exception of alpha ray exposure; risk assessment thus depends on an extrapolation form data on high doses/ dose rates. Studies on experimental animals should therefore clarify whether a reduction in dose rate is accompanied by a reduction in radiation-induced cancer. The doses used varied between 1 and 39 Gy and were delivered at dose rates from 1.34 mGy/ h to 15 Gy/h.

A comparison between two groups of rats receiving 3 Gy Co-60 gamma exposure either at 1.34 Gy/h during 14 weeks or 78 mGy/h during 5 days demonstrated a reduction in the incidence of carciomas by a factor of 5 at the low dose rate.

Since these exposures were still relatively short compared to the lifespan of the animals, it seemed important, for an assessment of the risk of long term exposure, to study the influence of age on the carcinogenic effect of radiation. Exposure to 3 Gy at an age of 9 months, 3 months or in utero showed little difference in cancer incidence compared to controls for rats aged 9 months whereas a significant increase was seen for rats exposed in utero or at an age of 3 months. The excess cancer incidence was only a 1/10 for the rats irradiated at 9 months compared to those irradiated in utero. The excess cancers after in utero exposure were mainly due to the great sensitivity of the central nervous system and the sex organs during their organogenesis.

References:

Morin, M. and J. Lafuma [eds.]. Les Cancer Radio-induits du Rat; Étude Expérimentale. CEA, Paris, Series Ed: CEA-R-5462., 1988.

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Experimental Groups:

Study 02.11
Tumors and Lifespan in Rats After Gamma Irradiation At Different Ages

Group Id	Dose Gy	Dose rate mGy/h	Age	No rats
1	2.66	53 (≈4,5h/d 5d/w)	mothers 3 months	11 ♀
2	5.96	53 (≈3,5h/d 5d/w)	mothers 3 months	20 ♀
3, 4	2.66	53 (≈4,5h/d 5d/w)	mother irrad.from 7d prior conception	10 ♀, 5 ♂
5, 6	2.66	53 (≈4,5h/d 5d/w)	day 8 postc. to birth	65 ♀, 66 ♂
7, 8	5.96	53 (≈3,5h/d 5d/w)	day 8 pc to 1 m	63 ♀, 69 ♂
9, 10	14.74	53 (≈3h/d 5d/w)	day 8 pc to 140 d	56 ♀, 48 ♂
11	1	78 (≈2.6h/d 5d)	3 months	505 ♂
12	2.83	1.34 (22h/d 7d/w 14w)	3 months	289 ♂
13	3	78 (≈6.3h/d 5d)	3 months	120 ♂
14, 15	3	38 mGy/h during 5 d	9 months	60 ♀, 120 ♂

02.12 Tumors and Lifespan in Rats After Irradiation From Different Neutron Sources

Institution: CEA, DSV-DPTE (IPSN) Fontenay-aux Roses, France

Scientist: M. Morin; active

Purpose: To evaluate the dose effect and dose rate relationships for irradiation with different sources of neutrons and compare different sources of neutrons, alpha particles and gamma radiation (a few experiments with a chemical co-carcinogen are also included)

Status: Part A 1977 - 1983, terminated
Part B 1982 - 1985, terminated
Part C 1990 - 1994, terminated
Data in ERAD except for those indicated in italics

Treatment: Exposure at the
TRITON facility (fission neutrons 0.01-0.1 Gy/h) , SILÈNE reactor (flash varying from 10 to 100 msec 1.10^{17} fissions); (gamma/neutron ratio 1-40)
Cf-252 Source: Gy/min, fission neutrons
Orleans: 8 Gy/min 1-30 MeV Neutrons from cyclotron protons on a Be target;
Saturne: 1-5 Gy/hr, 500 MeV alpha-particles from an accelerator at Saclay
Thalie: Bremstrahlung 2-6 MeV on a Tantal target from electron generated at 0-8 MeV;
some groups received 6 injections of 25 mg/kg BNF at an interval of 15 days
A) Triton and SILÈNE facilities
B) Orleans, Saturn and Thalie faclilities and low dose rate Cf-252 neutrons
C) Low dose rate neutron exposure to a Cf-252 source

Dosimetry: Neutrons: Carbon coated ionization chamber,: double ionization chamber (Ar Te Gas) activation detectors (S, Ni, Mg, Cu, Au) passive semicoductor devices.
Saturne ionization chamber
Gamma source: ionization chamber

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology

Animal: Sprague-Dawley SPF rats at an age of 3 months, one experiment with Wistar rats.

Results: These experiments using external whole body irradiation with neutrons yielded in our rat strain an RBE of about 45 for neutrons in relation to gamma irradiation. The experiments also revealed the different radiosensitivities of the various organs in dependence of dose.
For neutrons, the dose rate rate seemed to have less influence on the incidence of cancer than for gamma rays or alpha rays.
When the lung was exposed to radiation collimated at different diameters followed by the promoting agent BNF, serial sacrifices revealed that lung cancers appeared always within less than 3 months in the irradiated volume distributed over a surface corresponding to the diameter of the radiation beam.

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Experimental Groups:

Study 02.12

Tumors and Lifespan in Rats After Irradiation From Different Neutron Sources

A. Triton and Silène facility series

Group Id	TRITON Dose Gy	No rats	Group Id	SILÈNE Dose Gy	No rats
1	0.012	150			
2	0.020	150			
3	0.06	80	18	0.4	116
4	0.1	78	19	0.6	63
5	0.32	75	20	0.6	200
6	0.49	75	21	0.6	392
7	1.5	123	22	1.15	80
8	2.3	104	23	1.20	50
9	2.4	20	24	1.73	40
10	2.54	20	25	2	120
11	2.8	6			
12	3.5	60	26	2.86	40
13	3.86	20			
14	4.4	40			
15	5.3	40			
16	6	20			
17	8	20			

B. Orleans, Saturn and Thalie facilities and low dose rate Cf-252 neutrons
BNF β-naphthoflavone

Group Id	Facility	Dose Gy	Other Treatment	No Rats
27	Orleans	4		58
28	Saturne	5		12
29	Saturne	7.5		36
30	Saturne	7.5 Abdomen		24
31	Saturne	10		11
32	Saturne	15		34 (♂+♀)
33	Saturne	20		10
34	Saturne	25		9
35	Saturne	5	6*25mg/kg BNF IM /15d	6
36	Saturne	3.7 collim.10mm	6*25mg/kg BNF IM /15d	12
37	Saturne	3.7 collim.30mm	6*25mg/kg BNF IM /15d	12
38	Saturne	11.6 collim.10mm	6*25mg/kg BNF IM /15d	12
39	Saturne	18.4 collim.5.2mm	6*25mg/kg BNF IM /15d	12
40	Saturne	44.6 collim.3mm	6*25mg/kg BNF IM /15d	24
41	Thalie	1.5-3.5		60
42	Thalie	1.5-3.5	6*25mg/kg BNFIM /15d 3 groups	13
43	^{252}Cf hind paw	3.5 (38.2 mGy/h)		24
44	^{252}Cf lumbar region	8 (45mGy/h)		32
45	^{252}Cf total body	2 (4mGy/h) (Wistar rats)	control	23
46	^{252}Cf total body	2 (4mGy/h) (Wistar rats)	treated anti-cataractogene	22

C. Low dose rate neutron exposure to a Cf-252 source

Group Id	Dose mGy	Start Dose Rate µGy/h	Age Months Start-End Exposure	No Rats
47	0		Controls	501
48	25	950	3 - 3	150
49	25	758	14 - 14	250
50	25	3.58	3 - 15	205
51	53	7.72	3 - 15	50

02.13 Tumor and Lifetime Study on Rats After Acute Neutron Exposure and/or Treatment with Paradichlorobenzene and Tetrachlorobenzyltoluene

Institution: CEA, DSV-DPTE (IPSN) Fontenay-aux Roses, France

Scientists: M. Morin; active
G. Monchaux; active

Purpose: To assess the risks of neutrons in combination with a chemical carcinogen

Status: 1986 - 1990, data in ERAD

Treatment: Exposure to an about 100 msec flash of fission neutrons from the "SILENE" reactor (gamma/neutron ratio 1-40) and inhalation of para-dichlorobenzene (PCDB) or tetrachlorobenzyltoluene (TCBT); some groups received 6 injections of 25 mg/kg BNF at an interval of 15 days

Dosimetry: Double ionization chamber (Ar Te Gas) activation detectors (S, Ni, Mg, Cu, Au) passive semiconductor

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology

Animal: Male and female Sprague-Dawley SPF rats aged 3 months, data in ERAD

Results:

References:

Experimental Groups:

Study 02.13
Tumor and Lifetime Study on Rats After Acute Neutron Exposure and/or Treatment with Paradichlorobenzene and Tetrachlorobenzyltoluene

Group Id	Neutrons Gy	Chemical Treatment	No animals
1	1.2	none	50 ♀
2, 3	none	500 ppm PCDB	50 ♀, 50 ♂
4, 5	none	500 ppm PCDB and BNF	28 ♀, 25 ♂
6, 7	1.2	75 ppm PCDB	50 ♀, 50 ♂
8	1.2	500 ppm PCDB	50 ♂
9	none	15 mg TCBT	50 ♂
10	none	15 mg TCBT+ BNF 25mg/kg	30 ♂
11	none	50 mg TCBT	50 ♂
12	none	50 mg TCBT + BNF 25mg/kg	25 ♂
13, 14	none	150 mg TCBT	29 ♀, 28 ♂
15, 16	none	150 mg TCBT + BNF 25mg/kg	25 ♀, 25 ♂
17, 18	1.2	50 mg TCBT	50 ♀, 50 ♂
19, 20	1.2	150 mg TCBT	50 ♀, 50 ♂

02.14 Tumors and Lifespan in Rats After Irradiation From Neutrons or Co-60 Gamma Rays and Treatment with Chemicals

Institution: CEA, DSV-DPTE (IPSN) Fontenay-aux Roses, France

Scientist: M. Morin; active

Purpose: To evaluate the influence of cofactors on the effects from Triton neutrons or gamma rays.

Status: 1982 - 1985, terminated; data in ERAD except for unavailable groups indicated in italics

Treatment: Exposure at the
TRITON facility (fission neutrons 0.01-0.1 Gy/h)
Silène reactor: see under 02.12
Co-60 source: (0.12 Gy/min)

Dosimetry: Neutrons: Carbon coated ionization chamber, Gamma source: Ionization chamber

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology

Animal: Male Sprague-Dawley SPF rats at an age of 3 months, one experiment with Wistar rats ; for general controls see 02.01, for controls treated with BNF see 02.04, for controls with high dose neutron exposure only see 02.13.

Results: The only significant differences found in this study was an increase in lung cancers when BNF was used as cofactors

References: See 02.12

Experimental Groups:

Study 02.14
Tumors and Lifespan in Rats After Irradiation From Neutrons or Co-60 Gamma Rays and Treatment with Chemicals

Abbreviations: +### d: application ### days after (-### d before) radon exposure;
*x# d #: * applications over # days.
IM intramuscular, IP intraperitoneal, IT intratracheal, IPI intrapleural
BNF= β-naphthoflavone, BP= benzopyren.

Group Id	Exposure Facility Dose Gy	Treatment	No rats
1	Triton 1.5	Coffeine 15mg/d OR -105d	15
2	Triton 2.3	Coffeine 15mg/d OR +130d	20
3	Triton 1.5	Red Wine ad lib OR +130 d	20
4	Triton 1.5	Sugar OR +130 d	20
5	Triton 1.5	Aspirine 10mg/d OR +130d	20
6	Triton 2.3	Valium 0.1mg/d OR +130 d	20
7	Triton 2.8	α BNF IM +223 d	6
8	Triton 0.15	none	10
9	Triton 0.15	16*25 mg BNF IM +231d	10
10	Triton 0.23	none	10
11	Triton 0.23	16*25 mg BNF IM +231d	10
12	Triton 0.3	none	10
13	Triton 0.3	12*25 mg BNF IM +231d	10
14	Triton 0.45	none	9

Group Id	Exposure Facility Dose Gy	Treatment	No rats
15	Triton 0.45	12*25 mg BNF IM +231d	10
16	Silene 0.4	8*25 mg BNF IM +503d	4
17	Triton 0.75	8*25 mg BNF IM +105d	4
18	Triton 0.75	(7,6,5,4)*25 mg BNF IM +232d	16
19	Triton 1.1	4*25 mg BNF IM +105d	4
20	Triton 1.1	(6,5,4,3)*25 mg BNF IM +232d	16
21	Triton 1.5	12*25 mg BNF IM +4d	10
22	Triton 1.5	8*25 mg BNF IM +105d	4
23	Triton 1.5	(7,6,5,4)*25 mg BNF IM +232d	16
24	Triton 2.2	5*25 mg BNF +150d	4
25	Triton 2.2	4*25 mg BNF +232d	16
26	Triton 2.3	12*25 mg BNF -104d	15
27	Triton 2.3	12*25 mg BNF +4d	10
28	Triton 2.3	12*25 mg BNF +117d	20
29	Triton 0	0.06 mg BP IM	18
30	Triton 1.5	0.03 mg BP IM	20
31	Triton 1.5	0.06 mg BP IM	20
32	Triton 1.5	0.3 mg BP IM	5
33	Triton 1.5	3 mg BP IM	5
34	Triton 2.3	0.04 mg BP IM -104d	15
35	Triton 2.3	0.04 mg PB oral +22 d	20
36	Triton 0	Asbestos IT +126d	10
37	Triton 2.3	Asbestos IT +35d	10
38	Triton 2.3	Crocidolite (IPL) -69d 15	
39	Silène 0	Ozone 0.4 ppm acute	36
40	Silène 0	Ozone 0.75 ppm acute	30
41	Silène 0	Ozone 2 ppm chronic	50
42	Silène 0.6	Ozone 0.4 ppm acute	36
43	Silène 0.6	Ozone 0.75 ppm acute	30
44	Silène 0	Pb O	50
45	Silène 0	Pb O + BNF	25
46	Silène 0.6	Pb O	50
47	Silène 0	$Cd\ Cl_2$	25
48	Silène 0	$Cd\ Cl_2$ +BNF	25
49	Silène 0	$Cd\ Cl_2$ 700 µg/m3 inhaled	30
50	Silène 0.6	$Cd\ Cl_2$	50
51	Silène 0	As_2O_3 500 µg/m^3	50
52	Silène 0.6	As_2O_3 500 µg/m^3	50
53	Radon 500 WLM		25 ♂
54	Radon 500 WLM		25 ♂

Group Id	Exposure Facility Dose Gy	Treatment	No rats
55	Radon 1000 WLM		50
56	Radon 1000 WLM	Ozone 0.2 ppm acute	50
57	Radon 1000 WLM	Ozone 2 ppm	50
58	Radon 1000 WLM	Ozone 2 ppm	50
59	^{60}Coγ wholebody 4	BNF 5*25mg +56 d	10
60	^{60}Coγ wholebody 8	BNF 6(12)*25mg +56 d	10
61	^{60}Coγ wholebody 12	BNF 5(10)*25mg +56 d	10
62	^{60}Coγ wholebody 16	BNF 3(6)*25mg +56 d	9
63	^{60}Coγ wholebody 20	BNF 4(5)*25mg	24
64	^{60}Coγ 3mm coll. 15 0.5Gy/min	BNF 4(5,6,8)*25mg	24
65	^{60}Coγ 3mm coll. 20 0.5Gy/min	BNF 4(8)*25mg	12
66	^{60}Coγ 10mm coll. 20 1.4Gy/min	BNF 4(5)*25mg	24

02.15 Tumors and Lifespan in Rats After Treatment with Chemicals

Institution: CEA, DSV-DPTE (IPSN) Fontenay-aux Roses, France

Scientists: M. Morin; active
G. Monchaux; active
J.P. Morlier; active

Purpose: To evaluate the induction or promotion effect of inhalation (or injection) alone and together with β-naphthoflavone as promotor.

Status: 1977 - 1985, terminated; data in ERAD

Treatment: Various chemicals inhaled or injected as indicated on the table

Dosimetry: Amounts inhaled or injected

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology

Animal: Sprague-Dawley SPF rats at an age of 3 months; for untreated controls see 02.01, controls treated with BNF only see 02.04

Results: By way of varying both the concentration of the product studied and the amount of BNF injected, combined dose-effect relationships can be revealed. Both factors together determine the extent of the synergistic effect.

References:

Monchaux, G., J.P. Morlier, M. Morin, J. Chameaud, J. Lafuma and R. Masse. Carcinogenic and cocarcinogenic effects of radon and radon daughters in rats. *Environ. Health Perspect.* **102:**64-73, 1994.

Monchaux, G., J.P. Morlier, M. Morin, P. Fritsch, J. Tredaniel and R. Masse. Etude des effets cancérogènes et cocancérogènes de l'ozone chez le rat: résultats préliminaires. *Pollution Atmospherique:*84-88, 1994.

Monchaux, G., J.P. Morlier, M. Morin, R. Zalma, H. Ogata, H. Pézerat and R. Masse. Carcinogenic effects in rats of exposure to different minerals from metallic mine ores, radon and radon daughters, pp. 159-164. *In* J.M.G. Davis and M.C. Jaurand [eds.], *Cellular and Molecular Effects of Mineral and Synthetic Dusts and Fibres*, NATO ASI series ed., Vol. H 85. Springer Verlag, Berlin, Heidelberg, 1994.

Tredaniel, J., G. Monchaux, M. Bisson, J.P. Morlier, H. Richard, F. Lacroix, P. Fritsch, M. Morin, M.F. Olivier, R. Masse and A. Hirsch. Cocarcinogenic effect of ozone for lung tumors in rats after exposure to radon and its daughters, preliminary results. *Ann. Assoc. Belge Radioprot.* **19**:79-86, 1994.

Experimental Groups:

Study 02.15

Tumors and Lifespan in Rats After Treatment with Chemicals

Abbreviations:+### d: application ### days after (-### d before) radon exposure;
*x# d #: * applications over # days.
IM intramuscular, IP intraperitoneal, IT intratracheal, IPI intrapleural
BNF= β-naphthoflavone, BP= benzopyren

Group Id	Treatment	Cofactor	No Rats
1	0.003 mg BP IM	none	5 ♂
2	0.01 mg BP IM	none	5 ♂
3	0.03 mg BP IM	none	5 ♂
4	0.03 mg BP IM	none	10 ♀
5	0.1 mg BP IM	none	5 ♂
6	0.3 mg BP IM	none	5 ♂
7	1 mg BP IT	none	5 ♂
8	1 mg BP IT	BNF IM 4*25mg/kg +18d	5 ♂
9	1 mg BP IT	BNF IM 12*25mg/kg +18d	5 ♂
10	3 mg BP IT	BNF IM 4*25mg/kg +30d	6 ♂
11	3 mg BP IT	BNF IM 8*25mg/kg +30d	6 ♂
12	5 mg BP IT	none	5 ♂
13	5 mg BP IT	BNF IM 2*25/15 +18d	5 ♂
14	5 mg BP IT	BNF IM 4*25mg/kg +18d	5 ♂
15	5 mg Crocidolite IT	BNF 4*25mg/kg	8 ♂
16	5 mg Crocidolite IT	BNF 8*25mg/kg	8 ♂
17	10 mg Crocidolite IT	BNF 4*25mg/kg	11 ♂
18	10 mg Crocidolite IT	BNF 8*25mg/kg	11 ♂
19	10 mg Crocid.Lixif. IT	BNF 4*25mg/kg	11 ♂
20	10 mg Crocid.Lixif. IT	BNF 8*25mg/kg	12 ♂
21	10 mg Chrysotile IT	BNF 4*25mg/kg +30 d	5 ♂
22	10 mg Chrysotile IT	BNF 8*25mg/kg +30d	13 ♂
23	10 mg Chrysot.Lixif.IT	BNF 4*25mg/kg +30d	7 ♂
24	10 mg Chrysot.Lixif.IT	BNF 8*25mg/kg +30d	8 ♂
25	10 mg Chrysot.Son. IT	BNF 8*25mg/kg +30d	8 ♂
26	20 mg Chrysotile IT	BNF 4*25mg/kg +30d	8 ♂
27	20 mg Chrysotile IT	BNF 8*25mg/kg +30d	9 ♂
28	5 mg Hematite IT	BNF 8*25mg/kg	8 ♂
29	10 mg Hematite IT	BNF 4*25mg/kg	8 ♂
30	10 mg Hematite IT	BNF 8*25mg/kg	7 ♂
31	15 mg Hematite IT	BNF 8*25mg/kg	12 ♂
32	5 mg Quartz DQ12 IT	BNF 4*25mg/kg +30d	8 ♂
33	5 mg Quartz DQ12 IT	BNF 8*25mg/kg +30d	8 ♂
34	10 mg Quartz DQ12 IT	BNF 4*25mg/kg +30d	8 ♂

Group Id	Treatment	Cofactor	No Rats
35	10 mg Quartz DQ12 IT	BNF 8*25mg/kg +30d	8 ♂
36	20 mg Quartz DQ12 IT	BNF 8*25mg/kg +30d	12 ♂
37	0.6 mg Be dust IT	BNF 4*25mg/kg +30d	6 ♂
38	0.6 mg Be dust IT	BNF 8*25mg/kg +30d	6 ♂
39	Saline IPI	none	32 ♂
40	Crocidolite IPI	none	52 ♂
41	Crocidolit Chrysotyl mix IPI	none	5 ♂
42	Chrysotil Non-Lixif. IPI	none	52 ♂
43	Chrysotyl Lixif.20% Ox.Ac. IPI	none	32 ♂
44	Chrysotyl Lixif.50% Ox.Ac. IPI	none	48 ♂
45	Chrysotyl Lixif.70% Ox.Ac. IPI	none	32 ♂
46	Chrysotyl Lixif.100% Ox.Ac. IPI	none	48 ♂
47	Chrysotyl Lixif.100% HCl. IPI	none	16 ♂
48	Glas fiber IPI	none	52 ♂
49	20 mg Pb CrO_4 IT	none, serial sacrifice	12 ♂
50	20 mg Pb Sulfochromate IT	none, serial sacrifice	12 ♂
51	20 mg Mo Sulfochromate IT	none, serial sacrifice	6 ♂
52	5 (20) mg $K_2Cr_2O_7$ IT	none, serial sacrifice	6 ♂
53	5 (20 mg Zn CrO_4 IT	none, serial sacrifice	6 ♂
54	10 mg Zn CrO_4 IT	BNF 25mg/kg, serial sacrifice	6 ♂
55	10 mg Zn CrO_4 tetraoxyIT	BNF 25mg/kg, serial sacrifice	6 ♂
56	10 mg Sr CrO_4 IT	none, serial sacrifice	4 ♂
57	10 mg Sr CrO_4 IT	BNF 25mg/kg, serial sacrifice	6 ♂
58	20 mg Sr CrO_4 IT	BNF 25mg/kg, serial sacrifice	13 ♂
59	75 mg Ni La dust IT	BNF 25mg/kg, serial sacrifice	12 ♂
60	150 mg Ni La dust IT	BNF 25mg/kg serial sacrifice	12 ♂
61	1 mg Ni_3S_2	BNF 25mg/kg, serial sacrifice	12 ♂
62	3 mg Ni_3S_2	BNF 25mg/kg, serial sacrifice	12 ♂
63	10 mg Ni_3S_2	BNF 25mg/kg, serial sacrifice	12 ♂

02.16 Effects of Prenatal and Postnatal Gamma Irradiation on the Rat Testis

Institution: CEA, DSV-DPTE (IPSN) Fontenay-aux Roses, France

Scientists: H. Coffigny; active

Purpose: To determine the effect of acute irradiation during gestation and the neonatal period and of protracted exposure during the entire intra-uterine life on adult rat testis: influence of dose rate and threshold values.

Status: 1977 - 1988, terminated

Treatment: Acute and protracted Co-60 gamma irradiation: acute exposure to doses from 0 to 1.5 Gy at different dose rates on day 15 and 21 of gestation and day 0 and 2 of postnatal life.

A) Acute exposure to 1.5 Gy (dose rate 0.1 Gy/min) (sacrifice at an age of 3 months): Effect of intrauterine age
B) Protracted exposure during the entire intrauterine life (sacrifice at an age of 3 months): Effect of dose
C) Effect of dose rate for an exposure of 1 Gy to fetuses 16 or 21 days post conception (sacrifice at an age of 3 months).
D) Effect of low doses to determine threshold dose at a dose rate of 0.1 Gy/min, sacrificed at an age of 26 days

Dosimetry: Ionization chamber

Endpoints: Testis weight, histology and hormonal activity in prepueral and adult animals.

Animal: Sprague-Dawley SPF rats offspring

Results:

A) Following exposure from day 18 post conception (p.c.) until day 2 post birth (p.b.), all germ cells in the testis were found to be killed and the animal was sterile,
B) A dose as small as 0.1 Gy/d resulted in a loss of all germ cells from the testis,
C) Nearly all germ cells were killed following an exposure to 1 Gy at a dose rate of 0.6 mGy/min on day 15 p.c.; at the other dose rates, the histology of the irradiated testis was similar to that of the control testis. After a dose of 1 Gy on day 21 p.c., all germ cells were killed and no effect of dose rate could be observed.
D) The threshold dose at which a decrease in germ cells could be detected is 0.2 Gy at days 18 p.c., 21 p.c. and the day of birth; it increases to 0.4 Gy on day 2 p.b.

References:

Coffigny, H., P. Fritsch, M. Beauvallet, L. Court, H. Métivier and R. Masse. Late effects of protracted gamma irradiation during intra-uterine life on gonad development. *EULEP Newsletter* **57**:35-36, 1990.

Coffigny, H. Hormonal and cellular factors affecting immature Sertoli cells radiosensitivity in the fetal rat. *Int. J. Radiat. Biol:*746, 1987.

Coffigny, H.G., C.F.H. Pasquier, G. Perrault and J.P. Dupouy. Étude chez le rat adulte des conséquences d'une irradiation de 150 rad à différents stades de la gestation et de la période néo-natale. Éffets sur le développement des organes génitaux, pp. 207-220. *In* IAEA-SM224-805 [ed.], *Late Biological Effects of Ionizing Radiation*, Vol. II. Iaea, Vienna, 1978.

Coffigny, H. Modification de la radiosensibilité des gonocytes du rat nouveau-né pendant la périod quiescente, . *In* Reprod.Nutr.Dévelopm. 29 (2) Supp.30: Multiplication, Différenciation et Transformations Cellulaires., 15éme Réunion du Groupe *Dévelopment, Multiplication, Transformation Céllulaires* Paris 24-26 Mai, 1989.

Coffigny, H. and C.F.H. Pasquier. A comparative experimental study of gamma rays and neutron effects on germ cells during the prenatal period, pp. 416-417. *In* A. Kaul, R. Neider, J. Pensko, F.E. Stieve and H. Brunner [eds.], *Radiation-Risk-Protection,* Vol. 1. Fachverband für Strahlenschutz, Berlin, Proceedings VIth IRPA Congress Berlin, 1984.

Experimental Groups:

Study 02.16

Effects of Prenatal and Postnatal Gamma Irradiation on the Rat Testis

A. Acute exposure to 1.5 Gy (dose rate 0.1 Gy/min) (sacrifice at an age of 3 months): Effect of intrauterine age

Group Id	Age (days)	No testes assayed
1	14 days post conception	10
2	15 days post conception	34
3	16 days post conception	8
4	17 days post conception	8
5	18 days post conception	9
6	19 days post conception	9
7	20 days post conception	16
8	21 days post conception	8
9	0 days after birth	12
10	0 days after birth	12
11	0 days after birth	12
12	0 days after birth	6
13	0 days after birth	9
14	0 days after birth	4
15	0 days after birth	8

B. Protracted exposure during the entire intrauterine life (sacrifice at an age of 3 months): Effect of dose

Group Id	Dose Gy (Dose rate Gy/d)	No testes assayed
16	0	9
17	0.6 (0.03)	9
18	2.0 (0.10)	8
19	5.0 (0.25)	10
20	7.5 (0.375)	12

C. Effect of dose rate for an exposure of 1 Gy to fetuses 16 or 21 days post conception (sacrifice at an age of 3 months).

Dose rate mGy/min	15 days p.c.		21 days p.c.	
	Group Id	No testes	Group Id	No testes
0	21	29	26	29
0.6	22	12	27	6
3.3	23	12	28	10
16.6	24	7		
166	25	11	29	8

D. Effect of low doses to determine threshold dose at a dose rate of 0.1 Gy/min (sacrificed at an age of 26 days)

Dose Gy	Group Id / No of testes			
	18 days p.c.	21 days p.c.	day of birth	2 days old
0		30 / ?		
0.1	31 / 14	35 / 14	42 / 15	46 / 11
0.2	32 /?	36 16	43 / 16	47 / 23
0.3	33 /?	37 / 23	44 / 13	48 / 33
0.4	34 /?	38 / 14	45 / 12	49 / 8
0.5		39 / 8		
1.0		40 / 8		
1.5		41 / 5		

02.17 Brain Damage in 90-Day-Old Rats Exposed During the Entire Gestation to Co-90 Gamma Rays or Cf-252 Neutrons At Different Dose Rates

Institution: CEA, DSV-DPTE (IPSN) Fontenay-aux Roses, France

Scientists: H. Coffigny; active

Purpose: To determine the effect of dose rate and relative biological efficiency of neutron vs gamma irradiation for protracted, in utero exposure

Status: 1989 - 1992, terminated

Treatment: Protracted Co-60 gamma irradiation and Cf-252 neutrons plus gamma (ratio 2/1) irradiation at different dose rates delivered over the entire gestation

Dosimetry: Gamma: ionization chamber; neutrons: ionization chamber filled with circulating tissue-equivalent gas

Endpoints: Early and late effects on brain weight and late effects on brain histology

Animal: Sprague-Dawley SPF rats offspring

Results: Ninety day old rats exposed during the entire gestation to C0-60 gamma rays or Cf-252 neutrons at various dose rates showed a marked decrease in brain weight (RBE = 4) but no gross malformations of the brain when examined by histological methods.

References: Coffigny, H., P. Fritsch, M. Beauvallet, L. Court, H. Métivier and R. Masse. Dose-rate effect of gamma irradiation during the intra-uterine life on brain development. *In* 22nd Annual Meeting Europ. Soc. Radiation Biology Brussels., Abstract, 1989.

Coffigny, H. and M. Beauvallet. Effects of gamma or neutron protracted irradiatom during the whole gestation of rat. *EULEP Newsletter* 67:24, 1992.

Experimental Groups:

Study 02.17
Brain Damage in 90-Day-Old Rats Exposed During the Entire Gestation to Co-90 Gamma Rays or Cf-252 Neutrons At Different Dose Rates

Dose Gy	Dose Rate Gy/d	Gamma rays		Neutrons	
		Group Id	No rats	Group Id	No rats
0		1	56		
0.3	0.015			6	51
0.6	0.03	2	66	7	66
1	0.05			8	30
2	0.1	3	68	9	68
3	0.15			10	12
5	0.25	4	18		
7.5	0.375	5	24		

02.18 Comparative Radiosensitivity of Developing Brain Structures in the Rat After Gamma Irradiation

Institution: CEA, DSV-DPTE Fontenay-aux Roses, France

Scientists: F. Ménétrier; active

Purpose: To compare the radiosensitivities of proliferative layers of the olfactory bulb (OB), the dentate gyrus of the hippocampus (DG) and the cerebellum (C)

Status: 1990 - 1992, terminated

Treatment: Single whole body gamma irradiation with doses from 0.1 to 12 Gy (dose rate 0.19 Gy/min) from a Co-60 gamma source irradiation. Animals sacrificed and brains removed 3, 6 or 9 h after exposure

Dosimetry: Ionization chamber

Endpoints: Quantification of radiation-induced apoptosis in semi-thin sections, development with time of radiation-induced lesions, cell survival curves

Animal: Sprague-Dawley CFA albino rats at an age of 14 days, sham irradiated and irradiated rats randomly chosen.

Results: Irradiated injured cells in the central nervous system develop a typical apoptotic appearance. The number of apoptotic cells incrases dramatically with time 5 hours after exposure. The survival rate of immature granule cells was evaluated in function of the dose. In both, the olfactory bulb and the dentate gyrus, the dose-effect relationship was complex. In the cerebellum, this relationship followed a negative exponential function. These results suggest that, in the olfactory bulb and the dentate gyrus, the proliferative layer consists of two cell populations with different radiosensitivities whereas in the cerebellum only one homogeneous population is present.

References: Ménetrier, F., S. Denis, G. Azzi, D. Dormont and L. Court. Comparative study of radiation-induced apoptosis in the young rat olfactory bulb,hippocampus and cerebellum, . *In* Proc. *25th annual Meeting Europ. Soc. Radiation Biology* Stockholm.; 1993.

Alaloui, F., J. Pratt, F. Ménetrier, M. Stutzma and L. Court. Riluzol protects the dentate gyrus of gamma-irradiated immature rats, pp. 215-221. *In Neurodegenerative Diseases.* Academic Press Ltd, New York, 1994.

Fritsch, P., H. Richard-Le Naour, S. Denis and F. Ménetrier. Kinetics of radiation-induced apoptosis in the cerebellum of 14 days old rats after acute or during continuous exposure. *Int. J. Radiat. Biol.* **66**:111-117, 1994.

Experimental Groups:

Study 02.18

Comparative Radiosensitivity of Developing Brain Structures in the Rat After Gamma Irradiation

Dose Gy	Hours post Exposure	Group Id / No of Rats		
		Olfactory Bulb	Hippocampus	Cerebellum
0		1 / 6	20 / 6	37 / 4
0.1	6	2 / 6	21 / 5	38 / 6
0.25	6	3 / 6	22 / 6	39 / 6
0.5	3	-	-	40 / 2
0.5	6	4 / 6	23 / 5	41 / 6
0.5	9	-	-	42 / 2
1	6	5 / 6	24 / 5	43 / 6
1.5	6	6 / 7	25 / 5	44 / 6
2	3	7 / 3	26 / 3	-
2	6	8 / 7	27 /5	45 / 6
2	9	9 / 5	28 / 3	-
3	3	10 / 3	-	46 / 3
3	6	11 / 7	29 / 5	47 / 6
3	9	12 / 2	-	48 / 2
4	6	13 / 8	30 / 5	49 / 6
5	3	14 / 2	31 / 2	50 / 2
5	6	15 / 7	32 / 5	51 / 6
6	6	16 / 3	33 / 3	-
9	6	17 / 3	34 / 3	52 / 3
12	6	18 / 3	35 / 3	53 / 3
5	9	19 / 2	36 / 2	54 / 2

02.19 Brain Damage in 120-Day-Old Rats After Single Doses of Co-60 Gamma Irradiation

Institution: CEA, DSV-DRR-LRA Fontenay-aux Roses, 91191 Gif sur Yvette, France

Scientists: J-L. Lefaix; active

Purpose: To study radiation-induced necrosis of the brain and glucose metabolism

Status: 1990 - 1992, terminated

Treatment: Single exposure of the brain to doses from 0 to 40 Gy of Co-60 gamma irradiation collimated at a 20 mm diameter circular (whole brain) or a 8x3 mm quadratic field (left hemisphere)

Dosimetry: Ionization chamber

Endpoints: Lifespan, brain and body weight, histology, immuno-cytochemistry, C-14 glucose metabolism

Animal: Sprague-Dawley rats aged 120 days,

Results:

References:

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Experimental Groups:

Study 02.19
Brain Damage in 120 Day-Old-Rats After Single Doses of Co-60 Gamma Irradiation

Dose Gy	Collimation 20 mm Whole Brain		Collimation 8x3mm Hemisphere	
	Group Id	No Rats	Group Id	No Rats
0	1	7		
15	2	7	7	7
20	3	7	8	7
25	4	7	9	7
30	5	7	10	7
40	6	7	11	7

02.20 Regional Gamma Irradiation of Pigs

Institution: CEA, DSV-DRR Fontenay-aux Roses, Laboratoire de Radiobiologie Appliqué, 91191 Gif sur Yvette, France

Scientists: F. Daburon; active

Purpose: To study the gastro-intestinal syndrome in pigs exposed to the posterior part of the body with the aim to improve the management of accidental over-exposure in man.

Status: 1970 - 1978, terminated

Treatment: Single partial body irradiation of the posterior half part of the body of pigs from the xyphoid appendix downwards; the upper part of the body was shielded with lead plates. The midplane dose from eight Co-60 sources delivered at dose rates from 0.3 to 1 Gy/min ranged from 8 to 18.5 Gy. The animals were followed up to 1 year. Intestinal mucosa biopsies were performed using a cannula indwelling in the jejunal lumen.

Dosimetry: Ferro-sulfate dosemeter, LiF thermoluminescence detectors, ionization chamber

Endpoints: Histological and histoenzymological evolution of the irradiated intestinal mucosa dependent on time and dose; gastric secretion, intestinal absorption and balance of dietary minerals, nitrogen and lipids; treatment with pharmaceutics and/or surgery (graft and exeresis) in some animals

Animal: Large white pigs 4-5 months old, weighing 25-45 kg;
Adult miniature pigs, Pitman-Moore or Corsican as well as crossbreds, 1-2 years old, weighing 30-70 kg

Results: Supralethal doses (>15 Gy) result in a gastrointestinal syndrome with diarrhoea, increased Na excretion and dehydration and a survival of 4-5 days in large white pigs and 5-7 days in Pitman Moore pigs. Based on studies on DNA content in the ileum after different doses, it appears that at doses above 15 Gy recovery is impossible. Large white pigs supplied with a Pavlov pouch and exposed to 15 Gy show an immediate fall in gastric secretion with abnormalities still present at 3 days whereas histamine- stimulated secretion is but little altered. Corsican pigs provided with an indwelling gastric catheter had longlasting hypochlorhydria as well as an increase of DNA and exudative proteins during the regenerative phase. Induced hyperglycaemia also remained abnormal although insulin secretion was not affected. Exocrine pancreatic function declined progressively leading to poor absorption of feed. Although the intestinal mucosa recovered after doses of 11 Gy, nutritional balance, electrolyte metabolism and pancreatic functions did not recover fully until at least 5 months after exposure. Attempts to treat the gastrointestinal syndrome showed that antibiotics may help to avoid infections and that pigs given parenteral nutrition after 10 Gy with supplements of minerals and water recover more rapidly. Intestinal grafts shortened rather than prolonged survival. Ileoectomy seemed to result in somewhat longer lifespan.

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Experimental Groups:

Study 02.20
Regional Gamma Irradiation of Pigs

Aim of Research	Midplane Dose (Gy)	Group Id	No Pigs	Studies/tests performed
1) determine threshold dose for total denudation of intestinal mucosa after total body exposure	5	1	8	DNA content of intestinal mucosa
	40	2		
2) study time course of gastrointestinal syndrome	17	3	9	clinical symptoms, hematology, excretion and distribution of Na, K and Cl
	18.5	4	23	
3) Recovery of intestinal mucosa	8-15	5	17	histology, histoimmunology of the intestinal mucosa, intestinal absorption of xylose and ^{14}C labeled lipids
4) Gastric functions	15	6	5 lw	Pavlov pouch; spontaneous and gastrin-stimulated gastric secretion, histology
5) Gastric functions	11	7	8 wp	spontaneous and gastrin- stimulated gastric secretion
6) Function of endocrine and exocrine pancreas	11	8	9	hyperglycemia test (6), digestibility of feed (10)
7) Function of exocrine pancreas	6	9	6	secretion of proteases and lipases
	8	10	2	
8)Intestinal absorption, digestibility of feed	11	11	10 co	balance of dietary minerals (Na, K, Ca, P), nitrogen and lipids
9) Treatment by parenteral nutrition	10	12	10	balance of dietary minerals (Na, K, Ca, P), nitrogen and lipids
10) Surgical treament by grafts	8-12.5	13	13	intestinal grafts of half jejunum and/or ileum
11) Surgical treatment by removal	13.75-14.5	14	6	partial enterectomy 22-27 d before(2 pigs) 3-4h after (3 pigs) or subtotal (4 pigs) 3-4 h after irradiation
12) Medical treatments	13	15	11	therapy with antibiotics, gastro-intestinal protectors, parenteral and enteral nutrition
	12-13	16	8	
	13.75	17	5	
	15-16.5	18	5	
	18.5	19	4	

Lw large white pigs, pi Pitman Moore pigs, co Corsican pigs

02.21 Early and Delayed Radiation Effects After Localized Irradiation of Pigs and Rabbits

Institution: CEA, DSV-DRR-LRA Fontenay-aux Roses, 91191 Gif sur Yvette, France

Scientists: F. Daburon; active
J-L. Lefaix; active
M. Martin; active

Purpose: To study the early radiation-induced necrosis and late radiation-induced fibrosis of skin and underlying tissues after acute localized irradiation with a view to the management of accidental over-exposure of man

Status: 1981 -

Treatment:
1) Single collimated gamma exposure (Ir-192) (diameter 2 cm) of the outer side of the thigh and the back of pigs with skin surface doses from 0 to 140 Gy;
2) Single collimated gamma exposure (Ir-192) (diameter 2 cm) of the outer side of the back of rabbits with skin surface doses from 0 to 160 Gy ;
3) Single beta exposure with a collimated (4cm diameter) Sr-90/Y90 source (1.7 GBq) of the flanc of pigs;
4) Mixed exposure (11% Ir-192 gamma 91% Sr-90/Y90 beta) of the pig skin with doses from 3.2 Gy gamma + 32 Gy beta radiation to 8 Gy gamma + 80 Gy beta radiation

Dosimetry: LiF thermoluminescence dosimeter, ionization chamber

Endpoints:
1) Clinical, biochemical and biophysical evaluation of the diagnostic-prognostic evolution of the lesions in dependence of dose and time after exposure (serum biochemistry, microwave thermography, X-ray computerised tomography, NMR imaging and spectroscopy, vascular and metabolic scintigraphy, skin microrelief, cutaneous laser Doppler
2) Histological, histo-enzymological and immuno-cytochemical evolution in the irradiation skin and skeletal muscle;
3) Pharmacological trials and surgery early after acute local exposure;
4) Medical treatment of late radiation-induced fibrosis.
5) Molecular-biological studies: early and late response

Animal: Large white pigs (4 months old) and adult New Zealand rabbits

Results: The development of the lesions after dose levels such as encountered after accidental overexposure was studied in function of time, size of field and penetration of the radiation. The studies demonstrate the importance of an early assessment of the degree of damage for an effective therapy. The data show that a spectrum of tests rather than a single one is needed for such an evaluation. The methods most useful for such an early evaluation are microwave thermography and scintigraphic techniques. Enzymatic tests help to evaluated the inflammatory reaction and cutaneo-muscular necrosis. Early treatment with excision of irradiated skin only followed by early grafts is most effective after doses of 120-160 Gy to reduce the late extension of the fibronecrotic processes. Drugs which reduce aggregation of platelets and combat infection. Softening of the late fibrotic reaction could be achieved with superoxide dismutase.
Molecular-biological studies on the mechanism by which fibroblast proliferate and deposit extracellular matrix indicate that the fibrotic process after irradiation escapes normal control by the organism. It is thought that protooncogenes induced after irradiation, c-fos after as little as 0.5 Gy, result in an activation of the fibroblasts. An overproduction of transforming growth factors may play a role in the overproduction of collagen and the reduction in protein breakdown.

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Experimental Groups:

Study 02.21
Early and Delayed Radiation Effects After Localized Irradiation of Pigs and Rabbits

Group Id	Treatment	Dose Gy (skin surface)	No of fields/No of animals
1	1a) ^{192}Ir gamma rays thigh pigs	120	1 per animal / 15 pigs
2		160	1 per animal / 26 pigs
3		250	1 per animal / 36 pigs
4		340	1 per animal / 24 pigs
5	1b) ^{192}Ir gamma rays back pigs	16, 32, 48, 64, 80, 96	16, 32, 48 Gy to right side, 64, 80, 96 to left side of the back, a total of 8 pigs
6	2) ^{192}Ir gamma rays back rabbits	40	1 field per animal / 8 rabbits
7		80	1 field per animal / 8 rabbits
8		120	1 field per animal / 8 rabbits
9		160	1 field per animal / 8 rabbits
10	3) ^{90}Sr^{90}Y beta rays flank pigs	4 , 8, 16, 32, 64	each dose to a different field on each animal / 6 pigs
11		32, 64, 96	each dose to a different field on each animal / 5 pigs
12		32, 64	each dose to a different field on each animal / 6 pigs
13		48, 64, 80	each dose to a different field on each animal / 6 pigs
14	3) ^{192} Ir gamma+ ^{90}Sr^{90}Y beta rays flank pigs	3.2 γ + 32β 6.4 γ + 64β	2 fields each animal, / 5 pigs
15		8 γ +80 β	1 field each animal / 8 pigs
16		8 γ +80 β	1 field each animal / 6 pigs

03 ENEA, Laboratory of Pathology, Casaccia-Rome

03.01 Ovarian Tumors in Mice After X-Ray and Neutron Exposure

Institution: ENEA, Labor. of Pathology, Casaccia-Rome, Italy

Scientists: V. Covelli; active
M. Coppola; active
V. Di Majo; active
S. Rebessi; active

Purpose: To determine the dose relationship and RBE for ovarian murine tumors after X-ray and neutron exposure.

Status: 1982 - 1987, terminated, data in ERAD

Treatment: Single acute exposure to 250 kVp X-rays (1.5 mm HVL, 60 mGy/min) or 1.5 MeV neutrons from a van de Graaff accelerator at the JRC Ispra (1.83 mGy/min)

Dosimetry: Twin ionization chamber method, ENDIP

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology

Animal: Female (C57Bl/Cne x C3H/Cne)F1 (BC3F1) mice aged 3 months

Results: A significant increase in life-shortening was observed for single neutron exposure to 0.08 Gy. or more. Assuming a linear non-threshold dose-effect relationship, the RBE value is 12.3 for 1.5 MeV neutrons. A statistically significant increase in solid tumors is seen for single neutron exposure from 0.08 Gy and for X-ray exposure from 1 Gy. The data for neutrons at low doses can be fitted to a linear dose effect relationship. A separatei analysis of of ovarian tumor induction substantiates the hypothesis of a threslhold for X-rays, whereas such a threshold is not evident for neutrons. A trend analysis confirms these findings. When death rates are analysed, a general agreement between their shift to earlier times and tumor induction was found.

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Experimental Groups:

Study 03.01
Ovarian Tumors in Mice After X-ray and Neutron Exposure

Group Id	Treatment	Dose mGy	Number Mice
1	X-rays	0	353
2	X-rays	40	100
3	X-rays	80	84
4	X-rays	160	53
5	X-rays	320	58
6	X-rays	640	57
7	X-rays	1280	60
8	X-rays	2560	55
9	Neutrons	0	279
10	Neutrons	5	165
11	Neutrons	10	150
12	Neutrons	20	95
13	Neutrons	40	96
14	Neutrons	80	92
15	Neutrons	160	48

03.02 Late Somatic Effects in Mice After Fractionated X-Ray and Neutron Exposure

Institution: ENEA, Labor. of Pathology, Casaccia-Rome, Italy

Scientists: V. Covelli; active
M. Coppola; active
V. Di Majo; active
S. Rebessi; active

Purpose: To determine the dose rate reduction factor and RBE for X-ray and neutron exposure.

Status: 1987- ongoing

Treatment: Single exposure to 250 kVp X-rays (318 mGy/min, 1.5 mm HVL) and single and fractionated (5 fractions at one day interval) exposure to fission neutrons (0.4 MeV, 4 mGy/min) from the biological facility of the RSV-TAPIRO reactor at Casaccia

Dosimetry: Twin ionization chamber method, ENDIP

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology

Animal: Male (C57Bl/Cne x C3H/Cne)F1 (BC3F1) mice aged 4-6 weeks

Results: The data were analysed with the Peto test for myeloid leukemia and for selected solid tumors. Myeloid leukemia was absent in controls and rare in the irradiated groups. Nevertheles, a positive trend with dose for 0-0.17 Gy or more could be established. Epithelial tumors were induced from doses of 0.17 Gy or

more. Tumor occurrence was further evaluated as final incidences with age adjustement for the difference in rates of mortality. Survival and incidence for selected classes of tumors after 0.17, 0.36 and 0.71 Gy were compared with those from a previous experiment at corresponding doses given acutely (dose rates between 0.05 and 0.25 Gy/min). The results did not suggest any marked overall influence of the time regimen of neutron irradiation on survival and tumor induction.

References: Di Majo, V., M. Coppola, S. Rebessi, A. Saran, S. Pazzaglia, L. Pariset and V. Covelli. Neutron-induced tumors in BC3F1 mice: effects of dose fractionation. *Radiat. Res.* **138**:252-259, 1994.

Experimental Groups:

Study 03.02
Late Somatic Effects in Mice After Fractionated X-Ray and Neutron Exposure

Group Id	Treatment	Dose mGy	No Mice
1	X-rays **Single**	0	758
2	X-rays	500	44
3	X-rays	1000	108
4	X-rays	2000	139
5	X-rays	3000	110
6	X-rays	4000	137
7	X-rays	5000	125
8	X-rays	6000	58
9	X-rays	7000	133
10	Neutrons **Single**	170	49
11	Neutrons	360	47
12	Neutrons	710	48
13	Neutrons	1070	49
14	Neutrons	1430	49
15	Neutrons	1790	96
16	Neutrons	2140	22
17	Neutrons **Fractionated**	25	202
18	Neutrons	50	148
19	Neutrons	100	105
20	Neutrons	170	74
21	Neutrons	250	53
22	Neutrons	360	54
23	Neutrons	535	54
24	Neutrons	710	52

03.03 Myeloid Leukemia and Harderian Gland Tumors in Mice After X-Ray Exposure

Institution: ENEA, Labor. of Pathology, Casaccia-Rome, Italy

Scientists: V. Di Majo; active
M. Coppola; active
S. Rebessi; active
V. Covelli; active

Purpose: To determine, for myeloid leukemia and Harderian gland tumors, the neutron RBE .

Status: 1989 - 1992, X-rays terminated, neutrons ongoing

Treatment: Single exposure to 250 kVp X-rays (126 mGy/min, 1.5 mm HVL)

Dosimetry: Twin ionization chamber ENDIP

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology

Animal: Male CBA/H/Cne mice aged 3 months

Results: Harderian glands transplanted into the fat pad of isogenic recipients were used to quantitatively study cell survival and maligant transformation after X-ray exposure. The *in vivo* survival curve of the gland cells yielded a Do of 1.83 Gy and an extrapolation number of 7.23. The dose response for cell transplantation *in vivo* was compared with that for lesions in glands irradiated in situ. A high incidence of epithelial hyperplasias with severe dysplasia was observed in translantation nodules after X-irradiation. The rate of gland tumors was significantly increased in whole-body-irradiated animals with a maximum incidence after 3 Gy. The risk of transformation per surviving cell was estimated for both dysplastic lesions and tumors. These results approximated a dose-squared relationship in both cases, suggesting a common induction mechanism at the cellular level. Myeloid leukemia was observed at all doses in whole body irradiated mice, and the maximum tumor incidence was reached at doses around 3 Gy.

References: Covelli, V., V. Di Majo, M. Coppola and S. Rebessi. The dose-response relationships for myeloid leukaemia and malignant lymphoma in BC3F1 mice. *Radiat. Res.* **119**:553-561, 1989.

Experimental Groups:

Study 03.03
Myeloid Leukemia and Harderian Gland Tumors in Mice After X-Ray Exposure

Group Id	Dose (Gy)	No mice
1	0	60
2	1	60
3	3	60
4	5	59
5	7	57

03.04 Myeloid Leukemia and Malignant Lymphoma in Mice After X-Ray and Neutron Exposure

Institution: ENEA, Labor. of Pathology, Casaccia-Rome, Italy

Scientists: V. Di Majo; active
M. Coppola; active
S. Rebessi; active
V. Covelli; active

Purpose: To determine neutron RBE for myeloid leukemia and malignant lymphoma.

Status: 1980 - 1984, terminated

Treatment: Single exposure to 250 kVp X-rays (133 mGy/min, 1.5 mm HVL) or fission neutrons (4 mGy/min, 0.4 MeV) from the biological facility of the RSV-TAPIRO reactor at Casaccia.

Dosimetry: Twin ionization chamber method, ENDIP

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology

Animal: Male (C57Bl/Cne x C3H/Cne)F1 (BC3F1) mice aged 3 months

Results: The data on the induction of lymphoma and myleoid leukemia yielded some new interesting shapes of dose-effect relationships which were interpreted by radiobiological models of the process of induction in conjunction with cell inactivation. The dose-effect relationship for malignant lymphoma induced by X-rays can be described by a quadratic model corrected for cell inactivation wheras that for neutrons is best fitted to a linear model with also allows for cell inactivation. Myeloid leukemia yielded a bell-shaped curve after irradiation with X-rays or neutrons which can be explained by simultaneous mechanisms of cell transformation and cell inactivation.. The data on cell inactivation at higher doses agree with those reported in other mouse strains. A relative biological efficiency of 4 was found for neutrons at the lowest neutron dose used. The value of the inactivation parameters can be compared with those of the cell inactivation probablility per unit dose for bone marrow haemopoietic stem cells which are considered to be the target cells for these tumors.

References: Covelli, V., V. Di Majo, M. Coppola and S. Rebessi. The dose-response relationships for myeloid leukaemia and malignant lymphoma in BC3F1 mice. *Radiat. Res.* **119**:553-561, 1989.

Experimental Groups:

Study 03.04
Myeloid Leukemia and Malignant Lymphoma in Mice After X-Ray and Neutron Exposure

Group Id	Treatment	Dose Gy	Number of mice
1	**X-rays**	0	561
2	X-rays	0.5	44
3	X-rays	1	108
4	X-rays	2	139
5	X-rays	3	110
6	X-rays	4	137
7	X-rays	5	125
8	X-rays	6	58
9	X-rays	7	133
10	X-rays	9	335
11	**Neutrons**	0.17	49
12	Neutrons	0.36	47
13	Neutrons	0.71	48
14	Neutrons	1.07	49
15	Neutrons	1.43	49
16	Neutrons	1.79	96
17	Neutrons	2.41	22

03.05 Tumors and Survival in Mice in Dependence of Age After X-Ray and Neutron Exposure

Institution: ENEA, Labor. of Pathology, Casaccia-Rome, Italy

Purpose: To determine the RBE in function of the age of the animal.

Status: 1984 - 1989, terminated

Scientists: V. Di Majo; active
M. Coppola; active
S. Rebessi; active
V. Covelli ; active

Treatment: Single exposure to 250 kVp X-rays (133 mGy/min, 1.5 mm HVL) or fission neutrons (4 mGy/min, 0.4 MeV) from the biological facility of the RSV-TAPIRO reactor at Casaccia

Dosimetry: Twin ionization chamber method, ENDIP

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology

Animal: (C57Bl/Cne x C3H/Cne)F1 (BC3F1) male mice aged 17.5 days post conception, 3 and 19 months

Results: Liver tumors increase slightly in mice irradiated prior birth after X-ray doses of 0.3 to 2.1 of X-rays and more markedly after neutron doses of 0.09 to 0.62 Gy. At an age of 3 months, incidence is higher after 2 Gy of X-rays or 0.17 Gy of neutrons. At an age of 19 months, very few liver tumors could be induced by either type of radiation. The data from X-rays indicated a quadratic relationship, those from neutrons a linear one. The RBE for neutrons was 28 at a dose of 0.09 and 131 at a dose of 0.17 for irradiation at 3 months. On the other hand, prenatal irradiation or irradiation at an age of 19 months did not cause life-shortening although it increased the rate of solid tumors and reticulosarcoma. At an age of 3 month life-shortening associated with increased tumor incidence was noticeable. The RBE was ranged between 3 and 18 with the higher levels at the lower doses.

References: Covelli, V., V. Di Majo, B. Bassani, S. Rebessi, M. Coppola and G. Silini. Influence of age on life-shortening and tumor induction after X-ray and neutron irradiation. *Radiat. Res.* **100**:348-364, 1984.

Di Majo, V., M. Coppola, S. Rebessi and V. Covelli. Age-related susceptibility of mouse liver to induction of tumors by neutrons. *Radiat. Res.* **124**:227-234, 1990.

Experimental Groups:

Study 03.05
Tumors and Survival in Mice in Dependence of Age After X-Ray and Neutron Exposure

Group Id	Age	Treatment	Dose mGy	Number mice
1	17.5 days p.c.	Control	0	237
2	17.5 days p.c.	X-rays	300	48
3	17.5 days p.c.	X-rays	900	61
4	17.5 days p.c.	X-rays	1,500	46
5	17.5 days p.c.	X-rays	2,100	45
6	17.5 days p.c.	Neutrons	90	51
7	17.5 days p.c.	Neutrons	270	44
8	17.5 days p.c.	Neutrons	450	27
9	17.5 days p.c.	Neutrons	620	35
10	3 months	X-rays	500	44
11	3 months	X-rays	1,000	48
12	3 months	X-rays	2,000	50
13	3 months	X-rays	3,000	50
14	3 months	X-rays	4,000	48
15	3 months	X-rays	5,000	68
16	3 months	X-rays	6,000	58
17	3 months	X-rays	7,000	74
18	3 months	Neutrons	170	49
19	3 months	Neutrons	360	47
20	3 months	Neutrons	710	48
21	3 months	Neutrons	1,070	49
22	3 months	Neutrons	1,430	49
23	3 months	Neutrons	1,790	96
24	3 months	Neutrons	2,140	22
25	19 months	Control	0	46

Group Id	Age	Treatment	Dose mGy	Number mice
26	19 months	X-rays	500	47
27	19 months	X-rays	1,000	44
28	19 months	X-rays	2,000	47
29	19 months	X-rays	3,000	48
30	19 months	X-rays	4,000	46
31	19 months	X-rays	5,000	71
32	19 months	X-rays	6,000	85
33	19 months	X-rays	7,000	58
34	19 months	Neutrons	170	50
35	19 months	Neutrons	360	48
36	19 months	Neutrons	710	51
37	19 months	Neutrons	1,070	49
38	19 months	Neutrons	1,430	49
39	19 months	Neutrons	1,790	42
40	19 months	Neutrons	2,140	46

04 Deutsches Krebsforschungszentrum

04.01 Liver and Spleen Tumors in Rats After Injection of Th-230 Enriched Thorotrast

Institution: Deutsches Krebsforschungszentrum, Heidelberg, FRG

Scientists: H. Wesch; active
K. Wegener; active
K. Küttler; active

Purpose: To determine the respective roles of the radioactive and chemical component in thorotrast gel-induced tumors, alpha radioactivity in thorotrast was enriched about 50 times by addition of Th-230.

Status: 1975-1979, terminated

Treatment: Single i.v. injection with different amounts of variously enriched thorotrast (see below)

Dosimetry: Activity delivered

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology

Animal: Female Wistar rats aged 12±2 weeks at injection.

Results: The number of animals that developed liver or spleen tumors increased by a factor of 19 in the highest dose-rate groups compared to controls. There was a linear correlation between dose rate and the number of liver and spleen tumors. An increase of the number of injected Thorotrast particles, providing a constant dose rate, had little influence on tumor incidence. However, at a constant relative dose-rate of ten, a fifty-fold increase in the number of particles (12-600 µl) shortened the minimal tumor latency time by about 250 days. The induced liver tumors showed mostly the same morphology as those observed in thorotrast patients except for a special type of sarcoma which, so far, has not been seen in man and was interpreted as a Kupffer cell sarcoma. No excess lung tumors due to the exhalation of Rn-220 was observed.

References:

Wegener, K., K. Hasenöhrl and H. Wesch: Recent results of the German Thorotrast study: patho-anatomical changes in animal experiments and comparison to human thorotrastosis. pp. 307-316. *In* Rundo,J; Failla,P; Schlenker,RA [eds,] *The Radiobiology of Radium and Thorotrast. Health Physics* **44,** Suppl.1, 1983

Wesch, H., G. van Kaick, W. Riedel, A. Kaul, K. Wegener, K. Hasenöhrl, H. Immich and H. Muth. Recent results of the German Thorotrast study: statistical evaluation of animal experiments with regard to nonradioactive effects in human thorotrastosis, pp. 317-321. *In* J. Rundo, P. Failla and R.A. Schlenker [eds.], *The Radiobiology of Radium and Thorotrast. Health Physics*,, **44,** Suppl.1, 1983.

van Kaick, G., H. Wesch, H. Lührs, D. Liebermann, A. Kaul and H. Muth. The German Thorotrast study - report on 20 years follow-up, pp. 98-104. *In* D.M. Taylor, C.W. Mays, G.B. Gerber and R.G. Thomas [eds.], *Risks from Radium and Thorotrast*, Vol. **21**. BIR (British Institute of Radiology), London, Report, 1989.

Experimental Groups:

Study 04.01
Liver and Spleen Tumors in Rats After Injection of Th-230 Enriched Thorotrast

Enrichment factor (Bq/ml ^{232}Th +Bq/ml ^{230}Th)	Group Id / Relative Dose rates (Number of rats)				
	12µl	60µl	120µl	300µl	600µl
Na Cl control	-	-	-	-	1 / 0 (95)
Dextrin control	-	2 / 0 (96)	3 / 0 (96)	4 / 0 (95)	5 / 0 (96)
1 (895 + 0)	-	6 / 1 (95)	7 / 2 (95)	8 / 5 (96)	9 / 10 (95)
2 (895 +1650)	-	10 / 2 (96)	11 / 4 (96)	12 / 10 (92)	-
5 (895 + 6550)	-	13 / 5 (96)	14 / 10 (93)	15 / 25 (92)	-
10 (895 + 14760)	-	16 / 10 (94)	17 / 20 (94)	18 / 50 (96)	-
50 (895 + 80360)	19 / 10 (96)	20 / 50 (95)	-	-	-

Dose rates relative to the standard treatment of 60 µl thorotrast with the number of animals in parentheses for different ratios Th-232/ Th-230 and amounts injected.

04.02 Lung Tumors in Rats After Injection of Normal and Th-228 Enriched Thorotrast and Inhalation of Quartz Dusts

Institution: Deutsches Krebsforschungszentrum, Heidelberg, FRG

Scientists: H. Wesch; active
A. Spiethoff; active
K. Wegener; active
H.J. Klimisch; active

Purpose: To determine whether thoron exhaled from incorporated thorotrast whose alpha radioactivity was enriched about 25 times in some groups by an addition of Th-228 would cause lung tumors if combined with inhalation of quartz dust.

Status: 1986-1989, terminated

Treatment: Single i.v. injection of 600 µml enriched thorotrast (1776 Bq Th-228/ml) followed by inhalation of quartz dust (6 mg/m^3 or 30 mg/m ^{3}) over 29 days

Dosimetry: Activity injected

Endpoints: Serial killing (0, 6, 12, and 24 months after exposure) and life-span (spontaneous death) with macroscopic/microscopic pathology

Animal: Female Wistar rats aged 3 ± 0.5 months at injection.

Results: In all quartz-exposed groups, the incidence of lung tumors was greater than 40%, The additional Thorotrast treatment resulted in a marked reduction of tumor latency times and in a higher total incidence (65%) in the animals exposed to the high quartz level (30 mg/m^3. Eighty seven of the animals treated with Thorotrast only developed lung tumors. Statistical methods that correct for intercurrent mortality showed a significant increase of the lung tumor risk due to Thorotrast even for the groups receiving the lowest concentration of quartz. The study demonstrates a pronounced interaction between quartz and thorotrast in lung carcinogenesis.

References: Spiethoff, A., H. Wesch, K. Wegener and H.J. Klimisch. The effects of thorotrast and quartz on the induction of lung tumors in rats. *Health Phys.* **63**:101-110, 1992.

Experimental Groups:

Study 04.02
Lung Tumors in Rats After Injection of Normal and Th-228 Enriched Thorotrast and Inhalation of Quartz Dusts

Group Id	Treatment	No rats
1	Controls	90
2	Inhalation of 6 mg /m^3 Quartz dust	90
3	Inhalation of 30 mg /m^3 Quartz dust	90
4	Inhalation of 6 mg /m^3 Quartz dust +600 µl enriched thorotrast	90
5	Inhalation of 30 mg /m^3 Quartz dust +600 µl enriched thorotrast	90
6	600 µl enriched thorotrast	90

04.03 Liver Tumors and Diseases in Rats After Fractionated Neutron Exposure or Injection of Nonradioactive Zirconotrast

Institution: Deutsches Krebsforschungszentrum, Heidelberg, FRG

Scientists: A. Spiethoff; active
H. Wesch; active
K. Wegener; active
K.H. Höver; active

Purpose: To determine the respective roles of the radioactive and chemical component in thorotrast induced liver damage. The fractionated neutron exposure was to simulate the radioactive, the zirconotrast the chemical damage from thorotrast.

Status: 1986-1989, terminated

Treatment: Fifty fractions of 0.2 Gy of neutrons (14 MeV neutrons produced by deuterium-tritium reaction, dose rate 0.1 Gy/min) at intervals of 14 days (total 10 Gy) i.v. of 120 µl of zirconotrast (Zr dioxide 13% w/v)

Dosimetry: Activity injected, twin ionization chamber with tissue equivalent material

Endpoints: Serial killing (6 and 12 months) and life-span (spontaneous death) with macroscopic/microscopic pathology

Animal: Female Wistar rats aged 3-4 months at the start of the irradiation

Results: One year after the begining of neutron irradiation, the first liver tumors were detected. At the end of the study after almost three years, the incidence of irradiated animals with liver tumors was about 40%. The animals treated additionally with Zirconotrast displayed nearly the same incidence, time of onset and overall number of liver tumors indicating that the fractionated neutron exposure was the exclusive cause of tumor development. Zirconotrast had no tumor promoting or tumor inducing effect. In comparison to earlier animal studies with Thorotrast, the same histological types of benign and malignant liver tumors were found.

References: Spiethoff, A., H. Wesch, K. Wegener and K.H. Höver. Tumor induction in rat liver by fractionated irradiation with neutrons and a foreign body burden (zirconotrast); comparison to thorotrast-induced tumors, pp. 149-152. *In* D.M. Taylor, C.W. Mays, G.B. Gerber and R.G. Thomas [eds.], *Risks from Radium and Thorotrast.* Butterworth Sevenoaks, Stoneham MA, 1989.

Spiethoff, A., H. Wesch, K.H. Höver and K. Wegener. The combined and separate action of neutron radiation and zirconium dioxide on the liver of rats. *Health Phys.* **63**:111-118, 1992.

Experimental Groups:

Study 04.03
Liver Tumors and Diseases in Rats After Fractionated Neutron Exposure or Injection of Nonradioactive Zirconotrast

Group Id	Treatment	Number rats
1	Controls	120
2	Sham-irradiated controls	120
3	$Zr O_2$	120
4	10 Gy fract. neutrons	120
5	10 Gy fract. neutrons + $Zr O_2$	120

04.04 Liver and Spleen Tumors in Rats After Injection of Zirconotrast to Which Different Amounts of Th-228/Th-230 Were Added.

Institution: Deutsches Krebsforschungszentrum, Heidelberg, FRG

Scientists: H. Wesch; active
K. Wegener; active
K. Küttler; active

Purpose: To determine the respective roles of the radioactive and chemical component in thorotrast induced liver and spleen damage. The radioactive Th-228/Th-230 was added to the zirconotrast Zr dioxide to obtain different levels alpha-energy emissions compared to an original thorotrast solution.

Status: 1980-1984, terminated

Treatment: Single i.v. injection of 120 µl of zirconotrast (Zr dioxide) to which different amounts of Th-230/Th-228 had been added to obtain 0, 1, 2.5, 5, 10 and 25 times the alpha-energy emission of an original thorotrast solution.

Dosimetry: Activity injected

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology

Animal: Female Wistar rats aged 12 ± 2 weeks at the injection

Results: The distribution of Zirconotrast in the liver of the rats was similar to that of thorotrast in humans. The number of liver and spleen tumors increased by a factor of 15 in the highest dose-rate group compared to controns. The frequency of these tumors showed a dependence on the dose-rate, but was not correlated with the number of injected particles. The pure nonradioactive colloid did not induce an excess of liver and spleen tumors nor did it increase tumor incidence when added to radioactive colloid compared to the radioactive colloid give alone delivering the same dose rate. No excess lung tumors due to the exhalation of Rn-220 was observed.

References: Wesch, H., W. Riedel, K. Wegener, A. Kaul, H. Muth and G. van Kaick. German Thorotrast study: Results of the Long-term animal studies on the effects of incorporated radionuclides, pp. 186-188. *In* W. Gössner, G.B. Gerber, U. Hagen and A. Lüz [eds.], The Radiobiology of Radium and Thorotrast. Urban und Schwarzenberg, München, *Strahlentherapie* Suppl.**80**, 1986.

van Kaick, G., H. Wesch, H. Lührs, D. Liebermann, A. Kaul and H. Muth. The German Thorotrast study - report on 20 years follow-up, pp. 98-104. *In* D.M. Taylor, C.W. Mays, G.B. Gerber and R.G. Thomas [eds.], *Risks from Radium and Thorotrast*, Vol. **21.** BIR (British Institute of Radiology), London, Report, 1989.

Experimental Groups:

Study 04.04
Liver and Spleen Tumors in Rats After Injection of Zirconotrast to Which Different Amounts of Th-228/Th-230 Were Added.

Enrichment factor (Bq/ml ^{230}Th +Bq/ml ^{228}Th)	Group Id / Relative Dose rates (Number of rats) Group		
	120 µl inject.	300 µl inject.	600µl inject.
Na Cl Control			1 / 0 (174)
only Zr O_2	2 / 0 (57)	3 / 0 (58)	4 / 0 (59)
1 (914 + 499)*	5 / 2 (60)	6 / 2 (60)	7 / 2 (58) 1
2.5 (2287+1251)	8 / 5 (60)	9 / 5 (60)	10 / 5 (58)
5 (4570 + 2498)	11 / 10 (60)	12 / 10 (60)	13 / 10 (58)
10 (9139 + 4995)	14 / 20 (60)	15 / 20 (58)	16 / 20 (58)
25 (22866+12506)	17 / 50 (60)	18 / 50 (50)	-

Dose rates relative to the standard treatment of 60 µl thorotrast for an accumulated dose after 1.5 years obtained by adding different ratios ^{230}Th/^{228}Th and injecting various amounts; number of animals in parentheses.

05 GSF Forschungszentrum für Umwelt und Gesundheit GMBH

05.01 Osteosarcoma in Mice After Single or Multiple Injections of Ra-224

Institution: GSF, Neuherberg, FRG

Scientists: W. Gössner; retired
A. Luz; active
W.A. Müller; active

Purpose: To determine the risks of osteosarcoma from the short-lived (T½ = 3.64 d), bone-seeking α emitter Ra-224 in relation to dose and protraction. Since most of the dose during the short half life is deposited near the bone surface, a fractionated exposure mimics that of Pu-239.

Status: 1970 - 1984, terminated, data in ERAD except those indicated in italics

Treatment: Single or multiple i.p. injection of Ra-224 chloride (fractions twice weekly over the period indicated)

Dosimetry: Activity delivered (and calculated mean skeletal dose corrected for changes with age)

Endpoints: Life span study (spontaneous death) with macroscopic/microscopic pathology

Animal: NMRI mice of 4 weeks (or 5 months) age

Results: Single injections of Ra-224 resulted in an osteosarcoma incidence of 7% in females at the lowest activity applied and attained a maximum of of 22% at higher activicites. In males, the maximum incidence was 8.5%.Dose protraction, achieved by multiple application of the short-lived Ra-224, resulted in an increased incidence of osteosarcomas, and the effect became more pronounced the more dose and protraction time were increased. The highest incidence of more than 90% was observed after a dose of 10.8 Gy delivered over 36 weeks.

References:

Müller, W.A. Studies on short-lived internal alpha-emitters in mice and rats. Part I. *Int. J. Radiat. Biol.* **20**:27-93,1971.

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Luz, A., W.A. Müller, W. Gössner and O. Hug. Estimation of late effects in mice on temporal distribution of skeletal α-doses from ^{224}Ra and ^{227}Th, pp. 135-148. *In* W.A. Müller and H.G. Ebert [eds.], *Biological effects of ^{224}Ra.* Martinus Nijhoff Med. Divis., The Hague Boston, 1976.

Luz, A., W.A. Müller, W. Gössner and O. Hug. Estimation of tumor risk at low dose from experimental results after incorporation of short-lived bone-seeking alpha emitters ^{224}Ra and ^{227}Th in mice, pp. 171-181. *In* IAEA-Sm-202/404, *Biological and Environmental Effects of Low Level Radiation*, Vol. II. IAEA, Vienna, 1976.

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Müller, W.A., U. Linzner and A. Luz. Early induction of of leukaemia (malignant lymphoma) in mice by protracted low α-doses. *Health Phys.* **54**:461-463, 1978.

Luz, A., W.A. Müller, E.H. Schäffer, A.B. Murray, R.R. Wick, W. Gössner and O. Hug. Osteosarcoma induced by short-lived bone-seeking alpha-emitters in mice: the role of age. *Environm. Res.* **18**:115-119, 1979.

Müller, W.A., A. Luz, E.H. Schäffer and W. Gössner. The role of time-factor and RBE for the induction of osteosarcomas by incorporated short-lived bone-seekers. *Health Phys.* Suppl 1, **44**:203-212, 1983.

Gössner, W. Pathology of radiation-induced bone tumors. *Leukemia Res.* **10**:897-904, 1986.

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Müller, W.A., A. Luz, A.B. Murray and U. Linzner. The effect of dose protraction with a very low ^{224}Ra activity in mice, pp. 32-36. *In* D.M. Taylor, C.W. Mays, G.B. Gerber and R.G. Thomas [eds.], *Risks from Radium and Thorotrast*, Vol. **21**. BIR (British Institute of Radiology), London, Report, 1989.

Müller, W.A., A. Luz, A.B. Murray and U. Linzner. Induction of lymphoma and osteosarcoma in mice by single and protracted low α doses. *Health Phys.* **59**:305-310, 1990.

Experimental Groups:

Study 05.01
Osteosarcoma in Mice After Single or Multiple Injections of Ra-224

Group Id	^{224}Ra Bq/g	Mean Skeletal Dose Gy	Application and Scope	Sex	No of Mice
1	Controls		None, osteosarcoma only		187
2				♀	47
3					184
4				♂	50
5				♀	50
6					97
7					165
8					47
9				♂	48
10				♀	55
11				♂	19
12				♀	109
13				♂	79
14				♀	38
15				♂	44
16				♀	50
17					44
18					50
19					50
20	Controls		None, full pathology	♀	75
21					50
22					97
23	18.5	0.15	Single, full pathology	♀	295
24		0.11	72 inj. 36 w, full pathology		298
25	37		Single	♀	205
26	92.5		Single	♀	200

Group Id	^{224}Ra Bq/g	Mean Skeletal Dose Gy	Application and Scope	Sex	No of Mice
27	148	1.2	Single, full pathology	♀	75
28		0.9	72 inj. 36 w, full pathology		74
29	185		Single, osteosarcoma only	♀	48
30				♂	49
31				♀	43
32				♂	53
33				♀	50
34				♂	50
35	370		Single, osteosarcoma only	♀	49
36				♂	49
37				♀	44
38				♂	52
39				♀	49
40				♂	50
41	444	3.6	Single	♀	49
42					50
43			8 inj. 4 w		52
44		3.2	24 inj. 12 w		50
45		3.6	24 inj. 12 w, full pathology		50
46		3.6	24 inj. 3x8 w, full pathology		49
47	925		Single, osteosarcoma only	♀	150
48				♀	50
49				♂	?
50				♀	50
51				♂	?
52				♀	44
53				♂	?
54	1332		Single, osteosarcoma only	♀	50
55					50
56		10.8	8 inj. 4 w, osteosarcoma only		50
57			24 inj. 12 w		50
58		8.0	72 inj. 36 w, full pathology		99
59		8.0	9 inj. 4 w, full pathology		75
60	1850		Single, osteosarcoma only	♀	50
61				♂	?
62				♀	?
63				♂	?
64				♀	42
65				♂	?
66	2775	17.8	50 inj. 25 w, osteosarcoma only	♀	50

05.02 Osteosarcoma in Mice After A Single Injection of Ra-224 or Sr -90

Institution: GSF, Neuherberg, FRG

Scientists: W. Gössner; retired
A. Luz; active
W.A. Müller; active

Purpose: To determine the risks of osteosarcoma from alpha and beta emitters.

Status: 1976, terminated, data in ERAD except for groups indicated in italics

Treatment: Single i.p. injection of Ra-226 chloride or Sr-90 nitrate

Dosimetry: Activity delivered and calculated mean skeletal dose corrected for changes with age

Endpoints: Life-span study (spontaneous death) with radiography for osteosarcoma only

Animal: Female NMRI mice

Results: The incidence per unit total accumulated skeletal dose from Ra-226 (the specific bone tumor production diminishes steadily as the dose is increased. Consequently, mice given a single injection of the long-lived Ra-226 display, in general, a considerably lower incidence of bone tumors than those which received comparable skeletal doses by means of repeated injections of short-lived Ra-224 spread over a longer period of time.

References: Müller W.A., A. Luz, E.H. Schäffer and W. Gössner. The role of time-factor and RBE for the induction of osteosarcomas by incorporated short-lived bone-seekers. *Health Physics* **44**:203-212, 1983.

Müller W.A. and A. Luz. The osteosarcomogenic effectiveness of short-lived ^{224}Ra compared with that of the long-lived ^{226}Ra in mice. *Radiation Research* **70**:444-448, 1977.

Experimental Groups:

Study 05.02
Osteosarcoma in Mice After A Single Injection of Ra-224 or Sr -90

Group Id	Radionuclide (Bq/g)	Age (weeks)	No mice
1	^{226}Ra 0	4	50
2	37	4	150
3	185	4	50
4	^{90}Sr 0	3-4	50
5	3700	3-4	50 (+10 for dosimetry)
6	18500	3-4	50 (+10 for dosimetry)

05.03 Osteosarcoma in Mice After Single or Multiple Injections of Lu-177 and Comparison with the Effects of Np-239

Institution: GSF, Neuherberg, FRG

Scientists: W. Gössner; retired
A. Luz; active
W.A. Müller; active

Purpose: To compare the risks of osteosarcoma for the beta emitters Lu-177 with that of the alpha emitter Np-239

Status: 1977 - 1981, terminated, data in ERAD except for groups indicated in italics

Treatment: Intraperitoneal injection of Lu -177 citrate (=< 0.025mg/kg or 2 mg/kg carrier, the latter leading to a colloidal suspension) or Np-239 citrate. Experimental series were as follows:

A) NMRI mice of 3-4 weeks age were given 12 injections of Lu-177 at an interval of 1 week [6/77]
B) NMRI mice of 3-4 weeks age were given a single injection of Lu-177 [12/77]
C) NMRI mice of 3-4 weeks age were given a single injection of Lu-177 [6/78]
D) NMRI mice of 4 weeks age were given single or multiple (12 injections over 12 weeks or 24 injections over 24 weeks) injections of Lu -177[6/81] or Np-239

Dosimetry: Activity delivered and calculated mean skeletal dose corrected for reduction by age

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology, determination of osteosarcoma only

Animal: Female NMRI mice

Results: Injection of Np-239 gives rise to the long-lived alpha-emitting daughter Pu-239 whose exposure can be compared with that of the beta-emitting Lu-177. After a mean skeletal dose of 14 Gy Np-239 caused 21.5% bone cancers compared to a significantly lower incidence of only 4.5% from Lu-177

References:

Müller, W.A., U. Linzner and E.H. Schäffer. Organ distribution studies of Lutetium-177 in mouse. Int. *J. Nucl. Med. Biol.* 5:29-31, 1978.

Müller, W.A., E.H. Schäffer and U. Linzner. Studies on incorporated short-lived β-emitters with regard to the induction of late effects. *Radiat. Environm. Biophys.* **18**:1-11, 1980.

Müller, W.A. and U. Linzner. Distribution and dosimetry studies after incorporation of ^{239}Np (^{239}Pu) in mice. *Health Phys.* **44** (Suppl. 1):577-580, 1983.

Müller, W.A., A. Luz, E.H. Schäffer and W. Gössner. The role of time-factor and RBE for the induction of osteosarcomas by incorporated short-lived bone-seekers. *Health Phys.* **44** (Suppl. 1) :203-212, 1983.

Müller, W.A., E.H. Schäffer, U. Linzner and A. Luz. Incorporation experiments with combined application of different bone seekers. *Radiat. Environm. Biophys.* **23:**113-115, 1984.

Müller, W.A., A. Luz and E.H. Schäffer. The osteosarcomogenic activity of low 224- Radium doses in mice compared to that of the short-lived beta-emitting rare earth 177- Lutetium, pp. 79-82. *In* W. Gössner, G.B. Gerber, U. Hagen and A. Luz [eds.], *The Radiobiology of Radium and Thorotrast.* Urban Schwarzenberg, München, *Strahlentherapie*, Suppl. **80** 1986.

Experimental Groups:

Study 05.03

Osteosarcoma in Mice After Single or Multiple Injections of Lu-177 and Comparison with the Effects of Np-239

Group Id	Activity kBq/g	Mean skeletal dose Gy	Application	No mice
A ^{177}Lu				
1	0		none	50
2	370			50
3	370			50
B ^{177}Lu				
4	0		none	50
5	207		single	48
6	411		single	51
7	825		single	49
8	1265		single	47
9	1683		single	49
C ^{177}Lu				
10	0		none	50
11	370		single	50
D ^{177}Lu				
12	0	0	none	50
13	92.5	14	single	193
14	92.5	14	12 inj. 12 w	50
15	185	28	single	50
16	185	28	24 inj. 24 w	50
17	185		24 inj. 24 w	50
18	370	56	single	50
^{239}Np				
19	0	0		50
20	0.28	14	single	183
21	1.14	36	single	44

05.04 Comparison of the Effects of Lu-177 or Th-227 Given in One or Two Series of Injections to Mice At Different Ages

Institution: GSF, Neuherberg, FRG

Scientists: W. Gössner; retired
A. Luz; active
W.A. Müller; active

Purpose: To compare the risks at different ages with single series or multiple series applications.

Status: 1982, terminated, data in ERAD

Treatment: Lu-177 (12 ip injections twice weekly starting at an age of 3 months or of 40 months, or 6 injections at 3 and 6 injections at 40 months) or Th-227 citrate (2 injections at an age of 12 and 20 months, 12 and 52 months or 52 and 60 months)

Dosimetry: Activity delivered

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic full pathology

Animal: Female NMRI mice

Results: No difference in the delay of appearance of osteosarcoma is seen when part of the activity is given at an older age

References: Luz, A., W.A. Müller, E.H. Schäffer, A.B. Murray, U. Linzner and W. Gössner. The sensitivity of female NMRI mice of different ages for osteosarcoma induction with ^{227}Th, pp. 178-182. *In* W. Gössner, B. Gerber, U. Hagen and A. Luz [eds.], *Strahlentherapie* Suppl **80**: *The Radiobiology of Radium and Thorotrast.* Urban & Schwarzenberg, München, Wien, Baltimore, 1986

Luz, A., W.A. Müller, U. Linzner, A.B. Murray, R.R. Wick and W. Gössner. Time as a cofactor for radiation-induced bone tumors, pp. 119-125. *In* F.H.W. Heuck and E. Keck [eds.], *Fortschritte der Osteologie in Diagnostik and Therapie.* Springer Verlag, Berlin Heidelberg, 1988.

Experimental Groups:

Study 05.04
Comparison of the Effects of Lu-177 or Th-227
Given in One or Two Series of Injections to Mice At Different Ages

Group Id	Age weeks 1st inject. Dose	Age weeks 2nd inject. Dose	No animals
	^{227}Th		
1	none	none	50
2	1 months 2 x 37 Bq/g	5 months 2 x 37 Bq/g	58
3	3 months 2 x 37 Bq/g	12 months 2 x 37 Bq/g	54
4	12 months 2 x 37 Bq/g	14 months 2 x 37 Bq/g	79
	^{177} Lu		
5	none	none	50
6	3 months 12 x 31 kBq/g	none	50
7	3 months 6 x 31 kBq/g	10 months 6 x 31 kBq/g	80
8	none	10 months 12 x 31 kBq/g	99

05.05 Osteosarcoma From Th-227 Or Ra-224 in Mice in Dependence of Dose and Age

Institution: GSF, Neuherberg, FRG

Scientists: W. Gössner; retired
A. Luz; active
W.A. Müller; active

Purpose: To determine the risks of osteosarcoma from Th-227 or Ra-224 in dependence of age in different mouse strains.

Status: 1974 - 1985, terminated, data in ERAD

Treatment: Intraperitoneal injection of Th-227 citrate or Ra-224 chloride. The experimental designs were as follows:

A) Comparison of 4 weeks and 5 months old NMRI SPF mice given a single i.p. injection of 185 Bq/g of Th-227,
B) Comparison of 4 weeks and 5 months old NMRI SPF mice given 18 ip injections of Th -227 every two weeks (total dose 185 Bq/g, total injection period 9 months),
C) Comparison of 4 weeks and 5 months old NMRI SPF mice given a single i.p. injection of 185 Bq/g of Ra-224,
D) Effect of Th-227 dose on 1 and 12 months old NMRI mice,
E) Osteosarcoma incidence after an injection of 6x 37Bq/g every two weeks of Th-227 at different ages (3-4 weeks and 18 months),
F) Comparison of age-dependent ostoeosarcoma risk in NMRI mice (1 and 18 months) and CBA mice (3.5 and 18 months) after a single i.p. injecton of 37 or 185 Bq/g of Th-227;

Dosimetry: Activity delivered

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology

Animal: Female NMRI or CBA mice of different age

Results: Th-227 given to older animals and at low activity (37Bq/g) results in osteosarcomas occurring earlier.

References:

Luz, A., W.A. Müller, E.H. Schäffer, A.B. Murray, R.R. Wick, W. Gössner and O. Hug. Osteosarcoma induced by short-lived bone-seeking alpha-emitters in mice: the role of age. *Environm. Res.* **18**:115-119, 1979.

Luz, A., W.A. Müller, U. Linzner, A.B. Murray, R.R. Wick and W. Gössner. Time as a cofactor for radiation-induced bone tumors, pp. 119-125. *In* F.H.W. Heuck and E. Keck [eds.], *Fortschritte der Osteologie in Diagnostik and Therapie*. Springer Verlag, Berlin Heidelberg, 1986.

Luz, A., W.A. Müller, E.H. Schäffer, A.B. Murray, U. Linzner and W. Gössner. The sensitivity of female NMRI mice of different ages for osteosarcoma induction with ^{227}Th, pp. 178-182. *In* W. Gössner, B. Gerber, U. Hagen and A. Luz [eds.], *Strahlentherapie* Suppl **80:** *The Radiobiology of Radium and Thorotrast*. Urban & Schwarzenberg, München, Wien, Baltimore, 1986.

Müller, W.A. Age-related retention and dose burden after injection of ^{224}Ra and ^{227}Th in mice, pp. 30-33. *In* G.B. Gerber, H. Métivier and H. Smith [eds.], *Age-related Factors in Radionuclide Metabolism*. M.Nijhoff, Dordrecht, 1987.

Luz, A., V. Erfle, P.G. Strauβ, K. Müller, J. Schmidt, W.A. Müller, U. Linzner, W. Gössner and H. Höfler. The role of age and genetic background as cofactors in the pathogenesis of radiation-induced osteosarcoma, pp. 30-33. *In* N.J. Park [ed.], USDOE Report UCD-472-136: *Joint Bone Radiobiology Workshop*, Toronto, July 12-13, 1991. University of California, Davis CA, 1991.

Experimental Groups: **Study 05.05**

Osteosarcoma From Th-227 Or Ra-224 in Mice in Dependence of Dose and Age

Group Id	Experim. Strain dose Bq/g		Remarks or skeletal dose	No Mice
1	**A ^{227}Th♀ 4 w NMRI**	0		48
2		185	single injection	50
3	**♀ 5 m NMRI**	0		97
4		185	single injection	150
5	**B ^{227}Th♀ 4 w NMRI**	0		48
6		185	18 injections every two weeks	49
7	**♀ 5 m NMRI**	0		101
8		185	18 injections every two weeks Remainder killed at an age of 590 d	100
9	**C ^{224}Ra♀ 4 w NMRI**	0		94
10		925		94
11	**♀ 5 m NMRI**	0		239
12		925		236
13	**D ^{227}Th♀ 1 m NMRI**	0		49
14		37		50
15		185		50
16	**♀ 12 m NMRI**	0		50
17		37	1 Gy	123
18		185	10 Gy	75
19	**E ^{227}Th♀ 3-4w NMRI**	0		49
20		222	6 x37 Bq/g 2w	50
21	**♀ 18 m NMRI**	0		50
22		222	6 x37 Bq/g 2w	59
26	**F ^{227}Th♀ 1 m NMRI**	0		50
27		37		48
28		185		48
29	**♀ 18 m NMRI**	0		50
30		37		96
31		185		98
32	**♀ 3.5 m CBA**	0		50
33		37		43
34		185		50
35	**♀ 18 m CBA**	0		50
36		37		98
37		185		97

05.06 Osteosarcoma Due to Th-227 in Mice in Dependence of Strain

Institution: GSF, Neuherberg, FRG

Scientists: W. Gössner; retired
A. Luz; active
W.A. Müller; active

Purpose: To determine the risks of osteosarcoma from Th-227 in different mouse strains.

Status: 1976 - 1983, terminated, data in ERAD except groups indicated in italics

Treatment: Single i.p. injection of 18.5 or 185 Bq/g Th-227 citrate

Dosimetry: Activity delivered

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology

Animal: Mice of different strains and sexes usually one month old

Results: Latency of appearance of osteosarcoma depends on the mouse strain and is a measurement of the sensitivity of the respective strain. The order of strains in order of the latency period of osteosarcoma is: BALB/c < C57BL < NMRI =X/GF =102 < CBA

References: Luz, A., W.A. Müller, U. Linzner, P.G. Strauβ, J. Schmidt, K. Müller, M.J. Atkinson, A.B. Murray, W. Gössner, V. Erfle and H. Höfler. Bone tumor induction after incorporation of short-lived radionuclides. *Radiat. Environm. Biophys.* **30:**225-227, 1991.

Experimental Groups:

Study 05.06
Osteosarcoma Due to Th-227 in Mice in Dependence of Strain

Group Id	Experim. Strain	Dose Bq/kg	No of mice
1	♀ **102/Ghg 4 w**	0	48
2		185	96
3	♀ **NMRI 4 w**	0	49
4		185	50
5	♀ **C57Bl 4 w**	0	50
6		185	50
7	♀ **BALB/c 4 w**	0	50
8		185	49
9	♀ **XGF 4 w**	0	49
10		18.5	49
11		185	50
12	♀ **CBA 4 w**	0	49
13		185	58
14	♂ **CBA 4 w**	0	47
15		185	44
16	♀ **BALB/c 4 w**	0	50
17		185	49

05.07 Osteosarcoma in Mice After Injection of Two Different Radionuclides

Institution: GSF, Neuherberg, FRG

Scientists: W. Gössner; retired
A. Luz; active
W.A. Müller; active

Purpose: To determine the risks of osteosarcoma from Th-227, Ra-224 and Lu-177 in different combinations with Ac-227.

Status: 1976 - 1984, terminated, data in ERAD

Treatment: Single i.p. injection with Th-227, Ra-224, Lu-177 and/or Ac-227; the experimental designs were as follows:

A) Osteosarcoma risk after different Th-227 doses potentiated by 1.85 Bq/g of Ac-227; both radionuclides were given simultaneously as a single injection to 4 weeks old NMRI mice,

B) Osteosarcoma risk after different Th-227 doses potentiated by 1.85 Bq/g of Ac-227; a single injection of Ac-227 was given to 10 weeks old NMRI or CBA mice followed two weeks later by a single injection of Th-227.

C) Repeat of B,

D) Osteosarcoma risk after different Ra-224 doses potentiated by 1.85 Bq/g of Ac-227; a single injection of Ac-227 was given to 10 weeks old NMRI mice followed 2 weeks later by a single injection of Ra-224,

E) Osteosarcoma risk after different Lu -177doses potentiated by 1.85 Bq/g of Ac-227; a single injection of Ac-227 was given to 4 weeks old NMRI mice followed 1 day later by a single injection ofLu-177

Dosimetry: Activity delivered

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic full pathology

Animal: Female NMRI or CBA mice as indicated

Results: An injection of 1.85 Bq/g of long-lived Ac-227 simultaneously with or followed by higher doses of the short-lived radionuclides Th-227, Ra-224 or Lu-177 caused, in all cases, less osteosarcomas than the sum of the effects when both radionuclides were administered separately.

References:

Luz, A., U. Linzner, W.A. Müller, E. de Fries and W. Gössner. Osteosarcoma induction by simultaneous incorporation of ^{227}Th and ^{227}Ac, pp. 141-151. *In* IAEA [ed.], *Biological Implications of Radionuclides Released from Nuclear Industries*, IAEA-SM-237/65 ed., Vol. I. IAEA, Vienna, 1979.

Müller, W.A., E.H. Schäffer, U. Linzner and A. Luz. Incorporation experiments with combined application of different bone seekers. *Radiat. Environm. Biophys.* **23**:113-115, 1984.

Müller, W.A., A.B. Murray, U. Linzner and A. Luz. Osteosarcoma risk after simultaneous incorporation of the long-lived radionuclide ^{227}Ac and the short-lived radionuclide ^{227}Th. *Radiat. Res.* **121**:14-20, 1990.

Müller, W.A., A. Luz, U. Linzner and A.B. Murray. The combined effect of two different bone seeking radionuclides on the induction of osteosarcomas in mice, pp. 64-71. *In* C.B. Seymour and C. Mothersill [eds.], *New Developments in Fundamental and Applied Radiobiology*. Taylor & Francis, London, 1991.

Experimental Groups:

Study 05.07
Osteosarcoma in Mice After Injection of Two Different Radionuclides

Group Id	Experim. Strain Dose Bq/g first radionucl.	Dose Bq/g, second Radionucl. ^{227}Ac	No Mice
1	A ^{227}Th ♀ NMRI 0	0	50
2	0	1.8	49
3	18.5	0	50
4	74	0	50
5	148	0	50
6	185	0	50
7	185	1.8	50
8	B ^{227}Th♀ NMRI 0	0	50
9	0	1.8	49
10	18.5 (=1Gy)	0	48
11	74	0	49
12	185 (=10 Gy)	0	48
13	18.5	1.8 (-2 weeks)	60
14	74	1.8 (-2 weeks)	49
15	185	1.8 (-2 weeks)	50
16	♀ CBA 0	0	50
17	0	1.8	49
18	185	0	50
19	185	1.8 (-2 weeks)	50
20	C ^{227}Th ♀ NMRI 0	0	50
21	0	1.8	51
22	18.5	0	52
23	74	0	53
24	185	0	48
25	18.5	1.8 (-2 weeks)	53
26	74	1.8 (-2 weeks)	53
27	185	1.8 (-2 weeks)	53
28	♀ CBA 0	0	50
29	0	1.8	53
30	185	0	53
31	185	1.8 (-2 weeks)	52
32	D ^{224}Ra♀ NMRI 0	0	100
33	0	1.8	99
34	18.5	0	300
35	185	0	100

Group Id	Experim. Strain Dose Bq/g first radionucl.	Dose Bq/g, second Radionucl. ^{227}Ac	No Mice
36	18.5	1.8 (-2 weeks)	198
37	185	1.8 (-2 weeks)	100
38	E ♀ ^{227}Lu NMRI 0	0	47
39	0	1.8	49
40	185.000	0	75
41	370.000	0	99
42	185.000	1.8 (+1 day)	74
43	370.000	1.8 (+1 day)	97

05.08 Osteosarcoma in Mice After Multiple Injection of Th-227 Together with Chemicals

Institution: GSF, Neuherberg, FRG

Scientists: W. Gössner; retired
A. Luz; active
W.A. Müller; active

Purpose: To determine the influence of different promoting or cocarcinogenic chemicals on osteosarcoma (or leukemia) development after multiple injections of Th-227 and the influence of age.

Status: 1974 - 1987, terminated, data in ERAD

Treatment: Intraperitoneal injection of Th-227 citrate, for details see individual experiments

A) NMRI or BALB/c mice of 4 weeks age were given a single injection of 185 Bq/g of Th-227 followed, starting 4 weeks later by 8 ip injections of 20 µg twice a week of LPS (lipopolysaccharide from E.coli),

B) NMRI mice of 4 weeks age were given with 6 injections of 37 Bq/g of Th-227 (at intervals of 2 weeks) followed at an age of 230 - 800 days by a 6 times/w oral application of alkyl-lyso-phospholipid (ALP),

C) BALB/c mice of 4 weeks age were given a single injection of 185 Bq/g of Th-227 followed, at an age of 122 days, with ALP given daily orally 50 µg from an age of 207 days 100 µg from an age of 272 days until death,

D) BALB/c mice of 6 weeks age were given a single injection of 185 Bq/g of Th-227 and fed 2.5 g/kg food of beta-aminoproprionitril fumarate (BAPN) during the 5, 7, 9, 11, 13, 15, 17 month of life,

E) NMRI mice of 4 weeks age were given a single injection of 185 Bq/g of Th-227 and fed 25 ppm Cadmium chloride from the 5th to the 10th month of life,

F) BALB/c mice of 12 weeks age were given a single injection of 185 Bq/g of Th-227 preceded 1, 3 and 5 days earlier by an ip injection of 1 mg/kg 5-azacytidine (to inhibit DNA methylation),

G) BALB/c or CBA mice of 16 weeks age were given a single injection of 37 or 185 Bq/g of Th-227 followed, during an age of 17-52 weeks, by a weekly injection of 1 mg/kg 5-azacytidine (AZ) ,

H) mice of the NMRI, BALB/c, CBA, C57BL train of 16 weeks age were given an ip injection of 1 mg/kg 5-azacytidine every 3 weeks to study chemical induction of leukemia,

I) NRMI mice of 1 month age were given a single injection of 185 Bq/g of Th-227 followed by an ip injection of 60 mg/kg cyclophosphamide (CPA) monthly from an age of 4 to 10 months,

K) BALB/c mice of 1 month age were given a single injection of 185 Bq/g of Th-227 followed by 2 ip injections of 150 mg/kg cyclophosphamide (CPA) 1 and 29 days later,

L) BALB/c mice of 4 weeks age were given a single injection of 185 Bq/g of Th-227 followed by 6 ip injections of 1mg/kg daunomycine at weekly intervals starting 1 day after contamination,

M) NRMI mice of 3 months age were given a single injection of 37 Bq/g of Th -227followed by 28 oral administration of cyclosporine A (CS) given weekly from the 30th to the 57th week of age,

N) BALB/c mice of 16 weeks age were given a single injection of 185 Bq/g of Th-227 followed by 20 µg/ml indomethacine (IM) in drinking water from an age of 17 weeks until death to study inhibition of tumor development as a result of a reduced prostaglandine synthesis.

Dosimetry: Activity delivered

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology

Animal: Female NMRI, CBA, C57/Bl or BALB/c mice, see individual experiments

Results: Results not fully evaluated

References:

Experimental Groups:

Study 05.08
Osteosarcoma in Mice After Multiple Injection of Th-227 Together with Chemicals

Group Id	Experim. Strain, ^{227}Th dose Bq/g	Chemical Treatment	No Mice
1	**A ♀ NMRI** 0	none	49
2	0	8x20 µg LPS 2x/w	50
3	185 single	none	48
4	185 single	8x20 µg LPS 2x/w	48
5	**♀ BALB/c** 0	none	50
6	185 single	none	48
7	185 single	16x20 µg LPS 2x/w	30
8	**B ♀ NMRI** 0	none	47
9	0	ALP 10 mg/kg/d	35
10	0	ALP 20 mg/kg/d	40
11	222 in 6 inject.	none	49
12	222 in 6 inject.	ALP 10 mg/kg/d	40
13	222 in 6 inject.	ALP 20 mg/kg/d	40
14	**C ♀ BALB** 0	none	49
15	0	ALP	48
16	185 single	none	49
17	185 single	ALP	48
18	**D ♀ BALB** 0	none	50
19	0	2.5 g/kg BAPB oral	51
20	185 single	none	48
21	185 single	2.5 g/kg BAPN oral	50
22	**E ♀ NMRI** 0	none	49
23	0	25ppm Cd Cl_2 fed	48
24	185 single	none	48
25	185 single	25ppm Cd Cl_2 fed	49
26	**F ♀ BALB** 0	none	50
27	0	3x 1mg/kg Azacytid.	50
28	185 single	none	48
29	185 single	3x 1mg/kg Azacytid.	47

	G	Chemical treatment	No Mice BALB/c	CBA
30/31	0	none	50	50
32/33	0	35x1mg/kg/w Azacytid.	50	50

Group Id	Experim. Strain, ^{227}Th dose Bq/g	Chemical Treatment	No Mice	
34/35	37 single	none	80	79
36/37	185 single	none	57	61
38/39	37 single	35x1mg/kg/w Azacytid.	76	78
40/41	185 single	35x1mg/kg/w Azacytid.	58	58
42	**H ♀ BALB** 0	none	19	
43	0	1mg/kg/3w Azacytid.	29	
44	**♀ CBA** 0	none	23	
45	0	1mg/kg/3w Azacytid.	27	
46	**♀ C57/bl** 0	none	32	
47	0	1mg/kg/3w Azacytid.	30	
48	**♀ NMRI** 0	none	24	
49	0	1mg/kg/3w Azacytid.	28	
50	**I ♀ NMRI** 0	none	50	
51	0	12*60 mg/kg CPA	47	
52	185 single	none	49	
53	185 single	12*60 mg/kg CPA	50	
54	**K ♀ BALB** 0	none	49	
55	185 single	none	69	
56	185 single	2x 150 mg/kg CPA	73	
57	**L ♀ BALB** 0	none	50	
58	0	6x1mg/kg Daunam.	49	
59	185 single	none	50	
60	185 single	6x1mg/kg Daunam.	50	
61	**M ♀ NMRI** 0	none	49	
62	0	28x10 mg/kg oral CS	50	
63	0	28x50 mg/kg oral CS	51	
64	37 single	none	49	
65	37 single	28x10mg/kg oral CS	49	
66	37 single	28x50mg/kg oral CS	49	
67	**N ♀ BALB** 0	none	48	
68	0	20 µg/ml IM drink	46	
69	185 single	none	46	
70	185 single	20 µg/ml IM drink	47	

05.09 Consequences of Paternal Exposure to Ethylnitrosourea on Th-227-Induced Osteosarcoma in the Offspring

Institution: GSF, Neuherberg, FRG

Scientists: A. Luz; active

Purpose: To determine whether paternal exposure to a mutagenic agents will increase mutations and susceptibility to osteosarcoma in the offspring.

Status: 1991 -

Treatment: Eighty day old C3Hx102/F1 male mice received a single ip injection of 160 mg/kg body weight of ethylnitrosourea; following a recovery period of five months, they were mated with T-stock females. Half of the F1 generation received a single ip injection of 37 kBq/kg Th-227 citrate (about 2Gy mean skeletal dose) at an age of about 100 days. Since incidence of osteosarcoma is very low in male mice after this dose, only data from female mice are used in the experiment.

Dosimetry: Activity delivered

Endpoints: Life-.span study (spontaneous death) with macroscopic/microscopic pathology, determination of specific locus test

Animal: Offspring from male C3Hx102/F1 mice

Results: The latency period for osteosarcoma is shorter in the female offspring of fathers treated with ethylnitrosourea

References:

Experimental Groups:

Study 05.09
Consequences of Paternal Exposure to Ethylnitrosourea on Th-227-Induced Osteosarcoma

Group Id	ENU Treatment Parents mg/kg	^{227}Th Treatment Offspring kBq/kg	No Mice
1	0	0	69
2	0	37	65
3	160	0	69
4	160	37	65

06 KFK, Kernforschungszentrum Karlsruhe

06.01 Comparative Toxicity of Np-237, Pu-239, and Ra-226 in Rats

Institution: Kernforschungszentrum Karlsruhe, Institut für Genetik und Toxikologie, Karlsruhe FRG, pathological analysis carried out by Prof. A. Luz, GSF Neuherberg

Scientist: V. Volf; retired

Purpose: To determine the long-term risks from incorporation of different alpha emitters in rats and to allow an extrapolation to man by comparison with epidemiological data on radium.

Status: 1985- 1993

Treatment: Single i.v. injection of Np-239 nitrate, Pu-239 citrate or Ra-226 chloride; some animals received 0.001M ZDTPA in the drinking water starting from day 4 or day 30 after injection of Pu-239 until the end of their life

Dosimetry: Injected activity, activity at death, whole body counting

Endpoints: Life-span study with macroscopic/microscopic pathology; skin tumors removed surgically when they appeared to endanger life

Animal: Sprague-Dawley rats aged about 2 months

Results: To be published

References:

Experimental Groups:

Study 06.01
Comparative Toxicity of Np-237, Pu-239, and Ra-226 in Rats

Nuclide	Group Id / Injected Activity Bq/g (Number of Rats in group)					
Females Controls	1/ **0** (77)					
^{237}Np	2/ **7.4** (28)	3/ **25.9** (28)				
Males Controls	4/ **0** (201)			5/ **DTPA** (52) **DTPA** (51)		
^{237}Np	6/ **2.59** (40)	7/ **5.18** (44 +44)	8/ **14.8** (40)	9/ **25.9** (42)	10 **37** (40)	-
^{239}Pu	12/ **7.4** (20 +20)	13/ **18.5** (20 +20)	14/ **37** (20 +20)	15/ **62.9** (20 +20)	16/ **37** + **DTPA**[1] (40 +20)	17/ **37** +**DTPA**[2] (40 +20)
^{226}Ra	18/ **92.5** (68 +96)	19/ **185** (32+32)	20/ **277.5** (32)	21/ **370** (30)	22/ **555** (22)	-

1) Zn DTPA administration from 4 days, 2) from 30 days after Pu injection
rats from some groups were not treated at the same time, this is indicated by two numbers of animals. After evaluation, these animals can probably be combined into one group.
When the injection of the radionuclide was carried out at different times, two groups are indicated

07 Medical Research Council, Radiobiology Unit

07.01 Consequences (Osteosarcoma, Leukemia) of A Single, Low Dose Ra-224 Injection in Adult Mice

Institution: MRC Radiobiology Unit, Chilton, UK

Scientist: E.R. Humphreys; retired
V.A. Stones; retired

Purpose: To determine the long-term risks of alpha-particle emitters.

Status: 1985- ongoing

Treatment: Single i.p. injection of Ra-224 chloride in physiological saline

Dosimetry: Only injected dose; absorbed dose was not calculated because of uncertainties about the location of the relevant target cells

Endpoints: Life-span study with macroscopic/microscopic pathology

Animal: Male CBA/H mice aged 84 ± 5 days at injection

Results: Fifty three cases of myeloid leukemia and 22 cases of osteosarcoma were confirmed in the 2000 mice injected and, for both tumor types, direct relationships were shown to exist between the amount of Ra-224 administered and the incidence of tumor. The ratio myeloid leukemia/ osteosarcoma decreased with increasing injected amount of Ra-224 although this could not be shown to be significant by a chi square test (P=0.067); the overall ratio of myeloid leukemia to osteosarcoma was 2.48±0.64. It was concluded that the mouse is at a greater risk from myeloid leukemia than from osteosarcoma in the region of administered Ra-224 below that which causes a maximum yield of osteosarcoma.

The different micro-architectures of bone in mouse and man almost certainly contribute to different susceptibilities to induction of either type of tumor from injected Ra-224. It is likely, however, that these differences influence the induction of either tumor to a similar extent making the ratio of induced tumor types similar in mouse and man. These results, and those from epidemiological findings on humans given Ra-224, now question whether persons exposed to amounts of alpha-particle emitters previously thought to pose an acceptable risk from osteosarcoma, might not also be at risk from myeloid leukemia.

References:

Humphreys, E.R., J.F. Loutit, I.R. Major and V.A. Stones. Experiments using alpha-emitters in mice and their relevance to humans, Forum on alpha-emitters in bone and leukaemia, Comittee on the effects of ionizing radiation. *Int. J. Radiat. Biol.* **53**:527-529, 1988.

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Humphreys, E., K.R. Isaacs, T.A. Raine, J. Saunders, V.A. Stones and D.L. Wood. Myeloid leukaemia and osteosarcoma in CBA/H mice given ^{224}Ra. *Int. J. Radiat. Biol.* **64**:231-235, 1993.

Experimental Groups:

Study 07.01

Consequences (Osteosarcoma, Leukemia) of A Single, Low Dose Ra-224 Injection in Adult Mice

Group Id	Activity injected Bq/g	No of mice
1	0	400
2	69	400
3	138	400
4	278	400
5	550	400

07.02 Consequences (Osteosarcoma, Leukemia) of Single or Multiple Ra-224 Injections in Adult Mice

Institution: MRC Radiobiology Unit, Chilton, UK

Scientist: E.R. Humphreys; retired

Purpose: To determine the long-term risks of fractionated exposure to alpha-particle emitters.

Status: 1979- ongoing

Treatment: Single or multiple (16 injections over 8 weeks) i.p. injection of ^{224}Ra chloride in physiological saline

Dosimetry: Activity injected; absorbed dose was not calculated because of uncertainties about the location of the relevant target cells

Endpoints: Life-span study with macroscopic/microscopic pathology

Animal: Male CBA/H mice aged 84 ± 5 days at injection

Results Sixteen cases of myeloid leukemia were confirmed in the 1261 mice injected. Under none of the conditions tested was the incidence of myeloid leukemia significantly greater than from a single administration of the same total activity.

There is no comprehensive mechanism which explains the observations and contradictions in previously published *in vivo* and *in vitro* experiments designed to investigate the effects of low dose rate on high LET irradiation or contamination. Although an increased incidence of leukemia has been demonstrated in some of these experiments the present unpublished results indicate that further experiments may be needed to explore in more detail the effects of more prolonged exposure, perhaps for the lifetime of the animal.

References: Humphreys, E.R., J.F. Loutit, I.R. Major and V.A. Stones. The induction by ^{224}Ra of myeloid leukaemia and osteosarcoma in male CBA mice. *Int. J. Radiat. Biol.* **47**:239-247, 1985.

Experimental Groups:

Study 07.02
Consequences (Osteosarcoma, Leukemia) of Single or Multiple Ra-224 Injections in Adult Mice

Activity inject. Bq/g	Single injection		Multiple injection	
	Group Id	No mice	Group Id	No mice
0	1	40	2	41
68	3	40	4	41
140	5	41	6	41
270	7	42	8	41
550	9	40	10	41
1100	11	40	12	41
2200	13	42	14	41

07.03 Consequences (Osteosarcoma, Leukemia) of Multiple Ra-224 Injections in Mice

Institution: MRC Radiobiology Unit, Chilton, UK

Scientist: E.R. Humphreys; retired

Purpose: To determine the long-term risks of fractionated exposure to alpha-particle emitters.

Status: 1988- ongoing

Treatment: Multiple (16 injections over 8 weeks) i.p. injections of Ra-224 chloride in physiological saline

Dosimetry: Activity injected; absorbed dose was not calculated because of uncertainties about the location of the relevant target cells

Endpoints: Life-span study with macroscopic/microscopic pathology

Animal: Male CBA/H mice aged 84 ± 5 days at injection

Results: Under evaluation

References: Humphreys, E.R., I.R. Major and V.A. Stones. The effects of protracted alpha-particle- emitting radionuclides on mice. *Int. J. Radiat. Biol.* **58**:874-875, 1990.

Experimental Groups:

Study 07.03
Consequences (Osteosarcoma, Leukemia) of Multiple Ra-224 Injections in Mice

Group Id	Activity injected Bq/g	No Mice
1	0	200
2	32	200
3	64	200
4	128	200

07.04 Consequences (Osteosarcoma, Leukemia) of Single or Multiple Ra-224 Injections in Young Mice

Institution: MRC Radiobiology Unit, Chilton, UK

Scientists: E.R. Humphreys; retired

Purpose: To determine the long-term risks of fractionated exposure to alpha-particle emitters in young mice.

Status: 1989- ongoing

Treatment: Single or multiple (sixteen injections over eight weeks) i.p. injections of Ra-224 chlorid in physiological saline

Dosimetry: Activity injected; absorbed dose was not calculated because of uncertainties about the location of the relevant target cells

Endpoints: Life-span study with macroscopic/microscopic pathology

Animal: Male CBA/H mice aged 28 ± 2 days at start of injections

Results: Under evaluation

References:

Experimental Groups:

Study 07.04
Consequences (Osteosarcoma, Leukemia) of Single or Multiple Ra-224 Injections in Young Mice

Group Id	Activity injected Bq/g	No mice
	0	historical controls
1	**Single** 64	200
2	**Multiple** 64	100
3	128	80
4	256	80

07.05 Consequences (Osteosarcoma, Leukemia) in the Offspring of Pu-239 Contaminated Pregnant Mice

Institution: MRC Radiobiology Unit, Chilton UK

Scientists: E.R. Humphreys; retired

Purpose: To determine the long-term risks to offspring from contamination by alpha-particle emitters in utero.

Status: 1989- ongoing

Treatment: Single i.v. injection of Pu-239 citrate to mice on day 4 or day 13 of pregnancy, male offspring kept for late effects

Dosimetry: Activity injected; absorbed dose was not calculated because of uncertainties about the location of the relevant target cells

Endpoints: Life-span study with macroscopic/microscopic pathology

Animal: Male offspring from pregnant timed CBA/H mice 84 ± 5 days old at injection

Results: Interim results show that the distribution of Pu-239 in the tissues of the offspring of CBA/H mice contaminated on day 4 or day 13 of gestation was very similar to that obtained in previous experiments on BDF1 offspring similarly contaminated in utero. This indicates that the haemopoietic effects seen in the BDF1 offspring would also be seen in the CBA/H offspring. The long-term findings in the CBA/H offspring, however, indicate that there has been no tumorigenic effect. Further analysis are needed to validate those early findings.

References:

Experimental Groups:

Study 07.05

Consequences (Osteosarcoma, Leukemia) in the Offspring of Pu-239 Contaminated Pregnant Mice

Group Id	Activity injected to mothers Bq/g	Day of injection pC	No offspring
	(historical controls)		
1	16	13	195
2	32	4	200
3		13	200
4	64	4	200
5		13	200

07.06 Consequences (Osteosarcoma, Leukemia) of Pu-239 Contamination in Adult Mice

Institution: MRC Radiobiology Unit, Chilton, UK

Scientist: E.R. Humphreys; retired

Purpose: To determine the long-term risks of alpha-particle emitters .

Status: 1979- ongoing

Treatment: Single or multiple (sixteen injections over eight weeks) i.p. injection of Pu-239 citrate

Dosimetry: Activity injected; absorbed dose was not calculated because of uncertainties about the location of the relevant target cells

Endpoints: Life-span study with macroscopic/microscopic pathology

Animal: Female CBA/H mice aged 84 ± 5 days at injection

Results: Both osteosarcoma and myeloid leukemia were induced by 1.85, 5.5 and 18.5 Bq/g Pu-239 after single and multiple intraperitoneal injection and, for both tumor types, the yield increased with the amount injected. No differences in osteosarcoma yield were seen as a result of multiple injections; the yield of myeloid leukemia was slightly increased.

The observed osteosarcomas were classified either as "fully developed" (seen radiographically) or as "early" (not seen radiographically). Although the "early" osteosarcomas could be identified only in those bones either sampled routinely or because other pathology was suspected, their numbers were comparable with those of "fully developed" tumors.

References: Humphreys, E.R., J.F. Loutit and V.A. Stones. The induction by ^{239}Pu of myeloid leukaemia and osteosarcoma in female CBA mice (interim results), pp. 343-351. *In* N.D. Priest [ed.], *Metals in Bone.* MTP Press Lim, Lancaster, Boston, the Hague, Dordrecht, 1985.

Humphreys, E.R., J.F. Loutit and V.A. Stones. The induction, by ^{239}Pu, of myeloid leukaemia and osteosarcoma in female CBA mice. *Int. J. Radiat. Biol.* **51**:331-339, 1987.

Experimental Groups:

Study 07.06
Consequences (Osteosarcoma, Leukemia) of Pu-239 Contamination in Adult Mice

Group Id	Activity Injected Bq/g	Application	No Mice
1.	0	single	42
2		multiple	40
3	1.85	single	42
4		multiple	40
5	5.5	single	42
6		multiple	39
7	18.5	single	42
8		multiple	40

07.07 Consequences (Osteosarcoma, Leukemia) of Th-228 Contamination in Adult Mice

Institution: MRC Radiobiology Unit, Chilton, UK

Scientist: E.R. Humphreys; retired

Purpose: To determine the long-term risks of alpha-particle emitters.

Status: 1990- ongoing

Treatment: Two paratibial injections, separated by one year, of a colloidal solution of Th-228

Dosimetry: Activity injected; absorbed dose was not calculated because of uncertainties about the location of the relevant target cells

Endpoints: Life-span study with macroscopic/microscopic pathology

Animal: Male CBA/H mice aged 84 ± 5 days at first injection

Results Eight hundred CBA/H mice were injected paratibially with 3.9-27.6 Bq/g Th-228 when 12 weeks old and maintained for lifetime study. Activities of Th-228, Ra-224 and Pb-212 were measured in selected tissues of most of these mice at death.

Preliminary results indicate that Ra-224 is circulating continuously in these mice in range of amounts which would be expected to cause myeloid leukemia when present as the result of single injections. The yields of myeloid leukemia which have been obtained so far, however, appear to be no greater than this. On the other hand, the yields of osteosarcoma are surprisingly large and indicate that there may be a total yield of osteosarcoma of the order of 50%. This is greater than has been obtained in any previous experiment with CBA/H mice and suggests an additional effect caused possibly by continuous exposure to Ra-224. However, further analysis of the results may be necessary before an unequivocal statement can be made on the true effects of protraction since it is known that thorium is more osteosarcomogenic than plutonium. Furthermore, if a real protective effect is confirmed, then some explanation must be sought for why this effect appears to have been restricted to osteosarcoma.

References:

Experimental Groups:

Study 07.07
Consequences (Osteosarcoma, Leukemia) of Th-228 Contamination in Adult Mice

Group Id	Bq/g ^{228}Th injected	No of Mice
historical controls	0	
1	3.46	200
2	6.92	200
3	13.84	200
4	27.68	200

07.08 Life Span and Myeloid Leukemia Incidence After Single and Fractionated Irradiation with X-Rays or Neutrons in CBA Mice

Institution: MRC Radiobiology Unit, Chilton, UK

Scientist: R.H. Mole; deceased
With the participation of M.J. Corp, E.V. Hulse, G.J. Neary, I.R. Major, R.A. Meldrum, D.G. Papworth in various parts of these studies

Purpose: To determine leukemia incidence in CBA mice function of dose, dose application and radiation quality and evaluate the data in relation to human risks .

Status: 1955-1987

Treatment:
A) Lifetime gamma-ray or fission neutron (in the natural U "GLEEP" reactor) exposure of male and female CBA mice (lifespan studied only);
B) Co-60 gamma irradiation with 1000 R of CBA or C57BL female mice at different different fractionation modalities; the animals irradiated at day or at night were combined in the table;
C) Fractionated Co-60 gamma ray or neutron exposure of male CBA mice
D) Fractionated exposure to 2x 1.25 Gy 250 kVp X-rays at 5.5 Gy/min separated by intervals from 3 h to 7 days;
Role of immunity : some groups were immunized by irradiated (30 or 50 Gy) myeloid leukemia cells before being exposed to small numbers of viable cells or to a challenging X-ray dose. Only a part of this experiment has been incorporated in the table.
E) single exposure to X-rays (250 kVp) at different dose rates, Co-60 gamma rays, fission neutrons (low flux reactor at Petten (1.5 MeV neutrons) 10 mGy/min) of CBA mice (one study with R =F1(C3Hx101) mice.

Dosimetry: Ionization chamber

Endpoints: Life-span study with macroscopic/microscopic pathology with emphasis on leukemia

Animal: CBA/H and some C57 Bl mice aged about 100 days (in some earlier experiments also about 80 days

Results Dr. R.H. Mole died in 1993. The reconstruction of the experiments had, therefore, to be done from published information which was difficult and sometimes unreliable.

A) The data suggest an RBE of about 10 with no difference between sexes and doses per day.
B) The incidence of myeloid leukemia was highest in animals exposed to the largest dose rate Co-60 gamma irradiation, almost no leukemias were seen at the lowest dose rate exposure. There is no marked difference between the two strains
C) Fractionated exposure to Co-60 gamma rays at daily doses of 3-50 rem a minimum in survival-time was found after an exposure lasting less than half the duration of life exposure. RBE for fission neutrons was found to be independent of exposure but may perhaps vary with dose rate.
In the experiment protracted vs fractionated gamma irradiation, the incidence of myeloid leukemia was about the same regardless of dose or dose rate when exposure was delivered over a period of 4 weeks.
D) Protracted or fractionated exposure caused only a minor increase in myeloid leukemia compared to the marked dose-dependent increase after single exposure. Leukemia incidence decreased markedly when the fractionation interval was 3 days or more.
Injection of bone marrow cells 3 days (but not 1 day) after exposure shortened the latency period of myeloid leukemia but did not influence total incidence.
E) A single exposure to X-rays yields a bell-shaped dose-effect relationship with a maximal incidence of myeloid leukemia of about 20% at a dose of 3 Gy. The dose response curve can be fitted to a a curve of the type aDxDexp(-lD) with values of a = 0.00027 ± 0.00005 /mGy and l= 0.087 ± 0.007 /rad for X-rays and a=0.00017 ± 0.00004 /mGy and l= 0.064 ± 0.007 /rad for gamma rays. The saturation of the curve is explained by the inactivating action of radiation. The data suggest that

interaction between two adjoining cells is an essential element in radiation carcinogenesis. Some studies with higher (5.5 Gy/min) and lower (0.04 Gy/min) do not suggest a marked effect of dose rate in this range.

Neutron exposure at the low flux reactor at Petten yielded also a saturation type curve but of a linear type axD+ xexp(-lD) with a= 0.0405± 0.0125 /mGy and l =0.101± 0.028 /mGy.

References:

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Experimental Groups:

Study 07.08
Life Span and Myeloid Leukemia Incidence After Single and Fractionated Irradiation with X-Rays or Neutrons in CBA Mice

Dose and Radiation	Application	No of Animals
A. Lifetime exposure		
Fission neutrons (0.05, 0.1, 1 rad/d)	1st experiment: 16-24 h/d continuous lifespan	500
Doses for 1st experiment are only approximative because they were read from a figure and not from a table.		
Controls		39♂+38♀
Fission neutrons (0.287 rad/d)	2nd experiment: 16-24 h/d continuous lifespan	40♂+33♀
Fission neutrons (2.26 rad/d)		19♂+20♀
Reactor gamma rays (2.26 rad/d)		39♂+33♀
Reactor gamma rays (15.8 rad/d)		20♂+20♀
B. Fractionated exposure of two mouse strains		
Controls CBA mice		30
1000 R Gamma rays CBA mice	5 days/w 50 R 81 R/hr	30
1000 R Gamma rays CBA mice	5 days/w 50 R 21 R/hr	25
1000 R Gamma rays CBA mice	5 nights/w 50 R 81 R/hr	30
1000 R Gamma rays CBA mice	Continuously 32 R/dr	30
Controls C57 Bl mice		29
1000 R Gamma rays C57 Bl mice	5 days/w 50 R 81 R/hr	30
1000 R Gamma rays C57 Bl mice	5 days/w 50 R 21 R/hr	29
1000 R Gamma rays C57 Bl mice	5 nights/w 50 R 81 R/hr	25
1000 R Gamma rays C57 Bl mice	Continuously 32 R/d	28
C. Fractionated Exposure Gamma rays		
1400 R Gamma-rays	4 weekly doses of 350 R	30♀
2100 R Gamma-rays	6 weekly doses of 350 R	25♀
2800 R Gamma-rays	8 weekly doses of 350 R	20♀
2650 R Gamma-rays	duration of life weekly doses 350 R	10♀
900 R Gamma-rays	4 weekly doses of 220 R	30♀
2190 R Gamma-rays	10 weekly doses of 207 R	20♀
3100 R Gamma-rays	15 weekly doses of 208 R	20♀
4340 R Gamma-rays	20 weekly doses of 218 R	24♀
5170 R Gamma-rays	25 weekly doses of 207R	10♀
6180 R Gamma-rays	30 weekly doses of 205 R	10♀
7210 R Gamma-rays	duration of life weekly doses 170 R	20♀
7250 R Gamma-rays		10♀
560 R Gamma-rays	5 weekly doses of 112 R	19♀
1160 R Gamma-rays	10 weekly doses of 116 R	19♀
1690 R Gamma-rays	15 weekly doses of 112 R	15♀

Dose and Radiation	Application	No of Animals
2150 R Gamma-rays	20 weekly doses of 107 R	29♀
3150 R Gamma-rays	30 weekly doses of 105 R	25♀
6820 R Gamma-rays	duration of life weekly doses 112 R	20♀
1680 R Gamma-rays	duration of life weekly doses 16 R	38♀
Fission neutrons 75 rad neutrons	5 weekly doses 15 rad	19♀
150 rad neutrons	10 weekly doses 15 rad	15♀
350 rad neutrons	20 weekly doses 17rad	30♀
500 rad neutrons	30 weekly doses 17rad	29♀
820 rad neutrons	duration of life weekly doses 16 rad	19♀
66 rad neutrons	30 weekly doses 2.2 rad	24♀
126 rad neutrons	60 weekly doses 2.1 rad	25♀
178 rad neutrons	duration of life weekly doses 2 rad	38♀
Protracted vs fractionated gamma rays 150 rad gamma rays	28 days continuously 4-11 mrad/min	71
300 rad gamma rays		66
450 rad gamma rays		66
900 rad gamma rays		48
150 rad gamma rays	20 fractions 5 d/w for 4 weeks 25 rad/min	72
300 rad gamma rays		65
450 rad gamma rays		65
900 rad gamma rays		48
150 rad gamma rays	single exposure 25 rad/min	99
300 rad gamma rays		83
450 rad gamma rays		104
D. Different fractionation intervals		
2 x 1.25 Gy X-rays	Interval 1h	?
2 x 1.25 Gy X-rays	Interval 2h	?
2 x 1.25 Gy X-rays	Interval 3h	?
2 x 1.25 Gy X-rays	Interval 6h	?
2 x 1.25 Gy X-rays	Interval 12h	?
2 x 1.25 Gy X-rays	Interval 1 d	?
2 x 1.25 Gy X-rays	Interval 2 d	?
2 x 1.25 Gy X-rays	Interval 3 d	?
2 x 1.25 Gy X-rays	Interval 7 d	?
1.25 Gy X-rays single	$5x10^6$ cells 3 days after exposure	?♂
1.25 Gy X-rays single	$30x10^6$ cells 1 days after exposure	?♂
1.25 Gy X-rays single	$30x10^6$ cells 3 days after exposure	?♂
1.25 Gy X-rays single	$30x10^6$ cells 7 days after exposure	?♂
E. Single exposure		

Dose and Radiation	Application	No of Animals
Controls (1972-1980) CBA mice		800 ♂
0.25 Gy X-rays CBA mice	0.55 Gy/min	130 ♂
0.5 Gy X-rays CBA mice		133 ♂
0.75 Gy X-rays CBA mice		100 ♂
1.0 Gy X-rays CBA mice		53 ♂
1.5 Gy X-rays CBA mice		78 ♂
2.0 Gy X-rays CBA mice		40 ♂
2.5 Gy X-rays CBA mice		88 ♂
3.0 Gy X-rays CBA mice		118 ♂
4.5 Gy X-rays CBA mice		169 ♂
6.0 Gy X-rays CBA mice		42 ♂
X-rays unkown doses and numbers CBA mice	5.5 Gy/min	?
X-rays unkown doses and numbers CBA mice	0.4 Gy/min	?
X-rays unkown doses and numbers R mice		?
Co-60 gamma rays (7 point dose effect curve up to 8 Gy)	single dose 0.25 Gy/min	?
Co-60 gamma rays CBA mice (7 point dose effect curve up to 8 Gy)	protracted dose over 22 h	?
Fission neutrons (Petten reactor) Controls CBA mice		77
0.02 CBA mice	0.01 Gy/min	75
0.05 CBA mice		74
0.1 CBA mice		75
0.2 CBA mice		73
0.5 CBA mice		74
1.0 CBA mice		72
2.0 CBA mice		74

07.09 Deterministic Skin Damage and Skin Cancer After Local Irradiation

Institution: MRC Radiobiology Unit, Chilton, UK.

Scientist: E.V. Hulse; deceased
R.H. Mole; deceased
R.J. Berry; active

Purpose: To determine dose levels needed to elicit early and late skin reactions in guina pigs and to determine risks of skin cancer and relation to deterministic damage in mice after different fraction modalities.

Status: 1974- 1980

Treatment: Dr. R.H. Mole died in 1993. The reconstruction of the experiments had, therefore, to be done from published information which was difficult and sometimes unreliable

A) 140 kVp X-rays delivered to a 4x3 cm field on the right flanc of guinea pigs.
B) Beta irradiation from Tl-204 (0.765 MeV) delivered in different fractionation modalities. In the first experimental series some animals were exposed to two fields at the thorax and the pelvis (cylindrical field 1.1cm long, 2.5 cm diameter); in the second series, the field (1.1 cm long 8.6 sq cm) was at the middle of the torso.

Dosimetry: Ionization chamber

Endpoints:
A) Daily observation and scoring for 40 days and then at intervals for one year when the animals were sacrificed
B) Life span study with regular observation of skin and at death

Animal:
A) Female albino guinea pigs about 1 year old, 2-5 animals per group, 26 animals total exact number in individual groups unknown
B) Female CBA mice of 3 months age

Results
A) The peak of the early reaction occurred 14-21 days after exposure. Fractionation of the dose spared about 340 rad. Permanent partial or complete epilation was found after 1400 rad or 1740 rads respectively. Fibrosis was detectible after more than 2070 rad after 3 months and after 1800 rad after one year.
B) Malignant tumors were mainly squamous cell types, most dermal tumors were fibrosarcomas or fibromas. After single exposure, the dose effect relationship followed a square low at low doses with saturation or a downward bend at doses >60 Gy . For fractionated exposure, tumor incidence ranged from 28-55% and 57 - 65% after 6 and 12 Gy respectively with no significant difference between single and fractionated exposures except for the highly fractionated last groups where it was only 29% and 28%. However, fractionation reduced clearly deterministic damage. Thus, there was little or no correlation between tumor formation and deterministic damage.

References:
Hulse E.V. Tumors of the skin and other delayed effects of external beta irradiation of mice using ^{90}Sr and ^{32}P. *Brit. J. Cancer* **16**:72-86, 1962.

Hulse E.V. Incidence and pathogenesis of skin tumors in mice irradiated with single external doses of low energy beta particles. *Brit. J. Cancer* **21**:531-547, 1967.

Hulse E.V., R.H. Mole and D.G. Papworth. Radiosensitivities of cells from which radiation-induced skin tumors are derived. *Int. J. Radiat. Biol.* **14**:437-444, 1968.

Hulse E.V. and R.H. Mole. Skin tumor incidence in CBA mice given fractionated doses to low energy beta emitters. *Brit. J. Cancer* **23**:452-463, 1969.

Mole R.H. The induction of skin cancer by radiation. *Brit. J. Radiol.* **45**:795, 1972.

Berry R.J., R.G. Mole and D.W. Barnes. Skin response to X-irradiation in the guinea pig. *Int. J. Radiat. Biol.* **30**:535-541, 1976.

Experimental Groups:

Study 07.09
Deterministic Skin Damage and Skin Cancer After Local Irradiation

Dose	Application	No of Animals
Guinea pigs 1260 rad X-rays	single application	
1530 rad X-rays	single application	
1800 rad X-rays	single application	
2070 rad X-rays	single application	
2340 rad X-rays	single application	
2610 rad X-rays	single application	
1035+1035 rad X-rays	two fractions 24 h apart	
1350+1350 rad X-rays	two fractions 24 h apart	
CBA/H mice first series 0 Gy (controls)		58
7.5 Gy beta rays	two separate zones	60
15 Gy beta rays	one zone	59
15 Gy beta rays	two separate zones	60
15 Gy beta rays	two adjacent zones	60
30 Gy beta rays	one zone	60
30 Gy beta rays	two adjacent zones	60
60 Gy beta rays	one zone	31
120 Gy beta rays	one zone	30
CBA/H mice second series 0 Gy (controls)		60
60 Gy beta rays	single exposure	31
60 Gy beta rays	single exposure	30
60 Gy beta rays	given as 4 weekly exposures over 21 d	20
120 Gy beta rays	given as 4 weekly exposures over 21 d	40
60 Gy beta rays	given as 4 monthly exposures over 12 w	20
120 Gy beta rays	given as 4 monthly exposures over 12 w	40
60 Gy beta rays	given as 12 weekly exposures over 11 w	20
120 Gy beta rays	given as 12 weekly exposures over 11 w	40
60 Gy beta rays	given as 20 daily exposures (5d/w)over 25 d	20
120 Gy beta rays	given as 20 daily exposures (5d/w)over 25 d	40

08 National Radiological Protection Board NRPB

08.01 Comparative Toxicity and Retention of Am-241, Pu-239, and U-233 in Mice

Institution: NRPB, Chilton, UK

Scientists: M. Ellender; active
J.W. Haines; active
J.D. Harrison; active

Purpose: To determine the long-term risks from contamination by different alpha emitters

Status: 1986- ongoing

Treatment: Nine i.p. injections of Am-241 citrate, Pu-239 citrate or U-233 citrate (the activity was given as 9 injections over a short period to avoid any toxic effects due to the chemical toxicity of uranium; all groups were treated similarly)

Dosimetry: Activities calculated to give the same average bone dose at 500 days at each group on the basis of data on distribution and retention (serial killing 1, 7, 14, 28, 112, 224 ,448 days)

Endpoints: Life-span study with macroscopic/microscopic pathology

Animal: Male CBA/H mice aged 12 weeks

Results: Not terminated, only intermediate results available

References:

Ellender, M. and J.W. Haines. Retention and distribution of ^{233}U, ^{239}Pu and ^{241}Am in the CBA/H mouse. *EULEP Newsletter* **52**:14-15, 1989.

Ellender, M., J.W. Haines and J.D. Harrison. A comparison of the biokinetics and toxicity of plutonium-239, americium-241 and uranium-233 in CBA/H mice. *EULEP Newsletter* **57**:26-27, 1990.

Cox, R., G.M. Kendall, C.R. Muirhead, G.N. Stradling, J.D. Harrison and D.C. Lloyd. Biomedical Progress Report for the year to Febr. 1991, . *In* NRPB-M306. NRPB, Chilton, 1991.

Ellender, M., J.W. Haines, T.A. Cragg and J.D. Harrison. Distribution and toxicity of ^{239}Pu, ^{241}Am and ^{233}U in the mouse skeleton. *EULEP Newsletter* **62**:26-27, 1991.

Haines, J.W., M. Ellender, R.J. Talbot and J.D. Harrison. Autoradiographic studies and dose estimates for ^{239}Pu, ^{241}Am and ^{233}U in animal bones. *EULEP Newsletter* **62**:28-29, 1991.

Harrison, J.D. The dosimetry of incorporated radionuclides. Contract Bi6-089. *Progr. Rep. CEC Rad. Prot. Progr.*:1831, 1991.

Ellender, M., L. Robbins, S.D. Bouffler and J.D. Harrison. Induction of osteosarcoma and leukaemia by ^{239}Pu, ^{241}Am and ^{233}U in CBA/H mice. *EULEP Newsletter* **12**:12, 1993.

Robbins, L. and M. Ellender. Husbandry procedures and health problems associated with a long term mouse study. *Anim. Technol.* **44**:247-255, 1993.

Ellender, M., J.W. Haines and J.D. Harrison. Bone dosimetry of ^{239}Pu, ^{241}Am and ^{233}U in a log term effects study using CAB/H mice. *EULEP Newsletter* **77**:13-14, 1994.

Ellender, M., J.W. Haines and W.D. Harrison. The distribution and retention of plutonium, americium and uranium in CBA/H mice. *Human & Experimental Toxicology* **14**:38-48, 1995.

Experimental Groups:

Study 08.01
Comparative Toxicity and Retention of Am-241, Pu-239, and U-233 in Mice

Group Id	Radionuclide	Bq/g	Bone Dose (mGy)	No Mice
1	Control	0	0	100
2	^{239}Pu	5	200	100
3	^{239}Pu	15	600	60
4	^{239}Pu	25	1000	50
5	^{231}Am	5.8	250	100
6	^{231}Am	17.2	700	75
7	^{241}Am	28.9	1200	50
8	^{233}U	39.5	300	100
9	^{233}U	117.6	800	60
10	^{233}U	197.3	1300	50

09 SCK/CEN Studiecentrum voor Kernenergie, Centre d'Étude de l'Energie Nucléaire

09.01 Evaluation of Treatment with Zn DTPA Following Contamination with Am-241

Institution: SCK/CEN, Mol, Belgium

Scientists: G. Schoeters; active
O. Vanderborght; retired

Purpose: To determine whether treatment with Zn DTPA not only reduces contamination levels of Am-241 but also risks with respect to osteosarcoma, leukemia and other consequences. Comparison with Ra-226

Status: 1983-1986, terminated, data in ERAD

Treatment: Single i.p. injection of Am-241 citrate or Ra-226 followed, in some groups, by treatment with 50 µmol Zn DTPA per kg mouse 4 days later

Dosimetry: Am-241 retention in the femur measured after 4 days, 56 days and at death

Endpoints: Life-span study (spontaneous death) with radiographic determination of osteosarcomas and macroscopic/microscopic pathology

Animal: Male C57BL mice aged 12 weeks at the injection

Results: Treatment with Zn DTPA reduced Am concentration in bones between 33 and 45 % and in liver by 97 %. Treatment of mice given the low Am dose restored survival time to that of control mice and reduced incidence of bone tumors, liver carcinomas and all malignant tumors in relation to the reduction in tissue burdens. At the high Am dose,no maligancies were observed due to the much shortened survival of the mice (168 dats vs 576 days in controls). Zn DTPA treatment prolonged somewhat survival (236 days) and thereby allowed a small number of tumors to appear..

References:

Schoeters, G.E.R. and O.L.J. Vanderborght. The comparative carcinogenicity of ^{241}Am versus ^{226}Ra in various mouse strains, pp. 503-513. *In* K.F. Baverstock and J. Stather [eds.], *Low Dose Radiation: Biological Bases of Risk Assessment.* Taylor and Francis, London, 1989.

Schoeters, G.E.R., J.R. Maisin and O.L.J. Vanderborght. Protracted treatment of C57Bl mice with ZnDTPA after ^{241}Am injection reduces the long-term radiation effects. *Int. J. Radiat. Biol.* **59**:1027-1038, 1991.

Schoeters, G.E.R., J.R. Maisin and O.L.J. Vanderborght. Toxicity of ^{241}Am in male C57Bl mice: relative risk versus ^{226}Ra. *Radiat. Res.* **126:**198-205, 1991.

Experimental Groups: **Study 09.01**
Evaluation of Treatment with Zn DTPA Following Contamination with Am-241

	Without ZnDTPA		With ZnDTPA	
Bq/g	Group Id	No of mice	Group Id	No of mice
0	1	107	2	49
22 ^{241}Am	3	105		
58 ^{241}Am	4	102	5	102
190 ^{241}Am	6	103		
373 ^{241}Am	7	67	8	65
1197 ^{241}Am	9	57		
895 ^{226}Ra	10	80		

09.02 Evaluation of Treatment with Na Alginate Following Ra-226 Contamination

Institution: SCK/CEN, Mol, Belgium

Scientists: G. Schoeters; active
O. Vanderborght; retired

Purpose: To determine whether treatment with Na alginate not only reduces contamination levels but also risks with respect to osteosarcoma, leukemia and other consequences.

Status: 1978-1981, terminated, data in ERAD

Treatment: Single i.p. injection of Ra-226 chloride followed, in some groups, by Na alginate (5% added to food) for a period of 200 days starting 4 days after contamination

Dosimetry: Ra-226 retention in the femur and lumbar vertebrae at necropsy

Endpoints: Life-span study (spontaneous death) with radiographic determination of osteosarcomas and macroscopic/microscopic pathology

Animal: Male C57BL mice aged 12 weeks at injection

Results: Daily treatment with alginate substantially reduces the body burden of Ra-226 especially for higher doses of Ra-226 (48% at 24.8 Bq Ra-226, but only 10.7 % at 4.4 Bq). This treatment had, however, no influence on the reduction of survival time caused by the Ra treatment nor on the appearance of osteosarcomas.

References: Schoeters, G.E.R., A. Luz and O.L.J. Vanderborght. ^{226}Ra induced bone-cancers: the effects of a delayed Na-alginate treatment. *Int. J. Radiat. Biol.* **43**:231-247, 1983.

Experimental Groups:

Study 09.02
Evaluation of Treatment with Na Alginate Following Ra-226 Contamination

	Without alginate		With alginate	
Dose Bq/g	Group Id	No of mice	Group Id	No of mice
Control	1	117	2	114
170	3	100	4	108
350	5	104	6	109
920	7	68	8	68

09.03 Survival, Osteosarcoma and Leukemia in Adult Mice and the Offspring Following Contamination of Pregnant Mice with Am-241

Institution: SCK/CEN, Mol, Belgium

Scientists: R. van den Heuvel; active
G. Schoeters; active

Purpose: To determine the consequences of an adult and in utero exposure to the alpha emitter Am-241

Status: 1986- 1993, terminated, data in ERAD

Treatment: Single i.v. injection of Am-241 citrate to adult male or female mice or to pregnant mothers on day 14 post conception, transfer of offspring to a non-contaminated foster mother after birth.
A) Two groups of adult female mice and one group of adult male mice
B) One group of female and one group of male offspring.

Dosimetry: Am-241 retention measurements in fetal bone and liver at 15 and 17 days of gestation, 0, 3, 10, 30 and 90 days after birth of selected animals.

Endpoints: Lfe-span study (spontaneous death) with radiographic determination of osteosarcomas and macroscopic/microscopic pathology, determination of radioactivity in femur

Animal: Adult male or female BALB mice, timed pregnant BALB mice aged 12 weeks, male and female offspring

Results: Adults treated with Am-241 have a significantly shortened survival and increased incidence of osteosarcoma (to 40- 50%). The data also suggest that female mice are more susceptible to induction of osteosarcoma than male mice. There is also a significant increase in osteosarcoma, all bone tumors, all sarcomas and all leukemias in the offspring from the contaminated mothers, although this appeared to occur independently of dose. Calculations of the number of osteosarcomas induced per Gy varied for contamination of adult mice between 0.2 and 0.01 and for the offspring between 6 and 0.6. Thus, offspring seemed to be about 10 times more at risk if osteosarcomas induced per mouse Gy are compared. In view of the small transfer of Am-241 through the placenta it can, nevertheless, be concluded that the risk to the offspring from contamination of the mother is not that large. Surprisingly, offspring from mothers treated with Am-241 displayed a longer survival time than controls, possibly due to fewer deterministic lung diseases appearing early in life.

References:

Schoeters, G.R., R. van den Heuvel, C. Hurtgen and J. Colard. ^{241}Am distribution in fetal haemopoietic organs of Balc/c mice, pp. 193-200. *In* G.B. Gerber, H. Métivier and H. Smith [eds.], *Age-related Factors in Radionuclide Metabolism*. Martinus Nijhoff, Dordrecht, 1987.

Schoeters, G.E.R., R. van den Heuvel, H. Leppens, F. van der Plaetse and O.L.V. Vanderborght. Distribution of ^{241}Am in offspring of BALB/c mice injected with ^{241}Am at 14 days of gestation: relation to calcium and iron metabolism and comparison with distribution of ^{241}Am after injection of adults. *Int. J. Radiat. Biol.* **58:**371-382, 1990.

Schoeters, G.E.R., R. van den Heuvel, H. Leppens, F. van der Plaetse and O.L. Vanderborght V. Distribution of ^{241}Am in offspring of BALB/c mice injected with ^{241}Am at 14 days of gestation: relation to calcium and iron metabolism and comparison with distribution of ^{241}Am after injection of adults. *Int. J. Radiat. Biol.* **58:**371-382, 1990.

van den Heuvel, R., G.B. Gerber, H. Leppens, F. van der Plaetse and G.E.R. Schoeters. Long-term effects on tumor incidence and survival from ^{241}Am exposure of BALB/c mice in utero and during adulthood. *Int. J. Radiat. Biol.* **68,** 679-685: 1995.

Experimental Groups:

Study 09.03
Survival, Osteosarcoma and Leukemia in Adult Mice and the Offspring Following Contamination of Pregnant Mice with Am-241

A. Adult mice

Bq/g ^{241}Am Injected (kBq/mouse)	Female Mice		Male Mice	
	Group Id	No of mice	Group Id	No of mice
First series 0	1	11		
100 (2.1)	2	66		
Second series 0	3	31	7	30
45 (0.8)	4	46		
90 (1.6)	5	15		
103 (2.5)			8	59
212 (3.8)	6	62		

B. Offspring

Bq/g ^{241}Am average doses injected to mother (kBq/mouse)	Female Offspring		Male Offspring	
	Group Id	No of mice	Group Id	No of mice
Controls 0	9	50	10	91
100 (2.85)	11	46	12	51
500 (13.68)	13	45	14	59
1,500 (40.94)	15	56	16	81

09.04 Survival and Disease Incidence in BALB/C and C57BL Mice After X-Ray Exposure with and without Treatment with Chemical Protectors

Institution: SCK/CEN, Mol, Belgium

Scientists: J.R. Maisin; retired
G.B. Gerber; retired

Purpose: To determine the influence of chemical protectors on late effects in two mouse strains.

Status: 1970-1976, terminated, data in ERAD except for groups indicated in italics

Treatment: Single exposure to 250 kVp X-rays (100R/min HVL 0.7 mm Cu), C57Bl also 4 equal fractions at 1 week interval, injection of mixture before each exposure
in addition a group also i.p 8 mg 2 ß-aminoethylisothiouronium-Br-HBr (AET) before exposure, another 1 mg 5 hydroxytryptamine (5-HT) and a third a mixture of 8mg AET, 1 mg 5-HT, 5 mg MEA, 15 mg L-cysteine and orally 16 mg glutathione.

Dosimetry: Following the EULEP protocol and standardized within EULEP using a Phillips integrating dosimeter and an ionization chamber

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology. embedded in paraffin, stained HE

Animal: Male C57Bl/Cnb (LD50/30 650R), BALB/c/Cnb (LD50/30 576 R)respectively of 4 and 12 weeks of age

Results: The results demonstrate that a mixture of radioprotectors is more efficient than any substance given separately. However, the dose-effect relationships are not paralell for protected and non protected mice, and the dose reduction factor (DRF) varies with dose. The highest DRF obtained for long term survival of BALB/c/Cnb mice is 2.5 and thus nearly the same as for acute survival (2.8). The study of the causes of death indicates that AET treatment shifts the maximum of thymic lymphoma incidence to 1000 R at an unaltered frequency whereas treatment with the mixture not only displaces the maximum to a still higher dose but also reduces the peak incidence. BALB/c/Cnb mice can also be protected, although to a smaller extent, with respect to myeloid leukemia, sarcoma, deterministic kidney damage and non-cancerous lung lesions and protection against the two latter diseases is mainly responsible for the longer survival of treated mice in the higher dose range. Protection of C57Bl resembles that of BALB mice. Thus, protection is effective against thymic lymphoma and possibly also against liver adenomas, all carcinomas, myeloid leukemia, kidney and lung damage.

After fractionated exposure, the dose-effect relationship for life-shortening is sigmoid in protected and non protected mice with a DRF of 2.1 at 50% life-shortening. Thymic lymphoma is the principal cause of death in C57Bl mice exposed to fractionated radiation. Radioprotectors diminish the incidence of this disease but apparently are not effective against the other causes of death.

References:

Maisin, J.R., G. Mattelin and M. Lambiet-Collier. Chemical protection against the long term effects of a single whole-body exposure of mice to ionizing radiation. I. Life shortening. *Radiat. Res.* **71**:119-131, 1977.

Maisin, J.R., A. Decleve, G.B. Gerber, G. Mattelin and M. Lambiet-Collier. Chemical protection against the long term effects of a single whole-body exposure of mice to ionizing radiation. II. Causes of death. *Radiat. Res.* **74**:415-435, 1978.

Maisin, J.R., G.B. Gerber, G. Mattelin and M. Lambiet-Collier. Chemical protection against the long term effects of a single whole-body exposure of mice to ionizing radiation. III. The effects of fractionated exposure to C57bl mice. *Radiat. Res.* **82**:487-497, 1980.

Experimental Groups:

Study 09.04
Survival and Disease Incidence in BALB/C and C57BL Mice After X-Ray Exposure with and without Treatment with Chemical Protectors

	X-rays		X-rays+AET		X-rays+Mixt.		X-rays + 5HT	
Dose R	Group Id	No Mice*	Group Id	No Mice*	Group Id	No Mice*	Group Id	No Mice*
BALB Single Exposure								
0	1	155						
100	2	144			14	145		
175	3	149			15	136		
350	4	107			16	91		
500	5	76	9	160	17	164		
650	6	198	10	102	18	130	22	89
750	7	57						
900	8	19						
1000			11	77	19	89	23	*56*
1100			12	98				
1200			13	37	20	81		
1350					21	40		
C57Bl Single Exposure								
0	24	131						
350	25	100	27	98				
650	26	69	28	96				
C57Bl Fractionated								
200	29	101 (52)			36	106(42)		
300	30	98 (45)			37	108(47)		
400	31	143 (44)			38	97(45)		
500	32	*100*			39	98(55)		
700	33	102(48)			40	104		
1000	34	100(40)			41	103(37)		
1500	35	7(3)			42	44(44)		

* total number of mice (with number given pathological diagnoses shown in parentheses)

09.05 Survival and Disease Incidence in BALB/C Mice After Single or Fractionated Gamma-Ray or Neutron Exposure

Institution: SCK/CEN, Mol, Belgium

Scientists: J.R. Maisin; retired
G.B. Gerber; retired
A. Wambersie; retired

Purpose: To determine the influence of radiation quality and fractionation on late effects in BALB mice

Status: 1977-1984, terminated, data in ERAD

Treatment: Single exposure to a Cs-137 source (3-4 Gy/min), fractionated 10 fractions separated by one day, single exposure to neutrons from 50 MeV deuterons on a beryllium target (23 MeV neutron modal energy, gamma contamination < 5%, 0.01-1.5 Gy/min for constant exposure times)

Dosimetry: Gamma rays following the EULEP protocol and standardized within EULEP using a an ionization chamber, neutrons in a Shonka plastic A150 Te plate ionization chamber

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology. embedded in paraffin, stained HE

Animal: Male BALB/c/Cnb mice of 12 weeks of age

Results Life-shortening in BALB/c mice shows a linear dependency on dose and is about the same for fractionated (38.1 ± 3.1 days per Gy) as for single (46.2 ± 4.3 days) exposure. More mice die from tumor diseases and fewer from deterministic lung damage after fractionated than after single exposure. The dose dependency after neutron exposure also is linear (55.8 ± 4 days), and the incidence of different diseases ressembles that after acute gamma exposure except that more carcinomas, sarcomas and myeloid leukemias are seen after neutron exposure and that deterministic lung and kidney diseases occur already after lower doses than after gamma exposure.

References:

Maisin, J., G.B. Gerber, G. Mattelin and M. Lambiet-Collier. Chemical protection against life-shortening and causes of death after single and fractionated whole body exposure of mice, pp. 483-495. *In* IAEA-STI/PUB 489: *Late Biological Effects of Ionizing Radiation*, Vol. II. IAEA, Vienna, 1978.

Maisin, J.R., A. Wambersie, G.B. Gerber, J. Gueulette, G. Mattelin and M. Lambiet-Collier. Late effects in mice following whole-body exposure tp d(50)-Be neutrons and gamma rays, pp. 187-189. *In* J.J. Broerse and G.B. Gerber [eds.], *Neutron Carcinogenesis*. CEC, Brussels-Luxembourg, 1982.

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Maisin, J.R., A. Wambersie, G.B. Gerber, J. Gueulette, G. Mattelin and M. Lambiet-Collier. Life shortening and disease incidence in BALB/c mice following a single d(50)-Be neutron or gamma exposure. *Radiat. Res.* **94**:374-389, 1983.

Maisin, J.R., A. Wambersie, G.B. Gerber, G. Mattelin, M. Lambiet-Collier and J. Gueulette. The effects of fractionated gamma irradiation on life shortening and disease incidence in BALB/c mice. *Radiat. Res.* **94**:359-373, 1983.

Maisin, J.R., A. Wambersie, G.B. Gerber, G. Mattelin, M. Lambiet-Collier and J. Gueulette. Life-span shortening and disease incidence in male BALB/c and C57Bl mice after single or fractionated d(50)-Be neutron or gamma exposure, pp. 172-183. *In* R.C. Thompson and J.A. Mahaffey [eds.], *Life-span Studies in Animals. What can they tell us?*, Vol. CONF-830951. US Dep. of Energy, Washington, 1986.

Experimental Groups:

Study 09.05
Survival and Disease Incidence in BALB/C Mice
After Single or Fractionated Gamma-Ray or Neutron Exposure

Dose (Gy)	γ Rays single		γ Rays fraction.		Neutrons	
	Group Id	No mice	Group Id	No mice	Group Id	No mice
0	1	324				
0.02					14	254
0.06					15	225
0.18					16	190
0.25	2	193	8	111		
0.5	3	196	9	110		
0.54					17	176
1	4	198	10	115		
1.65					18	141
2	5	149	11	74		
3					19	130
4	6	94	12	74		
6	7	113	13	78		

09.06 Survival and Disease Incidence in C57BL Mice After Single or Fractionated Gamma-Ray or Neutron Exposure

Institution: SCK/CEN, Mol, Belgium

Scientists: J.R. Maisin; retired
G.B. Gerber; retired
A. Wambersie; retired

Purpose: To determine the influence of radiation quality and fractionation on late effects in C57Bl mice.

Status: 1980-1989, terminated, data in ERAD

Treatment: Single exposure to a Cs-137 source (3-4 Gy/min), fractionated 10 fractions separated by one day or in 8 equal doses separated by 3 hours (0.3 Gy/min).
Single exposure to neutrons or fractionated into 8 fractions 8 hours apart or irradiation of the thorax with 50 MeV deuterons on a beryllium target (23 MeV neutron modal energy, gamma contamination < 7%)

Dosimetry: Gamma rays following the EULEP protocol and standardized within EULEP using a an ionization chamber, neutrons in a Shonka plastic A150 Te plate ionization chamber

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology. embedded in paraffin, stained HE

Animal: Male C57Bl/Cnb mice of 12 weeks of age

Results: No significant difference is observed between a single gamma and neutron exposure with respect to life-shortening of C57Bl mice. Fractionated gamma exposure is significantly less effective in reducing survival than a single exposure. On the other contrary, fractionating neutron exposure reduces life-span slightly, but not significantly, more than a single neutron exposure. Life-shortening depended in a linear fashion on dose for the exposure modalities studied. Malignant tumors, particularly leukemia including thymic lymphoma, and deterministic late degenerative damage to the lung are the principal causes of death after a single gamma-ray exposure. Exposure delivered in 8 fractions 3 hours apart is more effective in causing leukemias and all carcinomas and sarcomas than a fractionation schedule of of 10 fractions 24 hours apart or a single exposure. Following neutron exposure, leukemias and all carcinomas and sarcomas seem to appear at lower doses than after gamma exposure. No significant differences in incidence of leukemias and all carcinomas and sarcomas is noted between a single and a fractionated neutron exposure.

References:

Maisin, J.R., A. Wambersie, G.B. Gerber, G. Mattelin, M. Lambiet-Collier and J. Gueulette. Life-span shortening and disease incidence in male BALB/c and C57Bl mice after single or fractionated d(50)-Be neutron or gamma exposure, pp. 172-183. *In* R.C. Thompson and J.A. Mahaffey [eds.], *Life-span Studies in Animals. What can they tell us?*, Vol. CONF-830951. US Dep. of Energy, Washington, 1986.

Maisin, J.R., A. Wambersie, G.B. Gerber, G. Mattelin, M. Lambiet-Collier and J. Gueulette. Life shortening and disease incidence in BALB/c mice following after single and fractionated τ and high energy neutron exposure. *Radiat. Res.* **113:**300-317, 1988.

Experimental Groups:

Study 09.06
Survival and Disease Incidence in C57BL Mice
After Single or Fractionated Gamma-Ray or Neutron Exposure

Dose (Gy)	GroupNo / No of mice					
	γ Rays Single	γ Rays Fract. 24h	γ Rays Fract. 3h	Neutron Single	Neutron Fract.	Thorax Neutron
0	1 / 473					
0.02				17 / 196		
0.06						25 / 96
0.18				18 / 182	22 / 96	26 / 94
0.25	2 / 242	8 / 108				
0.5	3 / 239	9 / 112				
0.54				19 / 210	23 / 232	27 / 90
1	4 / 246	10 / 116	14 / 106			
1.65				20 / 135	24 / 196	
2	5 / 217	11 / 115	15 / 93			
3				21 / 95		
4	6 / 143	12 / 118	16 / 115			
6	7 / 188	13 / 117				

09.07 Influence of Radiation Quality on Survival and Disease Incidence in C57BL Mice Exposed At Different Ages

Institution: SCK/CEN, Mol, Belgium and UCL, Brussels

Scientists: J.R. Maisin; retired
G.B. Gerber; retired
J. Vankerkom; active

Purpose: To determine the influence of radiation quality on late effects in C57Bl mice exposed at different ages.

Status: 1987- ongoing

Treatment: Single exposure to X-rays (250 kVp 1Gy/min, 2mm Cu HVL) and to neutrons (3.1 MeV modal energy, obtained from 6.2 MeV protons on a Be target at the linear accelerator of the BCMN, Geel, 0.04 Gy/min)

Dosimetry: X-rays following the EULEP protocol and standardized within EULEP using a Philipps ionization chamber, neutrons in a 0,053 cm^3 ionization chamber operated in continuous gas flow.

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology. embedded in paraffin, stained HE

Animal: Male C57BL/Cnb mice of different age

Results: Survival and causes of mortality were studied in 7 or 21 day old male C57BL/Cnb mice exposed to 0.5, 1 or 3 Gy of 250 kVp X-rays or 0.125, 0.25, 0.5 or 1 Gy of accelerator neutrons (modal energy 3.1 MeV). A total 1287 animals were used in the experiments. Survival of irradiated animals is reduced significantly only in the highest dose groups (1 Gy neutrons, 3 Gy X-rays). Mice exposed to the lowest doses (0.125 Gy of neutrons, 0.5 Gy of X-rays) live significantly longer than controls due mainly to a reduction in non-neoplastic lung and liver diseases. All malignant tumors increase significantly from (and including) doses of 0.5 Gy neutrons and 1 Gy X-rays. Hepatocellular carcinoma is the principal contributor to the increase in tumor incidence, at least after neutron exposure. No significant increase in hepatocellular carcinoma is seen for 21old mice exposed to X-rays. An increase, especially after 3 Gy of X-rays is also observed for all leukemias. Controls in the present study lived significantly longer than in our earlier studies on adult mice making a direct comparison of adult with infant mice difficult. Based on percentage life shortening, it appears that exposure during infancy does not shorten total survival or survival from cancer much more than that of adults although such exposure, especially that to neutrons, causes more hepatocellular carcinoma. Due to the non-linearity of the dose-effect relationships, it is difficult to calculate the RBE of neutrons. For survival time at higher doses an RBE of about 3 is obtained. When the incidence of all malignant tumors and of hepatocellular cancer is fitted to a linear or a linear-quadratic function an approximate RBE from 5 to 8 is obtained. No RBE can be estimated for hepatocellular carcinoma in mice of an age of 21 days because X-rays does not seem to cause this tumor at that age.

References: Maisin J.R, G.B. Gerber, J. VanKerkom and A. Wambersie. Mice Exposed to X-rays or 3.1 MeV Neutrons at an age of 7 or 21 days .*Radiat. Res.* In the press

Experimental Groups:

Study 09.07

Influence of Radiation Quality on Survival and Disease Incidence in C57BL Mice Exposed At Different Ages

Dose Gy	Neutrons 7 d old		Neutrons 21 d old		X-rays 7 d old		X-rays 21 d old	
	Group Id	No Mice	Group Id	No Mice	Group Id	No Mice	Group Id	No Mice
0	1	165						
0.125	2	47	6	31				
0.25	3	102	7	112				
0.5	4	105	8	121	10	72	13	66.
1	5	84	9	102	11	70	14	76
3					12	85	15	83

09.08 Influence of Carbon Tetrachloride Treatment on Liver Tumors and Other Late Effects in C57BL Mice

Institution: SCK/CEN, Mol, Belgium and UCL, Brussels

Scientists: J.R. Maisin; retired

Purpose: To determine the interaction between radiation and the promotor carbontetrachloride at different times.

Status: 1987-1992

Treatment: Single exposure to X-rays of the upper abdomen (250 kVp 1Gy/min, 2mm Cu HVL) and to C Cl_4 (0.1 ml of a 40% solution in miglycol) given by gavage 69 hours before or 3 months after radiation exposure

Dosimetry: X-rays following the EULEP protocol and standardized within EULEP using a Philipps ionization chamber.

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology, including evaluation of the number and size of the liver lesions. The tissues were embedded in paraffin and stained with HE

Animal: Male C57BL/Cnb mice aged 12 weeks

Results: Evaluation not yet terminated

References:

Experimental Groups:

Study 09.08
Influence of Carbon Tetrachloride Treatment on Liver Tumors and Other Late Effects in C57BL Mice

X-rays Gy	No C Cl_4		C Cl_4 69 h prior irrad		C Cl_4 3 m after irrad.	
	Group Id	No mice	Group Id	No mice	Group Id	No mice
0	1	68				
0.5	2	57	7	60	12	56
1	3	57	8	56	13	58
2	4	54	9	56	14	113
4	5	58	10	57	15	113
6	6	57	11	56	16	59

09.09 Induction of Liver Tumors in Infant Mice by Diethylnitrosamine in Combination with X-Rays

Institution: SCK/CEN, Mol, Belgium and UCL, Brussels, Belgium

Scientists: J.R. Maisin; retired
J. Vankerkom; active
L. de Saint-Georges; active
M. Janowski; active

Purpose: To investigate the interaction of radiation with a carcinogen during a critical period of mammalian development.

Status: 1988 terminated.

Treatment: Single exposure to X-rays (250 kVp 0.95 Gy/min, 1.85 mm Cu HVL), ip injection of diethylnitrosamine (DEN) in saline at an age of 14 days preceded or followed by X-irradiation 7 days before or 7 days later. Mice treated with X-rays only at an age of 7 or 21 days.

Dosimetry: X-rays following the EULEP protocol and standardized within EULEP using a 2750 Nuclear Enterprise dosimeter

Endpoints: Serial sacrifice of 10 mice of each group at 10 weeks intervals (from 10 to 70 weeks)); controls only at 10, 40 and 70 weeks; the following parameters were determined: body weight, liver weight, number and size of macroscopic liver lesions, number and total surface of the different types of microscopic liver lesions.

Animal: Male C57BL/CNb mice injected with DEN at an age of 14 days and irradiated 7 days before or 7 days after DEN treatment

Results: The number of foci and carcinomas induced in liver depends essentially on the dose of DEN. X-irradiation given 7 days before or after DEN administration does not affect the development of these foci or of carcinoma.

References: Maisin, J.R., J. Vankerkom, L. de Saint-Georges, M. Janowski, M. Lambiet-Collier and G. Mattelin. Effect of X-rays alone and in combination with diethylnitrosamine on tumor induction in infant mouse liver. *Radiat. Res.* **133**:334-339, 1993.

Experimental Groups:

Study 09.09
Induction of Liver Tumors in Infant Mice by Diethylnitrosamine in Combination with X-Rays

Irradiation Age	µg/g DEN	0 Gy Group Id / No mice	0.5 Gy Group Id / No mice	1 Gy Group Id / No mice	3 Gy Group Id / No mice
7 days	0	1 / 30	6 / 80	11 / 80	16 / 80
	0.31	2 / 80	7 / 80	12 / 80	17 / 80
	0.62	3 / 80	8 / 80	13 / 80	18 / 30
	1.25	4 / 80	9 / 80	14 / 80	19 / 30
	2.5	5 / 80	10 / 80	15 / 80	20 / 80
21 days	0		25 / 80	30 / 80	35 / 80
	0.31	21 / 80	26 / 80	31 / 80	36 / 80
	0.62	22 / 80	27 / 80	32 / 80	37 / 80
	1.25	23 / 80	28 / 80	33 / 80	38 / 80
	2.5	24 / 80	29 / 80	34 / 80	39 / 80

09.10 Induction of Liver Tumors in Infant Mice by Diethylnitrosamine in Combination with Neutrons

Institution: SCK/CEN, Mol, Belgium and UCL, Brussels, Belgium

Scientists: J.R. Maisin; retired
J. Vankerkom; active
L. de Saint-Georges; active
M. Janowski; active

Purpose: To investigate the interaction of radiation with a carcinogen during a critical period of mammalian development.

Status: 1988 terminated

Treatment: Single exposure to neutrons (d,n reaction on a Be target at Ea= 6..3 MeV). Average neutron energy 3.1 MeV. ip Injection of diethylnitrosamine (DEN) in saline at an age of 14 days preceded or followed by X-irradiation 7 days before or 7 days later. Mice treated with neutrons only at an age of 7 or 21 days.

Dosimetry: Thimble ionization chamber (0.5 cm^3) operated under continuous TE-gas flow measuring total charge and assuming W =31.9 ±1.5 eV

Endpoints: Serial sacrifice of 10 mice of each group at 10 weeks intervals (from 10 to 70 weeks); controls only at 10, 40 and 70 weeks; the following parameters were determined: body weight, liver weight, number and size of macroscopic liver lesions, number and total surface of the different types of microscopic liver lesions.

Animal: Male C57BL/CNb mice injected with DEN at an age of 14 days and irradiated 7 days before or 7 days after DEN treatment

Results: The rate of appearance of foci increased significantly at the different times studied when a dose of 0.125 Gy of neutrons was administered before or after a dose of 1.25 µg of DEN. No differences were observed in the total surface area of foci and/or adenomas and carcinomas when increasing doses of neutrons were given 7 days before or after the administration fo 1.25 or 2.5 µg of DEN.

References: Maisin, J.R., J. Vankerkom, L. de Saint-Georges, M. Janowski, M. Lambiet-Collier, G. Mattelin and A. Wambersie. Effect of neutrons alone or combined with diethylnitrosamine on tumor induction in infant C57Bl mice. *Radiat. Res.* **142**:78-84, 1995.

Experimental Groups:

Study 09.10
Induction of Liver Tumors in Infant Mice by Diethylnitrosamine in Combination with Neutrons

Irradiation Age	µg/g DEN	0 Gy Group Id / No mice	0.5 Gy Group Id / No mice	1 Gy Group Id / No mice	3 Gy Group Id / No mice
7 days	0	1 / 30	6 / 80	11 / 80	16 / 80
	0.31	2 / 80	7 / 80	12 / 80	17 / 80
	0.62	3 / 80	8 / 80	13 / 80	18 / 30
	1.25	4 / 80	9 / 80	14 / 80	19 / 80
	2.5	5 / 80	10 / 80	15 / 80	20 / 80
21 days	0		25 / 80	30 / 80	34 / 80
	0.31	21 / 80	26 / 80	31 / 80	35 / 80
	0.62	22 / 80	27 / 80	32 / 80	36 / 80
	1.25	23 / 80	28 / 80	33 / 80	37 / 80
	2.5	24 / 80	29 / 80	33 / 80	38 / 80

09.11 Survival and Disease Incidence in Wistar Rats After a Single X-Ray Exposure in Utero

Institution: SCK/CEN, Mol, Belgium

Scientists: J.R. Maisin; retired
H. Reyners; active
E. Gianfelici; active

Purpose: To determine survival and disease incidence after X-ray exposure in utero (15 days post coitum).

Status: 1982-1987, terminated

Treatment: Single exposure to X-rays (250 kVp, 0.55 Gy/min, 1mm Cu HVL)

Dosimetry: X-rays following the EULEP protocol and standardized within EULEP using a Philipps ionization chamber

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology; embedded in paraffin, stained HE

Animal: Male Wistar r/cnb (SPF or not) rats exposed in utero

Results: Data under evaluation

References:

Experimental Groups:

Study 09.11
Survival and Disease Incidence in Wistar Rats After A Single X-Ray Exposure in Utero

Dose Gy	SPF rats exposed 15d pC		Non-SPF rats exposed 10d pC		Non-SPF rats exposed 15d pC	
	Group Id	No rats	Group Id	No rats	Group Id	No rats
0	1	119	5	14		
0.1	2	97				
0.2	3	138				
0.5	4	83	6	9	8	6
1			7	13	9	22

09.12 Brain Damage in Wistar Rats After Prenatal Radiation Exposure to X-Rays, Gamma-Rays, or Neutrons

Institution: SCK/CEN, Mol Belgium

Scientists: H. Reyners; active
E. Gianfelici; active

Purpose: To determine the threshold and consequences of different types of radiation exposure at different periods of pregnancy on adult brain development.

Status: 1980- ongoing

Treatments:
A) Co-60 gamma-exposure:
acute: on day 15 p.c.
protracted: day 0-20 p.c., day 14-20 p.c. or day 12-16 p.c. 36 mGy/h at 1.6 m from source
B) Cs-137 gamma exposure:
acute on day 15 p.c. at different dose rates (4 - 200 mGy/min)
C) X-ray exposure:
acute: on day 15 p.c., 250 kVp, 500 mGy/min assayed at different ages (C1) or exposed at different dose rates and assayed at 1 month (C2)
D) neutron exposure:
acute: on day 15 p.c. proton beam on a Li target 2.5 MeV (7.8 mGy/min) and 0.6 MeV (4.2 mGy/min) from the IRMM Van de Graaf accelerator (Geel)
protracted: day 12-16 p.c. and day 16-20 p.c. from the Cf-252 source at the CEA-FAR and from the IRMM Van de Graaf accelerator (10 mGy/d)

Dosimetry: Gamma and X-rays using a Farmer dosimeter 2570-EMI, verified with a TLD following the EULEP protocol and standardized within EULEP. Neutrons by means of a TNO T2/1 dosimeter

Endpoints: Serial killing after 1 -24 months, brain pathology (brain weight, cortex cingulum size, glia density) , determination of amino acids, biogenic amines and receptors in different brain areas

Animal: Female or male offspring from timed pregnant Wistar rats, in some experiments Sprague-Dawley or Lewis rats were also used

Results: **An atrophy** of the Wistar rat brain can be induced by fetal irradiation during the critical period of the pregnancy from day 12 to day 16 post-conception (p.c.). Exposure before or after this period is less efficient.

As little as 100 mGy of X-rays of a **single acute exposure** given 15 days p.c. at a dose rate of 500 mGy/min causes a small (3.8%) but significant reduction of the weight of the adult brain. This reduction is irreversible and becomes slightly more marked as the animal ages. Ten mGy of 600 keV neutrons (4.2 mGy/min) causes a 1.94% reduction of brain weight. At these low doses, differences are not detectible by morphological or histochemical methods; at slightly higher doses (25 mGy of 600 keV neutrons), loss of white matter in the cingulum of the corpus callosum becomes evident.

Gamma ray exposure given continuously at very low dose rates (0.017 to 0.1 mGy/min) during the critical period of pregnancy from days 12 to 16 p.c. causes a reduction in brain weight nearly as important (dose rate reduction factor 1.5) as acute X-ray exposure on day 15 p.c.; this contrasts with most observations in other radiobiological models. The decrease in cingulum size is, however, less pronounced after protracted than after acute exposure, and a significant reduction has so far only be detected after 70 mGy/ day (0.05 mGy/min) of 252-Cf neutrons given between days 12-16 p.c.

Biochemical parameters are much less susceptible to the action of radiation than morphological ones. Increases in several biogenic amines and receptors were found if expressed on a per g basis. However, at the doses studied (1 Gy), brain weight decreases significantly so that total amounts in a brain structure seem to vary but little.

References:

Reyners, H., E. Gianfelici de Reyners, R. Hooghe, J. Vankerkom and J.R. Maisin. Irradiation prénatale à très faible dose de rayons X: lésions de la substance blanche. *Compt.Rend Soc. Biol.* **180**:224-228, 1986.

Reyners, H., E. Gianfelici de Reyners, L. Regniers and J.R. Maisin. A glial progenitor cell in the cerebral cortex of the adult rat. *J. Neurocytol.* **15**:53-61, 1986.

Reyners, H., E. Gianfelici de Reyners and J.R. Maisin. The role of glia in late damage after prenatal irradiation, pp. 117-122. *In* H. Kriegel [ed.], *Radiation Risks to the Developing Organism.* G. Fisher, Stuttgart, 1986.

Ferrer, I., E. Soriano, E. Marti, E. Digon, H. Reyners and E. Gianfelici de Reyners. Development of dendritic spines in the cerebral cortex of the microencephalic rat following prenatal X-irradiation. *Neuroscience Letters* **125**:183-186, 1991.

Ferrer, I., E. Soriano, E. Marti, E. Laforet, H. Reyners and E. Gianfelici de Reyners. Naturally occurring, postnatal cell death in the cerebral cortex of the micrencephalic rat induced by prenatal X-irradiation. *Neuroscience Research* **12**:446-451, 1991.

Janowski, M., G.B. Gerber, H. Reyners and E. Gianfelici de Reyners. Late effects of an in utero irradiation on the central nervous system. *Progr. Rep. CEC Rad. Prot. Progr. EUR* 13268 2:1298-1308, 1991.

Reyners, H., E. Gianfelici de Reyners, F. Poortmans, A. Crametz and J.R. Maisin. Brain atrophy after fetal exposure to very low doses of ionizing radiations. Int. J. Radiat. Biol. 62:619-626, 1992.

Reyners, H., I. Ferrer and H. Coffigny. Effects of protracted exposures to low doses of radiation during the prenatal development of the central nervous system. *Progr. Rep. CEC Rad. Prot. Progr. EUR* 15238 2:413-418, 1993.

Reyners, H., E., H. Coffigny and I. Ferrer. Effect of radiation on the development of the central nervous system. *Progress Report CEC Radiation Protection Programme* Contract Bi7-003:1009-1016, 1994.

Reyners, H., L. van Ravestyn and E. Gianfelici de Reyners. Neurologie du retard mental sévère causé par une irradiation prénatale. *Ann. Assoc. Belge Radioprot.* **18**:151-157, 1993.

Experimental Groups:

Study 09.12

Brain Damage in Wistar Rats After Prenatal Radiation Exposure to X-Rays, Gamma-Rays, or Neutrons

A. Acute and chronic ^{60}Co gamma-exposure (female Wistar rats except where indicated otherwise)

Dose mGy	Age assay	Group Id / No rats					
		Chronic ^{60}Co γ exposure 36mGy/h				Acute exposure	
		day 0-20	day 14-20	day 11-15	day 12-16	day 15	day 16
0	20d	1 / 6	12 / 10				
0	32d		13 / 11		39 / 14		
0	3m	2 / 6	14 / 9	31 / 11♀ 32 / 15♂	40 / 3	55 / 4	58 / 4
0	15m	3 / 6	15 / 9				
65	20d		16 / 6				
65	32d				41 / 13		
65	3m		17 / 19		42 / 24		
107	20d		18 / 7				
107	32d				43 / 13		
107	3m		19 / 11		44 / 31		
170	20d	4 / 8	20 / 6				
170	32d				45 / 8		
170	3m	5 / 20	21 / 20		46 / 18		
170	15m				47 / 8		
270	20d		22 / 6				
270	3m		23 / 12	33 / 15♀ 34 / 8♂		56 / 8	59 / 7
356	20d	6 / 8	24 / 6				
356	32d				48 / 7		
356	3m	7 / 12	25 / 12		49 / 11		
356	15m	8 / 10	26 / 11		50 / 13		
500	3m			35 / 10♀ 36 / 10♂			
564	32d				51 / 6		
564	3m				52 / 9		
850	20d	9 / 8	27 / 8				
850	32d		28 / 12		53 / 6		
850	3m	10 / 8	29 / 9		54 / 9		
850	15m	11 / 11	30 / 11				
905	3m					57 / 5	59 / 13
1415	3m			37 / 4♀ 38 / 3♂			

B. Acute ^{137}Cs γ- exposure on day 15 p.c. to 365 mGy at different dose rates, assay at 32 days (femaleWistar rats)

Dose Rate (mGy/min)	Group Id	No Animals
0	60	11
4	61	9
20	62	12
200	63	9

C-1. Acute X-ray exposure on dat 15 p.c. with assay at different times (second group reduced to 8 pups/litter) (female Wistar rats)

Dose (mGy)	Group Id / No rats Age at assay months					
	1	3	6	15	24	30
0	64 / 11	71 / 12	78 / 17	81 / 13	88 / 5	95 / 13
91	65 / 14	72 / 11	79 / 17	82 / 12	89 / 7	96 / 12
180	66 / 5	73 / 18	80 / 18	83 / 9	90 / 15	97 / 12
0	67 / 11	74 / 15		84 / 16	91 / 24	
50	68 / 10	75 / 14		85 / 21	92 / 21	
100	69 / 10	76 / 15		86 / 15	93 / 17	
150	70 / 12	77 / 15		87 / 7	94 / 19	

C-2. Acute X-ray exposure day 15 pc to 180 mGy at different dose rates, assay at 1 month age (female Wistar rats)

Dose rate mGy/min (total dose 180 mGy)	Group Id	No Animals
0	98	5
20	99	15
40	100	5
400	101	5
4000	102	20

D-1. Acute neutron exposure (0.6 and 2.5 MeV) on day 15 p.c., assay at different ages (female Wistar rats)

Dose (mGy)	Group Id / No rats				
	0.6 MeV			2.5 MeV	
	3 months	15 months	24 months	3 months	24 months
0	103 / 30	109 / 15	114 / 23	120 / 6	124 / 8
10	104 / 15	110 / 10	115 / 15	-	-
25	105 / 22	111 / 14	116 / 18	-	-
50	106 / 18	112 / 9	117 / 16	121 / 5	125 / 12
100	107 / 14	113 / 10	118 / 14	122 / 5	126 / 10
150	108 / 11	-	119 / 9	123 / 5	127 / 8

D-2. Chronic neutron exposure with Cf-252 neutrons (CEA-FAR, female Sprague-Dawley rats) or 0.6 MeV accelerator neutrons (IRMM, female Lewis rats), assay at an age of 3 months

Dose rate mGy/d	No of rats	
	Exposure day 12-16 p.c.	Exposure day 16-20 p.c.
CEA Paris		
0	128 / 25	136 / 4
10	129 / 35	137 / 16
17.5	130 / 20	-
25	131 / 15	138 / 17
70	132 / 11	-
IRMM		
0	133 / 26	-
10	134 / 19	-
100	135 / 11	-

10 St. Bartholomew Medical College, London

10.01 Cancer in Mouse Skin Following Alpha Irradiation

Institution: St. Bartholomew Medical College, Radiation Biology Department, London, UK

Scientists: J.E. Coggle; active
S.G. Needham; active

Purpose: To determine the risk of skin cancer from Cm-244 alpha radiation.

Status: 1988- 1993

Treatment: Single exposure to the flank area of the mice from a flat 2x4 cm 3.7 MBq source of Cm-244 (5.8 MeV alpha-rays)

Dosimetry: Calculated and then checked by an extrapolation ionization chamber measurement; surface dose rate 260 Gy/hr

Endpoints: Observation of visible/palpable tumors followed by sacrifice and macroscopic/ microscopic pathology

Animal: Male SAS/4 mice aged 11 weeks at irradiation

Results:

References:

Experimental Groups:

Study 10.01
Cancer in Mouse Skin Following Alpha Irradiation

Group Id	Dose Gy	No Animals	No Tumors	Weeks Incidence
1	0	77	0	-
2	2	99	0	-
3	5	93	1	76
4	10	93	1	108
5	20	92	0	-
6	40	75	2	60,79
7	80	76	0	-
8	120	76	0	-
9	180	84	1	103

10.02 Long-Term Effects of Low Energy Neutrons in Mice and Comparison with X-Rays

Institution: St. Bartholomew Medical College, Radiation Biology Department, London , UK

Scientists: J.E. Coggle; active
S.G. Needham; active

Purpose: To determine the risks mainly of skin cancer and eye changes from 24 keV neutrons in comparison with X-rays

Status: 1988- ongoing

Treatment: Single exposure of the entire body to 2 Gy of 24 keV neutrons (generated by the Pluto research reactor, Harwell, dose rate 2 Gy/hr) and 2 Gy of 320 kVp X-rays (2 Gy/hr)

Dosimetry: Uranium-235 fission chamber

Endpoints: Observation of visible/palpable tumors, eye changes or other pathology requiring sacrifice and macroscopic/microscopic pathology

Animal: Male SAS/4 mice aged 6-7 weeks at irradiation

Results: Under evaluation

References:

Experimental Groups:

Study 10.02
Long-Term Effects of Low Energy Neutrons in Mice and Comparison with X-Rays

Group Id	Radiation	Dose (Gy)	No of mice
1	Control	0	43
2	X-rays	2	50
3	Neutrons	2	80

10.03 Skin Cancer in Different Mouse Strains From Beta-Rays

Institution: St. Bartholomew Medical College, Radiation Biology Department, London, UK

Scientists: J.E. Coggle; active
S.G. Needham; active

Purpose: To determine the different response of various mouse strains to skin cancer from beta-irradiation.

Status: 1986-1990, terminated

Treatment: Single exposure of the flank of mice to 2x4 cm Tm-170 β sources (0.97 MeV)

Dosimetry: Extrapolation ionization chamber, dose rates between 4 and 11 Gy/min

Endpoints: Observation of visible/palpable tumors, followed by sacrifice and macroscopic/ microscopic pathology

Animal: Male SAS/4 mice, CBA/CA, C57BL/6 and CD1 mice aged 11 weeks at irradiation

Results: Under evaluation

References:

Experimental Groups:

Study 10.03
Skin Cancer in Different Mouse Strains From Beta-Rays

Group Id	Dose Gy	Strain	No Mice
1	0	CD1	59
2	12.5	CD1	63
3	25	CD1	63
4	50	CD1	62
5	100	CD1	66
6	0	CBA	61
7	12.5	CBA	58
8	25	CBA	64
9	50	CBA	56
10	100	CBA	64
11	0	C57BL	59
12	12.5	C57BL	63
13	25	C57BL	55
14	50	C57BL	62
15	100	C57BL	63
16	0	SAS	104
17	12.5	SAS	47
18	25	SAS	47
19	50	SAS	48
20	100	SAS	60

10.04 Lung Tumor Induction in Mice After X-Rays and Neutrons

Institution: St. Bartholomew Medical College, Radiation Biology Department, London, UK

Scientist: J.E. Coggle; active

Purpose: To determine the risk and RBE of lung tumors

Status: 1982- 1988

Treatment: Single exposure to the thorax with 200 kV X-rays (0.6 Gy/min) or 7.5 MeV neutrons (obtained from 16 MeV deuterons at a Be target, 3% gamma contamination, 1.06 Gy/min)

Dosimetry: Farmer ionization chamber and Li F thermoluminescent

Endpoints: Sacrifice and macroscopic/ microscopic pathology 12 months post-irradiation, a pilot experiment with groups of 32 three-month old mice sacrificed 3-24 months after thoracic X-ray doses of 0, 1 3 and 5 Gy showed this to be the optimal design.

Animal: Male SAS/4 mice aged 3 months at irradiation

Results: The dose effect curve for X-rays is bell-shaped consisting of a quadratic part and an exponential inactivation term. For neutrons, the curve is linear at low doses, peaks between 1-3 Gy and sharply declines at 4 Gy. The RBE at 1Gy is 7.4 for both males and females combined and 8.6 for females and 4.7 for males separately.

References:

Coggle, J.E. and D.M. Peel. Relative effects of uniform and non-uniform external radiation on the induction of lung tumors in mice, pp. 83-94. *In* IAEA [ed.], *Late Biological Effects of Ionizing Radiation*, Vol. II. IAEA, Vienna, 1978.

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Experimental Groups:

Study 10.04
Lung Tumor Induction in Mice After X-Rays and Neutrons

Dose Gy	Group Id	No ♂ Mice	No ♂ Mice with Tumors	Group Id	No ♀ Mice	No ♀ Mice with Tumors
X-rays						
0	1	291	48	12	210	19
0.25	2	61	12	13	62	7
0.5	3	62	11	14	61	6
1	4	67	13	15	64	8
2	5	56	15	16	63	10
2.5	6	69	23	17		
3	7	32	12	18	60	16
4	8	45	17	19	61	23
5	9	45	22	20	59	21
6	10	48	18	21	60	15
7.5	11	72	16	22	61	9
Neutrons						
0.1	23	60	17	31	57	10
0.25	24	52	17	32	54	13
0.5	25	58	16	33	55	14
0.75	26	55	16	34	61	17
1	27	71	33	35	59	18
2	28	64	27	36	59	20
3	29	69	31	37	61	18
4	30	45	9	38	58	9

10.05 In-Utero Exposure to Plutonium and Resultant Cancer Incidence in CBA/CA Mice

Institution: St. Bartholomew Medical College, Radiation Biology Department, London, UK

Scientist: P.G. Mountford-Lister; active
B.E. Lambert; active

Purpose: To investigate the carcinogenic effect of chronic exposure to plutonium throughout pregnancy with special emphasis on leukaemogenesis.

Status: 1988- 1994

Treatment: Chronic exposure of pregnant female CBA/Ca mice to Pu-239 citrate throughout pregnancy using osmotic pumps for intranvenous infusion

Dosimetry: Concurrent Pu-241 studies and confirmatory sampling of Pu-239 exposed animals to determine concentrations in critical organs. Trapezoidal methods used to calculate dose to tissues. Autoradiographic analysis of tissues sampled during pregnancy.

Endpoints: Lifespan study with sacrifice of moribund animals, necropsy observation and histopathology of macroscopically observed abnormalities, haematological analysis of animals killed in extremis.

Animal: Male and female offspring of exposed pregnant CBA/Ca female mice.

Results: In preparation

References:

Experimental Groups:

Study 10.05
In-Utero Exposure to Plutonium and Resultant Cancer Incidence in CBA/CA Mice

Group Id	Dose Kbq/kg Means± S.E	Range kBq/kg	Total Pregnant Dams	No Litters Born	No Pups Born
1	0	0	60	53	342
2	0	0	46	32	200
3	10.0 ± 0.14	7.9 - 12.1	46	42	306
4	20.0 ± 0.35	12.6 - 23.0	46	34	186
5	38.0 ± 0.97	19.2 - 47.2	42	33	210
6	83.0 ± 1.74	57.2 - 97.3	28	25	148

10.06 Lifespan-Shortening After Exposure of SAS/4 Mice to 15 MeV X-Irradiation

Institution: St. Bartholomew Medical College, Radiation Biology Department, London , UK

Scientist: P.J. Lindop; retired
J. Rotblat; retired

Purpose: To determine lifespan shortening in dependence of dose, age and oxygen tension.

Status: 1955- 1970

Treatment: Single exposure to 15 MeV photons from an accelerator

Dosimetry: Two paralell ionization chambers, one above, the other below, the cage

Endpoints: Lifespan study in some experiments including also necropsy and histopathological analysis. In one study number of oocytes and litter production were also assayed.

Animal: Male and female SAS/4 mice of different age; sexes were pooled in several evaluations.

Results: Dr. P.J. Lindop retired in the early 1980 for health reasons. The reconstruction of the experiments had, therefore, to be done from published information; this was difficult and sometimes unreliable since doses had often to be read from figures. Data on the number of mice in the individual experiments are not available except for the first experiment although it is known that more than 10.000 mice together were used in these experiments. It must also be pointed out that the mice used for life-span observations at higher doses were those which had survived the acute effects.

The most extensive experiments with mice of 4 weeks age covering a wide range of doses showed that lifespan-shortening in this strain of mice is proportional to dose over the range from 50 o 780 r, and amounts to 5.66 ± 0.18 weeks per 100 r or to to 38% of the median life span for a LD50 dose (698 R) There is no difference in sensitivity between sexes. The analysis of causes of death suggested that all causes of death contribute to the shortening of lifespan except for a clear increase in leukemia and a decrease in the high dose groups (>=549 R) of all neoplastic diseases.

Age at time of radiation had a marked effect on lifespan shortening with 7.63, 7.08, 5.77, 5.55 and 2.66 weeks/ 100 R for mice of an age of 1 day, 4 weeks, 8 weeks and 30 weeks respectively. Studies on hypoxic mice, on mice anaesthized and breathing air and on mice breathing oxygen were carried out concurrently. Shortening of lifespan in 4 weeks old mice was essentially independent of dose rate in the range from 77 to 158,000 rads/min regardless whether the mice were under anaesthesia or not.. Mice breathing nitrogen had a lifespan shortening of 1.3 and 0.5 weeks/r for the two older groups. In the younger age groups the survival-time vs dose relationship was no longer linear.

Another study dealing with the Do of oocytes of SAS/4 mice varied between 24 and 58 rad in air and 37-175 rad in nitrogen dependent on cell stage with immature cells (stage 3) being most sensitive). Reproductive lifespan is also shortened corresponding to a Do of 216 rad in air.

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Experimental Groups:

Study 10.06
Lifespan-Shortening After Exposure of SAS/4 Mice to 15 MeV X-Irradiation

Dose (R)	No males /for longevity study	No females /for longevity study	
SAS Mice 4 Weeks			
Control	583 / 420	569 / 434	
50	288 / 235	288 / 236	
98	296 / 248	280 / 233	
198	286 / 227	290 / 230	
350	291 / 246	285 / 241	
457	287 / 208	289 / 223	
549	72 / 55	72 / 48	
620	68 / 30	68 / 33	
703	72 / 38	72 / 33	
780	72 / 11	72 / 18	
Age dependency			
Dose R SAS/4 Mice 1 d old	**Dose R SAS/4 Mice 1 w old**	**Dose R SAS/4 Mice 8 w old**	**Dose R SAS/4 mice 30 w old**
396	202	103	101
500	403	206	203
596	592	412	408
686			
794			
882			

Effect of Hypoxia			
Dose (rad) SAS/4 Mice 1 day old	**Dose (rad) SAS/4 Mice 1 w old**	**Dose (rad) SAS/4 Mice 8 w old**	**Dose (rad) SAS/4 Mice 30 w old**
nitrogen 0	0	0	0
nitrogen 430	411	405	453
air 434	419	405	454
nitrogen 920	878	845	937

Effect of Dose Rate	
rad/min without aenasthesia	**rad/min with anaesthesia**
77	480
480	2,060
1,730	31,700
6,000	162,000
31,000	
158,000	

Oocyte Survival			
SAS/4 Mice age	**Total Number Mice**	**Dose range (rad) air**	**Dose range (rad) nitrogen**
1 day	235	66 - 375	148 - 775
1 week	51	6 - 44	88 and 197
2.5 weeks	156	5 - 74	13 - 210
4 weeks	581	5 - 190	10 - 640
16 weeks	240	11 - 328	21 - 630

11 TNO Organisatie Natuurwetenschappelijk Onderzoek, Centre Radiological Protection and Dosimetry, Rijswijk

11.01 Mammary Cancers in Different Rat Strains After Single Exposure to X-Rays and Fast Neutrons

Institution: RBI- TNO,Rijswijk and Rijksuniversiteit Leiden, the Netherlands

Scientists: J.J. Broerse; retired
D.W. van Bekkum; retired
R. Bartstra; active
C. Zurcher;active

Purpose: To determine the incidence of breast cancer in rats in dependence of strain, radiation quality, hormonal treatment, ovarectomy.

Status: 1974-1991, mostly terminated some still under evaluation, data in ERAD

Treatment: X-rays: 0.06 Gy/min, 300 kV
Mono-energetic neutrons: 0.5, 4.2 or 15 MeV from an accelerator beam, p+T d+D and d+T reactions respectively, 2 mGy/min, 4 mGy/min, 10 mGy/min).
Hormonal treatment: implantation of 2mg oestradiol-17-ß + cholesterol pellets, usually at an age of 7 weeks

A) Effect of estrogen treatment, ovarectomy and both combined on mammary tumors after a single total body exposure to X-rays or 0.5, 4.2 or 15 MeV neutrons in WAG/RIJ rats,
B) Effect of estrogen treatment, ovarectomy and both combined on mammary tumors after a single total body exposure to X-rays or 0.5, 4.2 or 15 MeV neutrons in SD/RIJ rats,
C) Effect of estrogen treatment, ovarectomy and both combined on mammary tumors after a single total body exposure to X-rays or 0.5, 4.2 or 15 MeV neutrons in BN/BI RIJ rats

Dosimetry: Tissue equivalent ionization chambers and Geiger Müller counters

Endpoints: Observation of visible/palpable tumors during the entire life span with macroscopic/microscopic pathology

Animal: Female rats aged usually 8 weeks (with some older groups as indicated).
Strains: WAG/Rij, Brown Norway (BN/BI RIJ), Sprague-Dawley (SD/RIJ)

Results: There are appreciable differences in susceptibility for radiation carcinogenesis in the three rat strains. Hystero-ovarectomy provides an appreciable protective effect for mammary carcinogenesis. The application of hormones resulted in a considerable increase in mammary tumors with a significant tendency to the induction of carcinomas versus fibroadenomas. The dose-effect relations for induction of mammary tumors are linear-quadratic for the X-irradiations and linear for the various neutron beams. The highest RBE values (with a maximum at 15 at a neutron dose of 10 mGy) are observed for the irradiation with 0.5 MeV neutrons.

References: See 11.02

Experimental Groups:

Study 11.01

Mammary Cancers in Different Rat Strains After Single Exposure to X-Rays and Fast Neutrons

A. Effect of estrogen treatment, ovarectomy and both combined on mammary tumors after a single total body exposure to X-rays or 0.5, 4.2 or 15 MeV neutrons in WAG/RIJ rats

		No Treatment		Estrogen		Ovarectomy		Ovarect.+Oestr.	
Radiatino	Dose Gy	Group Id	No rats	Grou p Id	No rats	Group Id	No rats	Group Id	No rats
control	0	1	80	2	40	3	40	4	40
X-rays	0.25	5	40	6	40	7	40	8	40
	1	9	50	10	20	11	18	12	19
	4	13	35	14	20	15	26	16	20
Neutr.0.5 MeV	0.05	17	39	18	40	19	38	29	40
	0.15					21	19		
	0.2	22	49	23	20	24	19	25	20
	0.8	26	20	27	20	28	20	29	20
Neutr.4.2 MeV	0.1	30	40	31	40	32	39	33	40
	0.15							34	40
	0.3	35	50	36	50	37	20		
	0.5							38	19
	1	39	40	40	20	41	20	42	19
	1.5							43	20
Neutr.15 MeV	0.15	44	39	45	40	46	38	47	40
	0.5	48	50	49	20	50	19	51	20
	1.5	52	20	53	20	54	38	55	19

B. Effect of estrogen treatment, ovarectomy and both combined on mammary tumors after a single total body exposure to X-rays or 0.5, 4.2 or 15 MeV neutrons in SD/RIJ rats

		No Treatment		Estrogen		Ovarectomy		Ovarect.+Oestr.	
Radiation	Dose Gy	Group Id	No rats	Group Id	No rats	Group Id	No rats	Group Id	No rats
control	0	56	79	57	40	58	82	59	39
X-rays	0.1	60	40	61	39	62	39	63	40
	0.3	64	49	65	39	66	19	67	20
	1	68	20	69	49	70	19	71	20
	2	72	20	73	18	74	20	75	18
Neutr.0.5 MeV	0.02	76	40	77	40	78	39	79	39
	0.08	80	49	81	20	82	20	83	20
	0.32	84	20	85	20	86	20	87	19

Radiation	Dose Gy	No Treatment		Estrogen		Ovarectomy		Ovarect.+Oestr.	
		Group Id	No rats	Group Id	No rats	Group Id	No rats	Group Id	No rats
Neutr.4.2 MeV	0.04	88	40	89	40	90	40	91	40
	0.05							92	40
	0.12	93	50	94	20	95	18	96	20
	0.4	97	20	98	20	99	20	100	20
	0.5			191	19				
Neutr.15 MeV	0.05	102	40	103	40	104	78	105	39
	0.15	106	50	107	20	108	20	109	19
	0.5	110	20	111	20	112	18	113	19

C. Effect of estrogen treatment, ovarectomy and both combined on mammary tumors after a single total body exposure to X-rays or 0.5, 4.2 or 15 MeV neutrons in BN/BI RIJ rats

Radiation	Dose Gy	No Treatment		Estrogen		Ovarectomy		Ovarect.+Oestr	
		Group Id	No Rats	Group Id	No Rats	Group Id	No Rats	Group Id	No Rats
control	0	114	114	115	40	116	52	117	42
X-rays	0.25	118	37	119	40	120	38	121	40
	1	122	49	123	20	124	20	125	20
	2	126	20					127	19
	4	128	19	129	33	130	30	131	29
Neutron 0.5 MeV	0.005	132	40	133	40	134	40	135	41
	0.02	136	50	137	20	138	20	139	20
	0.05			140	20				
	0.08	141	19	142	20	143	18	144	19
Neutron 4.2 MeV	0.1	145	38	146	40	147	76	148	39
	0.3	149	51	150	20	151	39	152	20
	1	153	20	154	20	155	20	156	20
	1.5							157	17
Neutron 15 MeV	0.15	158	38	159	39	160	38	161	40
	0.5	162	50	163	20	164	19	165	20
	1.5	166	18	167	20	168	19	169	20

11.02 Mammary Cancers in Rats After Fractionated Irradiation with X-Rays, Gamma-Rays, Beta-Rays and Fast Neutrons

Institution: RBI-TNO Rijswijk and Rijksuniversiteit Leiden, the Netherlands

Scientists: J.J. Broerse; retired
D.W. van Bekkum; retired
R. Bartstra, active
C. Zurcher; active

Purpose: To determine the incidence of breast cancer in rats in dependence of strain, radiation quality, fractionation, hormonal treatment.

Status: 1974-1991, mostly terminated some still under evaluation.

Treatment: X-rays: 0.06 Gy/min, 300 kV
Gamma-rays: Cs-137, 0.9 Gy/min single exposure, 1 mGy/min
Mono-energetic neutrons: 0.5, 4.2 or 15 MeV from an accelerator beam, p+T d+D and d+T reactions respectively, 2 mGy/min, 4 mGy/min, 10 mGy/min)
Fractionation code: total fractions/days between fractions
hormonal treatment: implantation of 2mg oestradiol-17ß + cholesterol pellets, usually at an age of 7 weeks,

A) Comparison between X-rays and 0.5 MeV neutrons in WAG/RIJ rats of single and fractionated and 0.4 Gy fractionated (2 modalities) exposure
B) Comparison between X-rays, gamma-rays and 0.5 MeV neutrons in WAG/RIJ rats of single and fractionated (different modalities, 3 for gamma-rays) exposure
C) Comparison of single and fractionated X-ray and neutron exposure in two rat strains
D) Effect of fractionation, oestradiol treatment and oestradiol plus ovarectomy in WAG/RIJ rats after total body irradiation with X-, gamma-rays or neutrons
E) Comparison of three rat strains for different total body radiation qualities and estrogen applications.
F) Single and fractionated total or partial body exposure to X-rays and neutrons in two rat strains

Dosimetry: Tissue equivalent ionization chambers and Geiger Müller counters

Endpoints: Observation of visible/palpable tumors during life span with macroscopic/microscopic pathology.

Animal: Female rats aged usually 8 weeks (with some older groups as indicated).
Strains: WAG/Rij, Brown Norway (BN/BI RIJ), Sprague-Dawley (SD/RIJ)

Results: Emphasis is placed on mammary carcinogenesis after irradiation with gamma rays either at fractionated exposure with fractions doses of 2.5 and 10 mGy or single dose exposures at different age. The relative excess hazards for tumor induction at a total dose of 0.3 Gy are not significantly different from the controls. At higher doses, fractionation does not any longer providea protective effect. The irradiation of older animals has demonstrated a reduction of the susceptibility for mammary carcinogenesis with age.

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Experimental Groups:

Study 11.02
Mammary Cancers in Rats After Fractionated Irradiation with X-Rays, Gamma-Rays, BetaRrays and Fast Neutrons

A. Comparison between X-rays and 0.5 MeV neutrons in WAG/RIJ rats of single and fractionated exposure

	Single			5 fractions 4w interval			5 fractions 2w interval		
Dose Gy Radiation	Group Id	No Rats	Gy	Group Id	No Rats	Gy	Group Id	No Rats	Gy
Control	1	44	0						
X-rays	2	40	2	3	40	4			
0.5 MeV Neutrons	4	40	0.2	5	40	0.3	6	40	0.3

B. Comparison between X-rays, γ-rays and 0.5 MEV neutrons in WAG/RIJ rats of single and fractionated exposure.

	Single Exposure		Fractionated Exposure			Single Expos.+ Oestrad.	
Dose Gy Radiation	Group Id	No Rats	Group Id	No Rats	Schedule	Group Id	No Rats
0 Control	7	100					
0.2 X-rays			8	60	10 fract. 1/m		
1 X-rays			9	60	10 fract. 1/m		
2 X-rays	10	60	11	60	10 fract. 1/m	14	60
			12	58	10 x 2d/w		
			13	60	2 x 5d/w		
4 X-rays						15	20
2 γ-rays	16	40	17	60	10 fract. 1/m		
			18	60	10 x 2d/w		
			19	60	2 x 5d/w		
0.1 Neutron			21	60	5 x 1 fract/2w		
0.2 Neutron	21	60	22	60	10 fract. 1/m		

C. Comparison between single and fractionated (5 days a week for 2 weeks) X-ray and neutron exposure in two rat strains

Dose Gy Radiation	Wag/RIJ				BN/BI RIJ			
	Single Exposure		Fraction.Expos.		Single Exposure		Fraction. Exposure	
	Group Id	No Rats	Group Id	No Rats	Group Id	No Rats	Group Id	No Rats
0 Controls	23	40			24	30		
0.1 Neutron	25	40	26	56	27	40	28	60
0.4 X-rays			29	59			30	60

D. Effect of fractionation (120 fractions 12 d interval), oestradiol treatment and oestradiol +ovarectomy in 4 week old or 17 week (*)WAG/RIJ rats after total body irradiation with X-, gamma-rays or neutrons

Dose Gy Radiation	Fraction Scheme	No other treatment		Estrogen		Ovarect.+ Oestrog.	
		Group Id	No Rats	Group Id	No Rats	Group Id	No Rats
0 Control		31	40	32	40	33	30
0.3 γ-rays	single	34	40	35	40		
		36	40	37	40		
	fract.	38	40	39	40		
1.2 γ-rays	single	40	40	41	40		
		42	40	43	40		
	fract.	44	40	45	40		
0.8 X-rays	single	46	60				
2 X-rays	single	47	40				
1 4.2 MeV Neut.	single					48	90

E. Comparison of three rat strains for different total body radiation qualities and estrogen applications

Dose Gy	Exposure Fraction	Treatment	WAG/RIJ		SD/RIJ		BN/BI RI	
			Group Id	No Rats	Group Id	No Rats	Group Id	No Rats
Control		none	49	60	50	60	51	140
		Oestr.7					52	40
0.025 X-rays	single	none					53	80
0.1 X-rays	single	none					54	80
0.25 X-rays	single	none					55	40
		Oestr.7					56	40

Dose Gy		Exposure Fraction	Treatment	WAG/RIJ		SD/RIJ		BN/BI RI	
				Group Id	No Rats	Group Id	No Rats	Group Id	No Rats
0.4	X-rays	single	none					57	80
		5 fract.	none					58	80
1	X-rays	single	none					59	20
			Oestr.7					60	20
2	X-rays	single	none	61	40	62	40		
			Oestr.7	63	40	64	40		
			Oestr.12	65	40	66	40		
			Oestr.20	67	38	68	40		
			Oestr.32	69	40	70	40		
		10 fract.	none	71	40	72	40		
			Oestr.1	73	40	74	40		
4	X-rays	single	none					75	20
			Oestr.7					76	20
		10 fract.	none	77	40	78	40		
1	γ- rays	single	none	79	19				
			Oestr.0	80	2				
2	γ- rays	single	none	81	7				
0.005	Neutron 0.5 MeV	single	none					82	80
0.02	Neutron 0.5 MeV	single	none					83	80
0.05	Neutron 0.5 MeV	single	none					84	120
			Oestr.7					85	40
0.1	Neutron 0.5 MeV	5 fract.	none					86	80
0.2	Neutron 0.5 MeV	single	none					87	20
			Oestr.7					88	20
0.075	Neutron 15 MeV	single	none					89	20
0.15	Neutron 15 MeV	single	none					90	38
			Oestr.7					91	39
0.5	Neutron 15 MeV	single	none	92	40	93	39	94	20
			Oestr.7					95	21
1.5	Neutron 15 MeV	single	none					96	20
			Oestr.7					97	20

fractionation schedule: exposure once per week; oestr.# :estrogen implantation at an age of # weeks

F. Single and fractionated total or partial body exposure to X-rays and neutrons in two rat strains

Radiation Dose Gy		Rat Strain	Single Exposure				Fractionated Exposure			
			Total-Body		Partial-Body		Total-Body		Partial-Body	
			Group Id	No rats	Group Id	No Rats	Group Id	No Rats	Group Id	No Rats
0	Control	WAG/RIJ	98	100						
		BN/BIRIJ	99	84						
0.02	X-rays	BN/BIRIJ	100	60	101	59				
0.08	X-rays	WAG/RIJ	102	60	103	59				
		BN/BIRIJ	104	60	105	60				
0.1	X-rays	WAG/RIJ							106	68
		BN/BIRIJ							107	60
0.4	X-rays	WAG/RIJ	108	60	109	60	110	60	111	60
		BN/BIRIJ	112	60	113	60	114	60	115	60
1.6	X-rays	WAG/RIJ	116	60	117	36	118	60		
		BN/BIRIJ	119	39	120	40	121	60		
2	X-rays	WAG/RIJ							122	60
		BN/BIRIJ							123	56
0.4	β-rays	WAG/RIJ			124	60				
		BN/BIRIJ			125	60				
0.6	β-rays	BN/RIBIJ			126	1				
1.6	β-rays	WAG/RIJ			127	40				
		BN/RIBIJ	128	1	129	19				
0.04	Neutrons 0.5 MeV	WAG/RIJ	130	62						
		BN/BIRIJ	131	84						
0.08	Neutrons 0.5 MeV	WAG/RIJ					132	60		
0.2	Neutrons 0.5 MeV	WAG/RIJ	133	58						
		BN/BIRIJ	134	57						

fractionation schedules: total body exposure 5d a week for 4 weeks, partial body exposure 10 fractions at 4 w interval, neutrons 5 fractions at 2 d interval

11.03 Life-Span Study on Monkeys Exposed to X-, Gamma- Or Neutron Irradiation with and without Bone Marrow Transplantation and Other Treatments

Institution: TNO MBL, Rijswijk, Rijksuniversiteit Leiden, the Netherlands

Scientists: D.W. van Bekkum; retired
J. Broerse; retired
C. Zurcher; active

Purpose: To determine long-term radiation risks from X-rays, gamma-rays and neutrons in a primate model.

Status: 1964- ongoing

Treatment: X-rays 300 kV 3mm Cu HVL, 0.36 Gy/min, gamma-rays from a linear accelerator 6 (8) MeV 0.56 Gy/min, fractions 24 hr interval, neutrons from a low flux reactor 0.08 Gy/min
Three experimental series respectively 1973-1978, 1978-1981, 1988-1990

Dosimetry: Tissue equivalent ionization chamber

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology, biochemical, haematological analysis, blood pressure measurements, cataract formation at different times after irradiation.

Animal: Rhesus monkeys (Macacca mulatta), at least 2-3 year old, weight 2-3 kg at the start of the experiment

Results: After exposure to high doses of X-rays (average dose 6.7 Gy) and fission neutrons (average dose 3.4 Gy), an appreciable number of malignancies (approximately 70% of all cases) has been observed after latency periods of many years (up to 18 years). The long-term surviving monkeys are kept under continuous observation and are presently screened for the occurrence of deterministic effects such as cararact, and hepatic and renal function.

References:

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Experimental Groups:

Study 11.03
Life-Span Study on Monkeys Exposed to X-, Gamma- or Neutron Irradiation with and without Bone Marrow Transplantation and Other Treatments

Group Id	Treatm.	Series	Gy	No Animals	Remarks
1	Control	1st	0	21	
2		2nd	0	3	
3		3rd	0	3	
4	X-rays	1st	4 - 9	20	0 long-term survivors from 13 untreated and 3 from 21 ABMT grafted monkeys
5		2nd	≈8.5	7	allBMT, 1 animal fraction.exposure
6		3rd	4	2	GF
7			5	12	4 untreated, 2 GM CSF, 3 GF, 3 IL-3
8			5	12	4 untreated, 4 GF, 4 GM-CSF, 2 IL-3
9			8	1	BMT
10			8.5	1	BMT
11			2x5	5	1 ABMT, 4 ABMT + GT
12	γ-rays	3rd	4	2	2 untreated
13			5	9	5 GM-CSF, 4 GF
14			6	3	1 untreat., 1 GM-SCF, 1 GF
15			7	1	GF
16			8	3	GM-CSF
17			8.5	5	1 IL-3, 2 BMT, 2 BMT+GF
18			9.5	1	BMT
19			2*6	3	1 untreat., 1 BMT, 1 ABMT*
20			2*6.8	3	ABMT+GT* (1 with 8 MeV γ)
21	Neutrons	1st	2.6- 4.1	9	long-term survivors from 15 untreated and 15 ABMT grafted monkeys

BMT	bone marrow transplantation,
allBMT	allogenic bone marrow transplantation
ABMT	autologous bone marrow transplantation
IL-3	treatment with rhesus monkey interleukin,
GM-SCF	treatment with human granulocyte macrophage colony-stimulating factor
GF	treatment with granulocyte colony-stimulating factor
GT	treatment with IL-3 gene transfer
*	partial lung shielding

11.04 Lung Cancer in Rats After Exposure to Radon and/or Acetaldehyde

Institution: RBI-TNO, Rijswijk, the Netherlands

Scientists: D.W. van Bekkum; retired
R.W. Bartstra, active
P.J.N. Meynders, active
J.S. Groer, active

Purpose: To determine the risk from radon alone or in combination with a chemical irritant.

Status: 1989- ongoing

Treatment: Radon inhalation at 1000 WL for 8 h/d 2-3 days per week (≈ 150 WLM/w), acetaldehyde exposure starting 1 week after termination of radon exposure at 1500 or 3000 ppm for 8 h/d 5 days per week (8 weeks total at 3000 ppm, 16 weeks total at 1500 ppm ,ie the same total dose)
In addition, an intercomparison experiment has been carried out by TNO and CEA, France. Rats from TNO (75 males and 75 females, 1-12 months of age) have been exposed at CEA to 1000 WLM at a rate of 1000 WL and were transported back again to TNO for lifespan observation.

Dosimetry: Thomas measurements of WL, Pb-214 measurements in lung of a "test" rat sacrificed after exposure

Endpoints: Life-span study (spontaneous death) with macroscopic/microscopic pathology

Animal: Male Sprague-Dawley rats aged 5-10 weeks

Results: In the group exposed to 200 WLM without additional acetaldehyde treatment 10% malignant lung tumor were found. The result from all other radon groups were obscured by severe lifespan shortening which was more pronounced at higher doses of both, radon and acetaldehyde. Kaplan-Meier correction for the phenomenon on the results of the group exposed to 800 WLM without aldehyde (2 tumors in 36 animals) resulted in a relative risk of 2 +/- 2 as compared to the group exposed to 200 WLM. The group exposed to 200 WLM with additional 1500 ppm acetaldehyde displayed no enhanced effect compared to the former (200 WLM without acetaldehyde) group. The reason for the observed lifespan shortening has not yet been clarified. In the intercomparison experiment, no lifespan shortening has been observed; tumor data are not yet available.

References: Bartstra, R.W., J.S. Groer and D.W. van Bekkum. Deterministic effects after radon exposure. *Int. J. Radiat. Biol.* **62**:363, 1992.

Experimental Groups:

Study 11.04
Lung Cancer in Rats After Exposure to Radon and/or Acetaldehyde

Radon WLM	Acetaldehyde 0 ppm		Acetaldehyde 1500 ppm		Acetaldehyde 3000 ppm	
	Group Id	No rats	Group Id	No rats	Group Id	No rats
0	1	130	5	40	8	60
200	2	80	6	40	9	40
800	3	40	7	40	10	60
1600	4	40				
Intercomparison TNO/CEA						
1000	11	75				
1000	12	75				

12 Universität Freiburg, Institut für Biophysik und Strahlenbiologie

12.01 Neuronal Alignment in Pre-Adult Mice Following Prenatal X-Irradiation

Institution: Universität Freiburg, Institut für Biophysik und Strahlenbiologie, Freiburg, FRG

Scientist: G. Konermann; active

Purpose: To determine the consequences on the adult mouse brain of a prenatal X-ray exposure.

Status: 1989-1990, similar work continuing

Treatment: Single 250 kV X-ray exposure (HWD 2 mm Cu, 0.5 Gy/min) of the pregnant mothers on day 12-18 post conception, sacrifice by decapitation under ether anaesthesia on post-irradiation day 31 (50 days p.c.).

Dosimetry: Monitored with an ionization chamber in the radiation exposure cage; energy doses assessed with a mouse phantom filled with a Fricke dosimeter (Fe SO_4)

Endpoints: Image analysis of neuronal structures; alignment quotients were computed from the ratios of points of intersection between video lines and neuronal processes at maximal crossing or parallel position.

Animal: Pregnant albino mice "Heiligenberg"

Results: Exposure to X-rays causes reduction in brain weight, disalignment of the neuronal processes in the Va cortex layer and decrease in size of different cortical areas and the corpuis callosum. The effects were most marked in animals exposed at an age of 12 days p.c. (effects could be detected after 120 mGy) and decreased for exposure at later times (effects were detectable after 250 mGy delivered on day 13 p.c., and after 500 mGy at later times). Dose rate effectiveness factors (DREF) were studied after exposure on day 13 using dose rates of 0.8 and 5 mGy/min and were compared to the standard dose rate of 500 mGy/min. DREFs for a 15% brain weight loss were 1.2 for 0.8 mGy/min and 2.0 at 0.8 mGy/min. For a 10% decrease in cortical diameter, these DREFs were respectively 1,6 and 1.8. DREFs were not significant for the changes observed in the corpus callosum and in neuronal alignment.

References:

Konermann, G. Postnatal brain maturation damage induced by prenatal irradiation: Modes of effect, manifestation and dose-response relations, pp. 364-376. *In* K.F. Baverstock and J. Stather [eds.], *Low Dose Radiation: Biological Bases of Risk Assessment.* Taylor and Francis, London, 1989.

Experimental Groups:

Study 12.01
Neuronal Alignment in Pre-Adult Mice Following Prenatal X-Irradiation

Dose mGy	Group Id / No of mice						
	Day 12 pc	Day 13 pc	Day 14 pc	Day 15 pc	Day 16 pc	Day 17 pc	Day 18 pc
0	1 / 19	2 / 19	3 / 19	4 / 19	5 / 19	6 / 19	7 / 19
30	8 / 17	9 / 18	-	-	-	-	-
60	10 / 20	11 / 20	-	-	-	-	-
120	12 / 20	13 / 20	14 / 18	15 / 19	16 / 18	17 / 18	18 / 19
250	19 / 17	20 / 20	21 / 1 8	22 / 20	23 / 15	24 / 18	25 / 19
500	26 / 19	27 / 19	28 / 14	29 / 19	30 / 19	31 / 17	32 / 20
1000	33 / 20	34 / 20	35 / 19	36 / 20	37 / 19	38 / 18	39 / 16
2000	-	-	-	40 / 20	41 / 18	42 / 20	43 / 19

13 Agricultural University, Department of Pathology, Uppsala; National Defense Research Institute Sundbyberg

These studies were carried out at Sundbyberg until 1981, later they were transferred to the University of Uppsala after a temporary stay at the University of Stockholm. The research team, however, remained the same.

13.01 Late Effects of Sr-90 and Am-241 and Metabolism of Some Alkaline Earths and Actinides in Adult CBA Mice

Institution: National Defense Research Institute, Divis. Radiobiology, Sundbyberg, Sweden

Scientist: A. Nilsson; retired

Purpose: To determine the incidence of osteosarcomas, their morpho-pathogenesis and type, and to study the occurrence and type of blood cell disorders in relation to the distribution of alkaline earths in the body of mice.

Status: 1962- 1980.

Treatment: Intraperitoneal injection of Sr-90 nitrate or Am-241 citrate (as well as other radionuclides as indicated under G)

A) Development and histogenesis of osteosarcoma following injection of Sr-90 to male mice,
B) Study of early phases of carcinogenesis following injection of Sr-90, first experiment by serial sacrifice of 5 male mice each at 6, 12, 24 h, 2, 3, 8,16 days and thereafter at monthly intervals following injection of 24.8 kBq/g Sr-90 (not shown as separate table); second experiment see table
C) Dose effect relationship of carcinogenesis following injection of Sr-90 in male mice,
D) Effect of age on Sr-90-induced carcinogenesis
E) Influence of gestation and lactation; injection of 25.6 kBq/g of Sr-90 to 100 females which were mated 2 days after injection and then whenever weaning was terminated up to a period of 224 days after injection.
F) Metabolism and carcinogenesis of Am-241 citrate
G) Studies on metabolism of actinides and alkaline earths i.v. injection of CBA or NMRI mice (either males 25-30 g, or females c. 40 g in late gestation with 18.5 Mbq of Ba-133 (for whole body autoradiography) or of Ba-140 in equilibrium with La-140 for impulse counting. Similar studies were carried out with Sr-85 and Sr-90/Y-90 (in equilibrium) in comparison to Ru-106 and Cs-137 as well as with Am-241. These studies are not presented in tables

Dosimetry: Activity administered

Endpoints: Life-span study, sacrificed when moribund or when tumor detected, macroscopic and microscopic pathology and blood cell analysis, also groups subject to serial sacrifice.

Animal: CBA or NMRI mice about 70 days old unless otherwise indicated

Results: A - C) Serial histogenetic studies showed an increase in osteoblasts and osteoclasts and later of fibers prior to the appearance of osteosarcoma buds 4-6 months after exposure to c. 25 kBq/g of Sr-90
The latency period was shortened and the incidence of bone tumors increased in dependence of dose. Even at the lowest dose (7.4 kBq/g) 4.9% osteosarcoma were observed. The bone marrow showed an early dose-dependent aplasia with recovery at later times. Beside osteosarcomas and haemopoietic lymphoid tumors, carcinomas of the external ear and the mucous membranes of the head also showed an increase in frequency
With respect to age, incidence of osteosarcoma was highest in the group injected at an age of 75 day and lower in the other two groups. The incidence of lymphoreticular tumor was inversely related to dose (highest at the lowest dose) and not dependent on age.

Gestation and lactation delayed and reduced the appearance of osteosarcoma apparently in relation to the decreased retention of Sr-90 during lactation

F) The two highest doses of Am-241 caused extensive damage to haemopoietic tissues, testes and bone. The highest frequency of skeleton (27%) and haemopoietic tumors were observed in the group receiving 296 Bq/g of Am-241. Animals receiving 592 Bq/g died too early to develop tumors. Even after a dose of 1.185 Bq/g life span was slightly shortened and degenerative lesions seemed to appear earlier and at a higher frequency.from

G) The distribution of Ba ressembles that of Sr but Ba is less rapidly incorporated into bone and more remains in soft tissues. Most marked uptake in soft tissues occurred in the pigmented tissues of the eye and in hair follicles.. With respect to its uptake by the eye and causing damage in the tapetum, choroid and iris, Ba-140 ressembles more Ra than Sr.

References:

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Experimental Groups:

Study 13.01

Late Effects of Sr-90 and Am-241 and Metabolism of Some Alkaline Earths and Actinides in Adult CBA Mice

A. Development and histogenesis of osteosarcoma following injection of Sr-90,.

Group Id	kBq/g of ^{90}Sr administered	No of animals
1	0 Controls	125
2	25	200

B. Early phases of carcinogenesis following Sr-90 injection (second experiment)

kBq/g	Days after injection Group Id / No of mice										
	200	215	230	245	260	275	290	305	320	335	350
29.6	3/5	4/5	5/5	6/5	7/5	8/5	9/5	10/5	11/5	12/5	13/5

C. Dose effect relationship of carcinogenesis following injection of Sr-90

Group Id	kBq/g of ^{90}Sr administered	Total No mice for tumor/haematology	No Sacrificed for tumor/haematology (last sacrifice at day)
14	0	95 \ 20	94 \ 50 (570 \ 300)
15	7.4	122 \ 20	103 \ 20 (540 \ 60)
16	14.8	122 \ 50	95 \ 50 (480 \ 300)
17	29.6	121 \ 20	75 \ 20 (360 \ 60)
18	59.2	120	65 (300)

D. Effect of age on Sr-90 induced carcinogenesis

kBq/g of ^{90}Sr administered	Group Id	Age at injection	No of animals
7.4	19	25	50
	20	75	47
	21	150	48
	22	300	50
14.8	23	25	50
	24	75	49
	25	150	49
	26	300	49
29.6	27	25	49
	28	75	47
	29	150	49
	30	300	50

E. Influence of gestation and lactation on Sr-90 induced carcinogenesis

Group Id	kBq/g of ^{90}Sr administered	No of animals
31	0	100
32	1.185	100
33	3.7	100
34	7.4	100
35	14.8	100

F. Metabolism and carcinogenesis of Am-241 citrate

Group Id	Bq/g ^{241}Am	Treatment	No of mice
36	0	Life-span study	50
37	1.48	Life-span study	51
38	7.4	Life-span study	48
39	14.8	Life-span study	40
40	296	Life-span study	100
41	592	Life-span study	40
42	592	Serial sacrifice up to 9 month	25

13.02 The Influence of Sex and Genetic Background on Late Effects from Sr-90

Institution: Swedish University of Agricultural Sciences, Dep. of Pathology, Uppsala, Sweden

Scientists: A. Nilsson; retired
P. Bierke; active

Purpose: To study the effect of a standardised Sr-90 dose on osteosarcoma incidence, type of early bone lesions and morpho-pathogenesis of intra-osseous early tumor "buds", as well as the variation of histological tumor types in different mouse strains and sexes. In addition, the incidence and type of lympho-reticular tumors were investigated.

Status: 1976 ,terminated , data in ERAD

Treatment: Intraperitoneal injection of Sr-90 nitrate

Dosimetry: Activity administered

Endpoints: Life-span study, sacrificed when moribund for macroscopic and microscopic pathology and blood cell analysis

Animal: Male and female mice of the CBA, C57Bl, BALB/c, Swiss Albino and F1 offspring of some of these strains aged 75 ± 5 days

Results: Significant differences are found between strains with Swiss mice (both sexes controls and Sr-treated) dying earliest but have few leukemias. The sensitivity of the different strains towards inductio of osteosarcoma increases in the following order: males CBA≈ C57> BALB; females CBA ≈C57 > BALB. For the F1 generation the order of sensitivity is: male CBA ≈CBAxC57> CBAxBALB >CBAxSwiss; females have all about the sensitivity except for the more sensitive CBAxSwiss . In general males have a shorter survival than females but are more resistant to the induction of osteosarcoma.

References: in preparation

Experimental Groups:

Study 13.02
The Influence of Sex and Genetic Background on Late Effects from Sr-90

Strain	Group Id / No of mice			
	Controls ♂	Controls ♀	11.1 KBq/g ♂	11.1 KBq/g ♀
CBA	1 / 54	2 / 52	3 / 51	4 / 49
C57Bl	5 / 50	6 / 52	7 / 51	8 / 52
BALB/c	9 / 60	10 / 60	11 / 51	12 / 49
Swiss Albino	13 / 13	14 / 170	15 / 25	16 / 34
F1 CBA x C57/Bl	17 / 53	18 / 50	19 / 51	20 / 52
F1 CBA x BALB/c	21 / 52	22 / 47	23 / 50	24 / 54
F1 CBA x Sw.alb.	25 / 64	26 / 55	27 / 57	28 / 51

13.03 Acute and Chronic Effects in Mice Exposed to Brief or Protracted Irradiation with 14-MeV Neutrons

Institution: National Defense Research Institute, Divis. Radiobiology, Sundbyberg, Sweden
Swedish University of Agricultural Sciences, Dep. of Pathology, Uppsala, Sweden

Scientist: A. Nilsson; retired

Purpose: To study the deleterious effects of neutrons and compare acute and protracted irradiation.

Status: 1970, terminated

Treatment: Acute or protracted exposure to fission neutrons from a reactor

Dosimetry: Carried out by the physicists at the National Defense Research Institut

Endpoints: Serial sacrifice and life-span study, with sacrifice when moribund for macroscopic and microscopic pathology and blood cell

Animal: Male mice of the CBA/S strain of 75 days of age

Results: Not fully published

References: Lüning, K.G., C. Rönnbäck and W. Sheridan. Genetic effects of acute and chronic irradiation with 14 MeV neutrons. *Acta Radiol.* **14**:401-415, 1975.

Experimental Groups:

Study 13.03
Acute and Chronic Effects in Mice Exposed to Brief or Protracted Irradiation with 14-MeV Neutrons

Dose and Exposure	Serial sacrifice days Group Id / *No of mice* Group	Lifespan study *No mice*
0	10d 30d 90d 1 / 5 2 / 5 3 / 5	4 / 76
Acute 0.65 Gy/h 0.75 Gy		5 / 29
1.5 Gy	3d 10d 20d 30d 45d 60d 90d 6 / 5 7 / 5 8 / 5 9 /5 10 / 5 11/ 5 12 / 5	13 / 55
2.5 Gy	3d 10d 20d 30d 45d 60d 90d 14 / 5 15 / 5 16 / 5 17 / 5 18 / 5 19 / 5 20 / 5	21 / 72
0 Gy	10d 60d 90d 210d 22 / 5 23 / 5 24 /5 25 / 5	
Protr. 8h/d 5d/w 2.5 Gy	3d 10d 21d 30d 45d 60d 90d 150d 210d 270d 26/ 5 27/ 5 28/5 29/5 30/ 5 31 /5 32 /5 33 /5 34/ 5 35 /5	

13.04 Fractionated X-ray Irradiation of Mouse Fetuses at Different Times After Conception

Institution: National Defense Research Institute, Divis. Radiobiology, Sundbyberg, Sweden
Swedish University of Agricultural Sciences, Dep. of Pathology, Uppsala, Sweden;

Scientist: A. Nilsson; retired

Purpose: To determine acute and late carcinogenic effects after irradiation in utero of the fetal ovary

Status: 1978, terminated

Treatment: Whole-body X-irradiation 260 kV, 0.47 Gy/min

Dosimetry: Ionization chamber

Endpoints: Life-span study, sacrificed when moribund, macroscopic and microscopic pathology and blood cell analysis.

Animal: Pregnant C57BL/S mice 75 ± 3 days old

Results: To be published

References:

Experimental Groups:

Study 13.04
Fractionated X-ray Irradiation of Mouse Fetuses at Different Times After Conception

Total dose Gy	Group Id	Days of exposure Group Id / *Doses (Gy)*	No Mice
0 (control)	1	*0 (control)*	
1.68	2	6 8 10 12 *0.7 0.4 0.26 0.34*	35
2.3	3	14.5 16.5 18.5 20 *0.5* 0.7 1.1 1.2	20
2.7	4	7 11 15 20 *0.72 0.22 0.56 1.2*	15

13.05 Effect of Sr-90 and X-rays on the Ovaries of Fetal Mice Following Administration at Different Times of Pregnancy

Institution: National Defense Research Institute, Divis. Radiobiology, Sundbyberg, Sweden
Swedish University of Agricultural Sciences, Dep. of Pathology, Uppsala, Sweden

Scientist: C. Rönnbäck; retired
B. Henricson,
A. Nilsson; retired

Purpose: To determine whether contamination of the dam with Sr-90 causes injury to the fetal ovary and compare the results with those due to X-rays.

Status: 1968- 1977-1978, terminated

Treatment: Intravenous injection of pregnant females with Sr-90 nitrate at different times of pregnancy;
A) Effect of age following a dose of 740 kBq/g delivered day 11 or 16 p.c.
B) Effect of age following a dose of 370 kBq/g delivered at day 8, 11, 13, 16 or 19 p.c.
C) Effect of dose of Sr-90 delivered on day 11 p.c., some animals also kept for fertility studies (see also study 13.08).
D) Effect dose of Sr-90 delivered on day 19 p.c.
E) Effect of 20 or 80 R of X-rays (260 kV 75 R/min) delivered on day 11p.c.

Dosimetry: Activity administered, ionization chamber

Endpoints: Microscopy of the ovary of the F1 females at different ages (number of germ cells in 9 different stages and follicles)

Animal: Female timed pregnant CBA/S mice (70-75 days old)

Results: A-D) ooocytes I to II were reduced to about 50% of controls after 740 kBq/g and the effect was more pronounced at 16 days p.c. than at 11 days. The number of growing or Graafian follicles was reduced although not to the same extent as that of oocytes.The most sensitive germ cell stage were the naked oocytes. The reduction in number of germ cells after Sr-90 treatment increased with dose and, for a given dose as the mouse approached the end of pregnancy. The reduction in the number of female germ cells correlated with the log of the Sr-90 dose with a significant reduction occurring already after 11.1 kBq of Sr-90, and the effect was most pronounced when Sr-90 was given on day 19 p.c. No significant difference seemed to occur in the reduction with age of germ cells between controls and Sr-exposed animals.
E) the decrease in oocytes was, depending on the X-ray dose, 20 and 45 % compared to controls. Reduction was less severe when assayed at an age of 56 days suggesting a repair process.

References:

Henricson, B. and A. Nilsson. Effects of radiostrontium on oocytes and follicles of adult mice. *Acta Radiol. Ther. Phys. Biol.* **4**:296-304, 1965.

Nilsson, A. and B. Henricson. The effect of ^{90}Sr on the ovaries of the fetal mouse, pp. 313-324. *In* M.R. Sikov and D.D. Mahlum [eds.], Ninth Annual Hanford Symposium: *Radiation Biology of the Fetal and Juvenile Mammal.* Batelle Memorial Institute, Richland WA, 1969.

Henricson, B. and A. Nilsson. Roentgen ray effects on the ovaries of fetal mice. *Acta Radiol. Ther. Phys. Biol.* **9**:443-448, 1970.

Rönnbäck, C., B. Henricson and A. Nilsson. Effect of different doses of ^{90}Sr on the ovaries of the fetal mouse. *Acta Radiol.*(Suppl. **310**):200-209, 1971.

Rönnbäck, C. Effect of ^{90}Sr on ovaries of fetal mice depending on time for administration during pregnancy. *Acta Radiol. Oncol.* **18**:225-233, 1978.

Experimental Groups:

Study 13.05

Effect of Sr-90 and X-rays on the Ovaries of Fetal Mice Following Administration At Different Times of Pregnancy

A. Effect of age following a dose of 740 kBq/g

Dose kBq/g (days post coitum)	Group Id / No of F1 mice assayed at days of age			
	2	14	28	56
Control (11)	1 / 5	2 / 5	3 / 5	4 / 5
Control (16)	-	-	5 / 5	-
740 kBq/g (11)	6 / 5	7 / 5	8 / 5	9 / 5
740 kBq/g (16)	-	-	10 / 8	-

B. Effect of age following a dose of 370 kBq/g

Time admin. 370 kBq/g (days post coitum)	Group Id / F1 mice assayed day 25	56	86
Controls	11 / 5	12 / 5	13 / 5
8	14 / 5	15 / 5	16 / 5
11	17 / 5	11 / 5	19 / 5
13	20 / 5	21 / 5	22 / 5
16	23 / 5	24 / 5	25 / 5
19	26 / 5	27 / 5	28 / 5

C. Effect of Sr-90 dose delivered on day 11 p.c., \ some animals also kept for fertility studies

kBq ^{90}Sr injected per dam	Group Id Mice assayed at an age of 56	170
0	29 / 5	30 / 29
175	31 / 5	32 / 26
370	33 / 5	34 / 19
740	35 / 5	36 / 19

D. Effect of Sr-90 dose delivered on day 19

kBq ^{90}Sr injected per dam	Group Id / Fetal mice assayed day 25	56	86
0	37 / 5	38 / 5	-
11.1 *	39 / 5	40 / 5	-
22.3 *	41 / 5	42 / 5	43 / 5
46.3 *	44 / 4	45 / 5	46 / 5
46.3 **	47 / 4	48 / 4	49 / 5
92.5 **	50 / 5	51 / 5	52 / 5
185. **	53 / 5	54 / 5	55 / 5
370. **	56 / 5	57 / 5	58 / 5

* 1st experimental series, ** 2nd experimental series. The remaining mice from the litters were kept for the lifetime study

E. Effect of X-rays delivered on day 11p.c.

X-ray dose R	Group Id / No of F1 mice assayed on day	
	28	56
0	59 / 5	60 / 5
20	61 / 5	62 / 5
80	63 / 5	64 / 5

13.06 Effect of Sr-90 on Male and Female Germ Cells of Adult CBA Mice

Institution: National Defense Research Institute, Divis. Radiobiology, Sundbyberg, Sweden

Scientists: A. Nilsson; retired
B. Henricson

Purpose: To study the effects of Sr-90 in comparison to X-rays on different male and female germ cell stages in adult mice.

Status: 1965-1967, terminated

Treatment: Intravenous. injection of mice with Sr-90 nitrate or X-irradiation (260 kV, 85 R/min) (male mice)

Dosimetry: Activity injected, ionization chamber

Endpoints: Male animals sacrificed 10 days after treatment, scoring of different stages of spermatogonia and primary spermatocytes and of Sertoli cells.
Female mice sacrificed at intervals of 7 days, scoring of oocyte stages and follicles.

Animal: Male and female CBA mice (aged ≈75 days)

Results: The LD50 of spermatogonia A is 12-25 R if the cells have to pass several spermatogonial divisions before scoring and 26 kBq/g Sr-90 corresponds to about 12 R. If cells are scored earlier sensitivity is lower and the effects in the range 12-50 R are similar. The effects between 3.7 and 51.8 kBq Sr-90 show a linear dose-dependency .
The predominating effect observed in females was an accelerated progression of oocytes to follicles and from those into later follicular stages. A lethal effect on young oocytes is suggested by the observations but could not be quantitatized.

References:
Henricson, B. and A. Nilsson. Effects of radiostrontium on oocytes and follicles of adult mice. *Acta Radiol. Ther. Phys. Biol.* 4:296-304, 1965.

Henricson, B. and A. Nilsson. Effects of radiostrontium and Roentgen rays on germ cells of male mice. *Acta Radiol. Ther. Phys. Biol.* 6:209-213, 1967.

Experimental Groups:

Study 13.06
Effect of Sr-90 on Male and Female Germ Cells of Adult CBA Mice
A. Male mice

Group Id	Dose	No of animals
X-rays R		
1	0	5
2	12	5
3	25	5
4	50	5
5	100	5
Sr-90 kBq/g		
6	3.7	5
7	11.1	5
8	18.5	5
9	25.9	5
10	51.8	5

B. Female mice

Group Id	Interval to sacrifice after injection of 25.9 kBq/g Sr-90	No of treated animals	No of controls
11	7	5	5
12	14	5	5
13	21	5	5
14	35	5	5
15	42	5	5
16	56	5	5

13.07 Influence of Sr-90-Contaminated Milk on the Ovaries of Fetal and Young Mice

Institution: National Defense Research Institute, Divis. Radiobiology, Sundbyberg, Sweden
Swedish University of Agricultural Sciences, Dep. Pathology, Uppsala, Sweden

Scientist: C. Rönnbäck; retired

Purpose: To study the risk to the fetal ovary of Sr-90 contamination transmitted from the dam mainly via the milk.

Status: 1980-1981, terminated

Treatment: Intravenous injection of pregnant females (group B and D) with 185 kBq of Sr-90 nitrate per animal on day 19 of pregnancy.

Dosimetry: Activity injected

Endpoints: Microscopic analysis of the ovary from F1 females at an age of 56 days

Animal: Female CBA/S mice (75-85 days old)

Results: Young female mice contaminated in utero that suckled contaminated milk showed a reduction (27.6%) in germ cells compared to controls. Injury was less marked (27.6%) when the contaminated mice were given non-contaminated milk. Mice which only received contamined milk had their germ cells reduced to 85.9% of controls. The effect was most marked in the younger oocytes.

References: Rönnbäck, C. Influence of ^{90}Sr contaminated milk on the ovaries of fetal and young mice. *Acta Radiol. Oncol.* 20:131-135, 1981

Experimental Groups:

Study 13.07
Influence of Sr-90-Contaminated Milk on the Ovaries of Fetal and Young Mice

Group Id	Treatment	No mothers (No F1)
1	A) Control	6 (7)
2	B) Exposed in utero, milk non-contaminated by exchange to foster mothers group C	6 (15)
3	C) Non-exposed in utero, exposed to contaminated milk from mothers of group B	6 (7)
4	D) Exposed in utero and during lactation	5 (4)

13.08 Disturbances of Fertility of Female Mice After Exposure to Sr-90 During the Fetal Period

Institution: National Defense Research Institute, Divis. Radiobiology, Sundbyberg, Sweden
Swedish University of Agricultural Sciences, Dep. of Pathology, Uppsala, Sweden

Scientist: C. Rönnbäck; retired

Purpose: To assess reproductive performance after application of different amounts of Sr-90 given at the end of pregnancy .

Status: 1981, terminated

Treatment: Intravenous injection of pregnant females with Sr-90 nitrate on day 19 of gestation

Dosimetry: Activity injected

Endpoints: Reproductive performance (number of litters and litter size) for at least 7 months, life-span and macro/microscopic pathology

Animal: Female CBA/S mice (80 ± 3 days old)

Results: Reproductive performance, ie littersize adnumber of litters when mated from day 80, was not affected at Sr-90 doses below 370 kBq per dam although microscopic examinatio revealed reduced germ cell numbers (by about one third) already after 46.3 kBq. Females exposed through their mothers to 370 kBq showed a slight reduction in litter size whereas those exposed to 740 kBq could only produce one single litter of reduced size.

References: Rönnbäck, C., B. Henricson and A. Nilsson. Effect of different doses of ^{90}Sr on the ovaries of the fetal mouse. *Acta Radiol.*(Suppl. **310**):200-209, 1971.

Rönnbäck, C. Disturbances of fertility in female mice ^{90}Sr contaminated as fetuses. *Acta Radiol. Oncol.* **20**:337-343, 1981.

Experimental Groups:

Study 13.08
Disturbances of Fertility of Female Mice After Exposure to Sr-90 During the Fetal Period

Group Id	kBq ^{90}Sr injected	No dams injected	No F1 females
1	0	3	7
2	46	7	28
3	92.5	6	21
4	185	6	20
5	370	5	15
6	740	8	24

13.09 OvarianTumors in CBA Mice Exposed to Sr-90 During the Fetal Period

Institution: National Defense Research Institute, Divis. Radiobiology, Sundbyberg, Sweden
Swedish University of Agricultural Sciences, Dep. of Pathology, Uppsala, Sweden

Scientists: A. Nilsson; retired
C. Rönnbäck; retired

Purpose: To study long-term risks of ovarial tumors after exposure to Sr-90 during pregnancy.

Status: 1981-1982, terminated

Treatment: Intravenous. injection of pregnant females with Sr-90 nitrateon day 19 of pregnancy

Dosimetry: Activity injected

Endpoints: Microscopic analysis of ovaries from F1 females at an age of 10 months

Animal: Female CBA/S mice (80 ± 5 days old)

Results: When the females were sacrificed at an age of 10 months, many ovaries from the mice exposed except from the two highest dose groups contained multiple corpora lutea. Ovarian cysts were also often found. Proliferative alterations, such as hyperplasia of luteinizing interstitial cells ad down-growth of the germinal epithelium did not occur at doses below 185 kBq. The findings suggest a non-linear dose relationship for ovarian tumors and a proportional dependency of down-growth and tubular adenomas above a threshold of about 14%.

References: Rönnbäck, C. and A. Nilsson. Neoplasms in ovaries of CBA mice ^{90}Sr treated as fetuses. *Acta Radiol. Oncol.* **21**:121-128, 1982.

Experimental Groups:

Study 13.09
Ovarian Tumors in CBA Mice Exposed to Sr-90 During the Fetal Period

Group Id	kBq Injected on Day 19	No Dams (F1 Females Analyzed)
1	0	3 (7)
2	46.3	7 (26)
3	92.5	6 (20)
4	185	6 (19)
5	370	5 (15)
6	740	8 (24)

13.10 Effects on Fetal Mouse Ovaries From Protracted External Gamma Irradation As Compared with Internal Contamination

Institution: National Defense Research Institute, Divis. Radiobiology, Sundbyberg, Sweden
Swedish University of Agricultural Sciences, Dep. of Pathology, Uppsala, Sweden

Scientist: C. Rönnbäck; retired

Purpose: To assess the relative risks on the fetal mouse ovary of Sr-90 compared to external gamma irradiation .

Status: 1983, terminated

Treatment: Gamma-irradiation from a Cs-137 source (1.11×10^{12}Bq) at a dose rate of 0.0268 Gy/h at 1 m distance

Dosimetry: Farmer ionization chamber

Endpoints: Microscopy of the F1 ovaries at an age of 56 and 165 days

Animal: Female CBA/S mice (75 ± 5 days old)

Results: The total number of germ cells in the ovary at 56 days of age was reduced to about 50% after a dose of 0.09 Gy (and to about 10 % after a dose of 0.91 Gy) given during 4 days from day 19 p.c. until 2 days after birth. Females exposed at an age of 85 days showed less injury. The number of litters per female after exposure around birth was also reduced in a dose-dependent manner. Compared to the early data on germ cell reduction after application of Sr-90 on day 90 of gestation, if appears that damage caused by 0.01 gamma irradiation corresponds about to that caused by 2-5 kBq of Sr-90

References: Rönnbäck, C. Effects on fetal ovaries after protracted, external gamma irradiation as compared with those from internal depositions. *Acta Radiol. Oncol.* **22**:465-471, 1983.

Experimental Groups:

Study 13.10
Effects on Fetal Mouse Ovaries From Protracted External Gamma Irradation As Compared with Internal Contamination

Dose (Gy)	No dams irradiated (No litters)	Group Id / F1 females analysed day 56	165
0	16 (10)	1 / 7	2 / 14
0.09	8 (7)	3 / 7	4 / 14
0.2	17 (15)	5 / 7	6 / 14
0.91	11 (10)	7 / 7	8 / 14

13.11 Age-Dependence of Radiation Sensitivity of the Gonads of Female Mice

Institution: Swedish University of Agricultural Sciences, Dep. of Pathology, Uppsala, Sweden;

Scientist: C. Rönnbäck; retired

Purpose: To assess the risk to the adult ovary of gamma-irradiation at different ages.

Status: 1987-1988

Treatment: Continuous gamma-irradiation during four days from a Cs-137 source (1.11 TBq) starting at an age of 50, 90, 135 or 190 days; dose rate at 1m from source 0.0268 Gy/h

Dosimetry: Farmer ionization chamber

Endpoints: Microscopy of the ovary 56 days after irradiation was terminated

Animal: Female CBA/S mice at ages from 50 to 190 days

Results: The total number of germ cells was reduced to about 70% of controls for all age groups after a low dose rate gamma exposure to 0.9 Gy. After 2.4 Gy, only 3-8% of the germ cells still remained with the larger number being preserved when older animals were exposed possibly because at the age the younger more radiosensitive germ cell stage had already been eliminated due to the normal ageing process. As in earlier studies, the youngest germ cell stages were most sensitive to radiation injury.

References: Rönnbäck, C. The age dependence of radiation sensitivity of the gonads of female mice. *Acta Radiol. Oncol.* **27**:399-405, 1988.

Experimental Groups:

Study 13.11
Age-Dependence of Radiation Sensitivity of the Gonads of Female Mice

Age days at begin of exposure	Group Id / No mice		
	0 Gy	0.9 Gy	2.4 Gy
50	1 / 10	2 / 10	3 / 10
90	4 / 7	5 / 15	6 / 15
135	7 / 9	8 / 15	9 / 15
190	10 / 9	11 / 15	12 / 15

13.12 Effects of Sr-90 Given During Fetal Development on Spermatogenesis of Offspring

Institution: Swedish University of Agricultural Sciences, Dep. of Pathology, Uppsala, Sweden

Scientists: C. Rönnbäck; retired
D.G. de Rooij; active (Utrecht NL)

Purpose: To compare the effects of Sr-90 during fetal development on spermatogenesis with those on the ovary

Status: 1987-1989, terminated

Treatment: Intravenous injection of pregnant females with Sr-90 nitrateon day 19 of gestation

Dosimetry: Activity injected

Endpoints: Number of litters from mating with 20 males, testicular weight and microscopic analysis of testis at an age of 56 days (with some experiments also sacrificing at 14 and 28 days)

Animal: Female CBA/S mice (about 70 days)

Results: The studies were carried out on the male littermates from the females used for the study of the ovary. Doses of 370 or 740 kBq Sr-90 administered to the dam caused a transient retardation in the appearace of more advanced types of testicular germ cells. Compared to control testes, fewer tubular cross-sections displayed spermatocytes or round spermatids at days 14 and 28 post birth. At 56 days, spermatogenesis in Sr-90 treated animals was similar to that in controls.. Doses of 92.5 or 185 kBq had no visible effects. Thus, fetal testis is much less vulnerable to Sr-90 damage than mouse ovary where 92.5 kBq permanently reduced germ cell number to 40% of controls. Presumably, the cell lost by radiation exposure in the testis are rapidly restored by division of surviving cells with, as result, only a delay in the appearance of differentiated cells. Other studies (not presented as a table) carried out on male mice mated 25, 35, 45 or 60 days after injection of 25.9 kBq/g of Sr-90 suggest abnormalities in chromosome number..

References:

Henricson,B. Nilsson,A.: Chromosome investigations on the embryo progeny of male mice treated with ^{90} Sr. *Acta Radiol. Ther. Phys. Biol.* **2**, 315-320, 1964.

Frölen, H. Genetic effects of ^{90}Sr on various stages of spermatogenesis in mice. *Acta Radiol. Ther. Phys. Biol.* **9**:596-608, 1970.

De Rooij, D.G. and C. Rönnbäck. The effect of ^{90}Sr given to pregnant mice on spermatogenesis in the male offspring: A comparison with the effect on the ovaries in the female offspring. *Int. J. Radiat. Biol.* **56**:151-159, 1989.

Experimental Groups:

Study 13.12
Effects of Sr-90 Given During Fetal Development on Spermatogenesis of Offspring

kBq Sr injected	Group Id / Studied for mating (No of litters)	Group Id /No studied for histology		
		14 day	28 day	56 day
0	1 / 8 (77)	2 / 5	3 / 4	4 / 4
92.5	-	5 / 6	6 / 4	7 / 4
185	-	8 / 4	9 / 4	10 / 4
370	11 / 19 (31)	12 / 4	13 / 4	14 / 4

13.13 Effects of Glucan on the RES and Tumor Development Following Sr-90 Injection of Adult Mice

Institution: Swedish University of Agricultural Sciences, Dep. of Pathology, Uppsala, Sweden

Scientists: G. Walinder ; retired

Purpose: To follow the effects of a substance activitating the reticuloendothelial system on Sr-90-induced tumors.

Status: 1979-1990

Treatment: Intraperitoneal injection with 14.8 kBq/g body weight of Sr-90 nitrate. Glucane (1.6 mg) was given i.p. every fortnight for 100 days either from 150-250 or from 250-350 days after Sr-90 administration

Dosimetry: Activity injected

Endpoints: Life-span study (sacrificed when moribund) with macroscopic/microscopic pathology

Animal: Male CBA/S mice (75 ± 5 days old)

Results: Glucane stimulates the reticulo-endothelial system as evidenced by a dose-related increase in lysozyme levels in the plasma and an enlargement of the liver. Weekly injections of glucane between 150 and 250 days after Sr-90 exposure suppressed actuarial appearance of the fibroblastic type of osteosarcomas and stimulated the emergence of malignant lymphoma. Glucane itself had no tumorigenic effect in mice not exposed to Sr-90.

References: Walinder, G., R.G. Arora, P. Bierke, A. Broomé-Karlsson and B.M. Svedenstål. Effects of glucan on the reticuloendothelial system and on the development of tumors in ^{90}Sr exposed mice. *Acta Oncol.* **31**:461-467, 1992.

Experimental Groups:

Study 13.13
Effects of Glucan on the Res and Tumor Development Following Sr-90 Injection of Adult Mice

Dose Sr-90 kBq/kg	No glucan		glucan day 150-250		glucan day 250-350	
	Group Id	No mice	Group Id	No mice	Group Id	No mice
0	1	50	2	50	3	50
14.8	4	50	5	50	6	50

13.14 Effect of 3,3',4,4'-Tetrachlorobiphenyl (TCB) on Ovaries of Fetal Mice

Institution: Unit. Exper. Pathology & Risk Research; Dep. Pathology; Swedish University of Agricult. Sciences, Uppsala

Scientists: C. Rönnbäck; retired

Purpose: To compare the effects of a chemical agent with those of Sr-90 on ovarial development.

Status: 1990-1991

Treatment: Intravenous injection of pregnant females with 3,3',4,4'-Tetrachlorobiphenyl (TCB on day 13 of pregnancy

Dosimetry: Amount injected

Endpoints: Ovarial histology at 28 days of age, reproductive capacity

Animal: Timed pregnant female C57/Bl- mice (85-90 days old)

Results: No effect of TCB treatment was observed below a dose of 15 mg /kg. At this dose, germ cell numbers decreased to about one half of control values. This decrease involved all stages of oocytes and follicles, a behavior contrasting with that seen after exposure to ionizing radiation. No sigificant difference in time intervals between litters, littersize or behavior of the offspring was observed at any of the dose of TCB applied.

References: Rönnbäck, C. Effect of 3,3',4,4'-Tetrachlorobiphenyl (TCB) on ovaries of fetal mice. *Pharmacol. Toxicol.* **68**:340-345, 1991.

Experimental Groups:

Study 13.14
Effect of 3,3',4,4'-Tetrachlorobiphenyl (TCB) on Ovaries of Fetal Mice

Group Id	Dose TCB mg/kg	F1 ♀ assayed
1	0 (control)	4
2	0 + 0.4 ml oil (control)	4
3	6	3
4	9	4
5	12	4
6	15	4

13.15 Late Effects of Fractionated X-Ray Exposure With and Without Cysteamine treatment

Institution: National Defense Research Institute, Divis. Radiobiology, Sundbyberg, Sweden
Swedish University of Agricultural Sciences, Dep. of Pathology, Uppsala, Sweden

Scientists: A. Nelson; retired
O. Hertzberg,
C. Rönnbäck; retired

Purpose: To determine the protective effect of cysteamine against late effects from fractionated irradation.

Status: 1960-1966

Treatment: Fractionated X-irradiation (260 kV, 72 R/min) at different time intervalls terminated at predefined doses (80 R interval 1 d: 640, 960, 1280, 1920 R; 80 R interval 3 d: exposure until death; 160 R interval 1 d: 480, 800, 1120, 1440, 1760 R; 160 R interval 3 d: 1600, 1920, 2240, 2560, 2880, 3200, 3250 R; 160R interval 7 d: 2880, 3200, 3250, 3840, 4160, 4480, 5760 R. Cysteamine 4 mg was injected i.p to the protected mice shortly before irradiation

Dosimetry: Ionization chamber

Endpoints: Macroscopic and microscopic pathology at spontaneous death

Animal: CBA mice

Results: Cysteamine was found to protect also against late effects of irradiation

References:

Nelson, A., O. Hertzberg and C. Rönnbäck. Protective effect of cysteamin at fractionated irradiation II Shortening of life span. *Acta Radiol.* **6**:449-463, 1967.

Nelson, A., B. Järplid, A. Nilsson, C. Rönnbäck and K.H. Eriksson. Protective effect of cysteamin at fractionated irradiation. Histopathologic diagnoses at death. *Acta Radiol.*(Suppl. **310**):181-199, 1971.

Ousavaplangchai, L., C. Rönnbäck, C. Rehbinder and A. Nilsson. Irradiation of mice pre-treated with radiation protective substances. *Acta Radiol. Oncol.* **17**:125-137, 1978.

Experimental Groups:

Study 13.15
Late Effects of Fractionated X-Ray Exposure With and Without Cysteamine

Group Id	Dose (R)	Treatment	No mice
1	0 R	none	95
2	0 R	saline	44
3	0 R	cysteamine 4 mg twice a week for lifespan	42
4	0 R	cysteamine 4 mg twice a week 24 times	20
5	80 R interval 1days	none	259
6	80 R interval 1 days	cysteamine 4 mg before exposure	173
7	80 R interval 3 days	none	
8	80 R interval 3 days	cysteamine 4 mg before exposure	
9	160 R interval 1 days	none	150
10	160 R interval 1 days	cysteamine 4 mg before exposure	150
11	160 R interval 3 days	none	209
12	160 R interval 3 days	cysteamine 4 mg before exposure	210
13	160 R interval 7 days	none	240
14	160 R interval 7 days	cysteamine 4 mg before exposure	239

13.16 The Role of the Immune System in Sr-90-Induced Tumorogenesis

Institution: National Defense Research Institute, Divis. Radiobiology, Sundbyberg, Sweden
Swedish University of Agricultural Sciences, Dep. of Pathology, Uppsala, Sweden

Scientists: P. Bierke; active
A. Nilsson; retired

Purpose: To study the influence of Sr-90 dose, adult thymectomy and antilymphocyte globulin(ALG) on the development of neoplastic and pre-neoplastic lesions in CBA mice.

Status: 1977-1990

Treatment: Intraperitoneal injection with different doses of Sr-90 nitrate; in addition, some groups were subjected to long-term non-specific immune suppression by thymectomy of young adult mice with subcutaneous transplantation of the removed thymus into intact recipient mice,and/or prolonged s.c. antilymphocyte globulin (ALG) treatment, other groups received syngenic bone marrow and/or thymus cells (5 million cells from syngeneic female donors injected every 30 days until 210 days (25.9 kBg/g) or for the entire life span (14.8 kBq/g).

A) Effect of thymectomy, thymus graft and ALG on Sr-90 induced tumors (one Sr-90 dose)
B) Effect of bone marrow and/or thymus cells grafts (two Sr-90 doses),
C) Effect of thymectomy, thymus graft and ALG on Sr-90 induced tumors (several Sr-90 doses),
D) Antigenicity of Sr-90-induced (25.9 kBq/g) osteosarcoma was studied by pre-treating recipients with heavily irradiated (147 Gy) cells or irradiating the mice with 3.8 Gy . The mice were then challenged with viable cells (50-500 000) 1 week after injection of the irradiated cells three times at weekly intervals or 24 hours after whole body irradiation, and the animals were observed for tumor growth
E) Tumor development was studied after injection of BCG (1mg dry mass Bacillus Calmette-Guerin) 209 days after application of 33.3 kBq/g Sr-90.

Dosimetry: Activity injected

Endpoints: Life-span with macroscopic/microscopic pathology

Animal: M ale CBA/SU mice (75 days old)

Results:

A). Immune suppression by antilymphocyte serum or thymectomy did not influece the neoplastic and preneoplastic responses to Sr-90.
B) Transplantation increased the number of lympho-reticular tumors in the low dose group compared to those treated with Sr-90 only; after high doses this was observed only after bone marrow transplantation. Data on osteosarcoma in transplanted animals were not very consistent.
C) The yield of bone, lymphoreticular and extracellular tumors depended on the Sr-90 dose. As the dose of Sr-90 increased and the latency period of appearance of bone tumors became shorter, the percentage of less-differenciated tumors increased at the expense of the more differentiated ones. Incidence or latency period of the tumors in controls and Sr-treated mice was not influeced by treatment with antilymphocytic globuline or thymectomy of the adult mice. However, tests showed that immune response was clearly suppressed.
D) Incidence of tumors was greater in whole body irradiated mice; injection of irradiated tumor cells decreased the frequency of growing tumors compared to an injection of non-tumor cells. The data were interpreted as an indication of specific transplantation antigens in osteosarcomas.
E) Growth of osteosarcomas was delayed and their incidence was reduced after injection of BCG, but survival time was unaltered. BCG treatment increased leukemia incidence

References:

Nilsson, A., L. Révész and J. Stjernswärd. Suppression of strontium-90-induced development of bone tumors by infection with Bacillus Calmette-Guéri (BCG). *Radiat. Res.* **25**:378-382, 1965.

Nilsson, A., L. Révész and K.H. Erikson. Antigenicity of radiostrontium-induced osteosarcomas. *Radiat. Res.* **52**:395-408, 1972.

Nilsson, A., P. Bierke and A. Broomé-Karlsson. Effect of syngeneic bone marrow and thymus cell transplantation to ^{90}Sr irradiated mice. *Acta Radiol. Ther. Phys. Biol.* **19**:29-36, 1980.

Bierke, P. and M. Gidlund. Influence of ^{90}Sr, adult thymectomy and antilymphocyte globulin-treated on T cells in mouse peripheral blood. *Acta Oncol.* **23**:61-64, 1984.

Gidlund, M., P. Bierke, A. Ör, I. Axberg, U. Ramstedt and H. Wigzell. Impact of ^{90}Sr on mouse natural killer cells and their regulation by interferone α and interleukin-2. *Scand. J. Immunol.* **23**:61-64, 1984.

Bierke, P. Immune competence in ^{90}Sr-exposed, adult thymectomized and antilymphocyte globulin-treated CBA mice. *Acta Oncol.* **28**:271-275, 1989.

Bierke, P. Role of immunosuppression in radiostrontium-induced oncogenesis. A histopathological and immunological study in ^{90}Sr-exposed normal and immuno-compromised CBA mice. Doctoral Thesis, Swedish University of Agricultural Sciences, Uppsala., 1989.

Bierke, P. and A. Nilsson. Radiostrontium-induced oncogenesis and the role of immuno- suppression. I. Influence of ^{90}Sr dose, adult thymectomy and antilymphocyte globulin on the development of neoplastic and pre-neoplastic lesions in the skeleton of CBA mice. *Acta Oncol.* **28**:87-102, 1989.

Bierke, P. Immune competence in ^{90}Sr-exposed, adult thymectomized and antilymphocyte globulin-treated CBA mice II. Reticulo-endothelial phagocytic function and *in vitro* mitogen responsiveness of spleen cells. *Acta Oncol.* **29**:615-621, 1990.

Bierke, P. and A. Nilsson. Radiostrontium-induced oncogenesis and the role of immuno-suppression. II. Influence of ^{90}Sr dose, adult thymectomy and antilymphocyte globulin on the development of lymphoreticular and extraskeletal neoplastic lesions in CBA mice. *Acta Oncol.* **29**:53-63, 1990.

Experimental Groups:

Study 13.16

The Role of the Immune System in Sr-90-Induced Tumorogenesis

A. Effect of thymectomy, thymus graft and ALG on Sr-90 induced tumors

Dose kBq/g	No addit. treatment		Thymectomy		Thymus graft		ALG	
	Group Id	No mice	Group Id	No mice	GroupId	No mice	Group Id	No mice
7.4	1	50	2	55	3	53	4	28

B. Effect of bone marrow and/or thymus cells grafts

Dose kBq/g	No addit.treatm.		Bone marrow cells		Thymus cells		BM + Thymus cells	
	Group Id	No mice	Group Id	No mice	Group Id	No mice	Group Id	No mice
0	5	47						
14.8	6	49	7	49	8	45	9	50
25.9	10	50	11	50			12	88

C. Effect of thymectomy, thymus graft and ALG on Sr-90 induced tumors

Sr inject. kBq/g	No addit. treat.		Thymect.		ALG		ALG+thymect	
	Group Id	No mice	Group Id	No mice	Group Id	No mice	Group Id	No mice
0	13	270 112 112 *			14	100	15	40 12 12
1.85	16	50	17	50			18	50
7.4	19	50	20	50			21	50
14.8	22	40 12 12					23	40 12 12
29.6	24	100 50 50	25	100 50 50	26	100 50 50	27	100 50 50

* The first number represents the animals used for survival and tumor incidence, the second those assayed for mitogen response, WBC counts and pre-neoplastic changes and the third those analysed for RES function. The untreated controls originate from several groups in the experiment.

D) Antigenicity of Sr-90-induced osteosarcoma

Group Id	X-ray dose Gy	Cells injected	Tumor type	No tumors (No of challenges)
28		none	fibroblastic	10 (185)
29	0	none	osteoblastic	13 (195)
30	0	none	fibroblastic- osteoblastic	23 (380)
31	0	irrad. normal	fibroblastic	5 (110)
32	0	irrad. normal	osteoblastic	7 (99)
33	0	irrad. normal	fibroblastic- osteoblastic	12 (209)
34	0	irrad. tumor	fibroblastic	5 (109)
35	0	irrad. tumor	osteoblastic	7 (100)
36	0	irrad. tumor	fibroblastic- osteoblastic	12 (209)
37	3.8	none	fibroblastic	9 (175)
38	3.8	none	osteoblastic	10 (164)
39	3.8	none	fibroblastic- osteoblastic	19 (339)
40	3.8	irrad. normal	fibroblastic	6 (100)
41	3.8	irrad. normal	osteoblastic	9 (155)
42	3.8	irrad. normal	fibroblastic- osteoblastic	15 (255)
43	3.8	irrad. tumor	fibroblastic	6 (100)
44	3.8	irrad. tumor	osteoblastic	9 (155)
45	3.8	irrad. tumor	fibroblastic- osteoblastic	15 (255)

E) Tumor development after injection of BCG

Group Id	Sr-90 kBq/g	BCG	No of mice
46	33.3	none	50
47	33.3	1 mg	50

13.17 Automated Flow-Cytometric Analysis of Acute and Chronic Effects of Sr-90 Application

Institution: Swedish University of Agricultural Sciences, Uppsala, Dep. of Pathology

Scientists: H. Amnéus; active
A. Nilsson; retired
B. Järplid.

Purpose: To develop automated methods for the identification of exposed individuals and the follow-up of the eventual pathological consequences. Acute effects are studied with respect to cell cycle analysis, cell counts, immuno-phenotyping and incidence of micronuclei. Late effects are studied with respect to cell proliferation, ploidity, immuno-phenotyping and cell counts supplemented by conventional histopathology.

Status: 1988- 1991

Treatment: Whole-body X-irradiation 260 kV: acute exposure (0.47 Gy/min), chronic exposure (50 mGy/d), fractionated exposure (4 fractions)
i.v. injection of 11.1 kBq/g Sr-90 nitrate
i.p. injection of 3 x 740 kBq/g of Cs-137 chloride

Dosimetry: Ionization chamber, activity injected

Endpoints: Acute effects: serial sacrifice: life-span study, sacrificed when moribund, macroscopic and microscopic pathology and blood cell analysis.

Animal: CBA/S mice sex as indicated 25 or 100 days old

Results: Not yet evaluated

Experimental Groups:

Study 13.17
Automated Flow-Cytometric Analysis of Acute and Chronic Effects of Sr-90 Application

Exposure	Sex Age	Acute (serial sacrifice)		Late effects (life span)	
		Group Id	No mice	Group Id	No mice
0 (control)	♂	1	50	12	50
0 (control)	♀	2	205	13	8
3 Gy acute X-rays	♂ 25d	3	50	14	51
	♂ 100d	4	100	15	52
50 mGy/d chronic X-rays [1]	♂ 25d			16	30
	♂ 100d			17	51
4 x 0.25 Gy	♀ 25d	5	18	18	90
4 x 0.5 Gy	♀ 25d	6	19	19	106
4 x 1 Gy	♀ 25d	7	17	20	51
4 x 1.375 Gy	♀ 25d	8	116	21	139
^{137}Cs 3x 740 kBq/g	♂ 25d	9	50	22	47
	♂ 100d	10	50	23	50
^{90}Sr 11.1 kBq/g	♀ 25d	11	50	24	50

1 Life time exposure, doses attaining up to 40 Gy until death

13.18 Myeloid Leukemia in CBA/S and Mice After Whole-Body X Irradiation

Institution: Swedish University of Agricultural Sciences, Dep. of Pathology, Uppsala, Sweden

Scientists: P. Bierke; active
A. Nilsson ; retired

Purpose: To compare two closely related sub-strains with respect to radiation-induced tumors, with special reference to myeloid leukemia.

Status: 1992

Treatment: External X-ray irradiation, 260 kV, 0.47 Gy/min

Dosimetry: Farmer ionization chamber

Endpoints: Life-span with macroscopic/microscopic pathology

Animal: Male CBA/S or CBA/H mice (100 days old)

Results: Under evaluation

References:

Experimental Groups:

Study 13.18
Myeloid Leukemia in CBA/S and Mice After Whole-Body X Irradiation

Dose (Gy)	CBA/S mice		CBA/H mice	
	Group Id	No mice	Group Id	No mice
0	1	50	5	90
2	2	50	6	100
3	3	50		-
4	4	50		-

13.19 Induction of Pituitary and Skeletal Tumors by Sr-90 Combined with Estrogens and Effect of Age on Tumor Induction

Institution: National Defense Research Institute, Divis. Radiobiology, Sundbyberg, Sweden
Swedish University of Agricultural Sciences, Dep. of Pathology, Uppsala, Sweden

Scientists: A. Nilsson; retired
I. Haraldsson,
P. Bierke; active

Purpose: to elucidate the possible synergism between radiation and estrogen treatment and the effects of age on tumor induction.

Status: 1978-1980, terminated

Treatment: Intraperitoneal injection of Sr-90 nitrate alone or together with three s.c. injections of of0.1 mg polyestradiol phosphate 1 day prior and 21 and 51 days after Sr injection, 0.25 mg nortestosterone or s.c. injections of 1 mg of methylprednisolon every second week for 2 months or the entire lifespan.

A) Induction of pituitary tumors, effect steroid hormones in 75 ± 3 days old mice,
B) Induction of osteosarcomas, effect of sexual steroid hormones in 75± 3 days old mice,

C) Induction of osteosarcomas, effect of prednisolon in 75± 3 days old mice,
D) Effect of age and dose on carcinogenicity of Sr-90 in mice of different ages
E) Influence of estrogen on metabolism of strontium; 1.5 kBq/g of Sr-85 were injected i.p. to all mice; some mice received also 29.6 kBq/g of Sr-90; three estrogen injections (1+0.5+0.25 mg were given at 4 weeks interval and the animals sacrificed at different times.

Dosimetry: Injected activity

Endpoints: Sacrificed when moribund with macroscopic and microscopic pathology

Animal: Male CBA/S mice

Results: Pituitary tumors are rare in mice treated with Sr-90 only (1 and 3% after 0.925 and 1.85 kBq/g respectively) but increase to 44 and 37% respectively when estrogens are administered in addition, presumably because this treatment induces the proliferation of pituitary cells. Estrogen treatment also increased the incidence and shortened the latency period of osteosarcomas, nortesteron did not change their incidence and methylprednisolone retarded and reduced their appearance. Incidence of osteosarcomas was highest in the groups exposed at an age of 75 days and lowest in the older groups. The incidence of lymphoreticulor tumors was inversely related to dose and independent of age at Sr-90 injection.
Estrogen results in an increased bone formation but in animals treated with Sr-90 this newly formed bone is later broken down. Lifespan of the mice treated with estrogens and Sr-90 is shorter than that treated with estrogens alone suggesting that stimulated cell populations are at greater risk of radiation damage than unstimulated ones.

References: Nilsson, A. and C. Rönnbäck. Influence of estrogenic hormones on carcinogenesis and toxicity of radiostrontium. *Acta Radiol. Ther. Phys. Biol.* **12**:209-228, 1973.

Rönnbäck, C. and A. Nilsson. Influence of estrogen on the excretion of stontium-90 and -85 in mice. *Acta Radiol. Ther. Phys. Biol.* **14**:485-496, 1975.

Experimental Groups:

Study 13.19
Induction of Pituitary and Skeletal Tumors by Sr-90 Combined with Estrogens and Effect of Age on Tumor Induction

A. Induction of pituitary tumors, effect steroid hormones in 75 ± 3 days old mice

kBq ^{90}Sr Injected	No Additional Treatment		Estrogen		Methylprednisolone	
	Group Id	No mice	Group Id	No mice	Group Id	No mice
0			1	70		
0.925	2	100	3	100	4	100
1.85	5	100	6	100	7	100
7.4	8	50	9	50	10	50

B. Induction of osteosarcomas, effect of sexual steroid hormones in 75± 3 days old mice

Group Id	Treatment	No of mice
11	Sr-90 14.8 kBq/g	50
12	Sr-90 14.8 kBq/g +methylprednisolone 2 months	50
13	Sr-90 14.8 kBq/g +estrogen	50
14	Sr-90 14.8 kBq/g + nortestosteroe	50

C. Induction of osteosarcomas, effect of prednisolon in 75± 3 days old mice

Group Id	Treatment	No Mice
15	Controls	50
16	methylprednisolone life time	49
17	Sr-90 14.8 kBq/g	50
18	Sr-90 14.8 kBq/g +methylprednisolone 2 months	49
19	Sr-90 14.8 kBq/g +methylprednisolone life time	42
20	Sr-90 14.8 kBq/g +methylprednisolone life time +adrenalectomy	42

D. Effect of age and dose on carcinogenicity of Sr-90 in mice of different ages

Dose kBq/g ^{90}Sr	Age 25 days		Age75 days		Age 150 days		Age 300 days	
	Group Id	No mice	Group Id	No mice	Group Id	No mice	Group Id	No mice
7.4	21	51	22	49	23	47	24	49
14.8	25	49	26	49	27	49	28	50
29.6	29	50	30	47	31	48	32	50

E. Influence of estrogen on metabolism of strontium in male mice

Group Id	kBq/g Sr-90	Estrogen treatment	No Mice	Remarks
1st experiment				
33	0	^{85}Sr 1week before start of estrogens	50	15 animals used for repeated measurements of ^{85}Sr, five animals each sacrificed 2, 3, 4, 5, 6, 7 months after Sr administration
34	0	^{85}Sr 1 week after start of estrogens	50	
35	0	^{85}Sr 1 week after last estrogen	50	
36	0	none	50	
2nd experiment				
37	0	none (also no Sr-85)	50	5 animals sacrificed at 28, 56, 84, 112, 140, 168 and 196 days after Sr administration
38	29.6	^{85}Sr +^{90}Sr 1week before start of estrogens	50	
39	0	^{85}Sr 1week before start of estrogens	50	
40	29.6	^{85}Sr +^{90}Sr 1week before start of estrogens	50	

13.20 Acute and Chronic Effects of Sr-90

Institution: Swedish University of Agricultural Sciences, Dep. of Pathology, Uppsala, Sweden

Scientists: H. Amnéus; active
A. Nilsson; retired

Purpose: To compare the effects of Sr-90 with those from earlier gamma-irradiation experiments with respect to acute survival and tumor induction.

Status: 1988-1990

Treatment: Intravenous injection of mice with 11.1 kBq/g of Sr-90 nitrate

Dosimetry: Activity injected

Endpoints: Life-span study, sacrificed when moribund; macroscopic and microscopic pathology

Animal: Male CBA/S mice (about 70 days)

Results: Not yet evaluated

References:

Experimental Groups:

Study 13.20
Acute and Chronic Effects of Sr-90

kBq/g Sr injected	Acute survival		Long-term study	
	Group Id	No mice	Group Id	No mice
0	1	50	2	50
11.1	3	50	4	50

13.21 Retention and Late Effects of Plutonium-239 in Mice

Institution: National Defense Research Institute, Divis. Radiobiology, Sundbyberg, Sweden

Scientists: A. Nilsson; retired
P. Bierke; active

Purpose: To study retention and late effects of Pu-239.

Status: 1974, terminated

Treatment: Intravenous injection of mice with Pu-239 nitrate.One experiment and its repeat; in addition 5 mice studied for retention after 20 days, and 10 mice for retention after 5 months. For controls use those of 13.01, 13.02 and 13.03.

Dosimetry: Activity injected

Endpoints: Life-span study, sacrificed when moribund; macroscopic and microscopic pathology, retention of Pu-239 after 20 days and 5 months

Animal: Male and female CBA/S mice (aged ≈75 days)

Results: To be published

References: Lüning, K.G., H. Frölen and A. Nilsson. Genetic effects of ^{239}Pu salt injections in male mice. *Mutation Res.* **34**:539-542, 1976.

Experimental Groups:

Study 13.21
Retention and Late Effects of Plutonium-239 in Mice

Group Id	kBq/g Pu injected	No ♂ Mice	No ♀ Mice
1, 2	0.37	10	10
3, 4	1.85	10	10
5, 6	3.7	10	10
7, 8	18.5	10	10

13.22 Long-Term Tumorigenic Effect of Cs-137 in Comparison with Gamma-Ray Exposure

Institution: Swedish University of Agricultural Sciences, Dep. of Pathology, Uppsala, Sweden

Scientists: H. Amnéus; active
A. Nilsson, retired

Purpose: To compare the long-term effects of protracted internal whole body irradiation with an acute or chronic gamma ray exposure in mice of different age.

Status: 1989-1991, terminated

Treatment: Intraperitoneal injection with 3x740 kBq of Cs-137, acute gamma ray exposure (3 Gy, dose rate), chronic gamma ray exposure (50 mGy/day) during the entire life time

Dosimetry: Activity injected, whole body dose calculated, Farmer ionization chamber for gamma ray exposure

Endpoints: Life-span study (sacrificed when moribund) with macroscopic/microscopic pathology

Animal: Male CBA/S mice (25 or 100 ± 5 days old)

Results: Evaluation under way

Experimental Groups:

Study 13.22
Long-Term Tumorigenic Effect of Cs-137 in Comparison with Gamma-Ray Exposure

Age (days) {type of study}	^{137}Cs 3x740 kBq		Acute 3 Gy γ-rays		Chronic 50 mGy/d	
	Group Id	No mice	Group Id	No mice	Group Id	No mice
Controls	1	50				
25 {acute}	2	50				-
100 {lifespan}	3	47			8	30
25 {acute}	4	50	6	50		-
100 {lifespan}	5	50	7	57	9	51

13.23 Bone Tumors in Beagle Dogs Exposed to Sr-90

Institution: Swedish University of Agricultural Sciences, Uppsala, Dep Pathology, with the Laboratory for Energy-Related Health Research, Univ. California, Davis CA, USA

Scientists: A. Nilsson, retired
J.P. Morgan,
S.A. Book

Purpose: To study long-term risks of injected Sr-90.

Status: 1984-1987, see studies 102.02-102.03.

Treatment: Sr-90 chronic feeding starting on day 21 of gestation until 540 days of age or intravenous injection at an age of 540 days .

Dosimetry: Activity fed or injected, mean skeletal dose calculated

Endpoints: Sacrifice when moribund, life-span study with macroscopic microscopic pathology

Animal: Male beagle dogs

Results: This investigation was carried out in cooperation with the Laboratory for Energy-Related Health Research, Davis Ca, USA and additional information will be found under 102.02-102.03. Osteosarcomas developed in a dose-dependent maner with tumors occurring earlier after higher doses. Intravenous application gave rise to somewhat more osteosarcomas than feeding the same dose of Sr-90. The tumors found occurred in the appendicular almost as frequently as in the axial skeleton and were predominatly localized in the diaphysis. Although the preferential sites of the tumor and deterministic lesions differed between dogs and mice, the underlying histological events appear to be similar.

References: Nilsson, A., J.P. Morgan and S.A. Book. Investigations of ^{90}Sr in dogs. I. Pathogenesis of radiation-induced bone tumors. *Acta Radiol. Oncol.* **24**:95-111, 1985.

Nilsson, A. and S.A. Book. Occurrence and distribution of bone tumors in beagle dogs exposed to ^{90}Sr. *Acta Oncol.* **26**:113-138, 1987.

Experimental Groups:

Study 13.23
Bone Tumors in Beagle Dogs Exposed to Sr-90

Group Id	Total kBq ^{90}Sr ingested	Mean Skeletal Dose Gy	No of Dogs
1	0	0	80
2	370	0.37	78
3	1480	1.16	40
4	8880	6.72	65
5	25900	21.98	65
6	81400	48.08	61
7	240500	79.07	60
8	717800	107.16	8
	Total kBq injected		
9	1.369	6.36	20
10	3.83	52.38	25

13.24 Late Effects of I-131 and X-rays After Exposure of Fetuses or Adult Mice

Institution: Swedish University of Agricultural Sciences, Dep. of Pathology, Uppsala, Sweden

Scientist: G. Walinder, retired

Purpose: To elucidate the risk of I-131 and X-rays to the fetus and the adult.

Status: 1970-1973, terminated

Treatment: Intraperitoneal injection of I-131 or X-irradiation (260 Kv 72 R/min) to the mother on day 18 of gestation or, for adult male mice at an age of 96 days

Dosimetry: Ionization chamber, exposure from I-131 calculated from injected activity

Endpoints: Sacrificed at an age of about 2 years (first experiment) or 323-348 days (exposure during gestation) or 374- 376 days (exposure of adults); macroscopic and microscopic pathology

Animal: CBA/S mice

Results: After exposure of the foeti, a substantial dose-dependent increase in neoplasms was seen after I-131 exposure to 19 to 73 Gy (with more tumors being found in males than in females) but not after X-ray exposure to 1.8 Gy. In adults, radiation-induced cell death gave rise increased production of TSH and elarged pituitary gland. Later, thyroid adenomas and some carcinomas were observed. In view of the variabilities encountered in mice born at different times, another experiment (2) was performed which again showed the resistance to tumor induction of the adult mice. This experiment also indicated that tumors following exposure during gestation arise earlier when the dose is higher.

References:

Walinder, G. Determination of the ^{131}I dose to the mouse thyroid. *Acta Radiol. Ther. Phys. Biol.* **10**:558, 1971.

Walinder, G. Late effects of irradiation on the thyroid gland in mice I Irradiation of adult mice. *Acta Radiol. Ther. Phys. Biol.* **11**:433-451, 1972.

Walinder, G. Late effects of irradiation on the thyroid gland in mice. II Irradiation of mouse fetuses. *Acta Radiol. Ther. Phys. Biol.* **11**:577-589, 1972.

Walinder, G. Late effects of irradiation on the thyroid gland in mice. III Comparison between irradiation of fetuses and adults. *Acta Radiol. Ther. Phys. Biol.* **12**:201-208, 1973.

Experimental Groups:

Study 13.24
Late Effects of I-131 and X-rays After Exposure of Fetuses or Adult Mice

Treatment	Dose (MBq) ^{131}I	Dose(Gy) (or R) X-rays	Males		Females	
			Group Id	No Mice	Group Id	No Mice
Fetuses Controls			1	263	2	225
^{131}I	0.7-0.78		2	172	4	160
^{131}I	1.41		5	89	6	58
^{131}I	1.74-1.81		7	16	8	20
^{131}I	2.52-2.70		9	102	10	83
X-rays		1.8 Gy	11	48	12	47
X-rays + ^{131}I	0.55-0.67	1.8 Gy	13	79	14	73
X-rays + ^{131}I	0.95-1.11	1.8 Gy	15	46	16	30
Adults ^{131}I	0.055		17	700		
^{131}I	0.11		18	700		
^{131}I	0.17		19	700		
X-rays		500 R	20	700		
X-rays		1000 R	21	700		
X-rays		1500 R	22	700		
2nd exp. Fetuses Controls			23	53	24	62
^{131}I	0.89		25	14	26	5
^{131}I	1.74		27	53	28	48
^{131}I	2.89		29	58	30	51
X-rays		1.8 Gy	31	47	32	35
X-rays + ^{131}I	0.89	1.8 Gy	33	5	34	4
X-rays + ^{131}I	1.74	1.8 Gy	35	45	36	29
^{131}I	3.15 ♂ 3.51 ♀		37	45	38	46

14 URCRM, Ural Research Center of Radiation Medicine

14.01 Osteosarcoma in Rats After Acute and Chronic Application of Sr-90

Institution: URCRM, Urals Research Center of Radiation Medicine, Chelyabinsk, Russia

Scientists: V.L. Shvedov; retired

Purpose: To determine the risk of osteosarcoma from the bone-seeking radionuclide Sr-90.

Status: 1972-1992, terminated

Treatment: **Experiment A:** Single iv injection of Sr-90 nitrate at different ages
Experiment B: Addition of Sr-90 nitrate to food

Dosimetry: Activity fed or injected, mean skeletal dose calculated for the life-span of the animals

Endpoints: Life-span study (spontaneous death) with macroscopic microscopic pathology

Animal: Male white rats

Results: The data demonstrate that the risk of Sr-90-induced osteosarcoma and latency period increase with dose and decrease exponentially with age. Osteosarcoma develops only late in the life of the animal due to the need for promotion which occurs in relation to age-related disorders in organ and system functions. Thus, osteosarcoma incidence has but little influence on the life span of the animals even when doses are high because other diseases reduce life-span in proportion.

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Experimental Groups:

Study 14.01
Osteosarcoma in Rats After Acute and Chronic Application of Sr-90

Experiment A: Single Injection

Group Id	kBq/g injected	Age (weeks) at injection	Mean Skeletal Dose Gy	No Rats
1	0	14	0	100
2	11.1	4	19.5	98
3	11.1	8	19	98
4	11.1	16	19	100
5	11.1	20	18.5	98
6	11.1	24	14	100
7	11.1	48	10	100
8	11.1	72	5	100

Experiment B: Ingestion with Food

Group Id	kBq Ingested Daily	Exposure	Mean Skeletal Dose Gy	No Rats
9	0	Lifetime	0	250
10	0.00185	Lifetime	0.024	250
11	0.0185	Lifetime	0.12	200
12	0.185	Lifetime	1.18	250
13	1.85	Lifetime	11.3	200
14	18.5	Lifetime	76.8	250
15	37	Lifetime	124	100
16	74	Lifetime	133	100
17	148	Lifetime	190	100
18	185	Lifetime	185	200
19	18.5	12 months	78	50
20	18.5	11 months	77	50
21	18.5	10 months	68	50
22	37	10 months	122	50
23	18.5	9 months	63	50
24	37	9 months	110	50
25	18.5	8 months	60	50
26	37	8 months	104	50
27	74	8 months	190	50
28	18.5	7 months	54	50
29	37	7 months	91	50
30	74	7 months	168	50
31	18.5	6 months	48	50
32	37	6 months	84	50
33	74	6 months	155	50
34	148	6 months	235	50
35	18.5	5 months	42	50
36	37	5 months	74	50
37	74	5 months	127	50
38	148	5 months	203	50
39	18.5	4 months	37	50
40	37	4 months	67	50
41	74	4 months	114	50
42	148	4 months	167	50

Group Id	kBq Ingested Daily	Exposure	Mean Skeletal Dose Gy	No Rats
43	18.5	3 months	29	50
44	37	3 months	55	50
45	74	3 months	91	50
46	148	3 months	154	50
47	18.5	2 months	25	50
48	37	2 months	50	50
49	74	2 months	85	50
50	148	2 months	134	50
51	18.5	1 month	16	50
52	37	1 month	32	50
53	74	1 month	68	50
54	148	1 months	119	50

14.02 Bone Tumors and Life Span in Rats After Combined Exposure to Sr-89, I-131, Pm-147, Gamma Rays, Immunoglobulin, and Pesticides

Institution: URCRM, Urals Research Center of Radiation Medicine, Chelyabinsk, Russia

Scientists: V.L. Shvedov; retired

Purpose: To determine the risk of osteosarcoma from combinations of different radionuclides and radiation schedules to simulate situations possibly occurring in accidents.

Status: 1972-1992, terminated

Treatment: **Experiment A:** Continuous intake of radionuclides in food for the times indicated in the table gamma ray exposure (0.9 Gy/min) for 7 days with a dose schedule declining exponentially (day 1= 100%, day 2 =70%, day 3 =50%, day 4 = 35%, day 5 = 25 %, day 6 = 15%, day 7 =10%) . No correction for decay were applied for the application of Sr-90 and I-131.
Experiment B: Single injection of 11.1 kBq/g of Sr-90 and feeding of pesticides during lifetime
Experiment C: Single injection of 11.1 kBq/g of Sr-90 and injection of 25 mg/g of rat immunoglobuline (Ig) at different times after Sr-90 application.

Dosimetry: Activity fed or injected, mean dose calculated for the life-span of the animals (Sr-89. Sr-90 for skeleton, I-131 for thyroid, Pm-147 for gastro-intestinal tract, gamma-rays (ionization chamber) for whole body.

Endpoints: Life-span study (spontaneous death) with macroscopic microscopic pathology

Animal: Male white rats

Results: **Experiment A**: Rats exposed to combined external (gamma rays) or internal irradiation (Sr-89 irradiating mainly bone, I-131irradiating mainly thyroid and Pm-147 irradiating mainly the GI tract) did not display any syngergistic effect.
Experiment B: Chlorophos or lindanes administered in the food over a wide range of doses during the entire lifespan did no show a carcinogenic effect per se or a co-carcinigenic effect in combination wih Sr-90
Experiment C: Application of homologous immunoglobulin reduces osteosarcoma incidence and increases the life span of the animals

References:

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Experimental Groups:

Study 14.02
Bone Tumors and Life Span in Rats After Combined Exposure to Sr-89, I-131, Pm-147,Gamma Rays, Immunoglobulin, and Pesticides
Experiment A:
feeding with different radionuclides alone or in combination, or gamma ray exposure

Group Id	Daily Dose (kBq or Gy)	Duration of exposure (Days)	Mean exposure to target organ (Gy)	No Rats
1	0 (Control)	0	0	50
2	^{89}Sr 1.85	60	0.2	50
3	18.5	60	2	50
4	185	60	20	50
5	1850	60	200	50
6	^{131}I 1.85	16	0.26	50
7	18.5	16	2.6	50
8	185	16	26	50
9	1850	16	266	50
10	^{147}Pm 18.5 (1st day)	7	0.013	50
11	185 (1st day	7	0.13	50
12	1850 (1st day	7	1.3	50
13	18500 (1st day	7	13	50
14	**Gamma rays (Gy)** 0.5 (first day)	7	1.5	50
15	1 (first day	7	3	50
16	2 (first day	7	6	50
17	4 (first day	7	12	50
18	^{89}Sr 1.85 (kBq) ^{131}I 1.85	60 16	0.2 0.26	50
19	^{89}Sr 18.5 (kBq) ^{131}I 18.5	60 16	2 2.6	50
20	^{89}Sr 185 (kBq) ^{131}I 185	60 16	20 26	50
21	^{89}Sr 1850 (kBq) ^{131}I 1850	60 16	200 260	50
22	^{89}Sr 1.85 (kBq) ^{147}Pm 18.5	60 7	0.2 0.013	50

Group Id	Daily Dose (kBq or Gy)	Duration of exposure (Days)	Mean exposure to target organ (Gy)	No Rats
23	^{89}Sr 18.5 (kBq) ^{147}Pm 185	60 7	2 0.13	50
24	^{89}Sr 185 (kBq) ^{147}Pm 1850	60 7	20 1.3	50
25	^{89}Sr 1850 (kBq) ^{147}Pm 185 00	60 7	200 13	50
26	^{131}I 1.85 (kBq) ^{147}Pm 18.5	16 7	0.26 0.013	50
27	^{131}I 18.5 (kBq) ^{147}Pm 185	16 7	2.6 0.13	50
28	^{131}I 185 (kBq) ^{147}Pm 1850	16 7	26 1.3	50
29	^{131}I 1850 (kBq) ^{147}Pm 18500	16 7	216 13	50
30	^{90}Sr 1.85 (kBq) ^{131}I 1.85 ^{147}Pm 18.5 Gamma rays first day 0.5 Gy	60 16 7 7	0.2 0.26 0.013 1.5 1.5	50
31	^{90}Sr 18.5 (kBq) ^{131}I 18.5 ^{147}Pm 185 Gamma rays first day 1 Gy	60 16 7 7	2 2.6 0.13 1.5 3	50
32	^{90}Sr 185 (kBq) ^{131}I 185 ^{147}Pm 1850 Gamma rays 2 Gy	60 16 7 7	20 26 1.3 1.5 6	50
33	^{90}Sr 1850 (kBq) ^{131}I 1850 ^{147}Pm 18500 Gamma rays first day 4 Gy	60 16 7 7	216 26 13 1.5 12	50

Experiment B:
Single injection of Sr-90 in combination with feeding of pesticides

Group Id	Dose (kBq/g or mg/day)	Duration of exposure	No rats
34	0 Control		100 (50+50)
35	^{90}Sr 11.1 kBq/g	single injection	100
36	Lindan 5 mg/d	life span feeding	100
37	Chlorophos 25 mg/d	life span feeding	100
38	^{90}Sr 11.1 kBq/g Lindan 1 mg/d	single injection life span feeding	100
39	^{90}Sr 11.1 kBq/g Lindan 2 mg/d	single injection life span feeding	100
40	^{90}Sr 11.1 kBq/g Lindan 5 mg/d	single injection life span feeding	100
41	^{90}Sr 11.1 kBq/g Lindan 10 mg/d	single injection life span feeding	100
42	^{90}Sr 11.1 kBq/g Chlorophos 5 mg/d	single injection life span feeding	100
43	^{90}Sr 11.1 kBq/g Chlorophos 10 mg/d	single injection life span feeding	100
44	^{90}Sr 11.1 kBq/g Chlorophos 25 mg/d	single injection life span feeding	100
45	^{90}Sr 11.1 kBq/g Chlorophos 50 mg/d	single injection life span feeding	100

Experiment C:
Effect of immunoglobulin treatment on Sr-90 osteosarcoma

Group Id	^{90}Sr kBq/g	Time of inject. of Ig following Sr application	No Rats
46	11.1	none	158
47	11.1	2 h	89
48	11.1	1 d	86
49	11.1	2 d	91
50	11.1	10 d	98
51	11.1	30 d	99
52	11.1	90 d	80
53	11.1	180 d	81

15 EULEP European Late Effect Project Group

15.01 Brain Damage in Adult Rats After X-Irradiation

Institutions: European Late Effect Project Group (EULEP)
Co-operative CNS-vascular project
I SCK/CEN, Mol Belgium
II TNO Rijswijk, the Netherlands
III Univ. of Oxford, UK
IV Univ.Cath. Louvain Brussels, Belgium
V Univ. of Ulm FRG

Scientists:
I H. Reyners; active
E. Gianfelici; active
G.B. Gerber; retired
II H.S. Reinhold; active
A. van der Berg; active
III J.W. Hopewell; active
J.H. Wilkinson;active
T.K. Yeung; active
IV A. Keyeux; active
V W. Calvo; retired

Purpose: To determine the threshold, mechanism of action and consequences of irradiation to the adult brain.

Status: 1973- ongoing

Treatment: Single acute 250 kVp X-ray exposure (1-2 Gy/min doses 10-40 Gy) to a defined area of the upper part of the head. The following experimental series were carried out:

A) Changes in glia cell population and damage to the corpus callosum and fimbria following X-irradiation of Wistar or Sprague-Dawley rats at an age of 3 months (I, III). In one experiment, 30-40 mg/kg/d pentoxifylline was given in food for the entire period after exposure until sacrifice
B) Changes in brain morphology and vascular architecture following X-irradiation (20 or 25 Gy) of female WAG/Rij X BN rats at an age of 3 months and studied 13 -104 weeks later (III, II)
C) Definition of vascular damage prior to the development of white brain matter necrosis following X-irradiation of female Sprague-Dawley rats at an age of 3 months (17.5, 20, 22.5 or 25 Gy) studied 13, 26, 39 and 52 weeks later (III, V, II, IV, I)
D) Changes in biogenic amines (serotonin, dopamine, adrenalin, noradrenalin) and receptors of serotonin and dopamin in Wistar rats irradiated (2.2, 3.3, 4.4 and 6.6. Gy) at an age of 3 months and assayed 1, 2, 3, 6, 9, 12 and 18 months later (I, II)
E) Bloodflow, blood volume and vascular permeability and intra/extra-vascular space in the brain of female Sprague-Dawley rats irradiated (20 Gy) at an age of 3 months and assayed 0.5, 1, 3, 6 , 9, 12 or 18 months later (IV)

Dosimetry: Local X-irradiation following an EULEP protocol and standardized within EULEP using an ionization chamber

Endpoints: Serial killing after 1 -24 months, brain pathology (changes in glia cell populations (I), cortical pathology and blood vessel structure (III, II), areas of white matter at greatest risk (III, I, V, II), brain biochemistry (I), brain haemodynamics (IV)

Animal: Three month old Wistar, WAG/Rij X BN, or Sprague-Dawley rats

Results: **Mol:** The adult brain is extremely radioresistant: a dose of 25 Gy induces relatively few early changes except for an immediate transitory loss of glial progenitor cells. During the first months after the exposure, the blood vessels progressively loose endothelial cells whilst their glial mantle becomes

more pronounced. This occurs in a few well-defined brain areas near the ventricles and, in particular at the fimbria hippocampi. The lumina of the fimbria vessels often become very dilated (telangiectasia), leucocytes penetrate the vascular walls (diapedesis) and accumulate in the perivascular spaces. At 9 months post-irradiation, a regenerative reaction with proliferation of endothelial and glial cells sets in but soon aborts and progresses towards an increasing necrose of the fimbria and the adjacent hippocampus. These late deterministic effects are only observed after doses of 20 Gy or more. The latency period is 30% longer in Wistar than in Sprague Dawely rats. Treatment with pentoxifylline had no influence on the development of late effects.
Biochemical studies of amino acids, biogenic amines and receptors in different brain areas show early changes in permeability followed by changes in DNA, serotonin and blood flow at about the same doses at which permanent morphological damage manifests itself.

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Experimental Groups:

Study 15.01
Brain Damage in Adult Rats After X-Irradiation
Experimental series A

Dose Gy	Group Id / Number of Wistar Rats at Months Assayed after Exposure					
	1-3		6-12		>12	
	Id	Rats	Id	Rats	Id	Rats
0	1	208	2	99	3	137
2.5	4	11	5	5		
5.5	6	22	7	5	8	3
10	9	20	10	10	11	4
14.5	12	50	13	5	14	2
20	15	88	16	42	17	40
25	18	12	19	17	20	6
30	21	24	22	17	23	13
40	24	50	25	8	26	13
60	27	54	28	17	29	10
100	30	17			31	2

SPRD Mol and Oxford Dose Gy	Group Id - Number of Animals at Months Assayed after Exposure													
	6		7		8		9		10		11		12	
0	32	10	33	8	34	17	35	20	36	6	37	7	38	5
20	39	10	40	8	41	18	42	6	43	1			44	1
25	45	25	46	18	47	20	48	25	49	7	50	8	51	11
30	52	4			53	1	54	2	55	2				

SPRD Mol and Oxford Treatment +Dose Gy	Group Id - Number of Aimals at Weeks Assayed after Exposure							
	26		39		52		75	
none +0	56	8	57	8	58	8	59	7
none +25	60	8	61	8	62	8	63	6
Pentoxifylline +25	64	8	65	8	66	7	67	6

16 University of Oxford, CRC Normal Tissue Radiobiology Research Group

16.01 Skin Damage from Single and Fractionated X-Ray or Neutron Exposure

Institution: CRC Normal Tissue Radiobiology Research Group, The Churchill Hospital, Oxford, UK

Scientists: J.W. Hopewell; active

Purpose: To determine the threshold, dependence on field size and radiation quality of different deterministic radiation effects in pig skin with the aim to recommend dose limits and assess risks.

Status: 1980- 1989

Treatments: Single or fractionated X-ray exposure (250 kV, HVL 1.3 mm Cu, dose rates 0.54-071Gy/min, 50 cm FSD) to 4x4 cm or 16x4 cm fields on the flank of pigs 52 large fields on 26 pigs, 48 small fields on 17 pigs
Single or fractionated exposure to 42 MeV d-Be cyclotron neutrons 0.54 Gy/min

Dosimetry: Tissue equivalent extrapolation chamber

Endpoints: Observation of the skin reaction with respect to erythema, moist desquamation and late dermal atrophy using a quantitative scoring scheme

Animal: 35 or 52 week old large white female pigs with 2-4 irradiation on the flank of each pig

Results: Moist desquamation developed with an ED50 of 27 Gy for a single dose of X-rays to more than 60 Gy for a highly fractionated X-ray exposure (fractionated over 18 days or more). For single exposure from neutrons this ED50 was >19.25 Gy and increased to about 24 Gy for similar fractionation schedules. Late dermal necrosis developed after about 4 months after X-irradiation and after about 2.5 months after neutron irradiation with ED 50 of about 21 Gy for a single exposure to an X-rays and more than 70 Gy for the most highly fractionated exposure (30 fractions over 39 days). For a single exposure to neutrons this ED50 was about 15 Gy increasing to more than 23 Gy for the most highly fractionated application. The observed upper RBE value was ca 2.75 for moist desquamation and > 3 for ischemic dermal necrosis when doses of 2- 5 Gy were given in a fraction. The upper limiting RBE value was calculated as 4.32. In order to spare late effects in skin and subcutaneous tissue a relatively small number of fraction delivered in a short overall treatment time appears to be optimal for fast neutron therapy.

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Experimental Groups:

Study 16.01

Skin Damage from Single and Fractionated X-Ray or Neutron Exposure

A. X-ray exposure

X-rays, single exposure Field size			X-rays, fractionated exposure fractions/ days field 16x4 cm							
			6F/18d		6F/39d		6F/18d		12F/18 d	
Gy	4x4 cm	4x16 cm	Gy	No	Gy	No	Gy	No	Gy	No
8	4	12	26.5	5	29	3	48	6	50.7	6
15.4	0/4	4	37.9	15	41.4	6	54	6	57.1	6
18	4/10	15/28	43.5	11	47.6	6	60	6	60.6	8
20.7	16/18	14/16	49.2	13	53.8	7			64.1	6
23.4	14/14	8/8	54.9	9					67.6	5
26.1	2/2								71.1	6
18[1]	6/8		14F/39d		18F/39d		30F/30d			
20.7	8/8		Gy	No	Gy	No	Gy	No		
23.4	8/8		50.7	6	62.1	2	52.5	7		
18[2]	8/10		58.3	6	65	5	61.5	12		
20.7	15/17		65.9	9	70.2	7	66.1	5		
23.4	10/10		73.6	8	74	3	70.7	8		
							80	18		

Pigs of 12-14 w of age except [1]35 w and [2]52 weeks

B. Neutron Exposure

Neutrons Single Exposure		Neutrons fractionated exposure fractions/ days field 16x4 cm									
		6F/18d		6F/39d		12F/18d		12F/39d		30F/39d	
Gy	No	Gy	No	Gy	No	Gy	No	Gy	No	Gy	No
11	6	17.5	4	16.6	6	19.5	5	18.3	6	21.5	6
13	8	19.3	7	19.5	8	21.5	6	21.5	5	23.5	6
15	9	22.4	7	22.4	4	23.5	5	24.7	5	25.5	6
17.3	2										
19.5	2	-									

16.02 Skin Damage from Single and Fractionated Beta-Ray Exposure Delivered from Radionuclides of Different Beta Energy, Different Applicator Sizes and Dose Rates

Institution: CRC Normal Tissue Radiobiology Research Group, The Churchill Hospital, Oxford, UK

Scientists: J.W. Hopewell; active
M.W. Charles; active, Radiobiology Laboratory Health Physics Research, Berkeley Nuclear Laboratories

Purpose: To determine the threshold, dependence on field size and radiation quality of different deterministic radiation effects in pig skin with the aim to recommend dose limits and assess risks.

Status: 1980- ongoing

Treatments: Exposure to Sr-90 (E-max 2.27 Mev), Tm-170 (E-max 0.97 Mev) or Pm-147 (E-max 0.225 Mev) beta rays via applicators of different diameters

Dosimetry: Tissue equivalent extrapolation chamber

Endpoints: Observation of the skin reaction with respect to erythema, moist desquamation and late dermal atrophy using a quantitative scoring scheme

Animal: 35 or 52 week old large white female pigs with 2-4 irradiation on the flank of each pig

Results: The proportion of fields developing moist desquamation increased with doses after an initital threshold dose and allowed to calculate ED50 values. These EDs declined markedly when the Sr-90 field was increased from 5 to 70 mm diameter. For the Tm-170 the dose effect curves were shallower than for Sr-90 and showed a less marked dependence on field size, possibly because of different stimulatory action and because more cells are preserved in the deeper part of the regions exposed to Tm-170.Studies with Sr-90 sources of different dose rate showed a reduction in ED 50 value of a factor of more than twice for a reduction in doses rate from 3Gy/min to 0.023 Gy/min and of a factor of more than 3 for a dose rate of 0.001 Gy/min. Pm-147, because of its low penetrating beta rays, produces a different response and shows only little dependence on field size. Regarding late atrophy, keeping doses below 10 and 15 Gy from 5-22.5 mm diameter sources for respectively Sr-90 and Tm-170 would avoid early skin damage. Studies using "hot particles" indicate that about 120 Gy can cause acute necrosis/ulceration.

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Experimental Groups:

Study 16.02

Skin Damage from Single and Fractionated Beta-Ray Exposure Delivered from Radionuclides of Different Beta Energy, Different Applicator Sizes and Dose Rates

Sr-90 No of reacting / No of irradiated fields by applicators of mm diameter

40mm		22.5mm		15mm		11mm		5mm		2mm		1mm	
Gy	No	Gy	No	Gy	No	Gy	No	Gy	No	Gy	No	Gy	No
16.7	9/5	16.7	0/10	30	2/8	23	0/6	25	0/18	150		70	
23:4	2/11	23.4	1/29	45	6/11.	33	4/12	40	1.5/8	300		150	
26.7	4/12	26.7	26.5/50	60	9.5/11	44	9.5/15	50	6/28	400		300	
30	8/8	33	26.5/31	75	9/11	66	11/14	75	18/28	500		500	
33	9/12	40	24.5/27	90	9/11	99	10/13	100	30/30	750		1000	
40	5/5	52	12/12	105	4/4	120	4/4	125	10/10				

Tm-170 No of reacting / No of irradiated fields by applicators of mm diameter

19mm		9mm		5 mm		2 mm		1 mm		0.5 mm		0.1 mm	
Gy	No	Gy	No	Gy	No	Gy	No	Gy	No	Gy	No	Gy	No
29.4	0/8	40	0/26	48.3	11/26	70	0/16	72.8	1/10	191	0/10	81.9	2/12
36.3	1/8	60	11/36	72.4	4.25/20	140	0/18	131	1/10	245	2.5/15	147	3.5/12
44	0/8	80	41.5/70	96.5	13/18	258	6/20	182	5/15	301	8.5/14	262	4/10
68.9	4.5/10	100	26.5/32	121	13.25/14	280	3.5/16	364	8.5/15	413	11/15	343	9/10
88	7/11	120	8/14	145	8.5/10	378	17.5/20	554	13/15	734	13.5/15	442	8/10
110	4/4			193	10/10	380	7.5/10	757	10/10	1010	5/5	786	10/10
140	4/4					420	7/8						
						514	15/18						
						771	13/18						
						1028	9.5/10						
						1541	10/10						

Pm-147 No of reacting / No of irradiated fields by applicators of mm diameter

15 mm		9 mm		5 mm		2 mm	
Gy	No	Gy	No	Gy	No	Gy	No
250	0/10	375	0/10	250	0/5	250	0/5
375	3.5/10	500	2/10	375	1/11	400	0/11
500	6/14	600	7/10	500	3/12	510	3/12
620	6.5/10	750	9.5/10	620	6/11	620	2/11
750	9.5/10	875	7/7	750	10/14	750	5.5/12

Effect of dose rate for Sr-90 beta rays exposure; for 3 Gy/min see above

107 mGy/min		52 mGy /min		22 mGy/min	
Gy	No	Gy	No	Gy	No
15		25		50	
22.5		30		60	
25		40		70	
30		45		80	
35		50		90	
40		55			
50					

16.03 Skin Damage from Sr-90 Beta-Rays Delivered at Different Fractionation Schedules

Institution: CRC Normal Tissue Radiobiology Research Group, The Churchill Hospital, Oxford, UK

Scientists: J.W. Hopewell; active
G.J.M.J. van den Aardweg; active, Dr Daniel den Hoed Cancer Centre, Rotterdam NL

Purpose: To determine the threshold, dependence on field size and radiation quality of different deterministic radiation effects in pig skin with the aim to recommend dose limits and assess risks.

Status: 1989- ongoing

Treatments: Exposure to Sr-90 (E-max 2.27 Mev) delivered from a 22.5 cm diameter applicator (dose rate ca 3Gy/min) in different fractionation schedules either fractionated at intervals which allowed complete repair or with 2 fractions each of which separated by an interval short enough that only incomplete repair could proceed. In several studies, the dose was supplemented by a "Top Up" (TU dose) of 17 Gy (half tolerance) 24 h after the last fractions. These schedules were chosen for a mathematical modelling of the results.

Dosimetry: Doses measured at 16 µm below surface with a tissue equivalent extrapolation chamber

Endpoints: Observation of the acute skin reaction with respect to erythema and moist desquamation using separate scoring systems and observations over a period of 9 weeks .

Animal: 35 or 52 week old large white female pigs with 2-4 exposure fields on the flank of each pig which were anaesthesized with 70% oxygen, 30% nitrous oxide and 2% halothane.

Results: The data were analysed by models (Thames) assuming mono- or bi-exponential kinetics for the repair of sublethal damage. For the monoexponential model a half time of 0.74 h was obtained, for the biexponential model a fast component with a half time of 0.09 h could be distinguished from a slow component with 4.5 h half time. The data were also analysed by the generalized LQ equation of Millar also yielding a slow and rapid component of repair. The presence of a slow component suggests the need for a careful control of the intervals in accelerated fractionation schedules used in tumor therapy.

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Experimental Groups: **Study 16.03**

Skin Damage From Sr-90 Beta-Rays Delivered at Different Fractionation Schedules

Values represent number of reacting/ number of total fields irradiated

Number of Fractions and TopUp dose (17 Gy) for "complete repair data"													
10 F		14 F		5F +TU		7 F+TU		TU + 10F		14 F +TU		TU +14F	
Gy	No	Gy	No	Gy	No	Gy	No	Gy	No	Gy	No	Gy	No
47	½/ 13	68	2½/12	28.5	3½/15	30	3/11	30	0/9	45	4/16	45	3/10
54	1½/ 12	73	2/10	31	4/16	34	5/22	35	2/10	47.5	5/16	47.5	2/9
56	1/14	78	2/8	33.5	7/16	36.5	2/12	40	2/8	50	4/15	50	3/10
57	3½/12	82	5/9	36	9½/16	38	6/10	45	5/9	52.5	7/15	52.5	3/9
60	5/13	87	7/8			39	2½/10	50	7/9	55	8½/ 14	55	5½/9
62	3½/11	92	9/10			41	4/10	55	6½/9	57.5	9/15	57.5	5/9
63	4/14					42	7/10	60	7/9	60	12/14	60	7/9
66	6½/12					43.5	6½/ 10			62.5	9½/ 14	62.5	6/9
67	6½/10					46	12½/19			65	10/14	65	7/9
70	5 ½/10					50	6/8			67.5	13/15	67.5	9/9
72	8½/11												
74	6/11												
77	6½/12												
84	11/11												

Number of Fractions and TopUp dose (17 Gy) for "incomplete repair data"													
14x2F/0.5h		14x2F/1.0h		14x2F/4h		14x2F/8h		7x2F/0.17h +TU		14x2F/0.33h +TU		14x2F/0.5h +TU	
Gy	No	Gy	No	Gy	No	Gy	No	Gy	No	Gy	No	Gy	No
55	0/12	77	4/10	82	0/11	90	3/9	32.5	1/11	38	8½23	32.5	2/12
65	0/12	82	3/10	87	2/9	95	4/11	35.5	1/12	41	11/23	37.5	2½/12
75	2½/10	87	8½/12	92	7/10	100	6/11	38.5	2 ½/10	44	9/19	42.5	2/10
85	3/10	92	7/10	97	9/12	105	8/10	41.5	5/10	47	12½/19	47.5	5/10
95	6/10	97	7 ½/9	102	7½/10	110	6/9	44.5	7 ½/10	50	10/19	52.5	6/10
105	7/10	102	10/11	107	9 ½/10	115	9/9	47.5	7/9	53	17/19	57.5	7/10
						120	7½/8			7x2F/1h +TU		7x2F/4h + TU	
						125	7½/8						
						130	9/9			Gy	No	Gy	No
						135	9/9			41	3/10	41	1/12
										43.5	6/12	43.5	1½/10
										46	4/9	46	3/10
										48.5	4/8	48.5	7/10
										51	7½/12	51	6/10
										53.5	8/10	53.5	5/10

17 Universität Ulm, Institut für Arbeits und Sozialmedizin

17.01 Repopulation of Aplastic Bone Marrow After Total-Body Irradiation by Transfusion of Blood-Derived Autologous Stem Cells

Institute: Institute of Clinical Physiology and Occupational Medicine, University of Ulm, FRG

Scientists: W. Nothdurft; active
C. Bruch; active
W. Calvo; retired
T. M. Fliedner; active

Purpose: To study the bone marrow repopulating capacity of blood-derived stem cells after total body irradiation under autologous conditions using transplants of different cell numbers.

Status: 1973 - 1975

Treatment: Total body irradiation (300 kV X-rays; HVL = 3.8 mm Cu; dose rate 65 mGy/min) by bilateral exposure; single dose of 11.7 Gy at the mid-line in soft tissue. Injection of autologous mononuclear and GM-CFC stem cells.

Dosimetry: Measurements with ionization chambers and LiF-TLDs in phantoms and dog cadavers at several reference positions including marrow spaces in different bones in situ

Endpoints: Hemopoietic recovery (bone marrow and blood cells) within the first weeks in relation to the cell numbers transfused in individual dogs; follow-up of hemopoietic function over 1 to 3 years after TBI; macroscopic/microscopic studies on lympho-/hemopoietic tissues and other organs at autopsy.

Animals: Dogs (Beagles); males and females of unknown age (1-4 years)

Results: The long-term survival obtained for 7 of the 8 dogs transplanted indicated that it was feasible to establish a "blood stem-cell bank" of cryopreserved blood leukocytes among which are cells capable of inducing and maintaining hematopoietic recovery in dogs rendered aplastic by means of lethal whole body x-irradiation. The pattern of bone marrow restoration was related to the number of mononuclear blood leukocytes transfused.
However, a lesion developed in the marrow, consisting of a fibrosis originating in conjunction with or from the endosteum. The fibrotic tissue substantially reduced the available marrow space in dogs with advanced lesions. The kidneys of all dogs showed glomerular sclerosis. Fibrotic lesions were noted in the pancreas in four of the seven long-term survivors.

References:

Fliedner, T.M., H.D. Flad, C. Bruch, W. Calvo, S.F. Goldmann, E. Herbst, E. Hügl, R. Huget, M. Körbling, K. Krumbacher, W. Nothdurft, W.M. Ross, H.P. Schnappauf and I. Steinbach. Treatment of aplastic anemia by blood stem cell transfusion: a canine model. *Haematologica* **61**:141-156, 1976.

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Experimental Groups:

Study 17.01
Repopulation of Aplastic Bone Marrow After Total-Body Irradiation by Transfusion of Blood-Derived Autologous Stem Cells

Group Id	TBI Conditioning (Gy)	No Dogs	Cells transfused per kg body weight		Survival (days)
			MNC* x 10^{-9}	GM-CFC x 10^{-5}	
1	11.7	8	0.32 - 1.63	0.02 - 1.38	(20), 259-898

* MNC = mononuclear cells

17.02 Repopulation of Aplastic Bone Marrow After Total-Body Irradiation by Transfusion of Blood-Derived Stem Cells From Allogeneic DLA-Identical MLC-Negative Donors

Institution: Institute of Clinical Physiology and Occupational Medicine, University of Ulm, FRG

Scientists: W. Nothdurft, T.M. Fliedner, W. Calvo (retired), F. Carbonell, H.D. Flad, R. Huget, M. Körbling, K. Krumbacher-von Loringhofen, W. M. Ross, H.P. Schnappauf, I. Steinbach (all others active)

Purpose: To study the bone marrow repopulating capacity of allogeneic blood-derived stem cells after total body irradiation for DLA-identical MLC-negative donor-recipient combinations
A) Without immunosuppressive treatment
B) With immunosuppressive treatment using methotrexate (MTX).

Status: 1972 - 1977

Treatment: Total body irradiation (300 kV X-rays; HVL = 3.8 mm Cu; dose rate 65 mGy/min) by bilateral exposure; single dose of 11.7 Gy at the midline in soft tissue. MTX ,0.25 mg per kg body weight was given on days 1, 3, and 6 after irradiation; on day 11 and therafter 0.5 mg per kg body weight was given at weekly intervals for 100 days.

Dosimetry: Measurements with ionization chambers and LiF-TLDs in phantoms and dog cadavers at several reference positions including marrow spaces in different bones in situ

Endpoints: Engraftment and hemopoietic recovery under allogeneic conditions, dependences on cell numbers in the transplant, GvH reaction in individual dogs
A) Without immunosuppressive treatment
B) Receiving treatment with methotrexate

Animal: Dogs (Beagles), males and females of uncertain age (probably 1-4 years)

Results: The kinetics of hemopoietic recovery and the long-term survival of some of the dogs indicated that cryopreserved blood-derived mononuclear cells were able to repopulate the aplastic bone marrow under allogeneic histocompatible transplantation conditions. Graft-versus-host disease was overcome in some of the dogs by methotrexate treatment. Chromosomal analysis of lymphohemopoietic cells

from 5 dogs which had received blood MNC from a donor of the opposite sex, revealed donor-type cells only, no recipient type cells, at least up to 1150 days in the long-term survivors (Carbonell et al. 1984).

References: Fliedner, T.M., H.D. Flad, C. Bruch, W. Calvo, S.F. Goldmann, E. Herbst, E. Hügl, R. Huget, M. Körbling, K. Krumbacher, W. Nothdurft, W.M. Ross, H.P. Schnappauf and I. Steinbach. Treatment of aplastic anemia by blood stem cell transfusion: a canine model. *Haematologica* **61**:141-156, 1976.

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Nothdurft, W. Use of peripheral blood stem cells for transplantation. Experimental protocols performed by the Ulm group, pp. 73-94. *In* E.P. Cronkite and H. Seidel [eds.], *The Haemopoietic Stem Cell.* Universitätsverlag, Ulm, 1989.

Experimental groups:

Study 17.02
Repopulation of Aplastic Bone Marrow After Total-Body Irradiation by Transfusion of Blood-Derived Stem Cells from Allogeneic DLA-Identical MLC-Negative Donors

Group No	TBI Conditioning (Gy)	Immuno-suppression	No dogs	Cells transfused per kg body w.		Survival (days)
				MNC[2] x 10^{-9}	GM-CFC x 10^{-5}	
1	11.7	no	12	0.39 - 2.76	0.02 - 1.91	6 - 1411
2	11.7	MTX[3]	12	0.51 - 1.87	0.07 - 1.42	8 - 1081
3[1]	11.7	MTX	2	0.68 - 0.73	0.33 - 0.35	29 - 129

[1] dogs of group 3 (homozygous for the haplotype 2.4) received cells from heterozygous (2.4/2.5) donors
[2] MNC = mononuclear cells
[3] MTX = methotrexate

17.03 Hematological Effects of Total-Body Irradiation with Small Radiation Doses in Dogs

Institution: Institute of Clinical Physiology and Occupational Medicine, University of Ulm, FRG

Scientists: W. Nothdurft, T.M. Fliedner, H. H. Gerhartz, W.M. Ross, K.H. Steinbach (all active)

Purpose: To study the acute effects and possible long-term alterations in the hemopoietic system after total body irradiation with small radiation doses in the range from 0.2 to 1.6 Gy, with special emphasis laid on comprehensive quantitative and qualitative analyses of the granulocyte-macrophage progenitor cell (GM-CFC) populations in the bone marrow and the blood.

Status: 1976 - 1982

Treatment: Total body irradiation (300 kV X-rays; HVL = 3.8 mm Cu; dose rate 65 mGy/min) by bilateral exposure; single doses of 0.21 Gy, 0.42 Gy, 0.8 Gy and 1.6 Gy at the midline in soft tissue

Dosimetry: Measurements with ionization chambers and LiF-TLDs in phantoms and dog cadavers at several reference positions including marrow spaces in different bones in situ

Endpoints: Different hematological parameters including determinations of GM-CFC in the bone marrow and the blood and colony stimulating activity (CSA) in the serum; sequential studies over 90 to 160 days after TBI

Animal: Dogs (Beagle), males and females, age 15 to 30 months

Results: The blood GM-CFC concentration was depressed in the first 21 days in a dose-dependent fashion. The regeneration within the first 30 to 40 days after TBI of the blood granulocyte values and the repopulation of the bone marrow GM-CFC compartment was associated with a dose-dependent increase in colony-stimulating activity (CSA) in the serum. The slow repopulation of circulating blood GM-CFC to about only 50% of normal even between days 157 and 164 after TBI could be related to a correspondingly delayed reconstitution of the mobilizable GM-CFC subpopulation in the bone marrow.

References:

Gerhartz, H.H., W. Nothdurft and T.M. Fliedner. Effect of low dose whole body irradiation on granulopoietic progenitor subpopulations: implications for CFU-C release. *Cell Tissue Kinet.* **15**:371-379, 1982.

Nothdurft, W. and T.M. Fliedner. The response of the granulocytic progenitor cells (CFU-C) of blood and bone marrow in dogs exposed to low doses of X-irradiation. *Radiat. Res.* **89**:38-52, 1982.

Nothdurft, W., K.H. Steinbach and T.M. Fliedner. Dose- and time-related quantitative and qualitative alterations in the granulocyte/macrophage progenitor cell (GM-CFC) compartment of dogs after total-body irradiation. *Radiat. Res.* **98**:371-379, 1984.

Experimental Groups

Study 17.03
Hematological Effects of Total-Body Irradiation with Small Radiation Doses in Dogs

Group Id	Treatment	Radiation Dose (Gy)	No Dogs	Days After TBI
1	Controls	0	2	90
2		0	3	160
3	TBI	0.21	2	90
4	TBI	0.42	2	90
5	TBI	0.84	2	90
6		0.78	3	160
7	TBI	1.57	3	160

17.04 Hematological Effects of Unilateral and Bilateral Exposures of Dogs to 300-kV X-rays

Institution: Institute of Clinical Physiology and Occupational Medicine, University of Ulm, FRG

Scientists: W. Nothdurft; active
K. Baltschukat; active

Purpose: To study the acute hematological effects and long-term alterations in the bone marrow function in dogs after total body irradiation with homogenous or inhomogenous dose distributions.

Status: 1986 - 1988

Treatment: Total body irradiation (300 kV X-rays; HVL = 3.8 mm Cu; dose rate 6.5 cGy/min) by unilateral or bilateral exposures resulting in inhomogenous or homogenous bone marrow dose distributions, but causing the same systemic damage to the progenitor cell pools as determined for the survival fractions of GM-CFC.

Dosimetry: Measurements with ionization chambers and LiF-TLDs in phantoms and dog cadavers at several reference positions including marrow spaces in different bones in situ

Endpoints: Different hematological parameters including determinations of GM-CFC in the bone marrow and blood, bone marrow stromal cell progenitors (CFU-F) and colony-stimulating activity (CSA) in the serum; sequential studies over 1 year after the exposure

Animal: Dogs (Beagles), males and females, 12 to 20 months

Results: In the unilaterally irradiated dogs showing a steep radiation dose gradient in the different bones of the skeleton the regeneration of the GM-CFC compartments in the various bone marrow spaces showed patterns which were independent of each other up to day 28. Certain residual hemopoietic and stromal defects could be observed 1 year after the exposure in the bone marrow of unilaterally as well as bilaterally exposed animals, i.e. a dose-dependent reduction in the number of progenitor cells of erythropoiesis (BFU-E) and granulocytes/monocytes (GM-CFC) and fibroblastoid-colony forming cells (CFU-F). A significant degree of emperipolesis, i.e. cytotoxic immigration of granulocytes into megakaryocytes could be established as another late consequence of irradiation.

References:

Baltschukat, K. and W. Nothdurft. Haematological effects of unilateral and bilateral exposures to 300 kVp X-rays. *Radiat. Res.* **123**:7-16, 1990.

Kreja, L., W. Weinsheimer, C. Selig and W. Nothdurft. Effects of total-body irradiation on bone marrow erythroid burst forming units (BFU-E) and hemopoietic regeneration in dogs. *Radiat. Res.* **135**:315-319, 1993.

Calvo, W., R. Alabi, W. Nothdurft and T.M. Fliedner. Cytotoxic immigration of granulocytes into megakaryocytes as a late consequence of irradiation. *Radiat. Res.* **138**:260-265, 1994.

Experimental Groups:

Study 17.04
Hematological Effects of Unilateral and Bilateral Exposures of Dogs to 300-kV X-rays

Group Id	Exposure	Radiation dose (Gy) Entrance	Exit	Mean marrow	No Dogs	Days after Exposure
1	Unilateral	3.8	0.9	1.8	6	370
2	Bilateral	2.1	2.1	1.7	3	370

17.05 Hematological Effects of Partial-Body Irradiation in Dogs with Large Radiation Doses Given to the Upper Or Lower Part of the Body

Institution: Institute of Clinical Physiology and Occupational Medicine, University of Ulm, FRG

Scientists: W. Nothdurft; active
K. Baltschukat; active
W. Calvo; retired
T.M. Fliedner; active
V. Klinnert; active
K.H. Steinbach; active
C. Werner; active

Purpose: To study the acute hematological effects and long term alterations in the bone marrow in the upper part of the body (70% of total mass) or the lower part (30% of total mass) after irradiation with a single dose of 11.7 Gy

Status:: 1982 - 1986

Treatment: Irradiation of the upper part of the body (UBI) including the 4th lumbar vertebra comprising 72% of the total bone marrow mass; or irradiation of the lower part (LBI, excluding the 4th lumbar vertebra) comprising 28 % of the total bone marrow mass; radiation dose at each exposure 11.7 Gy in soft tissue on the midline of the body.

Dosimetry: Measurements with ionization chambers and LiF-TLDs in phantoms and dog cadavers at several reference positions including marrow spaces in different bones in situ.

Endpoints: Different hematological parameters including determinations of GM-CFC in the bone marrow and blood, bone marrow stromal progenitor cells (CFU-F) and colony-stimulating activity (CSA) in the serum; sequential studies over 1 year after the exposure.

Animal: Dogs (Beagles), males and females, age 16 to 24 months

Results: After irradiation of the upper body (UBI) in the irradiated bone marrow, virtually no GM-CFC could be detected on day 1 after exposure. Beginning on day 7, a continuous increase took place up to day 21 when the GM-CFC concentration reached between 25% (sternum) and 43% (humerus) of the initial value. No further increase took place up to day 80. Between day 120 and 380 a secondary increase was observed which reached near-normal bone marrow GM-CFC concentrations. Apart from some quantitative differences, after irradiation of the lower body (LBI), the time-related pattern of changes in the concentration of granulocyte/macrophage progenitor cells (GM-CFC) in irradiated and shielded bone marrow sites was very similar to that observed after UBI. Interestingly, the progenitor-cells of the stromal fibroblastoid cells (CFU-F) in the irradiated bone marrow remained clearly subnormal for more than 1 year after UBI signalling some residual stromal damage.

References:

Nothdurft, W., W. Calvo, V. Klinnert, K.H. Steinbach, C. Werner and T.M. Fliedner. Acute and long-term alterations in the granulocyte/macophage progenitor cell (GM-CFC) compartment of dogs after partial body irradiatiaon: irradiation of the upper body with a single myeloablative dose. *Int. J. Radiat. Oncol. Biol. Phys.* **12**:949-957, 1986.

Baltschukat, K., T.M. Fliedner and W. Nothdurft. Hematological effects in dogs after irradiation of the lower part of the body with a single myeloablative dose. *Radiother. Oncol.* **14**:239-246, 1989.

Calvo, W., R. Alabi, W. Nothdurft and T.M. Fliedner. Cytotoxic immigration of granulocytes into megakaryocytes as a late consequence of irradiation. *Radiat. Res.* **138**:260-265, 1994.

Experimental Groups:

Study 17.05
Hematological Effects of Partial-Body Irradiation in Dogs with Large Radiation Doses Given to the Upper Or Lower Part of the Body

Group Id	Exposure	Radiation Dose (Gy)	% Total bone marrow	No dogs	Days After Exposure
1	Upper body	11.7	72 %	3	380
2	Lower body	11.7	28 %	6	380

17.06 Hematological Effects in Dogs of Sequential Irradiation of the Upper and Lower Part of the Body with Myeloablative Radiation Doses

Institution: Institute of Clinical Physiology and Occupational Medicine, University of Ulm, FRG

Scientists: W. Nothdurft; active
K. Baltschukat; active
T.M. Fliedner; active

Purpose: To study the compensatory mechanisms determining the tolerance of the hemopoietic system to sequential hemibody irradiation involving large fractions of the total bone marrow mass and late effects in bone marrow function

Status: 1984 - 1985

Treatment: Irradiation of the upper part of the body (UBI, including the 4th lumbar vertebra) comprising 72% of the bone marrow mass with a dose of 11.7 Gy followed after 56 days by irradiation with a dose of 11.7 Gy given to the lower part of the body (LBI) including 28 % of the total bone marrow mass

Dosimetry: Measurements with ionization chambers and LiF-TLDs in phantoms and dog cadavers at several reference positions including marrow spaces in different bones in situ

Endpoints: Different hematological parameters including determinations of GM-CFC in the bone marrow and blood, bone marrow stromal progenitor cells (CFU-F) and colony-stimulating activity (CSA) in the serum; sequential studies over 1 year after the second exposure

Animal: Dogs (Beagles), males and females, age 12 to 17 months

Results: UBI involving the abrogation of approximately 70% of the total active marrow was followed by an immediate increase in the proliferation and differentiation of GM-CFC in the protected bone marrow. Repopulation of the GM-CFC in the irradiated sites due to seeding of hemopoietic cells from the protected marrow already became evident at day 7 after UBI. At day 56 after UBI, when the irradiation of the lower body (LBI) was performed, the GM-CFC had recovered to between 30 and 40% of their pre-treatment values. Despite this incomplete regeneration, the GM-CFC compartment responded to LBI in a similar way as the GM-CFC had in the protected (normal) marrow after UBI, i.e. by an increased proliferation for at least 21 days. Already at day 7, the bone marrow of the iliac crest that had been exposed to LBI showed a considerable number of GM-CFC. Within 370 days all the bone marrow sites irradiated during either the first or the second treatment had regained nearly normal GM-CFC values.

References: Nothdurft, W., W. Calvo, V. Klinnert, K.H. Steinbach, C. Werner and T.M. Fliedner. Acute and long-term alterations in the granulocyte/macophage progenitor cell (GM-CFC) compartment of dogs after partial body irradiatiaon: irradiation of the upper body with a single myeloablative dose. *Int. J. Radiat. Oncol. Biol. Phys.* **12**:949-957, 1986.

Baltschukat, K., T.M. Fliedner and W. Nothdurft. Hematological effects in dogs after irradiation of the lower part of the body with a single myeloablative dose. *Radiother. Oncol.* **14**:239-246, 1989.

Nothdurft, W., K. Baltschukat and T.M. Fliedner. Hematological effects in dogs after sequential irradiation of the upper and the lower part of the body with single myeoloablative doses. *Radiother. Oncol.* **14**:247-259, 1989.

Nothdurft, W. Bone Marrow, pp. 113-169. *In* E. Scherer, C. Streffer and K.R. Trott [eds.], *Medical Radiology - Diagnostic Imaging and Radiation Oncology.* Springer Verlag, Berlin, Heidelberg, New York, London, Paris, 1991.

Experimental Groups:

Study 17.06
Hematological Effects in Dogs of Sequential Irradiation of the Upper and Lower Part of the Body with Myeloablative Radiation Doses

1st Exposure (UBI)			Interval Days	2nd Exposure (LBI)			Sacrifice Days
Field	Dose (Gy)	Bone Marrow		Field	Dose (Gy)	Bone Marrow	
Upper body	11.7	72 %	56	Lower body	11.7	28 %	380

No of animals = 3

17.07 Hematological Effects of rhGM-CSF in Dogs Exposed to Total-Body X-Irradiation with a Dose of 2.4 Gy

Institution: Institute of Clinical Physiology and Occupational Medicine, University of Ulm, FRG

Scientists: W. Nothdurft, C. Selig, T.M. Fliedner, P. Hintz-Obertreis, L. Kreja, D. Krumwieh, R. Kurrle, F.R. Seiler, W. Weinsheimer (all active)

Purpose: To study the role of (recombinant human) granulocyte-macrophage colony-stimulating factor as a stimulant of hemopoietic recovery after total body irradiation.

Status: 1989 - 1991

Treatment: Total body irradiation (300 kV X-rays; HVL = 3.8 mm Cu; dose rate 65 mGy/min) by bilateral exposure; single dose of 2.4 Gy at the midline in soft tissue; treatment with rhGM-CSF given as 2 dosages of either 10µg/kg or 30µg/kg per day by 2 daily subcutaneous injections for 21 days starting the first day after TBI

Endpoints: Different hematological parameters including determinations of GM-CFC in the bone marrow and the blood, colony stimulating activity (CSA), chGM-CSF and anti rhGM-CSF antibodies in the seriuml sequential studies over 1 year after exposure

Animal: Dogs (Beagles), males and females, age 12 to 48 months

Results: Treatment with rhGM-CSF decreased the severity and shortened the duration of neutropenia but had no significant influence on monocyte or lymphocyte recovery. The GM-CFC in the peripheral blood remained depressed during the whole treatment course, similar to the untreated irradiated controls. These results indicate that treatment with GM-CSF can be an effective biological monotherapy for radiation-induced bone marrow failure, but that for higher radiation doses the number of GM-CSF responsive target cells will become a critical determinant of therapeutic efficacy.

References: Nothdurft, W., C. Selig, T.M. Fliedner, A. Hintz-Obertreis, L. Kreja, D. Krumwieh, B. Kurrle, F.R. Seiler and W. Weinsheimer. Hematological effects of rhGM-CSF in normal dogs and in dogs exposed to total body irradiation with a radiation dose of 2.4 Gy. *Int. J. Radiat. Biol.* **61**:518-531, 1992.

Experimental Groups:

Study 17.07

Hematological Effects of rhGM-CSF in Dogs Exposed to Total-Body X-Irradiation with a Dose of 2.4 Gy

Group Id	Radiation Dose (Gy)	Treatment day 1 - day 21 after TBI	No Dogs	Sacrifice Days after TBI
1	0	Carrier, autolog. serum s.c.	3	360
2	0	rhGM-CSF, 10 µg/kg/day s.c.	2	360
3	0	rhGM-CSF, 30 µg/kg/day s.c.	2	360
4	2.4	Carrier, autolog. serum s.c.	4	360
5	2.4	rhGM-CSF, 10 µg/kg/day s.c.	2	360
6	2.4	rhGM-CSF, 30 µg/kg/day s.c.	2	360

17.08 Hematological Effects of rhIL-6 in Dogs Exposed to Total-Body X-Irradiation with a Dose of 2.4 Gy

Institution: Institute of Clinical Physiology and Occupational Medicine, University of Ulm, FRG

Scientists: W. Nothdurft, C. Selig, T.M. Fliedner, L. Kreja, H. Müller, E. Seifried (all active)

Purpose: To study the role of (recombinant human) interleukin 6 as a stimulant of hemopoietic recovery after total body irradiation.

Status: 1991 - 1993

Treatment: Total body irradiation (300 kV X-rays; HVL = 3.8 mm Cu; dose rate 65 mGy/min) by bilateral exposure; single dose of 2.4 Gy at the midline in soft tissue; treatment with rhIL-6 18 g/kg/day given by one subcutaneous injection for 14 days starting the first day after TBI

Dosimetry: Measurements with ionization chambers and LiF-TLDs in phantoms and dog cadavers at several reference positions including marrow spaces in different bones in situ

Endpoints: Different hematological parameters including determinations of GM-CFC in the bone marrow and blood and colony stimulating activity (CSA) and rhIL-6 levels in the serum; sequential studies over 1 year after the exposure

Animal: Dogs (Beagles), males and females, age 12 to 72 months

Results: No clear influence of IL-6 treatment on the pattern of recovery of lymphocytes could be detected in comparison to the irradiated control animals. In three of the four IL-6-treated dogs, thrombocyte counts increased 7 days earlier than in the non-treated controls. In two of the three dogs showing an accelerated recovery of platelet counts, however, treatment with IL-6 caused a strong decrease in the erythrocyte counts associated with a prolonged depression in reticulocyte concentration. There was no influence on the recovery of blood granulocytes. Another animal showed no influence of IL-6 on thrombocyte recovery but a strong depressive effect on erythrocyte and reticulocyte counts. The results show that for standardized conditions of radiation-induced bone marrow damage, the pattern of response to IL-6 in different hematopoietic lineages may show considerable variations between individuals.

References:

Selig, C., L. Kreja, H. Müller, E. Seifried, T.M. Fliedner and W. Nothdurft. Effects of recombinant human interleukin-6 (rhIL-6) on platelet counts, platelet functions and other hematological parameters in dogs exposed to a total body radiation dose of 2.4 Gy. Izotóptechnika *Diagnosztika* **37**(Suppl):65-72, 1994.

Selig, C., L. Kreja, H. Müller, E. Seifried and W. Nothdurft. Hematological effects of recombinant human interleukin-6 in dogs exposed to a total body radiation dose of 2.4 Gy. *Exp. Hematol.* **22**:551-558, 1994.

Experimental Groups:

Study 17.08
Hematological Effects of rhIL-6 in Dogs Exposed to Total-Body X-Irradiation with a Dose of 2.4 Gy

Group Id	Radiation Dose (Gy)	Treatment day 1 (day 14 after TBI)	No Dogs	Sacrifice Days after TBI
1	2.4	Carrier autolog. serum s.c.	5	360
2	2.4	rhIL-6 18 µg/kg/day s.c.	4	360

17.09 Hematological Effects of rhEpo and Recombinations of rhEpo with rhIL-1 or rhGM-CSF in Dogs Exposed toTotal-Body X-Irradiation with a Dose of 2.4 Gy

Institution: Institute of Clinical Physiology and Occupational Medicine, University of Ulm, FRG

Scientists: W. Nothdurft; active
C. Selig; active
L. Kreja, active

Purpose: To study the role of (recombinant human) erythropoietin and combinations of rhEpo with rh interleukin-1 or rh granulocyte-macrophage colony-stimulating factor as stimulants of hemopoietic recovery after total body irradiation.

Status: 1991 - 1993

Treatment: Total body irradiation (300 kV X-rays; HVL = 3.8 mm Cu; dose rate 6.5 cGy) by bilateral exposure; single dose of 2.4 Gy at the midline in soft tissue; treatment - with rhEpo 200 U/kg/day s.c. from day 3 to day 21 after TBI; - with rhIL-1 2.5 µg/kg/day i.v. from day 1 to day 7 after TBI; - with the combination in an overlapping application schedule; - with rhGM-CSF 30 µg/kg/day by two s.c. injections from day 1 to day 5 after TBI; - with the combination of rhGM-CSF with rhEpo in an overlapping application schedule

Dosimetry: Measurements with ionization chambers and LiF-TLDs in phantom and dog cadavers at several reference positions including marrow spaces in different bones in situ

Endpoints: Different hematological parameters including determinations of GM-CFC in the bone marrow and blood and colony stimulating activity (CSA) and rhEpo in the serum; sequential studies over 1 year after the exposure

Animal: Dogs (Beagles), males and females, age 12 to 48 months

Results: Epo when given alone caused a clear acceleration in erythropoietic regeneration. The attempt to improve platelet counts with a combination of rhGM-CSF and rhEpo failed, although rhEpo alone caused a weak elevation of the platelet counts in the thrombocytopenic state (day 7 to day 28). Treatment with rhIL-1 showed no or even a weak suppressive effect on the erythropoietic regeneration. The improvement of the reconstitution of platelet or granulocyte values was only marginal. RhEpo and its combination with rhIL-1 were able to support erythropoietic regeneration, even in a state of strongly reduced stem cell-reserve.

References: Baltschukat, K. and W. Nothdurft. Haematological effects of unilateral and bilateral exposures to 300 kVp X-rays. *Radiat. Res.* **123**:7-16, 1990.

Selig, C., W. Nothdurft, L. Kreja and T.M. Fliedner. Influence of combined treatment with interleukin 1 and erythropoietin on the regeneration of hemopoiesis in the dog after total body irradiation - A preliminary report. *Behring Institute Mitteilungen* **90**:86-92, 1991.

Experimental Groups:

Study 17.09

Hematological Effects of rhEpo and Recombinations of rhEpo with rhIL-1 or rhGM-CSF in Dogs Exposed to Total-Body X-Irradiation with a Dose of 2.4 Gy

Group Id	Radiation Dose (Gy)	Treatment		No Dogs	Sacrifice Days after TBI
1	0	rhEpo 200 U/kg/day	s.c. day 3 - day 21	1	~360
2	0	rhGM-CSF 30 µg/kg/d	s.c. day 1 - day 5	1	~360
3	0	rhIL-1 2.5 µg/kg/d	i.v. day 1 - day 7	1	~360
4	2.4	rhEpo 300 U/kg/d	s.c. day 3 - day 21	2	~360
5	2.4	rhGM-CSF 30 µg/kg/d rhEpo 300 U/kg/d	s.c. day 1 - day 5 s.c. day 3 - day 21	2	~360
6	2.4	rhIL-1 2.5 µg/kg/d rhEpo 300 U/kg/d	i.v. day 1 - day 7 s.c. day 3 - day 21	3	~360

17.10 Acceleration of Hemopoietic Recovery in Dogs After Extended Field, Partial-Body Irradiation by Treatment with Colony-Stimulating Factors: rhG-CSF and rhGM-CSF

Institution: Institute of Clinical Physiology and Occupational Medicine, University of Ulm, FRG

Scientists: W. Nothdurft; active
L. Kreja; active
C. Selig; active

Purpose: To study the role of (recombinant human) granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor as stimulants of hemopoietic recovery after partial body irradiation.

Status: 1993 - 1995, under evaluation

Treatment: Irradiation of the upper part of the body (UBI, including the 4th lumbar vertebra) comprising 72 % of the total bone marrow mass; or irradiation of the lower part (LBI, excluding the 4th lumbar vertebra) comprising 28 % of the total bone marrow mass; radiation dose at each exposure 11.7 Gy in soft tissue on the midline of the body; treatment with rhG-CSF or rhGM-CSF by subcutaneous injections of 30 µg/kg/day for 7 days starting day 1 after the exposure

Dosimetry: Measurements with ionization chambers and LiF-TLD in phantoms and dog cadavers at several reference positions including marrow spaces in different bones in situ

Endpoints: Different hematological parameters including determinations of GM-CFC and BFU-E in the bone marrow and blood, bone marrow stromal progenitor cells (CFU-F) and colony-stimulating activity (CSA) in the serum; DNA damage in blood and bone marrow cells using the comet assay; sequential studies over 1.5 years after the exposure

Animal: Dogs (Beagles), males and females, age 21 to 33 months

Results: Treatment with rhGM-CSF caused an accelerated, though incomplete, recovery of blood granulocutes in the period from day 8 to day 15. In contrast, treatment with rhG-CSF caused much stronger effects, as reflected by an early recovery to nearly normal levels at day 15 after UBI. RhG-CSF accelerated the hemopoietic recovery in the irradiated sites within the first 21 days after UBI in comparison to the controls and the rhGM-CSF treated animals. The enhanced repopulation in the irradiated bone marrow during and after treatment with rhG-CSF probably is due to enhanced seeding of stem cells from the protected marrow. These results indicate that under conditions of partial body irradiation short term treatment with G-CSF is superior to GM-CSF in stimulating the hemopoietic recovery.

References:

Nothdurft, W., W. Calvo, V. Klinnert, K.H. Steinbach, C. Werner and T.M. Fliedner. Acute and long-term alterations in the granulocyte/macophage progenitor cell (GM-CFC) compartment of dogs after partial body irradiatiaon: irradiation of the upper body with a single myeloablative dose. *Int. J. Radiat. Oncol. Biol. Phys.* **12:**949-957, 1986.

Nothdurft, W., L. Kreja and C. Selig. Acceleration of hemopoietic recovery in dogs after extended field partial body irradiation by treatment with colony-stimulating factors: rhG-CSF ad rhGM-CSF. *Blood,* 1995.

Experimental Groups:

Study 17.10
Acceleration of Hemopoietic Recovery in Dogs After Extended Field, Partial-Body Irradiation by Treatment with Colony-Stimulating Factors

Group Id	Exposure	Radiation Dose (Gy)	Treatment day 1 - day 7	No Dogs	Sacrifice Days after exposure
1	Upper body	11.7	Carrier-autolog. serum s.c.	3	72 - 540
2	Upper body	11.7	rhG-CSF 30 µg/kg/d s.c.	3	~540
3	Upper body	11.7	rhGM-CSF 30 µg/kg/d s.c.	2	160 - 540

18 Dr. Daniel den Hoed Cancer Centre, Rotterdam

18.01 Effects of High Dose Rate (HDR) and Low Dose Rate (LDR) Brachytherapy on Acute and Late Responses in Pig Skin

Institution: Dr Daniel den Hoed Cancer Centre (DDHCC), Rotterdam NL

Scientists: G.J.M.J. van den Aardweg; active
P.C.J. Hamm; active
E.J. Bakker; active
A.G. Visser; active
P.C. Levendag; active

Purpose: To compare continuous Low Dose Rate (LDR) and fractionated High Dose Rate (HDR) brachytherapy with multiple daily fractions with respect to acute and late normal tissue responses.

Status: 1993- ongoing

Treatment:
a) X-irradiation of 4x4 cm skin fields at the left flank of Yorkshire pigs with orthovoltage machine 200 kV 1 mm Cu filter. Total of 8 fields per flank. Dose rate 1.88 Gy/min
b) High Dose Rates (HDR) "optimized" brachytherapy of 3x3 cm skin fields at both flanks with a microSelectron (Nucletron) containing an Iridium-192 source resulting in uniform dose distribution over the field. Dose rate 0.7 -1.7 Gy/min with isodoses of 95% at the basal layer of the epidermis and of 80% at the dermal/fat layer.
c) Low Dose Rate (LDR) from Iridium-192 wires in 5x5 cm skin fields on both fields with 8 fields per flank. Dose rates ranging from 0.6 - 2 Gy/h

Dosimetry: Ionization chamber, TLD measurements

Endpoints: Incidence and latent period for
a) acute reactions of erythema (moderate/severe) and moist desquamation,
b) late responses of dusky/mauve erythema and dermal necrosis.

Animal: Purebred Yorkshire and Large White Pigs

Results: So far, data are only available for reactions following single doses. ED50-valuens obtained with logit analysis and the associated latent periods are presented below. Dose fractionation studies involving complete and incomplete repair between fractions are currently being performed.

Treatment:	X-rays		Brachytherapy (HDR microSelectron)			
Pig strain:	Yorkshire		Yorkshire		Large White	
Skin Response	ED50 ± SE (Gy)	Latent Period (days)	ED50 ± SE (Gy)	Latent Period (days)	ED50 ± SE (Gy)	Latent Period (days)
Erythema moderate/severe	20.1 ± 1.6	43 ± 8	24.8 ± 1.3	39 ± 7	17.7 ± 1.5	39 ± 9
Moist desquamation	27.4 ± 1.3	48 ± 8	31.9 ± 0.7	39 ± 9	29.2 ± 12	35 ± 9
Dusky/mauve erythema	17.7 ± 0.4	63 ± 6	16.3 ± 0.4	59 ± 7	13.7 ± 0.6	56 ± 9
Dermal necrosis	19.9 ± 0.4	80 ± 13	19.4 ± 0.4	76 ± 11	17.0 ± 0.6	82 ± 8

References: Hamm, P.C.J., E.J. Bakker, G.J.M.J. van den Aardweg, A.G. Visser and P.C. Levendag, Acude and late responses of pig skin after single doses of X-irradiation. In: Hagen, U., Jung, H. and Streffer,C [ed.], *Tenth International Congress of Radiation Research* Würzburg, Germany 337, 1995.

Experimental Groups:

Study 18.01
The Effects of High Dose Rate (HDR) and Low Dose Rate (Ldr) Brachytherapy on Acute and Late Responses in Pig Skin

X-irradiation Yorkshire pigs 1.88 Gy/min		HDR Brachytherapy Yorkshire */Large White* 1.13-1.23 Gy/min		HDR Brachytherapy Yorkshire 0.76-0.87 Gy/min		HDR Brachytherapy Yorkshire 1.67-1.79 Gy/min	
Skin Surface Dose Gy	No fields/ No animals	Skin Surface Dose Gy	No fields/ No animals	Skin Surface Dose Gy	No fields/ No animals	Skin Surface Dose Gy	No fields/ No animals
13.3	10/10	15	*10/3*	18	9/3	18	9/3
15.8	10/10	17	*12/4*	20	9/3	20	9/3
18.8	10/10	19	*12/4*	22	9/3	24	9/3
20.6	10/10	20	6/2	24	9/3	27	9/3
24.3	10/10	21	*12/4*	27	9/3	30	9/3
31.5	10/10	23	*12/4*	30	9/3	33	9/3
35.2	6/6	24	6/2	33	9/3	36	9/3
		26	*12/4*	36	9/3	39	9/3
		28	6/2	39	9/3	43	9/3
		29	*12/4*	43	9/3		
		32	6/2, *13/4*				
		44	6/2, *13/4*				
		40	6/1				
		44	6/1				

Large white pigs indicated in italics

National Radiobiological Archives of Animal Experiments (NRA)

List of Communicated Experiments

Prepared under the Auspices of

U.S. Department of Energy
Office of Health and Environmental Research

by

Charles R. Watson

101 University of Utah (UTAH)

The life-span studies involving beagle dogs at the University of Utah (101.01 - 101.14) were conducted by a team of scientists. The studies, which began in 1950 were of longer duration than the tenure of many of the investigators. Key personnel associated with these studies are listed here rather than being repeated 14 times on subsequent pages. Many others, who participated for short periods, or played supportive roles, will be found as co-authors on publications associated with these key scientists.

Utah Research Team:

Atherton, David R; deceased
Bruenger, Fred W; active
Dougherty, Jean H; retired
Dougherty, Thomas F; deceased
Jee, Webster SS; active
Lloyd, Ray D; active
Mays, Charles W; deceased
Miller, Scott C; active
Stevens, Walter; active
Stover, Betsy J; deceased
Taylor, Glenn N; retired
Wrenn, M Ed; retired

Of the multitude of scientific publications from these studies, the following cross-cutting, or summary, papers are presented here rather than as repeated entries under each of the 14 studies.

General references to University of Utah Radiobiology studies:

Loyd, R.D., S.C. Miller, G.N. Taylor, F.W. Bruenger, W.Angus, and W.S.S. Jee. Some similarities and differences between animals and humans for internal emitter radiobiology. *Health Physics* (in press).

Bruenger, F.W., S.C. Miller and R.D. Lloyd A Comparison of the natural survival of beagle dogs injected intravenously with low levels of plutonium-239, thorium-238, radium-226, radium-228, and strontium-90. *Radiation Research* **126**:328-337, 1991

F.W. Bruenger, R.D. Lloyd, and S.C. Miller. The influence of age at time of exposure to radium-226 or plutonium-239 on distribution, retention, postinjection survival and tumor induction in beagle dogs. *Radiation Research* **125**: 248-256, 1991.

101.01 Bone Tumor Risk: Single Injection of Plutonium-239 in Young Adult Beagles

Institution: Radiobiology Laboratory, University of Utah

Scientists: See introduction to Utah radiobiology studies.

Purpose: This study provides the plutonium-239 portion of the effort to predict the risk from plutonium-239 in people, based on the observed effects in the U.S. radium dial painters and the relative toxicity of plutonium-239 vs. radium-226 in young adult beagle dogs.

Status: Dogs injected between 1952 and 1974; last dog died in 1991; analysis is complete.

Treatment: Single intravenous injection of plutonium-239 citrate solution; dogs placed on experiment in 3 series: a relatively high level, "A", from 1952 to 1958; and two lower levels, "B", from 1964 to 1970; and "C", from 1973 to 1974.

Endpoints: Dogs were allowed to live out their life spans or until sacrifice was indicated for humane reasons, such as to prevent pain. To promote a long and healthy life, most soft tissue tumors were removed surgically under anesthesia, however, bone tumors were never removed. Particular emphasis has been given to bone fractures, the location of osteosarcomas and the evaluation of tumor growth rates based on sequential radiographs of the expanding tumors. At autopsy, the bones were defleshed and postmortem X-rays showing two views of each bone were taken to identify possible tumor sites that were then examined histologically.

Animal: 286 Beagle dogs (132 females, 154 males), 13 to 25 mo old, in 18 groups.

Results: Life shortening, primarily due to bone tumors, hematologic changes, or liver tumors at the higher levels.

References: R.D. Lloyd, G.N. Taylor, W. Angus, F.W. Bruenger, and S.C. Miller. Bone Cancer occurrence among beagles given plutonium-239 as young adults. *Health Physics*, **64**:45-51, 1993.

General description of study and summary of significant results, with extensive bibliography: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 9352, pp: 126-129.

Experimental Groups:

Study 101.01
Bone Tumor Risk: Single Injection of Plutonium-239 in Young Adult Beagles

Group Id	Series	Quantity Injected (kBq/kg)	Number of Dogs	Median Post-Exposure Survival (y)
01	A	Control	12	11.2
02	B	Control	31	12.1
03	C	Control	7	11.6
04	B	0.037	20	11.7
05	C	0.037	8	12.0
06	B	0.074	39	11.9
07	C	0.074	7	12.7
08	B	0.185	24	11.7
09	C	0.185	15	11.1
10	B	0.37	11	10.8
11	C	0.37	27	11.6
12	A	5.92	14	11.3
13	B	5.92	12	11.5
14	A	1.85	14	8.6
15	A	3.7	12	7.1
16	A	11.1	12	4.4
17	A	37	12	3.5
18	A	111	9	3.6
		Total	286	

101.02 Bone Tumor Risk: Single Injection of Radium-226 in Young Adult Beagles

Institution: Radiobiology Laboratory, University of Utah

Scientists: See introduction to Utah radiobiology studies.

Purpose: This study provides the radium-226 segment of the effort to predict the risk from plutonium-239 in people, based on the observed effects in the U.S. radium dial painters and the relative toxicity of plutonium-239 vs. radium-226 in young adult beagle dogs.

Status: Dogs injected between 1953 and 1970; last dog died in 1986; analysis is complete.

Treatment: Single intravenous injection of radium citrate solution; dogs placed on experiment in 2 series: "A", from 1953 to 1963; and "B", an extension to lower doses, from 1964 to 1970.

Endpoints: Dogs were allowed to live out their life spans or until sacrifice was indicated for humane reasons, such as to prevent pain. To promote a long and healthy life, most soft tissue tumors were removed surgically under anesthesia, however, bone tumors were never removed. Particular emphasis has been given to bone fractures, the location of osteosarcomas and the evaluation of tumor growth rates based on sequential radiographs of the expanding tumors. At autopsy, the bones were defleshed and postmortem X-rays showing two views of each bone were taken to identify possible tumor sites that were then examined histologically.

Animal: 164 Beagle dogs (94 females, 70 males), 12 to 28 mo old, in 11 groups.

Results: Eye lesions and intraocular melanomas were also significant effects.

References: General description of study and summary of significant results, with extensive bibliography: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 99352, pp: 130-132.

Experimental Groups:

Study 101.02
Bone Tumor Risk: Single Injection of Radium-226 in Young Adult Beagles

Group Id	Series	Quantity Injected (kBq/kg)	Number of Dogs	Median Post-Exposure Survival (y)
01	A	Control	12	9.6
02	B		32	12.8
03	B	0.222	10	10.6
04	B	0.74	25	12.0
05	A	2.22	12	10.9
06	B	2.22	11	10.2
07	A	5.92	14	9.2
08	A	12.21	13	10.3
09	A	37	12	5.9
10	A	111	13	4.2
11	A	370	10	2.9
		Total	164	

101.03 Bone Tumor Risk: Single Injection of Radium-228 in Young Adult Beagles

Institution: Radiobiology Laboratory, University of Utah

Scientists: See introduction to Utah radiobiology studies.

Purpose: This study provides information for comparing radium-228 with radium-226 (study 101.02) and with plutonium-239 (study 101.01). It was designed to supplement those studies by providing a link between epidemiologic studies of radium effects in humans, and studies in dogs with various radionuclides for which few effects have been documented in humans.

Status: Dogs injected between 1954 and 1963; last dog died in 1977; analysis is complete.

Treatment: Single intravenous injection of radium citrate solution.

Endpoints: Dogs were allowed to live out their life spans or until sacrifice was indicated for humane reasons, such as to prevent pain. To promote a long and healthy life, most soft tissue tumors were removed surgically under anesthesia, however, bone tumors were never removed. Particular emphasis has been given to bone fractures, the location of osteosarcomas and the evaluation of tumor growth rates based on sequential radiographs of the expanding tumors. At autopsy, the bones were defleshed and postmortem X-rays showing two views of each bone were taken to identify possible tumor sites that were then examined histologically.

Animal: 89 Beagle dogs (46 females, 43 males), 13 to 24 mo old, in 8 groups.

Results: Major radiation effects included bone and eye cancers. Hematologic changes were observed at the higher levels.

References: General description of study and summary of significant results, with extensive bibliography: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 99352, pp: 133-135.

Experimental Groups:

Study 101.03
Bone Tumor Risk: Single Injection of Radium-228 in Young Adult Beagles

Group Id	Quantity Injected (kBq/kg)	Number of Dogs	Median Post-Exposure Survival (y)
01	Control	13	12.6
02	0.74	12	11.5
03	1.85	13	10.6
04	5.55	12	8.1
05	11.1	12	6.4
06	33.3	12	4.0
07	99.9	8	3.0
08	333	7	2.1
	Total	89	

101.04 Bone Tumor Risk: Single Injection of Thorium-228 in Young Adult Beagles

Institution: Radiobiology Laboratory, University of Utah

Scientists: See introduction to Utah radiobiology studies.

Purpose: This study provides information for comparing thorium-228 with radium-226 (study 101.02) and with plutonium-239 (study 101.01).It was designed to supplement those studies by providing a link between epidemiologic studies of radium effects in humans, and studies in dogs with various radionuclides for which few effects have been documented in humans.

Status: Dogs injected between 1954 and 1963; last dog died in 1978; analysis is complete.

Treatment: Single intravenous injection of thorium citrate solution.

Endpoints: Dogs were allowed to live out their life spans or until sacrifice was indicated for humane reasons, such as to prevent pain. To promote a long and healthy life, most soft tissue tumors were removed surgically under anesthesia, however, bone tumors were never removed. Particular emphasis has been given to bone fractures, the location of osteosarcomas and the evaluation of tumor growth rates based on sequential radiographs of the expanding tumors. At autopsy, the bones were defleshed and postmortem X-rays showing two views of each bone were taken to identify possible tumor sites that were then examined histologically.

Animal: 89 Beagle dogs (44 females, 50 males), 10 to 24 mo old, in 9 groups.

Results: Radium-228 decays to thorium-228 and there was early concern that the intestinal absorption of the thorium-228 in dial paint might be high. Later, Maletskos et al. (1969) showed that absorption of thorium-228 from the human G.I. tract was low, about 0.02% compared to 20% for radium. However, the thorium-228 toxicity data from beagles proved very useful in evaluating the risk from radionuclides in the proposed Thorium Breeder Reactor (Lloyd et al., 1984).

References:

Lloyd, R.D., C.W. Jones, C.W. Mays, D.R. Atherton, F.W. Brunger and G.N. Taylor, Thorium-228 retention and dosimetry in beagles. *Radiation Research* **98**:614-628, 1984

General description of study and summary of significant results, with extensive bibliography: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 99352, pp: 136-138.

Experimental Groups:

Study 101.04
Bone Tumor Risk: Single Injection of Thorium-228 in Young Adult Beagles

Group Id	Quantity Injected (kBq/kg)	Number of Dogs	Median Post-Exposure Survival (y)
01	Control	13	12.5
02	0.074	13	12.5
03	0.185	12	11.1
04	0.555	12	9.2
05	1.11	13	6.5
06	3.33	13	3.0
07	11.1	12	2.4
08	33.3	4	2.1
09	99.9	2	0.4
	Total	94	

101.05 Bone Tumor Risk: Single Injection of Strontium-90 in Young Adult Beagles

Institution: Radiobiology Laboratory, University of Utah

Scientists: See introduction to Utah radiobiology studies.

Purpose: This study provides information for comparing strontium-90 with radium-226 (study 101.02) and with plutonium-239 (study **101.01**). It was designed to supplement those studies by providing a link between epidemiologic studies of radium effects in humans, and studies in dogs with various radionuclides for which few effects have been documented in humans.

Status: Dogs injected between 1955 and 1966; last dog died in 1977; analysis is complete.

Treatment: Single intravenous injection of strontium citrate solution.

Endpoints: Dogs were allowed to live out their life spans or until sacrifice was indicated for humane reasons, such as to prevent pain. To promote a long and healthy life, most soft tissue tumors were removed surgically under anesthesia, however, bone tumors were never removed. Particular emphasis has been given to bone fractures, the location of osteosarcomas and the evaluation of tumor growth rates based on sequential radiographs of the expanding tumors. At autopsy, the bones were defleshed and postmortem X-rays showing two views of each bone were taken to identify possible tumor sites that were then examined histologically.

Animal: 96 Beagle Dogs (47 females, 49 males), 14 to 21 mo old, in 9 groups.

Results: Strontium-90 toxicity was evaluated because of worldwide concern about radioactive fallout. Few effects were observed at average skeletal doses below 5000 rads, but bone sarcomas occurred frequently at higher doses. Most interesting was the relative ineffectiveness of strontium-90 in producing leukemia in adult beagles (Dougherty et al., 1972). This agrees with the low frequency of myeloproliferative syndrome (MPS) in beagles at Davis, California, injected with strontium-90 as adults. However, a high incidence of MPS was observed in Davis beagles exposed to high dosage of strontium-90 from fetal age to adulthood (Book et al., 1982).

References: General description of study and summary of significant results, with extensive bibliography: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 99352, pp: 139-140.

Experimental Groups:

Study 101.05
Bone Tumor Risk: Single Injection of Strontium-90 in Young Adult Beagles

Group Id	Quantity Injected (kBq/kg)	Number of Dogs	Median Post-Exposure Survival (y)
01	Control	12	12.6
02	22.2	12	14.1
03	66.6	12	12.7
04	133.2	12	10.6
05	407	12	13.0
06	1184	12	10.8
07	1285	12	6.1
08	3700	12	3.7
	Total	96	

101.06 Bone Tumor Risk: Single Injection of Americium-241 in Young Adult Beagles

Institution: Radiobiology Laboratory, University of Utah

Scientists: See introduction to Utah radiobiology studies.

Purpose: This study provides information for comparing americium-241 with radium-226 (study **101.02**) and with plutonium-239 (study **101.01**). It was designed to supplement those studies by providing a link between epidemiologic studies of radium effects in humans, and studies in dogs with various radionuclides for which few effects have been documented in humans.

Americium-241 was the first transplutonium radionuclide to be evaluated for toxicity in beagles at the U. of Utah. Because of strong interest in americium-241 the original test study was expanded into a full scale toxicity study with about 12 dogs per dosage level. Control dogs concurrently assigned to the low-level studies of plutonium-239 and radium-226 were considered suitable as controls for americium-241. In 1975, the number of beagles at the 1-level and 1.7-level were increased to 26 and 24 dogs, respectively, to investigate more extensively the induction of liver cancer by alpha-emitters.

Status: Dogs injected between 1966 and 1975; last dog died in 1990; analysis complete.

Treatment: Single intravenous injection of americium citrate solution; dogs placed on experiment in 2 series: "A", from 1966 to 1970; and "B", from 1974 to 1975.

Endpoints: Dogs were allowed to live out their life spans or until sacrifice was indicated for humane reasons, such as to prevent pain. To promote a long and healthy life, most soft tissue tumors were removed surgically under anesthesia, however, bone tumors were never removed. Particular emphasis has been given to bone fractures, the location of osteosarcomas and the evaluation of tumor growth rates based on sequential radiographs of the expanding tumors. At autopsy, the bones were defleshed and postmortem X-rays showing two views of each bone were taken to identify possible tumor sites that were then examined histologically.

Animal: 117 Beagle dogs (56 females, 61 males), 15 to 19 mo old, in 11 groups.

Results: The liver retention of americium-241 is higher than that for any other monomeric radionuclide studied in beagles at the University of Utah. Thyroid damage, hematologic changes, and liver and kidney failure were significant factors at the higher levels. Liver tumors were a major radiation effect at lower levels, while bone tumros predominate at higher levels..

References: Lloyd, R.D., C.W. Mays, C.W. Jones, D.R. Atherton, F.W. Brunger, L.R. Shabestari, L.R. and M.E. Wrenn. Retention and dosimetry of injected americium-241 in beagles. *Radiation Research* **100**:564-575, 1984.

General description of study and summary of significant results, with extensive bibliography: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 99352, pp: 141-142.

Experimental Groups:

Study 101.06
Bone Tumor Risk: Single Injection of Americium-241 in Young Adult Beagles

Group Id	Quantity Injected (kBq/kg)	Series	Number of Dogs	Median Post-Exposure Survival (y)
01	0.074	A	14	11.5
02	0.185	A	14	12.5
03	0.555	A	14	10.6
04		B	12	12.5
05	1.85	A	13	10.1
06		B	11	9.5
07	3.7	A	12	7.8
08	11.1	A	13	4.8
09	33.3	A	12	3.8
10	103.6	A	2	1.1
Total			117	

101.07 Bone Tumor Risk: Single Injection of Californium-249 in Young Adult Beagles

Institution: Radiobiology Laboratory, University of Utah

Scientists: See introduction to Utah radiobiology studies.

Purpose: The major goal of this study was to understand the RBE of alpha particles vs fission fragments. This study also provides information for comparing californium-249 with radium-226 (study **101.02**) and with plutonium-239 (study **101.01**). It was designed to supplement those studies by providing a link between epidemiologic studies of radium effects in humans, and studies in dogs with various radionuclides for which few effects have been documented in humans.

Status: Dogs injected between 1971 and 1974; last dog died in 1990,; analysis complete.

Treatment: Single intravenous injection of californium citrate solution.

Endpoints: Dogs were allowed to live out their life spans or until sacrifice was indicated for humane reasons, such as to prevent pain. To promote a long and healthy life, most soft tissue tumors were removed surgically under anesthesia, however, bone tumors were never removed. Particular emphasis has been given to location of osteosarcomas. At autopsy, the bones were defleshed and postmortem X-rays showing two views of each bone were taken to identify possible tumor sites that were then examined histologically.

Animal: 36 Beagle dogs (18 females, 18 males), 15 to 19 mo old, in 6 groups.

Results: Tracer amounts of beta-emitting berkelium-249 were present with the alpha-emitting californium-249, making it possible to establish simultaneously that the microscopic depositions of berkelium (element 97) and californium (element 98) were similar.

References: General description of study and summary of significant results, with extensive bibliography: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 99352, pp: 143-144.

Experimental Groups:

Study 101.07
Bone Tumor Risk: Single Injection of Californium-249 in Young Adult Beagles

Group Id	Quantity Injected (kBq/kg)	Number of Dogs	Median Post-Exposure Survival (y)
01	control	6	12.9
02	0.0222	6	13.2
03	0.185	6	11.0
04	0.555	6	11.2
05	3.33	6	7.1
06	11.1	6	4.4
	Total	36	

101.08 Bone Tumor Risk: Single Injection of Californium-252 in Young Adult Beagles

Institution: Radiobiology Laboratory, University of Utah

Scientists: See introduction to Utah radiobiology studies.

Status: Dogs injected between 1971 and 1973; last dog died in 1989; analysis complete.

Purpose: The major goal of this study was to evaluate the RBE of fission fragments vs alpha particles. This study also provides information for comparing californium-252 with radium-226 (study **101.02**) and with plutonium-239 (study **101.01**). It was designed to supplement those studies by providing a link between epidemiologic studies of radium effects in humans, and studies in dogs with various radionuclides for which few effects have been documented in humans.

Treatment: Single intravenous injection of californium citrate solution.

Endpoints: Dogs were allowed to live out their life spans or until sacrifice was indicated for humane reasons, such as to prevent pain. To promote a long and healthy life, most soft tissue tumors were removed surgically under anesthesia, however, bone tumors were never removed. Particular emphasis has been given to bone fractures, the location of osteosarcomas and the evaluation of tumor growth rates based on sequential radiographs of the expanding tumors. At autopsy, the bones were defleshed and postmortem X-rays showing two views of each bone were taken to identify possible tumor sites that were then examined histologically.

Animal: 36 Beagle dogs (18 females, 18 males), 15 to 19 mo old, in 6 groups.

Results: Carcinogenicity of californium-252 fission fragments is lower than that of radium alpha particles.

References: General description of study and summary of significant results, with extensive bibliography: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 99352, pp: 145-146.

Experimental Groups:

Study 101.08
Bone Tumor Risk: Single Injection of Californium-252 in Young Adult Beagles

Group Id	Quantity Injected (kBq/kg)	Number of Dogs	Median Post-Exposure Survival (y)
01	control	6	10.4
02	0.0222	6	11.8
03	0.185	6	12.2
04	0.592	6	12.1
05	3.33	6	10.4
06	11.1	6	4.9
	Total	36	

101.09 Bone Tumor Risk: Single Injection of Plutonium-239 in Immature (3-Month-Old) Beagles

In 1987, the University of Utah beagle kennels were demolished to make room for campus expansion. Remaining live dogs were transferred to ITRI. Responsibility for completion of this and two other studies was shifted to a team of ITRI investigators.

Institution: Radiobiology Laboratory, University of Utah,
Inhalation Toxicology Research Institute

Scientists:

Utah research team:
Bruenger, Fred W; active
Jee, Webster SS; active
Lloyd, Ray D; active
Mays, Charles W; deceased
Miller, Scott C; active
Polig, Erich; active
Taylor, Glenn N; active
Wrenn, M Ed; retired

ITRI analysis team:
Berry, MA; active
Boecker, Bruce B; active
Diel, Joe H; active
Griffith, William C; active
Guilmette, Richard A; active
Hahn, Fletcher F; active
Muggenburg, Bruce A; active
Nikula, Kristin J; active
Scott, Bobbie, R; active
Snipes, M Burt; active

Purpose: Extend study 101.01 by examining the effects of plutonium-239 in juvenile dogs which have rapidly growing skeletal systems.

Status: Dogs injected between 1972 and 1978; held for life time care and observation until remaining live dogs were transferred to ITRI in 1987. "Core" manuscript in press, records transfer to NRA in August 1996.

Treatment: Single intravenous injection of plutonium citrate solution.

Endpoints: Dogs were allowed to live out their life spans or until sacrifice was indicated for humane reasons, such as to prevent pain. To promote a long and healthy life, most soft tissue tumors were removed surgically under anesthesia, however, bone tumors were never removed. Particular emphasis has been given to the location of osteosarcomas and histopathologic evaluation of the liver. At autopsy, the bones were defleshed and postmortem X-rays showing two views of each bone were taken to identify possible tumor sites that were then examined histologically.

Animal: 75 Beagle dogs (37 females, 38 males), 2.9 to 3.5 mo old, in 7 groups.

Results: As compared to young adulst, these juvenile dogs deposited and retained less plutonium in liver and more in bone. Plutonium deposited on growing bone surfaces was rapidly buried and was less hazardous than plutonium deposited in older animals..

References: General description of study and summary of significant results, with extensive bibliography: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 99352, pp: 147-148.

Experimental Groups:

Study 101.09
Bone Tumor Risk: Single Injection of Plutonium-239 in Immature (3 Month-Old) Beagles

Group Id	Quantity Injected (kBq/kg)	Number of Dogs	Median Post-Exposure Survival (y)
01	control	8	12.6
02	0.185	11	13.2
03	0.592	10	13.0
04	1.85	11	12.2
05	3.7	11	11.4
06	11.1	12	7.1
07	111	12	3.5
	Total	75	

101.10 Bone Tumor Risk: Single Injection of Einsteinium-253 in Young Adult Beagles

Institution: Radiobiology Laboratory, University of Utah

Scientists: See introduction to Utah radiobiology studies.

Purpose: The major goal of this study was to evaluate the effects of brief skeletal irradiation by alpha rays. This study also provides information for comparing einsteinium-253 with radium-226 (study **101.02**) and with plutonium-239 (study **101.01**). It was designed to supplement those studies by providing a link between epidemiologic studies of radium effects in humans, and studies in dogs with various radionuclides for which few effects have been documented in humans.

Status: Dogs injected between 1973 and 1974; last dog died in 1987; analysis complete.

Treatment: Single intravenous injection of einsteinium citrate solution.

Endpoints: Dogs were allowed to live out their life spans or until sacrifice was indicated for humane reasons, such as to prevent pain. To promote a long and healthy life, most soft tissue tumors were removed surgically under anesthesia, however, bone tumors were never removed. Particular emphasis has been given to the location of osteosarcomas. At autopsy, the bones were defleshed and postmortem X-rays showing two views of each bone were taken to identify possible tumor sites that were then examined histologically.

Animal: 6 Beagle dogs (3 females, 3 males), 16 mo old, in 2 groups.

Results: Einsteinium (element 99) was the highest atomic number element to be investigated for radionuclide toxicity in beagles. Einsteinium appeared to resemble californium most closely in its excretion, retention and tissue distribution (Lloyd et al., 1975). No bone sarcomas occurred among the beagles injected with einsteinium-253, excluding the one dog that subsequently received a large dose of californium-249. This suggests that 20-d einsteinium-253 does not seem appreciably more toxic than the other transplutonium elements studied.

References: Lloyd, R.D., J.G. Dockum, D.R. Atherton,C.W. Mays and J.L. Williams. The early retention, excretion and distribution of injected einsteinium citrate in beagles. *Health Physics* **28**:585-589, 1975.

Brief description of study and summary of significant results, with limited bibliography: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 99352, pp: 149.

Experimental Groups:

Study 101.10
Bone Tumor Risk: Single Injection of Einsteinium-253 in Young Adult Beagles

Group Id	Quantity Injected (kBq/kg)	Number of Dogs	Median Post-Exposure Survival (y)
01	11.1	3	12.9
02	111	3	7.9
Total		6	

101.11 Bone Tumor Risk: Single Injection of Plutonium-239 in Aged (4- to 5-Year-Old) Beagles

Institution: Radiobiology Laboratory, University of Utah

Scientists: See introduction to Utah radiobiology studies.

Purpose: Extend study 101.01 by examining the effects of Pu-239 in mature dogs which have relatively static skeletal systems.

Status: Dogs injected between 1975 and 1978; last dog died in 1989 at ITRI; analysis complete.

Treatment: Single intravenous injection of plutonium citrate solution.

Endpoints: Dogs were allowed to live out their life spans or until sacrifice was indicated for humane reasons, such as to prevent pain. To promote a long and healthy life, most soft tissue tumors were removed surgically under anesthesia, however, bone tumors were never removed. Particular emphasis has been given to the location of osteosarcomas and histopathologic evaluation of the liver. At autopsy, the bones were

defleshed and postmortem X-rays showing two views of each bone were taken to identify possible tumor sites that were then examined histologically.

Animal: 34 Beagle dogs (21 females, 13 males), 4.1 to 5.2 y old, in 4 groups.

Results: As compared to young adults, the aged dogs retain more plutonium on bone surfaces and thus may be more sensitive to bone-tumor production despite their restricted life expectancy..

References: General description of study and summary of significant results, with extensive bibliography: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 99352, pp: 150.

Experimental Groups:

Study 101.11

Bone Tumor Risk: Single Injection of Plutonium-239 in Aged (4- to 5-Year-Old) Beagles

Group Id	Quantity Injected (kBq/kg)	Number of Dogs	Median Post-Exposure Survival (y)
01	0.592	4	8.2
02	1.85	10	8.7
03	3.7	10	5.8
04	11.1	10	3.9
	Total	34	

101.12 Bone Tumor Risk: Single Injection of Radium-226 in Immature (3- to 5-Month-Old) Beagles

In 1987, the University of Utah beagle kennels were demolished to make room for campus expansion. Remaining live dogs were transferred to ITRI. Responsibility for completion of this and two other studies was shifted to a team of ITRI investigators.

Institution: Radiobiology Laboratory, University of Utah,
Inhalation Toxicology Research Institute

Scientists:

Utah research team:
Bruenger, Fred W; active
Jee, Webster SS; active
Lloyd, Ray D; active
Mays, Charles W; deceased
Miller, Scott C; active
Polig, Erich; active
Taylor, Glenn N; active
Wrenn, M Ed; retired

ITRI analysis team:
Berry, MA; active
Boecker, Bruce B; active
Diel, Joe H; active
Griffith, William C; active
Guilmette, Richard A; active
Hahn, Fletcher, F; active
Muggenburg, Bruce A; active
Nikula, Kristin J.; active
Scott, Bobbie, R; active
Snipes, M Burt; active

Purpose: Extend study 101.02 by examining the effects of radium-226 in juvenile dogs which have rapidly growing skeletal systems.

Status: Dogs injected between 1975 and 1978; held for life time care and observation until remaining live dogs were transferred to ITRI in 1990. "Core" manuscript in press, records transfer to NRA in August 1996.

Treatment: Single intravenous injection of radium citrate solution.

Endpoints: Dogs were allowed to live out their life spans or until sacrifice was indicated for humane reasons, such as to prevent pain. To promote a long and healthy life, most soft tissue tumors were removed surgically under anesthesia, however, bone tumors were never removed. Particular emphasis has been given to the location of osteosarcomas, liver histopathology, and ocular changes. At autopsy, the bones were defleshed and postmortem X-rays showing two views of each bone were taken to identify possible tumor sites that were then examined histologically.

Animal: 53 Beagle dogs (26 females, 27 males), 3 to 5 mo old, in 6 groups.

Results: Retention of radium-226 was substantially greater in juveniles than in young adults.

References: General description of study and summary of significant results, with extensive bibliography: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 99352, pp: 151-152.

Experimental Groups:

Study 101.12
Bone Tumor Risk: Single Injection of Radium-226 in Immature (3- to 5-Month-Old) Beagles

Group Id	Quantity Injected (kBq/kg)	Number of Dogs	Median Post-Exposure Survival (y)
01	control	3	
02	0.74	10	13.8
03	1.85	10	11.6
04	5.92	10	12.2
05	11.1	10	10.5
06	37	10	7.1
	Total	53	

101.13 Bone Tumor Risk: Single Injection of Radium-226 in Aged (5- to 6-Year-Old) Beagles

Institution: Radiobiology Laboratory, University of Utah

Scientists: See introduction to Utah radiobiology studies.

Purpose: Extend study 101.02 by examining the effects of radium-226 in mature dogs which have relatively static skeletal systems.

Status: Dogs injected between 1975 and 1980; last dog died in 1987; analysis complete.

Treatment: Single intravenous injection of radium citrate solution.

Endpoints: Dogs were allowed to live out their life spans or until sacrifice was indicated for humane reasons, such as to prevent pain. To promote a long and healthy life, most soft tissue tumors were removed surgically under anesthesia, however, bone tumors were never removed. Particular emphasis has been given to the location of osteosarcomas, ocular changes, and histopathology of the kidney and liver. At autopsy, the bones were defleshed and postmortem X-rays showing two views of each bone were taken to identify possible tumor sites that were then examined histologically.

Animal: 33 Beagle dogs (20 females, 13 males), 4.9 to 6.2 y old, in 3 groups.

Results: Retention of radium-226 in aged dogs was somewhat lower than that observed in young adults. There was high mortality, associated with kidney degeneration, at higher dose levels..

References: General description of study and summary of significant results, with extensive bibliography: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 99352, pp: 153.

Experimental Groups:

Study 101.13
Bone Tumor Risk: Single Injection of Radium-226 in Aged (5- to 6-Year-Old) Beagles

Group Id	Quantity Injected (kBq/kg)	Number of Dogs	Median Post-Exposure Survival (y)
01	37	9	5.7
02	111	20	3.7
03	370	4	1.2
	Total	33	

101.14 Bone Tumor Risk: Single or Multiple Injections of Radium-224 in Young Adult Beagles

In 1987, the University of Utah beagle kennels were demolished to make room for campus expansion. Remaining live dogs were transferred to ITRI. Responsibility for completion of this and two other studies was shifted to a team of ITRI investigators.

Institution: Radiobiology Laboratory, University of Utah,
Inhalation Toxicology Research Institute

Scientists:

Utah research team:
Bruenger, Fred W; active
Jee, Webster SS; active
Lloyd, Ray D; active
Mays, Charles W; deceased
Miller, Scott C; active
Polig, Erich; active
Taylor, Glenn N; active
Wrenn, M Ed; retired

ITRI analysis team:
Berry, MA; active
Boecker, Bruce B; active
Griffith, William C; active
Hahn, Fletcher, F; active
Muggenburg, Bruce A; active

Purpose: This study provides information for comparing radium-224 with radium-226 (study **101.02**) and with plutonium (study **101.01**). It was designed to supplement those studies by providing a link between epidemiologic studies of radium effects in humans, and studies in dogs with various radionuclides for which few effects have been documented in humans. Because of the 3.6 d half-life of radium-224, virtually all of the radiation dose is received within the first mo following final injection.

Status: Dogs injected between 1977 and 1979; held for life time care and observation until remaining live dogs were transferred to ITRI in 1987. "Core" manuscript in press, records transfer to NRA in August 1996.

Treatment: Single or multiple intravenous injection of radium chloride solution. Series "A" received a single injection; series "B", 10 injections at 1-w intervals; and series "C", 50 injections at 1-w intervals.

These studies were undertaken to understand the modifying effect of protraction on the dose- response of radium-224 observed in German patients (Spiess & Mays 1973; Mays et al., 1986). Four graded dose levels were administered over three injection spans. Groups 1-12 received their radium-224 in 50 weekly fractions to correspond to the average injection span in the German children; Groups 41-52 received a single injection, and Groups 81-92 received 10 weekly injections to correspond to the present treatment in Germany for ankylosing spondylitis.

Dosimetry: Most of the radium-224 given the beagles was prepared by the German Amersham-Buchler Firm which also prepared the radium-224 for the German patients. In a few instances, radium-224 of the same high radiochemical purity was prepared by Dave Atherton and Fred Bruenger at the University of Utah.

Endpoints: Dogs were allowed to live out their life spans or until sacrifice was indicated for humane reasons, such as to prevent pain. To promote a long and healthy life, most soft tissue tumors were removed surgically under anesthesia, however, bone tumors were never removed. Particular emphasis has been given to bone fractures, the location of osteosarcomas and the evaluation of tumor growth rates based on sequential radiographs of the expanding tumors. At autopsy, the bones were defleshed and postmortem X-rays showing two views of each bone were taken to identify possible tumor sites that were then examined histologically.

Animal: 128 Beagle dogs (64 females, 64 males), 15 to 24 mo old, in 15 groups.

Results: The studies of radium-224 in beagles are among the most important with respect to understanding the mechanisms of alpha-particle-induced cancer. The short half-life of radium-224 causes much of it to decay on bone surfaces and some to decay within bone volume, giving a local distribution of dose in bone somewhat similar to that from plutonium-239. In the beagles receiving 278 rad from radium-224 protracted over 50 w the bone sarcoma appearance times and incidence were similar to that at the same skeletal dose from plutonium-239. The bone tumor occurrence was highest in the dogs receiving the highest level of Ra-224 in 50 injections. Thus, protraction of the amount received over a 1-y period was more carcinogenic that the same amount of Ra-226 given in 1 or 10 injections in agreement with available human data.

References: Muggenburg, B.A., F.F. Hahn, W.C. Griffith, R.D. Lloyd, and B.B. Boecker, The biological effects of radium-224 injected into dogs. *Radiation Research* **146**:171-, 1996.

Experimental Groups:

101.14

Bone Tumor Risk: Single or Multiple Injections of Radium-224 in Young Adult Beagles

Injection Regimen	Group Id	Quantity Injected (kBq/kg)	Number of Dogs	Post-Exposure Survival (y)		
				Min	Median	Max
Single	01	control	6	9.7	11.5	14.4
	02	13	12	5.7	11.4	14.6
	03	42	12	5.9	11.8	13.6
	04	120	6	11.0	11.4	14.4
	05	380	8	0.025	8.1	10.4
10 Weekly	06	control	6	6.8	12.3	14.6
	07	13	12	8.0	10.2	14.4
	08	40	12	7.1	11.3	14.6
	09	120	6	7.5	11.7	14.6
	10	350	6	2.7	7.6	9.4
50 Weekly	11	control	6	3.4	8.1	13.6
	12	13	12	3.6	10.3	13.8
	13	38	12	7.4	10.4	12.5
	14	120	6	4.3	9.3	10.4
	15	340	6	4.5	5.5	6.5
		Total	128			

102 University of California at Davis (DAVIS)

102.01 Life-Span Health Risks: Single or Fractionated X-Irradiation of Young Adult Female Beagles

Institution: Institute of Toxicology and Environmental Health (ITEH) University of California at Davis,CA

Scientists: Andersen, A. C. (Bud); deceased
Bustad, Leo K; retired
Goldman, Marvin; active
Parks, N. James; active
Raabe, Otto G; active
Rosenblatt, Leon S; deceased

Status: Exposure between 1952 and 1958, death of last dog in 1970. Final

Purpose: To study in young adult dogs the risks of single or fractionated X-ray exposure with respect to lifespan and tumor risks.

Treatment: Bilateral, 250 kVX-ray exposures, delivered in different numbers of fractions and different fractionation intervals.

Endpoints: Survival, cause of death.

Animal: 352 female Beagle dogs (352 females, 0 male) in 15 groups. Dogs received first exposures at 8 to 15 mo old, from 1952 to 1958. Some were bred subsequent to exposure.

Results: All irradiated beagles exhibited life shortening relative to controls, averaging, on a linear scale, 6.7% per 100 R. An effect of fractionation was seen only at total doses of 300 R, attributable solely to amelioration of nonmammary neoplasia. Major causes of death were similar in irradiated and control dogs. The development of malignant neoplasms at an earlier age in irradiated dogs explains, in large part, the observed life-span shortening.

References:

Andersen, A.C. and L.S. Rosenblatt. The effect of whole-body x-irradiation on the median lifespan of female dogs (begales). *Radiation Research* **39**:177-200, 1969.

Rosenblatt, L.S., S.A. Book and M. Goldman. Effects of x-irradiation of young female beagles on life span and tumor incidence. In *Life-Span Radiation Effects Studies in Animals: What Can They Tell Us?* (R.C. Thompson and J.A. Mahaffey, eds, CONF-830951, NTIS, Springfield, VA) 628-645, 1986.

For a general description of study and summary of significant results, with extensive bibliography: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 9352, pp: 156-157.

Experimental Groups:

Study 102.01
Life-Span Health Risks: Single or Fractionated X-Irradiation of Young Adult Female Beagles

Group Id	Exposure (R)	Number of Exposures	Interval (d)	Total Exposure (R)	Number of Dogs	Median Post-Exposure Survival (y)
01	Control			0	56	11.2
02	25	4	28	100	22	12.1
03	25	4	14	100	25	11.6
04	25	4	7	100	20	11.7
05	50	2	28	100	21	12.0
06	50	2	14	100	21	11.9
07	50	2	7	100	20	12.7
08	100	1		100	19	11.7
09	75	4	28	300	21	11.1
10	75	4	14	300	23	10.8
11	75	4	7	300	27	11.6
12	150	2	28	300	23	11.3
13	150	2	14	300	21	11.5
14	150	2	7	300	22	8.6
15	300	1		300	11	7.1

102.02 Life-Span Health Risks: Daily Ingestion of Strontium-90 in Immature (Fetal to 540-Day-Old) Beagles

Institution: Institute of Toxicology and Environmental Health (ITEH) University of California at Davis, CA

Scientists: Andersen, A. C. (Bud); deceased
Bustad, Leo K; retired
Goldman, Marvin; active
Parks, N. James; active
Raabe, Otto G; active
Rosenblatt, Leon S; deceased

Status: Ingestion of strontium-90 between 1961 and 1969, death of last dog in 1986. Final papers written, information and specimens transferred to NRA in 1990.

Purpose: This study (known as the "D" series) was initiated in response to the concern for possible long-term human health effects from strontium-90 in the fallout from tests of nuclear weapons. Beagles were to be surrogates for the human population and as such were to receive strontium-90 in the same way as people would, and were to be treated, medically, in the same way as people. It is the largest, and probably the most extensively described and interpreted, of the life-span dog studies. It is linked to the University of Utah strontium-90 injection study (101.05) through a companion injection study (102.03).

Treatment: Feeding of strontium-90 chloride to pregnant dogs began at 21 d after conception (at the start of the second trimester, at the initiation of fetal ossification) and was continued until their offspring were weaned at age 42 d. After weaning and until 540 d (18 mo) of age the offspring received the same diet, in which a constant ratio of strontium-90 was maintained relative to well-controlled dietary calcium levels. After the 540 d exposure period, animals were observed for life span (about 14 y). A few dogs were continued on the strontium-90 diet for their life span.

Because the results of this study were to be scaled to humans, a significant amount of time was devoted to prophylactic and elective health programs. Vaccination schedules and internal and external parasite control programs were instituted. Initially, the dogs were weighed and physically examined biweekly (in a seriatim fashion, over a 2-month period). Later, quarterly physical examinations were instituted. Annual physical exams were conducted throughout, as were radiographic skeletal surveys.

Since many clinical veterinarians were employed over the course of the study, a well documented "clinical philosophy" was developed to insure that idiosyncratic methods of treatment be prevented. A decision was made early on that osteosarcomas and other tumors of bone - one of the major end points - would be treated surgically, if possible. Those tumors in the axial skeleton could not be treated and the dogs would have to be euthanized on humane grounds. Clinically significant bone lesions in the appendicular skeleton would be removed (amputated).

Further, amputations were proscribed as it was not feasible to keep alive a non-ambulatory dog. Surgical interventions were extremely common, for example, female beagles are subject to mammary neoplasms. Nodules in the breast of a certain size (1.0 cm in diameter or larger) were excised and, if malignant, regional mammectomies followed. The prevalence of mammary neoplasms was quite high. Other surgeries, e.g. splenectomies, for malignant melanomas of the eye, testicular tumors, etc., were carried out. Therapy for chronic or degenerative diseases was given where possible, e.g., for cardiovascular and kidney diseases. During the 25-y history of the clinical treatment program there were changes instituted as new drugs and new techniques became available. Heroic treatments, however, such as hormone treatments, multiple amputations, for non-responsive paralysis and heart-lung machines were not permitted.

Dogs were euthanized when moribund or to prevent unnecessary pain. The necropsy protocol following euthanasia or spontaneous death included a complete gross pathological evaluation, with emphasis on those tissues or organs that had been clinically dysfunctional, had demonstrable lesions when examined radiographically, or were considered target tissues for strontium or radium deposition.

Endpoints: Cause of death and extensive SNOMED coded histopathology and clinical records are available for each dog. Other records include: problem oriented medical records summarizing each significant clinical episode, serial hematology values, whole body counts, and body weights.

Animal: 483 Beagle dogs (239 females, 244 males) in 11 groups

Results: Skeletal uptake averaged about 2% of the administered dose. Daily dose rate to the skeleton declined slowly to about 45% of peak value late in life. The time-weighted average dose rate for fed Sr-90 and injected Ra-226 was a robust measure that declined from peak values only about 20% late in life.

A threshold like response was observed; no sarcomas were observed in the lowest three dose groups, but the number of primary bone sarcomas increased rapidly in the higher dose groups. Of the 66 primary sarcomas, 49 were osteosarcomas, which occured primarily in the higher dose groups. The ratio of appendicular to axial sarcomas was 40:26. The distribution of sarcoma among 16 bone groups was correlated with the distribution of cancellous bone volume-to-surface ratio and not with either skeletal mass or dose distribution.

References: O.G. Raabe and N.J. Parks. Skeletal uptake and retention of strontium-90 and radium-226 in beagles. *Radiation Research*, **133**: 204-218, 1993.

R.G. White, O.G. Raabe, M.R. Culbertson, N.J. Parks, S.J. Samuels, and L.S. Rosenblatt. Bone sarcoma characteristics and distribution in beagles fed strontium-90. *Radiation Research* **136**:178-189, 1993.

Experimental Groups:

The dose ladder for the strontium-90 "D" dogs and the radium-226 "R" dogs were 0, 0.33, 1, 6, 18,54 and 162, a 486- fold range. The base dose was R10, 10 times the maximum permissible skeletal burden for man, adjusted for the difference in retention between man and beagle. The strontium-90 D10 level was designed to yield a dose-equivalent rate that was one-twentieth of R10 (for Q=10), so that D30 and R10 would have similar dose-equivalents.

Experimental Groups:

Study 102.02
Life-Span Health Risks:
Daily Ingestion of Strontium-90 in Immature (Fetal to 540-Day-Old) Beagles

Group Id	DAVIS Group Id	^{90}Sr kBq/g Dietary Calcium	Days of Ingestion	Total Ingested (kBq)	Number of Dogs	Median Survival (y)
01	D00				80	14.4
02	D05	0.259	540	37	78	14.2
03	D10	0.777	540	148	40	13.5
04	D20	4.55	540	888	65	14.4
05	D30	13.7	540	2590	65	14.1
06	D30C		life		7	12.5
07	D40	41.1	540	8140	61	12.0
08	D40C		life		4	6.4
09	D50	123	540	24100	60	5.2
10	D50C		life		4	5.1
11	D60	370	540	71800	19	2.2

102.03 Life-Span Health Risks: Single Injection of Strontium-90 in Young Adult Beagles

Institution: Institute of Toxicology and Environmental Health (ITEH) University of California at Davis, CA

Scientists: Andersen, A. C. (Bud); deceased
Bustad, Leo K; retired
Goldman, Marvin; active
Parks, N. James; active
Raabe, Otto G; active
Rosenblatt, Leon S; deceased

Status: Injection of strontium-90 between 1965 and 1969, death of last dog in 1983. Final papers written, information and specimens transferred to the NRA in 1990.

Purpose: This study (known as the "S" series) supplemented the strontium-90 chronic feeding study (102.02), providing a comparison of single and repeated administration, and also serving as a link to the more extensive single injection study at the University of Utah (101.05).

Treatment: Single intravenous injection of strontium-90 in 0.1 N hydrochloric acid in saline administered when animals were 540 d old.

Because the results of this study were to be scaled to humans, a significant amount of time was devoted to prophylactic and elective health programs. Vaccination schedules and internal and external parasite control programs were instituted. Initially, the dogs were weighed and physically examined biweekly (in a seriatim fashion, over a 2-month period). Later, quarterly physical examinations were instituted. Annual physical exams were conducted throughout, as were radiographic skeletal surveys.

Since many clinical veterinarians were employed over the course of the study, a well documented "clinical philosophy" was developed to insure that idiosyncratic methods of treatment be prevented. A decision was made early on that osteosarcomas and other tumors of bone - one of the major end points - would be treated surgically, if possible. Those tumors in the axial skeleton could not be treated and the dogs would have to be euthanized on humane grounds. Clinically significant bone lesions in the appendicular skeleton would be removed (amputated).

Further, amputations were proscribed as it was not feasible to keep alive a non-ambulatory dog. Surgical interventions were extremely common, for example, female beagles are subject to mammary neoplasms. Nodules in the breast of a certain size (1.0 cm in diameter or larger) were excised and, if malignant, regional mammectomies followed. The prevalence of mammary neoplasms was quite high. Other surgeries, e.g. splenectomies, for malignant melanomas of the eye, testicular tumors, etc., were carried out. Therapy for chronic or degenerative diseases was given where possible, e.g., for cardiovascular and kidney diseases. During the 25-y history of the clinical treatment program there were changes instituted as new drugs and new techniques became available. Heroic treatments, however, such as hormone treatments, multiple amputations, for non-responsive paralysis and heart-lung machines were not permitted.

Dogs were euthanized when moribund or to prevent unnecessary pain. The necropsy protocol following euthanasia or spontaneous death included a complete gross pathological evaluation, with emphasis on those tissues or organs that had been clinically dysfunctional, had demonstrable lesions when examined radiographically, or were considered target tissues for strontium or radium deposition.

Endpoints: Cause of death and extensive SNOMED coded histopathology and clinical records are available for each dog. Other records include: problem oriented medical records summarizing each significant clinical episode, serial hematology values, whole body counts, and body weights.

Animal: 45 Beagle dogs (25 females, 20 males), 540 d old, in 3 groups

Results: Skeletal uptake was about 33% of administered dose. Daily dose to the skeleton fell rapidly after injection and declined to about 10% of peak values late in life.

For a general description of study and summary of significant results, with extensive bibliography: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 9352, pp: 161.

References: O.G. Raabe and N.J. Parks. Skeletal uptake and retention of strontium-90 and radium-226 in beagles. *Radiation Research*, **133**: 204-218, 1993.

Experimental Groups:

Study 102.03
Life-Span Health Risks:
"S" Series—Single Injection of 90-Sr in 540 Day Old Beagles

Group Id	DAVIS Group Id	Total Injected (kBq/kg)	Number of Dogs	Median Post-Exposure Survival (y)
01	S20	137	20	13.5
02	S40	1220	25	13.3

102.04 Life-Span Health Risks: Multiple Injections of Radium-226 in Young Adult Beagles

Institution: Institute of Toxicology and Environmental Health (ITEH) University of California at Davis, CA

Scientists: Andersen, A. C. (Bud); deceased
Bustad, Leo K; retired
Goldman, Marvin; active
Parks, N. James; active
Raabe, Otto G; active
Rosenblatt, Leon S; deceased

Status: Injection of radium-226 between 1964 and 1969, death of last dog in 1985. Final papers written, information and specimens transferred to the NRA in 1990.

Purpose: This study (known as the "R" series) was designed to simulate the exposure pattern of the human dial painters and thus to provide a link between radium-226 effects in humans and the dog. The extended period of exposure also allows direct comparison with the chronic strontium-90 ingestion study (**102.02**) and complements the University of Utah single injection radium-226 study (**101.02**).

Treatment: Eight injections of radium-226 in a nitric acid-saline carrier at 14 d intervals, beginning at 435 d of age ending at 540 d. Dogs of both sexes placed on experiment from 1964 to 1969. After the injections, the dogs were held for life-span care and observation.

Because the results of this study were to be scaled to humans, a significant amount of time was devoted to prophylactic and elective health programs. Vaccination schedules and internal and external parasite control programs were instituted. Initially, the dogs were weighed and physically examined biweekly (in a seriatim fashion, over a 2-month period). Later, quarterly physical examinations were instituted. Annual physical exams were conducted throughout, as were radiographic skeletal surveys.

Since many clinical veterinarians were employed over the course of the study, a well documented "clinical philosophy" was developed to insure that idiosyncratic methods of treatment be prevented. A decision was made early on that osteosarcomas and other tumors of bone - one of the major end points - would be treated surgically, if possible. Those tumors in the axial skeleton could not be treated and the dogs would have to be euthanized on humane grounds. Clinically significant bone lesions in the appendicular skeleton would be removed (amputated).

Further, amputations were proscribed as it was not feasible to keep alive a non-ambulatory dog. Surgical interventions were extremely common, for example, female beagles are subject to mammary neoplasms. Nodules in the breast of a certain size (1.0 cm in diameter or larger) were excised and, if malignant, regional mammectomies followed. The prevalence of mammary neoplasms was quite high.

Other surgeries, e.g. splenectomies, for malignant melanomas of the eye, testicular tumors, etc., were carried out. Therapy for chronic or degenerative diseases was given where possible, e.g., for cardiovascular and kidney diseases. During the 25-y history of the clinical treatment program there were changes instituted as new drugs and new techniques became available. Heroic treatments, however, such as hormone treatments, multiple amputations, for non-responsive paralysis and heart-lung machines were not permitted.

Dogs were euthanized when moribund or to prevent unnecessary pain. The necropsy protocol following euthanasia or spontaneous death included a complete gross pathological evaluation, with emphasis on those tissues or organs that had been clinically dysfunctional, had demonstrable lesions when examined radiographically, or were considered target tissues for strontium or radium deposition.

Endpoints: Cause of death and extensive SNOMED coded histopathology and clinical records are available for each dog. Other records include: problem oriented medical records summarizing each significant clinical episode, serial hematology values, whole body counts, and body weights.

Animal: 335 Beagle dogs (169 females, 166 males), 435 d old at first injection, in 9 groups

Results: The distribution of bone sarcomas among 16 separate bone groups showed a statistically significant correlation to cancellous skeletal surfaces. It is postulated that the distribution of bone sarcomas reflects primarily the relative cell division rates in the bone groups and secondarialy the radiation dose distribution, with the highest occurrence of bone sarcoma in the humeri, pelvis, femora and tibiae/fibular tarsal, and no occurance in the cocdcygeal vertebrae, sternum, forepaws or hindpaws.

References: O.G. Raabe and N.J. Parks. Skeletal uptake and retention of strontium-90 and radium-226 in beagles. *Radiation Research*, **133**: 204-218, 1993.

R.G. White, O.G. Raabe, M.R. Culbertson, N.J. Parks, S.J. Samuels, and L.S. Rosenblatt. Bone sarcoma characteristics and distribution in beagles injected with radium-226. *Radiation Research* **137**:361-370, 1993.

Experimental Groups:

The dose ladder for the strontium-90 "D" dogs and the radium-226 "R" dogs were 0, 0.33, 1, 6, 18,54 and 162, a 486- fold range. The base dose was R10, 10 times the maximum permissible skeletal burden for man, adjusted for the difference in retention between man and beagle. The strontium-90 D10 level was designed to yield a dose-equivalent rate that was one-twentieth of R10 (for Q=10), so that D30 and R10 would have similar dose-equivalents.

Experimental Groups:

Study 102.04
Life-Span Health Risks:
"R" Series—multiple Injections 226-Ra in Young Adult Beagles

Group Id	DAVIS Group Id	Total Injected (kBq)	Number of Dogs	Median Post-Exposure Survival (y)
01	R00		82	14.6
02	R05	0.789	46	14.5
03	R10	2.37	39	13.8
04	R20	13.9	42	10.9
05	R30	41.4	41	7.4
06	R40	124	41	5.1
07	R50	370	44	4.3

103 Argonne National Laboratory (ANL)

103.01 Life-Span Health Risks: Transplacental Strontium-90 in Immature (1- to 9-Day-Prepartum) Beagles

Institution: Argonne National Laboratory, Argonne IL

Scientists: Miriam P Finkel; retired

Purpose: Investigate health risks in beagles for extrapolation to possible effects on children born to mothers exposed to strontium-90 from fallout from atmospheric nuclear weapons testing.

Status: Injection of strontium-90 in 1956, results unpublished. Copies of laboratory record books are available at NRA.

Treatment: Beagle dogs exposed by transplacental exposure from dams injected with strontium-90 chloride.

Endpoints:

Animal: 53 Beagle dogs at 1 to 9 d prepartum in 3 groups.

Results:

References:

Experimental Groups:

Study 103.01
Life-Span Health Risks:
Transplacental Strontium-90 in Immature (1- to 9-Day-Prepartum) Beagles

Group Id	Burden at birth (MBq/kg)	Number of Dogs
01	Control	29
02	0.259 to 1.517	15
03	16.440 to 11.100	9
	Total	53

103.02 Life-Span Health Risks: Daily injections Strontium-90 in Beagles

Institution: Argonne National Laboratory, Argonne IL

Scientists: Miriam P Finkel; retired

Purpose: Investigate health risks in beagles for extrapolation to possible effects on humans continuously exposed to strontium-90 from fallout from atmospheric nuclear weapons testing.

Status: Injection of strontium-90 started in 1960, results unpublished. Copies of laboratory record books are available at NRA.

Treatment: Multiple subcutaneous injections with strontium-90 chloride (5 injections/w).

Endpoints:

Animal: 98 Beagle dogs of various ages and both sexes in 8 groups

Results:

References:

Experimental Groups:

Study 103.02
Life-Span Health Risks: Daily injections Strontium-90 in Beagles

Group Id	Total Injected (MBq/kg)	Number of Injections	Age at First Injection (y)	Number of Dogs
01	Control			29
02	55.13	257	0	6
03	17.76 to 24.9	83 to 116	0	11
04	55.5	259	0.6 to 0.8	16
05	55.5	259	2.4	6
06	5.55	259	0	17
07	5.55	259	0.5	14
			Total	99

103.03 Life-Span Health Risks: Single Injection of Cerium-144 in Young Adult Beagles

Institution: Argonne National Laboratory, Argonne IL

Scientists: Bill Norris; retired
Tom Fritz; retired

Purpose: To study the long-term effects of soluble Ce-144.

Status: Injection of cerium-144 between 1964 and 1969, death of last dog in 1985. Final

Treatment: Single intravenous injection of cerium-144 citrate solution.

Endpoints: Dogs were provided with life-time clinical care, including annual physical examination and blood work-ups. At necropsy a thorough gross examination was conducted, and a preliminary cause of death was determined. After histopathological examination of tissues from suspected lesions and an extensive suite of representative tissues, a "final" cause of death was determined and entered into the database.

Animal: 49 Beagle dogs (11 females, 38 males), "approximately 13 mo" of age, in 2 groups

Results:

References:

Experimental Groups:

Study 103.03
Life-Span Health Risks: Single Injection of Cerium-144 in Young Adult Beagles

Group Id	Quantity Injected (MBq/kg)	Number of Dogs
	Control	Selected age matched dogs from Colony controls
01	0.851 to 19.61	49
	Total	49

103.04 Life-Span Health Risks: Single Injection of Cesium-137 in Beagles

Institution: Argonne National Laboratory, Argonne IL

Scientists: Bill Norris; retired
Tom Fritz; retired

Purpose: Eexamine the organs and tissues at risk following the internal deposition of cesium-137 in a soluble form and the influence of age at exposure on these risk patterns.

Status: Injection of cesium-137 between 1961 and 1963, death of last dog in 1970. Collaborative summary prepared at the Inhalation Toxicology Research Institute in 1995 (see study 105.05).

Treatment: Single intravenous injection of cesium chloride solution.

Endpoints: Dogs were provided with life-time clinical care, including annual physical examination and blood work-ups. At necropsy, a thorough gross examination was conducted, and a preliminary cause of death was determined. After histopathological examination of tissues from suspected lesions and an extensive suite of representative tissues, a "final" cause of death was entered into the database.

Animal: 63 Beagle dogs (28 females, 35 males), of 3 age categories (5, 13, and ~60 mo), in 8 groups. NOTE - NCRP 52 (1977) & RCT (1989) subdivide the 13 mo group by dose.

Results: Although a detailed description has not been published, information from this study was summarized in NCRP report 52. Acute toxicity in older dogs was attributed to higher radiation doses associated with increased biological retention of cesium with age. Nearly all the long-term dogs showed significant liver degeneration Compare with study 105.05..

References: Nikula, K.J., B.A. Muggenburg, W.C. Griffith, W.W. Carlton, T.E. Fritz, and B.B. Boecker. Biological effects of cesium-137 chloride injected in beagle dogs of different ages, *Radiation Research* (submitted in 1996).

Experimental Groups:

Study 103.04
Life-Span Health Risks: Single Injection of Cesium-137 in Beagles

Group Id	Age at Injection	Initial Body Burden (kBq/kg)			Number of Dogs	Post-Injection Survival (y)		
		Min	Median	Max		Min	Median	Max
01	Control				17	8.1	13.7	15.6
Late-Occurring Deaths < 11.5 Gy								
02	Juvenile	120	120	140	5	6.5	9.0	13.2
03	Young Adult	61	64	81	9	6.4	8.4	12.8
	Middle Aged				0			
Late-Occurring Deaths > 11.5 Gy								
04	Juvenile	120	130	150	5	5.1	8.8	9.6
05	Young Adult	61	99	160	19	4.4	9.2	12.1
	Middle Aged				0			
Early-Occurring Deaths								
06	Juvenile	140	150	150	3	0.074	0.074	0.11
07	Young Adult	100	140	160	10	0.066	0.077	0.14
08	Middle Aged	120	130	140	10	0.055	0.066	0.080
				Total	80			

103.05 Life-Span Health Risks: Duration-of-Life Gamma-Irradiation of Young Adult Beagles

Institution: Argonne National Laboratory, Argonne IL

Scientists: Bill Norris; retired
Tom Fritz; retired

Purpose: To investigate the effects of duration-of-life exposure at different dose rates on survival and cancer inductions in dogs

Status: Exposure initiated between 1968 and 1978, death of last dog at ANL in 1990. Study terminated /22/91; 18 remaining lowest level (0.3 rad/d) dogs transferred to ITRI.

Treatment: External cobalt-60 gamma-ray exposure, continued until death; dogs placed on experiment in two series: "A" from 1968 to 1970, and "B" form 1976 to 1978. Dogs were irradiated 22 h/d, 7 d/w, in a specially constructed facility. Particular attention was given to dosimetry; all factors contributing to the dose rate and total dose were normalized in the irradiation field by migrating dogs through all positions and orientations with respect to the irradiation source. Control dogs were similarly housed in cages and migrated through positions in the control animal room.

Dosimetry: Radiation was delivered with a cobalt-60 gamma beam apparatus equipped with steel attenuators which were changed every few mo to compensate for radioactive decay. Beagles were caged singly in two-tiered fiberglass cages placed at calculated distances from the source; cages were rotated 90 degrees daily to compensate for the propensity of the dog to occupy the rear of the cage. Dose rate at the center of the cage was measured and converted to absorbed dose.

Endpoints: Dogs were provided with life-time clinical care, including annual physical examination and blood work-ups. At necropsy, a thorough gross examination was conducted, ant a preliminary cause of death was determined. After histopathological examination of tissues from suspected lesions and an extensive suite of representative tissues, a "final" cause of death was determined and entered into the database.

Animal: 276 Beagle dogs (138 females, 138 males), 13 mo old, in 10 groups

Results: Hazard models indicated that hematopoietic failure occurring early in life was positively associated with dose and dose rate. The risk of death from causes other than cancer that occurred later in the life span also depended on dose and dose rate but was lower than the cancer risk. Once a dog survived long enough to die from cancer, failure times depended only on dose.

References: Carnes, B.A., T.E. Fritz. Continuous irradiation of beagles with gamma rays. *Radiation Research* **136** 103-110, 1993.

Experimental Groups:

Study 103.05
Life-Span Health Risks: Duration-of-Life Gamma-Irradiation of Young Adult Beagles

Group Id	Radiation Dose Rate (mGy/d)	Initiation of Exposures	Number of Dogs
01	caged controls		46
02	3	1976 to 1978	92 (18 terminated)
03	8	1976 to 1978	46
04	19	1976 to 1978	46
05	38	1968 to 1970	24
06	75	1968 to 1970	
07	128	1968 to 1970	13
08	263	1968 to 1970	16
09	365	1968 to 1970	8
10	540	1968 to 1970	4
		Total	295

103.06 Life-Span Health Risks: Continuous-Exposure Gamma-Irradiation until Various Total Doses in Young Adult Beagles

Institution: Argonne National Laboratory, Argonne IL

Scientists: Bill Norris; retired
Tom Fritz; retired

Purpose: Investigate the effect of total dose and dose rate in beagles given protracted whole-body cobalt-60 gamma ray exposure to: (1)provide a basis of comparison for beagles given continuous irradiation (**103.05**), (2) complement research on mice at ANL, and (3) address practical issues in radiation health hazards in man.

Status: Exposure initiated between 1968 and 1978, death of last dog at ANL in 1991.

Treatment: External cobalt-60 gamma-ray exposure, 22 h/d, at various dose rates, terminated at various total doses. Dogs were irradiated 22 h/d, 7 d/w, in a specially constructed facility. Particular attention was given to dosimetry; all factors contributing to the dose rate and total dose were normalized in the irradiation field by migrating dogs through all positions and orientations with respect to the irradiation source. Control dogs were similarly housed in cages and migrated through positions in the control animal room.

Dosimetry: Radiation was delivered with a cobalt-60 gamma beam apparatus equipped with steel attenuators which were changed every few mo to compensate for radioactive decay. Beagles were caged singly in two-tiered fiberglass cages placed at calculated distances from the source; cages were rotated daily to compensate for the propensity of the dog to occupy the rear of the cage. Dose rate at the center of the cage was measured and converted to absorbed dose.

Endpoints: Dogs were provided with life-time clinical care, including annual physical examination and blood work-ups. At necropsy, a thorough gross examination was conducted, ant a preliminary cause of death was determined. After histopathological examination of tissues from suspected lesions and an extensive suite of representative tissues, a "final" cause of death was determined and entered into the database.

Animal: 257 Beagle dogs (118 females 139 males), mean age 490 d, in 14 groups, plus 86 age matched dogs from the colony controls. Constraints on the availability of space in the irradiation facility resulted in a range in age at initiation of exposure from 368 to 756 d.

Results: Hazard models indicated that the probability of acute death (related to hematopoietic aplasia) was positively associated with total dose and dose rate. Once a dog survived the initial hematopoietic effects of irradiation, the risk of death from causes other than cancer, while elevated, was far less responsive than the neoplastic end points. No relationship between tumor or chronic nontumor deaths and dose rate could be identified. However, survival curves for tumor mortality did separate into a pattern clearly dependent on accumulated dose.

References: Carnes, B.A. and T.E. Fritz. Responses of the beagle to protracted irradiation. I. Effect of total dose and dose rate. *Radiation Research* **128** 125-132, 1991.

Experimental Groups:

Study 103.06
Life-Span Health Risks:
Continuous-Exposure Gamma-Irradiation until Various Total Doses in Young Adult Beagles

Group Id	Dose Rate (mGy/d)	Day of Exposure	Total Dose (rad)	Number of Dogs
01	caged controls	0	0	86
02	38	118	450	20
03		276	1050	24
04		395	1500	20
05	75	60	450	20
06		140	1050	24
07		200	1500	19
08		400	3000	20
09	128	35	450	20
10		82	1050	21
11		117	1500	19
12		234	3000	10
13	263	17	450	20
14		40	1050	20
			Total	343

103.07 Leukemogenesis: Duration-of-Life Gamma-Irradiation of Young Adult Beagles

Institution: Argonne National Laboratory, Argonne IL

Scientists: Tom Seed; retired.

Purpose: To investigate the consequences of duration-of-life exposure at low dose rates on leukaemogenesis.

Status: Terminated Jan 1991; survivors dispersed.

Treatment: External cobalt-60 gamma ray exposure, 22 hrs/d, 75 mGy/d. Dogs were irradiated 22 h/d, 7 d/w, in a specially constructed facility. Particular attention was given to dosimetry; all factors contributing to the dose rate and total dose were normalized in the irradiation field by migrating dogs through all positions and orientations with respect to the irradiation source. Control dogs were similarly housed in cages and migrated through positions in the control animal room.

Dosimetry: Radiation was delivered with a cobalt-60 gamma beam apparatus equipped with steel attenuators which were changed every few months to compensate for radioactive decay. Beagles were caged singly in two-tiered fiberglass cages placed at calculated distances from the source; cages were rotated daily to compensate for the propensity of the dog to occupy the rear of the cage. Dose rate at the center of the cage was measured and converted to absorbed dose.

Endpoints: evaluation of bone marrow structure and function leading to aplastic anemia, myelogenous leukemia, or protracted survival.

Animal: Young adult Beagle dogs

Results:

References:

Experimental Groups: not available

103.08 Effects (Survival and Carcinogenesis): Duration-of-Life Gamma-Irradiation of LAF1 Mice

Institution: Argonne National Laboratory, Argonne IL

Scientists: Lorenz, Egon; deceased
Heston, W.E.; deceased

Status: This classic study was performed at the National Cancer Institute in 1943, and a follow-up comparison of 0 and 0.11 R/d was conducted between 1949 and 1953. A detailed report was published by Lorenz in 1954. The archived data are held by Dr. Bruce Carnes at ANL as reported by D. Grahn in ANL-94/26 p 6 as study 2.1.

Purpose: To investigate the effects of duration of life exposure on survival of mice

Treatment: Mice were exposed 8 h/d to gamma rays from sealed radium sources. Daily exposure levels were: 0, 0.11, 1.1, 2.2, 4.4, and 8.8 R/d

Dosimetry: Reported as roentgens in air from a radium-226 point source, instrumentation not stated.

Endpoints: Survival, carcinogenesis

Animal: Initial study: 302 LAF1 mice, of both sexes, mean age at entry (60 to 85 d) varied by group.
Follow-up study: 449 LAF1 mice, of both sexes, age 31 d at entry

Results: The data from these studies is almost legendary for those who wish to believe that extremely low doses of radiation may be harmless or beneficial. There appears to be over-survival in several groups. However, pathology data are not available, and there are many experimental design issues which complicate retrospective reanalysis of the information.

References: Lorenz, E., L.O. Jacobson, W.E. Heston, M. Shimkin, A.B. Eschenbrenner, M/K. Deringer, J. Doniger, and R. Schweisthal. Effects of long-continued total-body gamma irradiation on mice, guinea pigs, and rabbits, III. Effects on life span, weight, blood picture and carcinogenesis and the role of the intensity of radiation. in *Biological Effects of External X and Gamma Radiation, Part I* (R.E. Zirkle, editor) National Nuclear Effects Series IV-22B, McGraw-Hill Book Co., New York, pp. 24-148, 1954.

A description of the study and documentation of available archived information will be found in ANL-94/26, pp. 6-7.

Experimental Groups:

See ANL-94/26, TABLE 1 Mean After-Survival Values for the NCI Initial Low-Dose Study, p. 42 for a tabulation of the 308 mice in 6 dose rate groups. The follow-up study is tabulated as, TABLE 2, Mean After-Survival Values for the NCI Low-Dose Follow-Up Study, on page 43 of ANL 94/26.

103.09 Survival and Mammary Tumor Induction: Duration-of-Life Gamma-Irradiation of Female C3Hf Mice

Institution: Argonne National Laboratory, Argonne IL

Scientists: Lorenz, Egon; deceased
Heston, W.E.; deceased

Purpose: To investigate the effect of duration-of-life exposure on survival and mamary carcinogenesis

Status: This classic study was performed at the National Cancer Institute between 1946 and 1951. Some groups were reported in detail by Lorenz in 1951; others remain to be analyzed. The archived data are held by Dr. Bruce Carnes at ANL as reported by D. Grahn in ANL-94/26 p 7 in section 2.2.

Treatment: Female C3Hf mice, normal and "castrate", were exposed 8 h/d to gamma rays from sealed radium sources. Daily exposure levels were: 0, 4.4, and 8.8 R/d.

Dosimetry: Reported as roentgens in air from a radium-226 point source, instrumentation not stated.

Endpoints: Survival, induction of mammary tumors

Animal: Female C3Hf mice, normal and "castrate".

Results: Life shortening in these data was on the high side, but the data are internally consistent. Pathology data are not available.

References: Lorenz, E., A.B. Eschenbrenner, W.E. Heston, D. Uphoff. Mammary tumor incidence in female C3Hb mice following long-continued gamma radiation. *Journal of the National Cancer Institute* **11**:947-965, 1951.

A description of the study and documentation of available archived information will be found in ANL-94/26, pp. 7.

Experimental Groups:

ANL-94/26 does not contain a tabulation of this study, but does describe archived data files.

103.10-103.19 General Summary: Studies of Acute and Chronic Radiation Injury at Argonne National Laboratory, 1953-1970

Institution: Argonne National Laboratory, Argonne IL

Scientists: G.A. Sacher; deceased
D. Grahn; retired
S. Lesher; deceased
R.J.M. Fry; retired - presently at ORNL
J.H. Rust; retired

Purpose: Between 1953 and 1970, studies on the long-term effects of external x-ray and gamma irradiation on inbred and hybrid mouse stocks were carried out at Argonne National Laboratory.

Status: These studies, conducted between 1953 and 1970, are known as the "pre-JANUS" studies. Information from these rodent studies is archived and is being analyzed by Bruce Carnes at Argonne. D. Grahn compiled a comprehensive document (ANL 94/26) describing these studies. Rather than duplicate details from the Grahn document here, the following descriptions of studies (103.10 through 103.19) refer the reader to appropriate pages. Additional information about these studies may be obtained from:

Dr. Bruce Carnes
Argonne National Laboratory
Building 202
Argonne, IL 60439

Treatment: The X-ray facility could irradiate up to 18 mice at once. Large walk-in, live-in radiation rooms were used for cobalt-60 gamma irradiation of large numbers of small mammals.

Dosimetry: Victoreen thimble chamber (ICC), dose measured in air.

Endpoints: Survival, carcinogenesis

Animal: Various mouse strains

References: Grahn, D., *Studies of Acute and Chronic Radiation Injury at the Biological and Medical Research Division, Argonne National Laboratory, 1953-1970: Description of Individual Studies, Data Files, Codes, and Summaries of Significant Findings*, ANL-94/26, 99 pages, 1994.

Experimental Groups:

Studies 103.10-103.19
Studies of Acute and Chronic Radiation Injury at Argonne National Laboratory, 1953-1970

Duration and Type of Exposure	Study Id	ANL Designation	Study Title	Number of Mouse Records
single exposure to X irradiation	10	XAM-3-I	Comparison of mouse strains	22540
	11	XAM-3-II	Outcross and Backcross of Radiosensitive and Radioresistant Mouse Strains	
	12	XAM-3-III	Iowa State University (ISU) Strains and Mutant Mouse Stocks	
	13	XAM-6	Sub Lethal Dose	1121
	14	XAM-7	Age Dependence	1561
chronic gamma ray exposure (8-12 h/d, 7 d/w)	15	GCM-4	LAF_1 Mice	4704
	16	GCM-8	Various Mouse Strains	5160
	16	GCM-12	Low Daily Doses	8862
	16	GCM-9	Age Dependence	669
	19	GAM-2, GFM-1	Single- or Split-Dose Comparison	1848
			Total	46465

103.10 Genetic Variation in Resistance to Single-Exposure X-Irradiation: Comparison of Mouse Strains

Institution: Argonne National Laboratory, Argonne IL

Scientists: Grahn, D; retired
Sacher, George A; deceased

Purpose: Provide consistent data set for studying 3 variables - reproductive performance, radiation resistance, and live expectancy - plus major pathologic findings at death for 15 inbred strains in 4 genetic marker stocks.

Status: The ANL study designation was XAM-3. These studies were initiated in 1953, and continued for nearly 20 y. The archived data are held by Dr. Bruce Carnes at ANL as reported by D. Grahn in ANL-94/26 p 8 in section 3.1.

Treatment: Groups of about 18 mice were exposed to 200 kVp, 15 mA, X-rays at a dose rate of 21-23 R/min in air at a target distance of 27 in. for 20-40 min to achieve doses between 400 and 900 R. The mice were restrained in celluloid centrifuge tubes on a rotating Bakelite disk.

Dosimetry: Victoreen thimble-chamber dosimeter (1 cubic cm). The dosimetric readings included backscatter from walls, floor, and the tabletop.

Endpoints: Acute survival (LD50/30), life expectancy, pathology at death.

Animal: Mice, of both sexes, of 6 inbred strains (A/He, A/Jax, BALB/c, C3Hf/He, C57BL/6, and C57L) and the F1, F2, and F3 hybrids of strains C57BL/6 and BALB/c.

Results: Significant differences in strain specific acute survival values were observed. Hybrid vigor was shown by increased acute survival times in the F1 and F2 generations. Long term survival was positively correlated with acute LD50. After correction for strain differences in lymphoreticular and ovarian tumor incidence, life shortening was estimated to be 28 d per 100 R.

References: Grahn, D., and K.F. Hamilton. Genetic variation in the acute lethal response of four inbred mouse strains to whole body x-irradiation. *Genetics* **42**:189-198, 1957.

Grahn, D. Genetic control of physiological processes: the genetics of radiation toxicity in animals. in *Radioisotopes in the Biosphere* (R.S. Caldecott and L.A. Snyder, editors), University of Minnesota Press, Minneapolis, pp 181-200, 1960.

A description of the study and documentation of available archived information will be found in ANL-94/26, pp. 8-15.

Experimental Groups:

See ANL-94/26, TABLE 3 Distribution of Strains and Hybrids across the Single X-Ray Exposures used in the XAM-3 Experiment, pp. 44-45 and TABLE 4 Number of Mice in XAM-3 Experiment by Strain, Hybrid, or Genetic Stock; Sexes and Doses Combined pp. 46-47. Table 4 lists a total of 22,540 mice (9,510 held for lifetime observation, 16,030 surviving less than 60 d).

103.11 Genetic Variation in Resistance to Single-Exposure X-Irradiation: Outcross and Backcross of Radiosensitive and Radioresistant Mouse Strains

Institution: Argonne National Laboratory, Argonne IL

Scientists: Grahn, D; retired
Sacher, George A; deceased

Purpose: This portion of the study involved a classic recurrent backcross series. The goal was to define the genetic behavior or transmissibility of radiation response and its corollary of life expectancy. A secondary goal was to quantify the linkage between the qualitative color-coat trait at the albino locus and the quantitative trait of radiosensitivity.

Status: The ANL study designation was XAM-3. These studies were initiated in 1953, and continued for nearly 20 y. The archived data are held by Dr. Bruce Carnes at ANL as reported by D. Grahn in ANL-94/26 p 8 in section 3.1.

Treatment, Dosimetry, Endpoints: Identical to those for study 103.10

Animal: Mice, of both sexes, of various crosses between C57BL/6 and BALB/c strains.

Results: This portion of the XAM-3 study was never fully reported. The LD50 values and life expectancies declined as the proportion of BALB/c genotype increased.

References: Grahn, D. Acute radiation response of mice from a cross between radiosensitive and radioresistant strains. *Genetics* **43**:835-843, 1958.

A description of the study and documentation of available archived information will be found in ANL-94/26, pp. 8-15.

Experimental Groups: included with those for study 103.10

103.12 Genetic Variation in Resistance to Single-Exposure X-Irradiation: Iowa State University (ISU) Strains and Mutant Mouse Stocks

Institution: Argonne National Laboratory, Argonne IL

Scientists: Grahn, D; retired

Purpose: Characterize 9 inbred strains and 4 mutant marker stocks brought to Argonne from Iowa State University, where they had been maintained since the early 1930s. The goal was to extend the range of known genetic variation available for radiation studies and preserve the stocks for other uses.

Status: The ANL study designation was XAM-3. These studies were initiated in 1953, and continued for nearly 20 y. This portion of the study was initiated in 1963. The archived data are held by Dr. Bruce Carnes at ANL as reported by D. Grahn in ANL-94/26 p 8 in section 3.1.

Treatment, Dosimetry, Endpoints: Identical to those for study 103.10

Animal: Mice, of both sexes, of 9 inbred strains and 4 mutant marker stocks from the Department of Genetics at Iowa State University.

Results: LD50 ranged from 475 to 750 R. Acute survival in some strains did not correlate with strain specific response to bacterial infection, while it did for others. Control mean life expectancy did not correlate with LD50, in contrast with regular inbreds (103.10 and 103.11).

References: A description of the study and documentation of available archived information will be found in ANL-94/26, pp. 8-15.

Experimental Groups: included with those for study 103.10

103.13 Genetic Variation in Resistance to Single-Exposure X-Irradiation: Sublethal Doses in Several Mouse Strains

Institution: Argonne National Laboratory, Argonne IL

Scientists: Grahn, D; retired

Purpose: XAM-6 was a follow-on to XAM-3. Sublethal single doses were employed to bring the dose-response curve for life-shortening into the low-dose range. The purpose was to improve estimation of the regression coefficient at sublethal doses and to provide a broad, multi strain database for extrapolation to exposures below 100 R

Status: The ANL study designation was XAM-6. The archived data are held by Dr. Bruce Carnes at ANL as reported by D. Grahn in ANL-94/26 p 8 in section 3.5.

Treatment, Dosimetry, Endpoints:
Identical to those for study 103.10. Dose levels of 0, 100 R, and a level equal to 0.6 of the LD50 for each strain.

Animal: 117 BALB/c, 263 A/He, 310 C3Hf, 215 C57BL/6, and 216 BCF1 mice of both sexes, entered into the study at age 100 d.

Results:

References: No peer reviewed description was published. See the description of the study and documentation of available archived information found in ANL-94/26, pp. 27-29.

Experimental Groups:
See ANL-94/26, TABLE 11 Number of Mice for the XAM-6 Test of Life Shortening Induced at Doses below the XAM-3 Range of Approximately 0.8-1.2 LD50 Values, p. 54 for a tabulation of the 1121 mice of 5 strains in this study.

103.14 Genetic Variation in Resistance to Single-Exposure X-Irradiation: Age Dependence in Three Mouse Strains

Institution: Argonne National Laboratory, Argonne IL

Scientists: Grahn, D; retired
Sacher, George A; deceased

Purpose: XAM-7 was a follow-on to XAM-3. The influence of age on response to single doses was studied; ages of 40, 300, and 500 d at time of exposure were to be compared with 100 d in XAM-3.

Status: The ANL study designation was XAM-7. The archived data are held by Dr. Bruce Carnes at ANL as reported by D. Grahn in ANL-94/26 p 8 in section

Treatment, Dosimetry, Endpoints: Identical to those for study 103.10.

Animal: 638 A/He, 834 C3Hf/He and 89 C57BL/6 mice of both sexes, exposed at age 40, 300 or 500 d.

Results: For both strains and sexes, there was no consistent response to the single exposure of 100 R, but there was a consistent life-shortening response to 450 R at all ages of exposure. This indicates the existence of a non-linear dose-response curve in the 0 to 100 to 450 R range.

References: No peer reviewed description was published. See 1958 ANL semi-annual report, and the description of the study, with extensive documentation of available archived information found in ANL-94/26, pp. 29-31.

Experimental Groups:
See ANL-94/26, TABLE 12 Number of Mice for the XAM-7 Study of Age Dependance of Response to Single Doses of 200-kVp X-Rays below the Acute Lethal Level, p. 55, for a tabulation of the 1561 mice in this study.

103.15 Effects of Duration-of-Life Gamma-Irradiation: Characterization of LAF1 Mice

Institution: Argonne National Laboratory, Argonne IL

Scientists: Grahn, D; retired
Lesher, S; deceased
Sacher, George A; deceased

Purpose: These duration-of-life studies evolved from the Lorenz studies (103.08 and 103.09). The goals were to test the concept of tolerance dose, provide data on responses to protracted irradiation compared with acute exposure, and give data on all of the typical radiation syndromes over a continuum of responses.

Status: The ANL study designation was GCM-4. The archived data are held by Dr. Bruce Carnes at ANL as reported by D. Grahn in ANL-94/26 p 8 in section 3.1.

Treatment: Animals were housed in an underground room (7.3 x 7.3 x 3.65 m high) and exposed to a central cobalt-60 source each night. Cylindrical, 1600 cubic cm, plastic cages, containing 3 mice, were placed along dose-rate arcs. Over the years, the duration of exposure was gradually adjusted from 8 to 12 h to compensate for radioactive decay.

Dosimetry: A Victoreen thimble-chamber was used to measure exposure in air. A phantom, designed by Sinclair used to obtain "cage average" absorbed dose. Animals were not housed in areas of the room with non-uniform exposure rates. The absorbed dose for mice was 0.9 rad per roentgen in air.

Endpoints: Mean after survival (MAS) from start of irradiation, life expectancy, pathology at death.

Animal: 4704 LAF1 mice of both sexes, entered into the exposure room at age 100 d.

Results:

References: Sacher, G.A., and D. Grahn. Survival of mice under duration-of-life exposure to gamma rays, I. The dosage-survival relation and the lethality function. *Journal of the National Cancer Institute* **32**:277-321, 1964:

Lesher, S, G.A. Sacher, D. Grahn, K. Hamilton, and A. Sallese. Survival of mice under duration-of-life exposure to gamma rays. II. Pathologic effects. *Radiation Research* **24**:239-277, 1965.

A description of the study and documentation of available archived information will be found in ANL-94/26, pp. 15-23.

Experimental Groups:

See ANL-94/26, TABLE 5 Distribution of Experiments GCM-4, 8, and 12 across Strains and Daily Dose Levels, p. 48 and TABLE 6 Number of Mice Entered into Studies CGM-4 and CGM-8 According to Dose and Strain; Sexes Combined, p. 49 for a tabulation of the 4704 mice in this study.

103.16 Effects of Duration-of-Life Gamma-Irradiation: Characterization of Various Mouse Strains

Institution: Argonne National Laboratory, Argonne IL

Scientists: Grahn, D; retired
Sacher, George A; deceased
Lescher, S; deceased

Purpose: These duration-of-life studies evolved from the Lorenz studies (103.08 and 103.09). The goals were to test the concept of tolerance dose, provide data on responses to protracted irradiation compared with acute exposure, and give data on all of the typical radiation syndromes over a continuum of responses.

Status: The ANL study designation was GCM-8. The archived data are held by Dr. Bruce Carnes at ANL as reported by D. Grahn in ANL-94/26 p 8 in section 3.1.

Treatment: Animals were housed in an underground room (7.3 x 7.3 x 3.65 m high) and exposed to a central cobalt-60 source each night. Cylindrical, 1600 cubic cm, plastic cages, containing 3 mice, were placed along dose-rate arcs. Over the years, the duration of exposure was gradually adjusted from 8 to 12 h to compensate for radioactive decay.

Dosimetry: A Victoreen thimble-chamber was used to measure exposure in air. A phantom, designed by Sinclair used to obtain "cage average" absorbed dose. Animals were not housed in areas of the room with non-uniform exposure rates. The absorbed dose for mice was 0.9 rad per roentgen in air.

Endpoints: Life expectancy (MAS), pathology at death.

Animal: 6273 mice of both sexes, 8 strains: A/He, A/Jax, BALB/c, C3Hf, C57BL/6, C57L, BCF1, and BCF2

Results:

References: Grahn, D., G.A. Sacher, R.A. Lea, R.J.M. Fry, and J.H. Rust. Analytical approaches and interpretations of data on time, rate and cause of death of mice exposed to external gamma radiation. In: *Late Biological Effects of Ionizing Radiation*, IAEA, Vienna, pp. 43-58, 1978.
Unfortunately, the data from this study were not fully reported in the peer-reviewed literature. Several ANL reports are available, and a description of the study, with extensive documentation of available archived information will be found in ANL-94/26, pp. 8-15.

Experimental Groups:
See ANL-94/26, TABLE 6 Number of Mice Entered into Studies GCM-4 and GCM-8 According to Dose and Strain; Sexes Combined, p. 49, and TABLE 7 Number of Mice Entered into the GCM-12 Study According to Dose, Strain, and Sex, p. 50 for a tabulation of the 6273 mice in this study.

103.17 Effects of Duration-of-Life Gamma-Irradiation: Low Dose Rate in Various Mouse Strains

Institution: Argonne National Laboratory, Argonne IL
Scientists: Grahn, D; retired
Sacher, George A; deceased

Purpose: These duration-of-life studies evolved from the Lorenz studies (103.08 and 103.09). The goals were to test the concept of tolerance dose, provide data on responses to protracted irradiation compared with acute exposure, and give data on all of the typical radiation syndromes over a continuum of responses.

Status: The ANL study designation was GCM-12. The archived data are held by Dr. Bruce Carnes at ANL as reported by D. Grahn in ANL-94/26 p 8 in section 3.2.

Treatment: Animals were housed in an underground room (7.3 x 7.3 x 3.65 m high) and exposed to a central cobalt-60 source each night. Cylindrical, 1600 cubic cm, plastic cages (improved by additional ventilation), containing 3 mice, were placed along dose-rate arcs. Over the years, the duration of exposure was gradually adjusted from 8 to 12 h to compensate for radioactive decay. A 2.5 cm, 120 degree, lead shield placed adjacent to the source provided a lower dose rate in part of the room for this study.

Dosimetry: A Victoreen thimble-chamber was used to measure exposure in air. Animals were not housed in areas of the room with non-uniform exposure rates. Absorbed dose measures were not made in the shielded areas, but pulse-height dosimetry was obtained. The characteristic 1.2 Mev energy prevailed, although there was considerable increase in the degraded energy spectrum. Thus, the reported absorbed dose of 0.9 rad/R in air could be an overestimate.

Endpoints: Life expectancy (MAS), pathology at death.

Animal: 8862 mice of both sexes and 4 strains (A/Jax. BALB/c, C57BL/6, and B6CF1).

Results: This data demonstrated unequivocally that most (>85%) radiation-induced excess risk of mortality at low doses could be attributed to neoplastic disease. Induced life-shortening in d per roentgen is linearly and additively a function of accumulated dose and is independent of dose rate up to daily doses of 12 R/d.

References: Grahn, D. Biological effects of protracted low dose radiation exposure of man and animals. In: *Late Effects of Radiation*, Taylor and Francis, London, pp 101-136, 1970.
Grahn, D., G.A. Sacher, R.A. Lea, R.J.M. Fry, and J.H. Rust. Analytical approaches and interpretations of data on time, rate and cause of death of mice exposed to external gamma radiation. In: *Late Biological Effects of Ionizing Radiation*, IAEA, Vienna, pp. 43-58, 1978.
A description of the study and documentation of available archived information will be found in ANL-94/26, pp. 15-23.

Experimental Groups:
See ANL-94/26, TABLE 7 Number of Mice Entered into the GCM-12 Study According to Dose, Strain, and Sex, p. 50 for a tabulation of the 8862 mice in this study.

103.18 Effects of Duration-of-Life Gamma-Irradiation: Age Dependence in Various Mouse Strains

Institution: Argonne National Laboratory, Argonne IL

Scientists: Grahn, D; retired
Sacher, George A; deceased

Purpose: GCM-9 was a adjunct to GCM-4 (103.15) in which the mice were entered into the exposure room at various ages. The scientific question was: "Does radiosensitivity vary significantly as a function of age at exposure or at initiation of protracted or periodic exposure?"

Status: The ANL study designation was GCM-9. The archived data are held by Dr. Bruce Carnes at ANL as reported by D. Grahn in ANL-94/26 p. 24 in section 3.3.

Treatment: Animals were housed in an underground room (7.3 x 7.3 x 3.65 m high) and exposed to a central cobalt-60 source each night. Cylindrical, 1600 cubic cm, plastic cages (improved by additional ventilation), containing 3 mice, were placed along dose-rate arcs. Over the years, the duration of exposure was gradually adjusted from 8 to 12 h to compensate for radioactive decay. Dose levels of 170, 125, 97, 74, 43, and 12 R/d.

Dosimetry: A Victoreen thimble-chamber was used to measure exposure in air. A phantom, designed by Sinclair was used to obtain "cage average" absorbed dose. Animals were not housed in areas of the room with non-uniform exposure rates. The absorbed dose for mice was 0.9 rad per roentgen in air.

Endpoints: Life expectancy (MAS), pathology at death

Animal: 669 LAF1 mice of both sexes, 601 mice of other strains: A/He, A/Jax, BALB/c, C3Hf, C57BL/6, C57L, and BCF1, aged 250 to 925 d were compared with similar animals in study 103.15 which were 100 d at study entry.

Results: With the 100-d GCM-4 values as the starting point, resistance increased up to the 400-d age level for all dose groups (except 43 R/d). Beyond 400 d of entry age, resistance tended to diminish steadily.

References: No peer reviewed description was published. See 1958 ANL semi-annual report, and the description of the study, with extensive documentation of available archived information found in ANL-94/26, pp. 24-25.

Experimental Groups:
See ANL-94/26, TABLE 8 Number of LAF1 Mice Entered in the GCM-9B Test of Age Dependence of Response to Daily Irradiation by Co-60 gamma Rays (exposure levels as in GCM-4) p. 51 and TABLE 9 Number of Mice Entered in the GCM-9B Test of Age Dependence of Response to Daily Irradiation by Co-60 Gamma Rays, p. 52, for a tabulation of the 669 LAF1 mice and 601 mice of other strains in this study.

103.19 Effects of Duration-of-Life Gamma-Irradiation: Single- or Split-Dose Comparison in LAF1 Mice

Institution: Argonne National Laboratory, Argonne IL

Scientists: Grahn, D; retired
Sacher, George A; deceased

Purpose: These studies were an adjunct to GCM-4 (103.15). These mice were exposed once at age 100 d, or twice, at intervals between 3 h and 28 d. The goal was to provide a comparison between the chronic irradiated GCM-4 study and acute exposure studies conducted at other institutions.

Status: The ANL study designation was GCM-2 and GFM-1. The archived data are held by Dr. Bruce Carnes at ANL as reported by D. Grahn in ANL-94/26 p. 25 in section 3.4.

Treatment: Dose levels of 150 to 1100 R, 450 and 750 R levels also given as split doses. The high level cobalt-60 (nominally 1200Ci) room was used, groups of 3 animals were housed in cylindrical cages. Exposures averaged 1 h.

Dosimetry: A Victoreen thimble-chamber was used to measure exposure in air. A phantom, designed by Sinclair was used to obtain "cage average" absorbed dose. Animals were not housed in areas of the room with non-uniform exposure rates. The absorbed dose for mice was 0.9 rad per roentgen in air.

Endpoints: Life expectancy (MAS), pathology at death.

Animal: LAF1 mice of both sexes, 984 given a single exposure at age 100, 114, or 128 d. An additional 864 mice were exposed twice, at 100 d of age and 0.125, 0.4, 1, 3, 5, 7, 14, or 28 d later.

Results: The LD50/30 value for cobalt-60 gamma ray exposure of the two sexes combined was about 975 R compared with 630 R for 200 kVp x-rays for a relative biological effectiveness of 0.6 to 0.7. The split-dose procedure had no significant influence.

References: Grahn, D. And G.A. Sacher. Fractionation and protraction factors and the late effects of radiation in small mammals. In: *Dose Rate in Mammalian Radiation Biology,* USAEC Report CONF-680410, pp. 2.10-2.27, 1968.
No peer reviewed description was published. See the description of the study and documentation of available archived information found in ANL-94/26, pp. 25-27.

Experimental Groups:
See ANL-94/26, TABLE 10 Number of LAF1 Mice (equal numbers of each sex) in the GAM-2/GFM-1 Test of Response to Single Exposures of Co-60 Gamma Rays at 100 D of Age (GAM-2), Plus a Split-Dose Series at 450 and 750 R (GFM-1), p. 53 for a tabulation of the 1848 LAF1 mice in this study.

103.20-103.30 General Summary: Studies of Exposure of Mice to JANUS Fission Neutrons at Argonne National Laboratory, 1970-1994

Institution: Argonne National Laboratory, Argonne IL

Scientists: Ainsworth, E. John; presently at AFFRI
Carnes, Bruce; active
Fry, R.J. Michael; retired, presently at ORNL
Grahn, D; retired
Lombard, Louise S; deceased
Stearner, SP; retired
Thomson, JF; deceased
Williamson, Frank; retired

Purpose: The primary program objectives were to obtain data for the development of realistic models of chronic radiation morbidity and mortality whereby long-term radiation injury can be understood and predicted in terms of: (1) cell injury and recovery; (2) tissue and organ injury, repair and regulation; (3) the actuarial statistics of disease and death. These data can then be used to estimate the neutron/gamma-ray RBE.

Status: Studies of external exposure to fission neutrons were conducted at Argonne National Laboratory from 1971 until the decommissioning of the JANUS medical research reactor in 1994. An extensive collection of archived data is being analyzed by Dr. Bruce Carnes at ANL. A technical document describing the JANUS program provides detailed guidance to the information archive is available. Rather than duplicate details from the Grahn documents here, the following descriptions of ANL rodent studies refer the reader to appropriate pages. Additional information about these studies may be obtained from:

Dr. Bruce Carnes
Argonne National Laboratory
Building 202
Argonne, IL 60439

Treatment: Cages of 5 mice were exposed in the JANUS reactor or the cobalt-60 gamma ray exposure room for various times. The power level of the reactor was adjusted to produce the desired dose rate.

Dosimetry: Neutrons - acetylene and argon ionization chamber. The JANUS fission-spectrum neutrons had a KERMA-weighted mean energy of 0.85 MeV.
Gamma - Victoreen Model 415 Intercomparison Standard chamber.

Endpoints: Life expectancy, cause of death

Animal: Specific pathogen free B6CF1 mice of both sexes were used for most of the experiments. In some cases, single sex populations were studied. In one experiment (103.27) the white-footed mouse, Peromyscus leucopus, was studied. The standard age at exposure was 100 d; three groups of mice (see 103.20 and 103.25) were exposed at 200, 300, and 500 d. Almost 50,000 mice were used in these studies.

Results: There is no single best estimate of the neutron/gamma-ray RBE. Grahn, et al, 1995 (ANL95/3) includes a lengthy summary section (pp. 35-39) discussing the major variables that influence the RBE value.

References: Carnes, B.A., D. Grahn, J.F. Thomson. Dose-response modeling of life shortening in a retrospective analysis of the combined data from the JANUS program at Argonne National Laboratory. *Radiation Research* **119**:39-56, 1989.

Carnes, B.A., and D. Grahn. Issues about neutron effects: the JANUS program. *Radiation Research* **128**: S141-S146, 1991.

Grahn, D., L.S. Lombard, and B.A. Carnes. The comparative tumorigenic effects of fission neutrons and cobalt-60 gamma rays in the B6CF1 mouse. *Radiation Research* **129**:19-36, 1992.

Grahn, D., J.F. Thomson, B.A. Carnes, F.S. Williamson, and L.S. Lombard. Comparative biological effects of low dose, low dose-rate exposures to fission neutrons from the JANUS reactor of to co-60 gamma rays. *Nuclear Science Applications* 2:385-396, 1986.

Grahn, D, B.J. Wright, B.A. Carnes, F.S. Williamson, and C. Fox. *Studies of Acute and Chronic Radiation Injury at the Biological and Medical Research Division, Argonne National Laboratory, 1970-1992: The JANUS Program Survival and Pathology Data*, ANL-95/3, 150 pages, 1995.

Experimental Groups:

Studies 103.20-103.30

Studies of Exposure to JANUS Fission Neutrons at Argonne National Laboratory, 1970-1994*

Study Id	JANUS Study Id and Description		Number of Mouse Records			
			Input	Death	Gross	Histo
20	JM-2	short-term fractionated and single exposures	11590	9947	9205	7838
21	JM-3	single exposures	3280	2867	2732	2204
22	JM-4K JM-4W	short-term fractionated exposures	8270	6258	5927	3193
23	JM-4L1 JM-4L2	protracted gamma ray exposures	1145	1104	1075	735
24	JM-7	long-term fractionated exposures	2735	2676	2554	438
25	JM-8	duration-of-life exposures	1880	1292	1197	239
26	JM-9	single exposures to very low doses	5450	5385	7923	1465
27	JM-10	species comparison	2390	2187	1959	0
28	JM-12	reverse dose-rate study	600	600	537	0
29	JM-13	simulation of working lifetime exposures	7895	6317	5935	2760
30	JM-14	evaluation of radioprotectors	4000	3978	3668	623
		Total	49235	42621	39712	19495

*Adapted from "TABLE 4 JANUS Program Records Summary", p. 46, ANL 95/3

103.20 Effects of Exposure to JANUS Fission Neutrons or Gamma-Irradiation: Short-Term, Fractionated and Single Exposures of B6CF1 Mice

Institution: Argonne National Laboratory, Argonne IL

Scientists: Ainsworth, E. John; presently at AFFRI
Fry, R.J. Michael; retired, presently at ORNL
Grahn, D; retired
Lombard, Louise S; deceased

Purpose: This study tested the additivity of small increments of neutron dose when given in different patterns of exposure over a 24 w period., as compared to the effects of single exposures.

Status: The ANL study designated as JM-2 was conducted in 1971-1972. The archived data are held by Dr. Bruce Carnes at ANL as reported by D. Grahn in ANL-95/3 p. 28-29 in section 3.2.1.

Treatment: A basic dose was 2.4 Gy neutron or 8.5 Gy gamma, delivered in 5 patterns ranging from a single exposure to 3/w for 24 w. Other doses: single: gamma-ray @ 90, 268, or 788 cGy; neutron @ 20, 80, or 240 cGy; 1/w X 24 w: gamma-ray @ 1.11 Gy; neutron @ 80 cGy.

Dosimetry: Neutrons - acetylene and argon ionization chamber. Gamma - Victoreen Model 415 Intercomparison Standard chamber.

Endpoints: Life expectancy, cause of death.

Animal: Specific pathogen free B6CF1 mice (over 11,000 of both sexes)

Results: The 24 weekly fractionation of the 2400 mGy dose augmented the life-shortening response from about 1 d lost per 10 mGy to about 1.5 d (opposite of gamma ray pattern). Super-additivity in neutron dose response was observed; 6 larger once-monthly exposures were less effective than 24 smaller weekly exposures.

References:

Ainsworth, E.J., R.J.M. Fry, D. Grahn, F.S. Williamson, P.C. Brennan, S.P. Stearner, A.V. Carrano, and J.H. Rust. Late effects of neutron or gamma radiation in mice. in *Biological Effects of Neutron Irradiation*, International Atomic Energy Agency, Vienna, pp. 359-379, 1974.

Thomson, J.F., F.S. Williamson, D. Grahn, and E.J. Ainsworth. Life shortening in mice exposed to fission neutrons and gamma rays. I. Single and short-term fractionated exposures. *Radiation Research* **86**:559-572, 1981.

Experimental Groups:

See ANL-95/3, TABLE 7 Inventory of Death and Pathology Records for Experiment JM-2, p. 48 for a tabulation and mean after survival of the 5390 female and 6200 male B6CF1 mice in 58 groups for this study.

103.21 Effects of Exposure to JANUS Fission Neutrons or Gamma-Irradiation: Single Exposures of B6CF1 Mice

Institution: Argonne National Laboratory, Argonne IL

Scientists: Ainsworth, E. John; presently at AFFRI
Fry, R.J. Michael; retired, presently at ORNL
Grahn, D; retired
Lombard, Louise S; deceased

Purpose: This experiment was a straightforward single-dose study composed of 7 replications.

Status: The ANL study designated as JM-3 was conducted between 1974 and 1977. The archived data are held by Dr. Bruce Carnes at ANL as reported by D. Grahn in ANL-95/3 p. 30 in section 3.2.2.

Treatment: The basic dose pattern was one 20 min exposure to neutrons or gamma rays.

Dosimetry: Neutrons - acetylene and argon ionization chamber. Gamma - Victoreen Model 415 Intercomparison Standard chamber.

Endpoints: Life expectancy, cause of death

Animal: Specific pathogen free B6CF1 mice (3280 of both sexes)

Results: Life shortening response to a single neutron dose of 200, 400, 600, 1200, 1600 and 2400 mGy was non-linear, concave downward, with the effect at 200 mGy being 4 x that at 2400 mGy. Per unit dose.

References: Thomson, J.F., F.S. Williamson, D. Grahn, and E.J. Ainsworth. Life shortening in mice exposed to fission neutrons and gamma rays. I. Single and short-term fractionated exposures. *Radiation Research* **86**:559-572, 1981.

Experimental Groups:
See ANL-95/3, TABLE 8 Inventory of Death and Pathology Records for Experiment JM-3, p. 49 for a tabulation and mean after survival of the 1330 female and 1950 male B6CF1 mice in 24 groups for this study.

103.22 Effects of Exposure to JANUS Fission Neutrons or Gamma-Irradiation: Short-Term, Fractionated, Low-Dose Exposures of B6CF1 Mice

Institution: Argonne National Laboratory, Argonne IL

Scientists: Ainsworth, E. John; presently at AFFRI
Fry, R.J. Michael; retired, presently at ORNL
Grahn, D; retired
Lombard, Louise S; deceased
Stearner, SP; retired
Thomson, JF; deceased
Williamson, Frank; retired

Purpose: This experiment extended the 1/w x 24 w exposure regimen of JM-2 to lower doses.

Status: The ANL study designation was JM-4. The archived data are held by Dr. Bruce Carnes at ANL as reported by D. Grahn in ANL-95/3 p. 30 in section 3.2.3.

Treatment: Cages of 5 mice were exposed in the JANUS reactor or the cobalt 60 gamma ray exposure room for 45 min, once/w for 24 w.

Dosimetry: Neutrons - acetylene and argon ionization chamber. Gamma - Victoreen Model 415 Intercomparison Standard chamber.

Endpoints: Life expectancy, cause of death

Animal: Specific pathogen free B6CF1 mice (8220 of both sexes)

Results:

References: Thomson, J.F., F.S. Williamson, D. Grahn, and E.J. Ainsworth. Life shortening in mice exposed to fission neutrons and gamma rays. I. Single and short-term fractionated exposures. *Radiation Research* **86**:559-572, 1981.

Experimental Groups:

See ANL-95/3, TABLE 9 Inventory of Death and Pathology Records for Experiment JM-4K and JM-4W, p. 50 for a tabulation and mean after survival of the 4030 female and 4190 male B6CF1 mice in 31 groups for this study.

103.23 Effects of Exposure to JANUS Fission Neutrons or Gamma-Irradiation: Protracted Gamma-Irradiation of B6CF1 Mice

Institution: Argonne National Laboratory, Argonne IL

Scientists: Ainsworth, E. John; presently at AFFRI
Fry, R.J. Michael; retired, presently at ORNL
Grahn, D; retired
Lombard, Louise S; deceased
Thomson, JF; deceased
Williamson, Frank S; retired

Purpose: Protracted exposure study to parallel the 60 x 1/w study (103.29), and the 24 X 1/w study (103.22).

Status: The ANL study designation was JM-4L1 and JM-4L2. The archived data are held by Dr. Bruce Carnes at ANL as reported by D. Grahn in ANL-95/3 p. 28-29 in section 3.2.1.

Treatment: Cages of 5 mice were exposed in the cobalt 60 gamma ray exposure room for 22 h/d, 5 d/w for 23 or 59 w to achieve weekly total doses of 90, 180, 420 and 800 mGy.

Dosimetry: Victoreen Model 415 Intercomparison Standard chamber.

Endpoints: Life expectancy, cause of death

Animal: Specific pathogen free B6CF1 mice (1145 males)

Results:

References: Thomson, J.F., and D. Grahn, Life shortening in mice exposed to fission neutrons and gamma rays. VIII. Exposures to continuous gamma radiation. *Radiation Research* **118**:151-160, 1989.

Experimental Groups:

See ANL 95/3, TABLE 10, Inventory of Death and Pathology Records for Experiment JM-4L1 and JM-4L2 (only males used), p. 51 for a tabulation and mean after survival of the 1145 male B6CF1 mice in 9 groups for this study

103.24 Effects of Exposure to JANUS Fission Neutrons or Gamma-Irradiation: Long-Term, Fractionated Exposures of B6CF1 Mice

Institution: Argonne National Laboratory, Argonne IL

Scientists: Ainsworth, E. John; presently at AFFRI
Fry, R.J. Michael; retired, presently at ORNL
Grahn, D; retired
Williamson, Frank; retired

Purpose: Extend protraction period from 24 to 60 w (about 50% of life expectancy); test single exposure at age 520 d.

Status: The ANL study designation was JM-7. The archived data are held by Dr. Bruce Carnes at ANL as reported by D. Grahn in ANL-95/3 p. 31 in section 3.2.4.

Treatment: Single exposure/w, for 60 weeks.

Dosimetry: Neutrons - acetylene and argon ionization chamber. Gamma - Victoreen Model 415 Intercomparison Standard chamber.

Endpoints: Life expectancy, cause of death

Animal: Specific pathogen free B6CF1 mice (2735 of both sexes)

Results:

References: Thomson, J.F., F.S. Williamson, D. Grahn, and E.J. Ainsworth. Life shortening in mice exposed to fission neutrons and gamma rays. II. Duration-of-life and long-term fractionated exposures. *Radiation Research* **86**:573-579, 1981.

Experimental Groups:
See ANL-95/3, TABLE 11 Inventory of Death and Pathology Records for Experiment JM-7, p. 52 for a tabulation and mean after survival of the 1080 female and 1655 male B6CF1 mice in 18 groups for this study.

103.25 Effects of Exposure to JANUS Fission Neutrons or Gamma-Irradiation: Duration-of-Life Exposures of B6CF1 Mice

Institution: Argonne National Laboratory, Argonne IL

Scientists: Ainsworth, E. John; presently at AFFRI
Fry, R.J. Michael; retired, presently at ORNL
Grahn, D; retired
Williamson, Frank; retired

Purpose: Duration-of-life exposure for comparison with pre-JANUS studies and protracted 1/w exposure.

Status: The ANL study designation was JM-8. The archived data are held by Dr. Bruce Carnes at ANL as reported by D. Grahn in ANL-95/3 p. 32 in section 3.2.5.

Treatment: Cages of 5 mice were exposed in the JANUS reactor or the cobalt-60 gamma ray exposure room once per w for life, starting at age 100 d.

Dosimetry: Neutrons - acetylene and argon ionization chamber. Gamma - Victoreen Model 415 Intercomparison Standard chamber.

Endpoints: Life expectancy, cause of death

Animal: Specific pathogen free B6CF1 mice (1880 of both sexes)

Results:

References: Thomson, J.F., F.S. Williamson, D. Grahn, and E.J. Ainsworth. Life shortening in mice exposed to fission neutrons and gamma rays. II. Duration-of-life and long-term fractionated exposures. *Radiation Research* **86**:573-579, 1981.

Experimental Groups:
See ANL-95/3, TABLE 12 Inventory of Death and Pathology Records for Experiment JM-8, p. 53 for a tabulation and mean after survival of the 480 female and 1400 male B6CF1 mice in 14 groups for this study.

103.26 Effects of Exposure to JANUS Fission Neutrons or Gamma-Irradiation: Single, Very-Low-Dose Exposures of B6CF1 Mice

Institution: Argonne National Laboratory, Argonne IL

Scientists: Grahn, D; retired
Lombard, Louise S; deceased
Thomson, JF; deceased
Williamson, Frank; retired

Purpose: Further investigate low dose end of response curve to compare with super-linear response observed earlier.

Status: The ANL study designated as JM-9 was conducted between 1977 and 1978. The archived data are held by Dr. Bruce Carnes at ANL as reported by D. Grahn in ANL-95/3 p. 30 in section 3.2.2.

Treatment: The basic dose pattern was one 20 min exposure to neutrons or gamma rays. Neutron doses of 10, 25, 50, 100, 200 and 400 mGy were compared to gamma-ray doses of 225, 450, and 900 mGy.

Dosimetry: Neutrons - acetylene and argon ionization chamber. Gamma - Victoreen Model 415 Intercomparison Standard chamber.

Endpoints: Life expectancy, cause of death.

Animal: Specific pathogen free B6CF1 mice (5450 of both sexes)

Results: The 10 mGy neutron dose had a null response.

References: Thomson, J.F., F.S. Williamson, and D. Grahn. Life shortening in mice exposed to fission neutrons and gamma rays. III. Neutron exposures of 5 and 10 rad. *Radiation Research* **93**:205-209, 1983.

Thomson, J.F., F.S. Williamson, and D. Grahn. Life shortening in mice exposed to fission neutrons and gamma rays. V. Further studies with low single doses. *Radiation Research* **104**:420-428, 1983.

Experimental Groups:
See ANL-95/3, TABLE 13 Inventory of Death and Pathology Records for Experiment JM-9, p. 54 for a tabulation and mean after survival of the 5050 female and 400 male B6CF1 mice in 17 groups for this study.

103.27 Effects of Exposure to JANUS Fission Neutrons or Gamma-Irradiation: Species Comparison, Male White-Footed Field Mice (*Peromyscus leucopus*)

Institution: Argonne National Laboratory, Argonne IL

Scientists: Grahn, D; retired
Sacher, George A; deceased
Thomson, JF; deceased
Williamson, Frank S; retired

Purpose: Provide data for interspecies comparisons.

Status: The ANL study designated as JM-10 was conducted between 1977 and 1979. The archived data are held by Dr. Bruce Carnes at ANL as reported by D. Grahn in ANL-95/3 pp. 32-33 in section 3.2.7.

Treatment: Same as 103.21. and 103.22.

Dosimetry: Neutrons - acetylene and argon ionization chamber. Gamma - Victoreen Model 415 Intercomparison Standard chamber.

Endpoints: Life expectancy, cause of death

Animal: Laboratory reared white footed field mouse, Peromyscus leucopus (2390 males)

Results: Response in terms of life-shortening was not particularly different from that of the B6CF1 mouse, but a different spectrum of pathology was seen.

References: Thomson, J.F., F.S. Williamson, and D. Grahn. Life shortening in mice exposed to fission neutrons and gamma rays. VI. Studies with the white-footed mouse, Peromyscus leucopus. *Radiation Research* **108**:176-188, 1983.

Experimental Groups:
See ANL-95/3, TABLE 14 Inventory of Death and Pathology Records for Experiment JM-10, p. 55 for a tabulation and mean after survival of the 2390 male B6CF1 mice in 12 groups for this study.

103.28 Effects of Exposure to JANUS Fission Neutrons or Gamma-Irradiation: Reverse Dose Rate in B6CF1 Mice

Institution: Argonne National Laboratory, Argonne IL

Scientists: Grahn, D; retired
Thomson, JF; deceased

Purpose: Investigate reverse-dose effect (as neutron doses are protracted or fractionated, life-shortening is augmented).

Status: The ANL study designated as JM-12 was conducted between 1979 and 1980. The archived data are held by Dr. Bruce Carnes at ANL as reported by D. Grahn in ANL-95/3 p. 33 in section 3.2.8.

Treatment: Total dose of 2400 mGy was delivered in 1, 2, 4, or 6 fractions at 1 w intervals.

Dosimetry: Neutrons - acetylene and argon ionization chamber. Gamma - Victoreen Model 415 Intercomparison Standard chamber.

Endpoints: Life expectancy, cause of death.

Animal: Specific pathogen free B6CF1 mice (600 males)

Results: Histopathology not performed.

References: Thomson, J.F., F.S. Williamson, and D. Grahn. Life shortening in mice exposed to fission neutrons and gamma rays. IV. Further studies with fractionated neutron exposures. *Radiation Research* **103**:77-88, 1983.

Experimental Groups:
See ANL-95/3, TABLE 15 Inventory of Death and Pathology Records for Experiment JM-12, p. 55 for a tabulation and mean after survival of the 600 male B6CF1 mice in 5 groups for this study.

103.29 Effects of Exposure to JANUS Fission Neutrons or Gamma-Irradiation: Simulation-of-Working-Lifetime Exposures in B6CF1 Mice

Institution: Argonne National Laboratory, Argonne IL

Scientists: Grahn, D; retired
Lombard, Louise S; deceased
Thomson, JF; deceased
Williamson, Frank; retired

Purpose: Evaluate potential risks to utility workers by exposing mice to low doses delivered in 60 once-weekly exposures; evaluate life-shortening and genetic alterati

Status: The ANL study designated as JM-13 was conducted between 1981 and 1982. The archived data are held by Dr. Bruce Carnes at ANL as reported by D. Grahn in ANL-95/3 pp. 33-34 in section 3.2.9. ons.

Treatment: Cages of 5 mice were exposed in the JANUS reactor or the cobalt-60 gamma ray exposure room for 20 min once per w for 60 w. Lowest neutron dose rate studied was 0.0167 mGy/min.

Dosimetry: Neutrons - acetylene and argon ionization chamber. Gamma - Victoreen Model 415 Intercomparison Standard chamber.

Endpoints: Life expectancy, genetic changes, cause of death

Animal: Specific pathogen free B6CF1 mice (7895 of both sexes)

Results:

References: Thomson, J.F., and D. Grahn. Life shortening in mice exposed to fission neutrons and gamma rays. VII. Effects of 60 once-weekly exposures. *Radiation Research* **115**:347-360, 1988.

Experimental Groups:
See ANL-95/3, TABLE 16 Inventory of Death and Pathology Records for Experiment JM-13, p. 56 for a tabulation and mean after survival of the 3200 female and 4695 male B6CF1 mice in 24 groups for this study.

103.30 Effects of Exposure to JANUS Fission Neutrons or Gamma-Irradiation: Evaluation of Radioprotectors in B6CF1 Mice

Institution: Argonne National Laboratory, Argonne IL

Scientists: Grdina, DJ; active

Purpose: Evaluate the efficacy of several radioprotector agents against the induction of late effects (life-shortening and tumorigenesis).

Status: The ANL study designated as JM-14 was conducted between 1984 and 1985. The archived data are held by Dr. Bruce Carnes at ANL as reported by D. Grahn in ANL-95/3 p. 34 in section 3.2.10.

Treatment: Cages of 5 mice were exposed in the JANUS reactor or the cobalt-60 gamma ray exposure room for 20 min at levels used in 103.21 and 103.26. Protective agent or saline injected 30 min prior to irradiation.

Dosimetry: Neutrons - acetylene and argon ionization chamber. Gamma - Victoreen Model 415 Intercomparison Standard chamber.

Endpoints: Life expectancy, cause of death

Animal: Specific pathogen free B6CF1 mice (4000 of both sexes)

Results:

References:

Grdina, D.J., B.A. Carnes, D. Grahn, and C.P. Sigdestad. Protection against late effects of radiation by S-2-(3-aminopropylomino)-ethylphosphorothioic acid. *Cancer Research* **51**:4125-4130, 1991.

Grdina, D. J., B.J. Wright, and B.A. Carnes. Protection by WR-151327 against late-effect damage from fission-spectrum neutrons. *Radiation Research* **128**:S124-S127, 1991.

Carnes, B.A., and D.J. Grdina. *In vivo* protection by the aminothiol WR-2721 against neutron-induced carcinogenesis. *International Journal of Radiation Biology* **61**:567-576, 1992.

Experimental Groups:

See ANL-95/3, TABLE 17 Inventory of Death and Pathology Records for Experiment JM-14, p. 57 for a tabulation and mean after survival of the 2000 female and 2000 male B6CF1 mice in 20 groups for this study.

104 Pacific Northwest Laboratory (PNL)

104.01 Life-Span Health Risks: Single-Inhalation Exposure of Plutonium-239 Oxide in Beagles

Institution: Pacific Northwest Laboratory, Richland WA

Scientists: Bair, William J; Retired
Park, James F; Retired

Status: Aerosol exposure in 1959-1962; no detailed information available at NRA

Purpose: Radiation dose range finding and aerosol administration technique refinement.

Treatment: Single inhalation of plutonium oxide aerosol, count median diameter (CMD) 0.1 to 0.5 μm; dogs 12 to 43 mo old, of both sexes, placed on experiment between 1959 and 1962. After exposure, the dogs were held for life time care and observation and were euthanized when moribund or to prevent unnecessary pain. The necropsy protocol following euthanasia or spontaneous death included a complete gross pathological evaluation, with emphasis on those tissues or organs that had been clinically dysfunctional, had demonstrable lesions when examined radiographically, or were considered target tissues for plutonium deposition.

Dosimetry: There was no acceptable method for estimation of the quantity of aerosol actually inhaled and deposited in the lung of the dog. Plutonium alpha particles are not detectable outside the body, and detectors sensitive to measure low energy x-rays associated with the decay had not yet been developed. Therefore, serial sacrifice and tissue radioanalysis was the primary dosimetric technique.

Endpoints: Survival, lung morphology, neoplastic changes.

Animal: 35 Beagle dogs of both sexes, 12 to 43 mo old, in 4 groups survived more than 855 d. Acute effects were observed in an additional 31 dogs.

Results: Plutonium distribution and retention were determined from excreta and postmortem tissue analysis. Percent of terminal body burden present in lungs decreased from 71% in dogs surviving less than 3 y, to 17% in dogs surviving more than 10 y; comparable values for pulmonary lymph nodes were 18% and 33%; for liver 7% and 33%; and for skeleton, 2% and 7%. This was the first study to demonstrate that inhaled plutonium could cause lung tumors.

References: For a general description of study and summary of significant results, with extensive bibliography: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 9352, pp: 174-175.

Experimental Groups:

Study 104.01
Life-Span Health Risks:
Single-Inhalation Exposure of Plutonium-239 Oxide in Beagles

Group Id	Initial Body Burden (kBq/kg)	Number of Dogs Surviving > 855 d	Median Post-Exposure Survival (y)
01	2.22	11	8.4
02	4.81	13	5.5
03	7.4	6	4.4
04	11.47	5	2.7
	Total	35	

104.02 Life-Span Health Risks: Single-Inhalation Exposure of Plutonium-238 Oxide in Beagles

Institution: Pacific Northwest Laboratory, Richland WA

Scientists: Bair, William J; Retired
Park, James F; Retired

Purpose: Investigate the difference in biological effectiveness between inhaled Pu-238 dioxide and Pu-239 dioxide (104.01).

Status: Aerosol exposure in 1967; no detailed information available at NRA

Treatment: Single inhalation of plutonium oxide aerosol, count median diameter (CMD) 0.1 μm; dogs 8 to 42 mo old, of both sexes. After exposure, the dogs were held for life time care and observation and were euthanized when moribund or to prevent unnecessary pain. The necropsy protocol following euthanasia or spontaneous death included a complete gross pathological evaluation, with emphasis on those tissues or organs that had been clinically dysfunctional, had demonstrable lesions when examined radiographically, or were considered target tissues for plutonium deposition.

Dosimetry: There was no acceptable method for estimation of the quantity of aerosol actually inhaled and deposited in the lung of the dog. Plutonium alpha particles are not detectable outside the body, and detectors sensitive to measure low energy x-rays associated with the decay had not yet been developed. Therefore, serial sacrifice and tissue radioanalysis was the primary dosimetric technique.

Endpoints: Survival, lung morphology, neoplastic changes.

Animal: 32 Beagle dogs (10 female, 14 males), 8 to 42 mo old, in 3 groups.

Results: Distribution and retention, as determined from excreta and postmortem tissue analysis, were very different for inhaled Pu-238 dioxide than for Pu-239 dioxide with Pu-238 dioxide being more rapidly translocated from the lung and depositing in much higher concentrations in bone. The high incidence of bone, rather than lung, tumors in the Pu-238 dioxide dogs correlates with this greater and more rapid translocation.

References: For a general description of study and summary of significant results, with extensive bibliography, see: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 9352, pp: 176-177.

Experimental Groups:

Study 104.02
Life-Span Health Risks:
Single-Inhalation Exposure of Plutonium-238 Oxide in Beagles

Group Id	Terminal Body Burden (kBq/kg)	Number of Dogs	Median Post-Exposure Survival (y)
01	0.74 to 29.6	10	4.9
02	0.74 to 11.1	12	6.0
03	>74	10	.5
	Total	32	

104.03 Life-Span Health Risks: Single-Inhalation Exposure to Low Levels of Plutonium-239 Oxide in Young Adult Beagles

Institution: Pacific Northwest Laboratory, Richland WA

Scientists: Park, James F; retired
Buschbom, Ray L; retired
Dagle, Gerald E; currently at Washington State University - Tri Cities
Watson, Charles R; active
Weller, Richard E; active

Purpose: This study was initiated when it became clear that dogs in the lowest exposures of the earlier Pu-239 dioxide experiment (104.01) were nearly all developing lung tumors. The lowest exposure level in this study was 200 times lower than in the earlier study, and improved administration and dosimetric evaluation techniques were employed.

Status: Aerosol exposure between 1970 to 1972, death of last dog in 1988. Publications in progress; information in NRA is final; no revisions anticipated.

Treatment: Single inhalation of plutonium oxide aerosol, mean activity median aerodynamic diameter (AMAD) 2.3 μm, mean geometric standard deviation 1.9; 153 dogs 14 to 22 mo old, of both sexes. After exposure, the dogs were held for life time care and observation and were euthanized when moribund or to prevent unnecessary pain. The necropsy protocol following euthanasia or spontaneous death included a complete gross pathological evaluation, with emphasis on those tissues or organs that had been clinically dysfunctional, had demonstrable lesions when examined radiographically, or were considered target tissues for plutonium deposition.

Dosimetry: There was no acceptable method for estimation of the quantity of aerosol actually inhaled and deposited in the lung of the dog. Plutonium alpha particles are not detectable outside the body, but thin NaI crystal detectors sensitive to the low energy x-rays associated with the decay were developed and employed for this study. These 17 keV x-rays emanating from the thorax were counted in a low-background steel room. Estimates of initial lung deposition were developed for each dog, based on thorax monitoring within 1 mo of exposure. Variability in thorax counting after the initial post-exposure period was very large. Therefore, serial sacrifice and tissue radioanalysis was performed for dosimetric purposes as well. In the final analysis, retention curves were fit to groups of dogs, and individual doses were estimated based on final body burdens.

Endpoints: Survival, lung morphology, neoplastic changes.

Animal: 153 Beagle dogs (75 females, 78 males), 14 to 22 mo old, in 14 groups.

Results: Lymphopenia developed in all but the 2 lowest groups soon after exposure, with a trend toward total recovery after about 3 y. Radioimmunoassay techniques revealed a significant decrease in primary antibody response in exposed versus unexposed dogs. the predominant lung tumor was bronchiolar-alveolar carcinoma, with a lesser number of adenosquamous carcinoma, adenocarcinoma, and epidermiod carcinoma.

References: For a general description of study and summary of significant results, with extensive bibliography, see: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 9352, pp: 178-179.

Experimental Groups:

Study 104.03
Life-Span Health Risks:
Single-Inhalation Exposure to Low Levels of Plutonium-239 Oxide in Young Adult Beagles

Group Id	Initial Lung Burden (kBq)	Designation	Number of Dogs	Median Post-Exposure Survival (y)
01	control	life-span	20	12.2
02	control	dosimetry	3	
03	0.0111	life-span	21	12.8
04	0.0111	dosimetry	2	
05	0.0740	life-span	22	13.0
06	0.0740	dosimetry	2	
07	0.259	life-span	21	13.1
08	0.259	dosimetry	2	
09	0.962	life-span	24	10.1
10	0.962	dosimetry	2	
11	3.33	life-span	20	6.2
12	3.33	dosimetry	4	
13	22.2	life-span	8	1.5
14	22.2	dosimetry	2	
		Total	153	

104.04 Life-Span Health Risks: Single-Inhalation Exposure to Low Levels of Plutonium-238 Oxide in Young Adult Beagles

Institution: Pacific Northwest National Laboratory, Richland WA

Scientists: Park, James F; retired
Buschbom, Ray L; retired
Dagle, Gerald E; currently at Washington State University - Tri Cities
Watson, Charles R; active
Weller, Richard E; active

Purpose: Pu-238 dioxide is an alpha-emitter with a relatively short physical half-life of 88 y, and a high specific activity (530 GBq/g. Sufficient heat is generated by the radioactive decay of Pu-238 for this material to be used in radioisotope thermoelectric generators (RTGs), which provide electric power for orbiting satellites and long space flights. There is a potential for accidental human exposure to Pu-238 dioxide during the manufacturing of RTGs or as a result of a launch or reentry accident during a mission. In the event of such accidents, inhalation is the most likely route of human exposure. Accordingly, we have conducted life-span studies with beagle dogs exposed to Pu-238 dioxide aerosols in order to identify the tissues at risk and the dose–effect relationships needed to predict the consequences of human inhalation exposure.

Status: Aerosol exposure between 1972 to 1975, death of last dog in 1989. Publications in progress; information in NRA is final; no revisions anticipated.

Treatment: Single inhalation of plutonium oxide aerosol, mean activity median aerodynamic diameter (AMAD) 1.8 μm, mean geometric standard deviation 1.9; 165 dogs 15 to 20 mo old, of both sexes. After exposure, the dogs were held for life time care and observation and were euthanized when moribund or to prevent unnecessary pain. The necropsy protocol following euthanasia or spontaneous death included a complete gross pathological evaluation, with emphasis on those tissues or organs that had been clinically dysfunctional, had demonstrable lesions when examined radiographically, or were considered target tissues for plutonium deposition.

Dosimetry: There was no acceptable method for estimation of the quantity of aerosol actually inhaled and deposited in the lung of the dog. Plutonium alpha particles are not detectable outside the body, but thin NaI crystal detectors sensitive to the low energy x-rays associated with the decay were developed and employed for this study. These 17 keV x-rays emanating from the thorax were counted in a low-background steel room. Estimates of initial lung deposition were developed for each dog, based on thorax monitoring within 1 mo of exposure. Variability in thorax counting after the initial post-exposure period was very large. Therefore, serial sacrifice and tissue radioanalysis was performed for dosimetric purposes as well. In the final analysis, retention curves were fit to groups of dogs, and individual doses were estimated based on final body burdens.

Endpoints: Survival, lung morphology, neoplastic changes.

Animal: 165 Beagle dogs (74 females, 91 males), 15 to 20 mo old, in 12 groups.

Results: Of the 116 plutonium-exposed beagles held for life-span observations, 34 (29%) developed bone tumors, 31 (27%) developed lung tumors, and 8 (7%) developed liver tumors. Although the lungs accumulated a higher average radiation dose than the skeleton, there were more deaths due to bone tumors than lung tumors. Non-neoplastic effects included radiation pneumonitis, osteodystrophy, hepatic nodular hyperplasia, lymphopenia, neutropenia, sclerosing tracheobronchial lymphadenitis, and hypoadrenocorticism. Although liver tumors were not frequent causes of death, increased levels of serum alanine aminotransferase (ALT), indicative of liver damage, were observed in exposure-level groups ≥ 3.1 kBq initial lung deposition.

References: For a general description of study and summary of significant results, with extensive bibliography, see: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 9352, pp: 180-181.

Experimental Groups:

Study 104.04
Life-Span Health Risks:
Single-Inhalation Exposure to Low Levels of Plutonium-238 Oxide in Young Adult Beagles

Group Id	Initial Lung Deposition (kBq)	Number of Dogs	Median Post-Exposure Survival (y)
01	control	20	13.7
02	control	8	dosimetry sacrifice
03	0.082	20	12.6
04	0.082	5	dosimetry sacrifice
05	0.67	21	13.0
06	0.67	3	dosimetry sacrifice
07	2.9	22	12.8
08	2.9	9	dosimetry sacrifice
09	13	20	11.7
10	13	4	dosimetry sacrifice
11	52	20	7.7
12	200	13	5.2
	Total	165	

104.05 Life-Span Health Risks: Single-Inhalation Exposure to Low Levels of Plutonium-239 Nitrate in Young Adult Beagles

Institution: Pacific Northwest National Laboratory, Richland WA

Scientists: Dagle, Gerald E; currently at Washington State University - Tri Cities
Buschbom, Ray L; retired
Park, James F; retired
Watson, Charles R; active
Weller, Richard E; active

Purpose: This experiment was designed to compare the behavior and effects of inhaled Pu-239 nitrate with those of inhaled Pu-239 dioxide and Pu-238 dioxide in concurrent experiments (104.03 and 104.05). Plutonium nitrate is much more soluble than plutonium oxide.

Status: Aerosol exposure between 1975 to 1977, death of last dog in 1992. Publications in progress.

Treatment: Single inhalation of plutonium nitrate aerosol, mean activity median aerodynamic diameter (AMAD) 0.81 μm, mean geometric standard deviation 1.7; 176 dogs 17 to 23 mo old, of both sexes. After exposure, the dogs were held for life time care and observation and were euthanized when moribund or to prevent unnecessary pain. The necropsy protocol following euthanasia or spontaneous death included a complete gross pathological evaluation, with emphasis on those tissues or organs that had

been clinically dysfunctional, had demonstrable lesions when examined radiographically, or were considered target tissues for plutonium deposition.

Dosimetry: The exposure aerosol was produced by nebulizing a 0.27 N nitric acid solution. Data on the translocation and retention of the deposited plutonium have been described. A supporting 1-y sacrifice study compared the early distribution and retention of inhaled 238 Pu Nitrate and 239 Pu Nitrate; although 238 Pu was initially translocated more rapidly from the lung, the rate of translocation was similar at 1 y postexposure. In another periodic sacrifice study extending 5 y postexposure, estimates were made of radiation doses to various tissues following 239-Pu Nitrate inhalation.

There was no acceptable method for estimation of the quantity of aerosol actually inhaled and deposited in the lung of the dog. Plutonium alpha particles are not detectable outside the body, but thin NaI crystal detectors sensitive to the low energy x-rays associated with the decay were developed and employed for this study. These 17 keV x-rays emanating from the thorax were counted in a low-background steel room. Estimates of initial lung deposition were developed for each dog, based on thorax monitoring within 1 mo of exposure. Variability in thorax counting after the initial post-exposure period was very large. Therefore, serial sacrifice and tissue radioanalysis was performed for dosimetric purposes as well. In the final analysis, retention curves were fit to groups of dogs, and individual doses were estimated based on final body burdens.

Endpoints: Survival, lung morphology, neoplastic changes.

Animal: 176 Beagle dogs (89 females, 87 males), 17 to 23 mo old, in 12 groups.

Results: Lymphopenia was less pronounced than was the case following exposure to Pu-239 dioxide or Pu-238 dioxide; it occurred only in the 2 highest groups. Osteosarcomas developed in the 3 highest groups, and were fatal; whereas lung tumors tended to be incidental findings at necropsy. Liver damage was noted.

References: For a general description of study and summary of significant results, with extensive bibliography, see: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 99352, pp 182-183.

Experimental Groups:

Study 104.05
Life-Span Health Risks:
Single-Inhalation Exposure to Low Levels of Plutonium-239 Nitrate in Young Adult Beagles

Group Id	Initial Lung Burden (kBq)	Number of Dogs	Median Post-Exposure Survival (y)
01	control	20	12.1
02	control	6	dosimetry sacrifice
03	vehicle	20	12.9
04	0.0074	20	13.2
05		3	dosimetry sacrifice
06	0.0259	20	12.4
07	0.185	20	11.3
08		19	dosimetry sacrifice
09	0.962	20	9.9
10	5.55	20	5.3
11		3	dosimetry sacrifice
12	19.24	5	1.4
	Total	176	

104.06 Life-Span Health Risks: Single-Inhalation Exposure to Low Levels of Plutonium-239 Oxide in Female Wistar Rats

Institution: Pacific Northwest National Laboratory, Richland WA

Scientists: Charles (Chuck) L. Sanders; retired

Purpose: Define the dose and dose distribution patterns in the rat lung following inhalation of plutonium-239 dioxide to better understand lung dose/lung tumor relationships for occupational and environmental risk assessment.

Status: Animals were exposed in 1982 - 1983, the study is complete, and manuscripts have been published. Laboratory records, electronic information, histopathology slides and paraffin tissue blocks are available at the NRA.

Treatment: A total of 74 groups, each approximately 35 rats, were exposed to ytterbium-169 trioxide - plutonium-239 dioxide aerosols for 30 min.

Dosimetry: Whole body counting for ytterbium-169 at 14 d post exposure provided an accurate (r=0.99) estimate of plutonium-239 lung content. Lung doses were calculated for each exposed rat based on individually determined initial lung burden, survival time, and individually computed clearance function.

Endpoints: Survival time; lung tumor incidence

Animal: Female Wistar rats (2105 exposed, 1052 sham-exposed controls). There were also 788 rats for system check, plutonium clearance, ytterbium dosimetry, low dose lung clearance, serial sacrifice, and sentinel purposes.

Results: Dosimetry: Alpha irradiation of the tracheal epithelium was at least 50 times less than for bronchiolar epithelium due principally to preferential retention of plutonium-239 dioxide in preribronchiolar alveoli as compared to other alveolar regions. Clumping and aggregation resulted in a highly nonhomogeneous dose distribution pattern. Alveolar clearance was best represented by a biphasic clearance curve (80% fast, 20% slow).

Health Effects: Lung tumor incidence appears to exhibit a threshold dose-response, increasing only after lung doses are > 1 Gy, while overall lung tumor incidence appears to bbe best fit by a quadratic model.

References:

C.L. Sanders, K.E. Lauhala, K.E. McDonald, and G.A. Sanders. Lifespan studies in rats exposed to plutonium-239 dioxide aerosol. *Health Physics*, **64**, 509-521, 1993.

C.L. Sanders, K.E. McDonald, B.W. Killand, J.A. Mahaffey and W.C. Cannon. Promotion of pulmonary carcinogenesis by plutonium particle aggregation following inhalation of plutonium-239 dioxide. *Radiation Research* **116**, 393-405, 1988.

Experimental Groups:

Study 104.06
Life-Span Health Risks:
Single-Inhalation Exposure to Low Levels of Plutonium-239 Oxide in Female Wistar Rats

Group Id	Whole Body Count (kB)	Lung Dose (Gy)	Number of Rats	Mean Post-Exposure Survival (d)
01	control		1052	733
02	0.014	0.040	523	708
03	0.024	0.067	866	730
04	0.047	0.13	223	710
05	0.093	0.27	120	709
06	0.17	0.53	98	718
07	0.25	0.81	47	733
08	0.44	1.6	34	637
09	0.71	3.35	24	663
10	0.85	4.4	21	761
11	1.05	5.8	17	697
12	1.29	7.00	18	727
13	2.31	15.7	33	608
14	3.18	25.1	17	585
15	3.67	34.5	32	566
16	4.74	44.4	17	536
17	6.35	55.1	15	441
		Total	3157	

105 Inhalation Toxicology Research Institute (ITRI)

105.01 Life-Span Health Risks: Single-Inhalation Exposure of Strontium-90 (in a Soluble Form) in Young Adult Beagles

Institution: Inhalation Toxicology Research Institute

Scientists: Benjamin, Stephen A; currently at Colorado State University
Boecker, Bruce B; active
Gillett, Nancy A; currently at Sierra Biomedical, Inc.
Griffith, William C; active
Hahn, Fletcher F; active
McClellan, Roger O; currently at Chemical Industry Institute of Toxicology (CIIT)
Muggenburg, Bruce A; active
Pickrell, John A; currently at Kansas State University
Redman, Hamilton C; retired
Scott, Bobby R; active

Purpose: This experiment was designed to compare the behavior and effects of inhaled, Sr-90 with those observed in injection and dietary studies at other laboratories (101.5, 102.2, and 102.3). The major issues were the determination of organs at risk for this soluble form of internally deposited beta-emitter and quantification of the life-span risks of radiation-induced disease, especially cancer.

Status: Dogs were placed on experiment from 1965 to 1967 and held for life time observation until death of last dog in 1982. "Core" manuscript published, records transfer to NRA in May, 1996.

Treatment: Single inhalation of strontium chloride in a cesium chloride vector aerosol with mean activity median aerodynamic diameter (AMAD) 1.4 to 2.7 μm with a geometric standard deviation (GSD) of about 2.

Endpoints: Dogs were given semi-annual medical examinations including radiographic surveys and complete blood work-ups throughout life. Dogs were euthanized when moribund or to prevent unnecessary pain. The necropsy protocol included histopathological observation of all body tissues, with special emphasis on the respiratory tract and tissues or organs that had been clinically dysfunctional.

Dosimetry, based on individual dog, included: whole-body retention, lung clearance, and tissue distribution, and organ- and time-specific dose calculations. Medical reviews by a clinician and pathologist determined the primary cause of death, the immediate cause of death, and any major contributing diseases. Incidental diseases, with emphasis on neoplasia, were also determined.

Animal: 88 Beagle dogs (44 females, 44 males), 12 to 15 mo old, in 7 groups.

Results: About 60% of the initial deposit was lost with a half-time of 0.3 d, reflecting rapid clearance from the respiratory and gastrointestinal trace. The retention of the remainder was described by 3 approximately equal components with half-times of 6 d, 130 d, and 8 y, all reflecting loss from the skeleton. Neoplastic changes were similar to those observed in dogs injected with Sr-90 at Utah or Davis.

References: Gillett, N.A., B.A. Muggenburg, B.B. Boecker, F.F. Hahn, F.A. Seiler, A.H. Rebar, R.K. Jones, and R.O. McClellan. Single inhalation exposure to strontium-90 chloride in the beagle dog: Hematological effects. *Radiation Research* **110**:267-288, 1987.

Gillett, N.A., B.A. Muggenburg, B.B. Boecker, W.C. Griffith, F.F. Hahn, and R.O. McClellan. Single inhalation exposure to strontium-90 chloride in the beagle dog: Late biological effects. *JNCI* **79**:359-376, 1987.

Experimental Groups:

Study 105.01
Life-Span Health Risks: Single-Inhalation Exposure of Strontium-90 (in a Soluble Form) in Young Adult Beagles

Group Id	Long Term Retained Burden (kBq/kg)			Number of Dogs	Post-Exposure Survival (y)		
	Min	Median	Max		Min	Median	Max
01	control			22	8.2	13.6	16.2
02	0.036	0.067	0.12	12	6.2	12.9	16.3
03	0.21	0.29	0.36	12	6.7	12.7	15.6
04	0.56	1.0	1.3	12	1.6	7.4	11.6
05	1.3	1.6	1.9	12	0.08	4.3	10.2
06	1.9	2.6	3.7	12	0.05	3.1	5.3
07	3.7	4.3	4.4	6	0.06	1.8	2.5
Total				88			

105.02 Life-Span Health Risks: Single-Inhalation Exposure of Cerium-144 (in a Soluble Form) in Young Adult Beagles

Institution: Inhalation Toxicology Research Institute

Scientists: Benjamin, Stephen A; currently at Colorado State University
Boecker, Bruce B; active
Griffith, William C; active
Hahn, Fletcher F; active
Jones, Robert, K; retired
McClellan, Roger O; currently at Chemical Industry Institute of Toxicology (CIIT)
Muggenburg, Bruce A; active
Newton, George J; active
Pickrell, John A; currently at Kansas State University
Redman, Hamilton C; retired
Scott, Bobby R; active

Purpose: The major issues were the determination of organs at risk for this soluble form of internally deposited beta-emitter and quantification of the life-span risks of radiation-induced disease, especially cancer.

Status: Dogs were placed on experiment from 1966 to 1967 and held for life time observation until death of last dog in 1984."Core" manuscript published, records transfer to NRA in May, 1996.

Treatment: Single inhalation of cerium chloride in a cesium chloride vector aerosol with mean activity median aerodynamic diameter (AMAD) 1.5 to 2.4 μm with a geometric standard deviation (GSD) of about 1.6 to 2.1.

Endpoints: Dogs were given semi-annual medical examinations including radiographic surveys and complete blood work-ups throughout life. Dogs were euthanized when moribund or to prevent unnecessary pain. The necropsy protocol included histopathological observation of all body tissues, with special emphasis on the respiratory tract and tissues or organs that had been clinically dysfunctional.

Dosimetry, based on individual dog, included: whole-body retention, lung clearance, and tissue distribution, and organ- and time-specific dose calculations. Medical reviews by a clinician and pathologist determined the primary cause of death, the immediate cause of death, and any major contributing diseases. Incidental diseases, with emphasis on neoplasia, were also determined.

Animal: 70 Beagle dogs (34 females, 36 males), 12 to 15 mo old, in 6 groups

Results: During the first wk after inhalation exposure, the cerium-144 translocated from the respiratory tract to other body organs and tissues, primarily liver and skeleton. Radiation-induced neoplasms occurred in lung, liver, skeleton and bone-associated tissues (oral and nasal mucosae and bone marrow).

References: Hahn, F.F., B.B. Boecker, W.C. Griffith, and B.A. Muggenburg: Biological effects of inhaled cerium-144 chloride in beagle dogs, *Radiation Research* (submitted in 1996).

Hahn, F.F., B.A. Mugenburg, and B.B. Boecker. Hepatic lesions in dogs that inhaled cerium-144 chloride, *Toxicol. Pathol.* (In press, 1996).

Experimental Groups:

Study 105.02
Life-Span Health Risks: Single-Inhalation Exposure of Cerium-144 (in a Soluble Form) in Young Adult Beagles

Group Id	Long Term Retained Burden (kBq/kg)			Number of Dogs	Post-Exposure Survival (y)		
	Min	Median	Max		Min	Median	Max
01	control			15	7.0	13.9	16.5
02	0.10	0.18	0.30	13	8.0	12.0	15.1
03	0.44	0.57	0.96	13	5.0	11.1	14.1
04	1.0	2.0	3.5	12	4.5	6.3	11.9
05	3.7	5.3	7.1	12	0.07	0.61	5.0
06	2.2	7.7	13	5	0.06	0.08	1.0
Total				70			

105.03 Life-Span Health Risks: Single-Inhalation Exposure of Yttrium-91 (in a Soluble Form) in Young Adult Beagles

Institution: Inhalation Toxicology Research Institute

Scientists: Benjamin, Stephen A; currently at Colorado State University
Boecker, Bruce B; active
Griffith, William C; active
Hahn, Fletcher F; active
McClellan, Roger O; currently at Chemical Industry Institute of Toxicology (CIIT)
Muggenburg, Bruce A; active
Newton, George J; active
Pickrell, John A; currently at Kansas State University
Redman, Hamilton C; retired
Scott, Bobby R; active

Purpose: The major issues were the determination of organs at risk for this soluble form of internally deposited beta-emitter and quantification of the life-span risks of radiation-induced disease, especially cancer.

Status: Dogs were placed on experiment from 1966 to 1967 and held for life time observation until death of last dog in 1983. "Core" manuscript in preparation, records transfer to NRA in May, 1996.

Treatment: Single inhalation of yttrium chloride in a cesium chloride vector aerosol.

Endpoints: Dogs were given semi-annual medical examinations including radiographic surveys and complete blood work-ups throughout life. Dogs were euthanized when moribund or to prevent unnecessary pain. The necropsy protocol included histopathological observation of all body tissues, with special emphasis on the respiratory tract and tissues or organs that had been clinically dysfunctional.

Dosimetry, based on individual dog, included: whole-body retention, lung clearance, and tissue distribution, and organ- and time-specific dose calculations. Medical reviews by a clinician and pathologist determined the primary cause of death, the immediate cause of death, and any major contributing diseases. Incidental diseases, with emphasis on neoplasia, were also determined.

Animal: 54 Beagle dogs (27 females, 27 males), 12 to 15 mo old, in 5 groups

Results: During the first wk after the inhalation exposure, the yttrium-91 translocated from the respiratory tract to other body organs and tissues, primarily the liver and skeleton. Late-occurring effects related to the radiation exposure were found primarily in these three organs.

References: [In preparation]
For a general description of study and summary of significant results, with extensive bibliography, see: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 9352, pp: 188-189.

Experimental Groups:

Study 105.03
Life-Span Health Risks: Single-Inhalation Exposure of Yttrium-91 (in a Soluble Form) in Young Adult Beagles

Group Id	Initial Burden (kBq/kg)	Number of Dogs	Median Post-Exposure Survival (y)
01	control	12	13.9
02	177.6	12	11.5
03	518	12	11.1
04	1,628	12	7.4
05	5,180	12	1.2
06	7,770	6	0.1
	Total	66	

105.04 Life-Span Health Risks: Single-Inhalation Exposure of Cerium-144 (in an Insoluble Matrix) in Young Adult Beagles

Institution: Inhalation Toxicology Research Institute

Scientists: Boecker, Bruce B; active
Gillett, Nancy A; currently at Sierra Biomedical Inc.
Griffith, William C; active
Hahn, Fletcher F; active
Hobbs, Charles H; active
Jones, Robert K; retired
Jones, Susan E; active
McClellan, Roger O; currently at Chemical Industry Institute of Toxicology (CIIT)
Mauderly, Joe L; active
Muggenburg, Bruce A; active
Pickrell, John A; currently at Kansas State University
Scott, Bobby R; active

Purpose: The major issues were the health risks produced by chronic beta-particle irradiation of the respiratory tract, dose protraction associated with this insoluble form of internally deposited beta-emitter and quantification of the life-span risks of radiation-induced disease, especially cancer.

Status: Dogs were placed on experiment from 1967 to 1971 and held for life time observation until death of last dog in 1988. Analysis of this experiment is incomplete.

Treatment: Single inhalation of cerium adsorbed in an insoluble fused aluminosilicate vector aerosol (FAP) with mean activity median aerodynamic diameter (AMAD) 1.5 to 2.7 μm with a geometric standard deviation (GSD) of about 2. Placed on experiment from 1967 to 1968 (Series A), and from 1969 to 1971 (Series B). Series A differs from Series B only in that aluminosilicate particles were fused prior to, rather than during, exposure.

Endpoints: Dogs were given semi-annual medical examinations including radiographic surveys and complete blood work-ups throughout life. Dogs were euthanized when moribund or to prevent unnecessary pain. The necropsy protocol included histopathological observation of all body tissues, with special emphasis on the respiratory tract and tissues or organs that had been clinically dysfunctional.

Dosimetry, based on individual dog, included: whole-body retention, lung clearance, and tissue distribution, and organ- and time-specific dose calculations. Medical reviews by a clinician and pathologist determined the primary cause of death, the immediate cause of death, and any major contributing diseases. Incidental diseases, with emphasis on neoplasia, were also determined.

Animal: 126 Beagle dogs (60 females, 66 males), 12 to 14 mo old, in 15 groups.

Results: The quantity of Ce-144 deposited and retained was determined by whole-body counting and by analysis on 24 dogs sacrificed at intervals to 2 y post-exposure; the effective half-life for lung clearance was about 200 d. Dogs exposed to the highest levels died within the first 18 mo from radiation pneumonitis and pulmonary fibrosis. The late-occurring effects in the remaining dogs were cancers, primarily those in the respiratory tract.

References: For a general description of study and summary of significant results, with extensive bibliography, see: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 9352, pp: 190-192.

Experimental Groups:

Study 105.04
Life-Span Health Risks: Single-Inhalation Exposure of Cerium-144 (in an Insoluble Matrix) in Young Adult Beagles

Group Id	Initial Burden (kBq/kg)	Series	Number of Dogs	Median Post-Exposure Survival (y)
01	control	A	3	13.0
02	control	B	12	12.7
03	0.555	B	12	14.2
04	2.553	B	12	13.7
05	12.58	B	12	12.8
06	51.8	B	12	11.6
07	225.7	B	12	9.9
08	555	A	3	6.8
09	481	B	12	6.7
10	999	A	3	3.6
11	888	B	12	4.6
12	1,665	B	12	0.8
13	2,442	A	3	0.7
14	4,440	A	3	0.5
15	7,030	A	3	0.5
		Total	126	

105.05 Life-Span Health Risks: Single Injection of Cesium-137 (in a Soluble Form) in Young Adult Beagles

Institution: Inhalation Toxicology Research Institute

Scientists: Benjamin, Stephen A; currently at Colorado State University
Boecker, Bruce B; active
Griffith, William C; active
Hahn, Fletcher F; active
Jones, Robert K; retired
McClellan, Roger O; currently at Chemical Industry Institute of Toxicology (CIIT)
Muggenburg, Bruce A; active
Nikula, Kristin J; active
Pickrell, John A; currently at Kansas State University
Redman, Hamilton C; retired
Scott, Bobby R; active

Purpose: The major issues were the determination of organs at risk for this soluble form of internally deposited beta-emitter and quantification of the life-span risks of radiation-induced disease, especially cancer. This study may be compared with a similar study at ANL (103.4).

Status: Dogs were placed on experiment from 1968 to 1969 and held for life time observation until death of last dog in 1985. "Core" manuscript published, records transfer to NRA in May, 1996.

Treatment: Single intravenous injection of cesium chloride solution.

Endpoints: Dogs were given semi-annual medical examinations including radiographic surveys and complete blood work-ups throughout life. Dogs were euthanized when moribund or to prevent unnecessary pain. The necropsy protocol included histopathological observation of all body tissues, with special emphasis on the respiratory tract and tissues or organs that had been clinically dysfunctional.

Dosimetry, based on individual dog, included: whole-body retention, lung clearance, and tissue distribution, and organ- and time-specific dose calculations. Medical reviews by a clinician and pathologist determined the primary cause of death, the immediate cause of death, and any major contributing diseases. Incidental diseases, with emphasis on neoplasia, were also determined.

Animal: 66 Beagle dogs (33 females, 33 males), 12 to 14 mo old, in 6 groups.

Results: Dogs died from 19 to 5342 d after injection of Cs-137. Eleven died within 81 d due to severe pancytopenia. An additional 25 dogs had transient hematologic dyscrasia. Dogs which survived this lived for long times and died from diseases unrelated to the blood forming organs (except 1 hemolytic anemia at 9 y). There were no myeloproliferative diseases. A higher-than-expected incidence of tumors occurred in the liver, nasal cavity, and possibly the urinary tract. Complete atrophy of the testicular tubular germinal epithelium was found in nearly all exposed dogs. Compare with study 103.04.

References: Nikula, K.J., B.A. Muggenburg, J.-Y Chang, W.C. Griffith, F.F. Hahn, and B.B. Boecker. Biological effects of cesium-137 chloride injected in beagle dogs, *Radiation Research* **142:**347-361, 1995.

Nikula, K.J., B.A. Muggenburg, W.C. Griffith, W.W. Carlton, T.E. Fritz, and B.B. Boecker. Biological effects of cesium-137 chloride injected in beagle dogs of different ages, *Radiation Research* (submitted in 1996).

Experimental Groups:

Study 105.05
Life-Span Health Risks: Single Injection of Cesium-137 (in a Soluble Form) in Young Adult Beagles

Group Id	Initial Body Burden (MBq/kg)			Number of Dogs	Post-Exposure Survival (y)		
	Min	Median	Max		Min	Median	Max
01	control			12	1.8	13.7	16.5
02	32	36	42	12	6.8	12.4	14.6
03	43	52	58	12	5.9	12.3	14.5
04	68	71	76	12	0.21	11.3	14.1
05	96	100	110	12	0.07	6.0	12.4
06	130	140	150	6	0.05	0.07	0.09
			Total	66			

105.06 Life-Span Health Risks: Single-Inhalation Exposure of Yttrium-90 (in an Insoluble Matrix) in Young Adult Beagles

Institution: Inhalation Toxicology Research Institute

Scientists: Boecker, Bruce B; active
Griffith, William C; active
Hahn, Fletcher F; active
Hobbs, Charles H; active
Jones, Robert K; retired
McClellan, Roger O; currently at Chemical Industry Institute of Toxicology (CIIT)
Mauderly, Joe L; active
Muggenburg, Bruce A; active
Pickrell, John A; currently at Kansas State University
Scott, Bobby R; active

Purpose: The major issues were the health risks produced by chronic beta-particle irradiation of the respiratory tract and dose protraction associated with this insoluble form of internally deposited beta-emitter.

Status: Dogs were placed on experiment from 1969 to 1971 and held for life time observation until death of last dog in 1987. Analysis of this experiment is incomplete.

Treatment: Single inhalation of yttrium adsorbed in a polydisperse, insoluble, fused aluminosilicate vector aerosol (FAP) with mean activity median aerodynamic diameter (AMAD) 0.8 to 1.4 μm with a geometric standard deviation (GSD) of about 2.

Endpoints: Dogs were given semi-annual medical examinations including radiographic surveys and complete blood work-ups throughout life. Dogs were euthanized when moribund or to prevent unnecessary pain. The necropsy protocol included histopathological observation of all body tissues, with special emphasis on the respiratory tract and tissues or organs that had been clinically dysfunctional.

Dosimetry, based on individual dog, included: whole-body retention, lung clearance, and tissue distribution, and organ- and time-specific dose calculations. Medical reviews by a clinician and pathologist determined the primary cause of death, the immediate cause of death, and any major contributing diseases. Incidental diseases, with emphasis on neoplasia, were also determined.

Animal: 101 Beagle dogs (50 females, 51 males), 12 to 14 mo old, in 11 groups.

Results: Dogs with initial burdens of 23.68 MBq/kg or greater died of radiation pneumonitis and pulmonary fibrosis within 1 y of exposure. Late-occurring effects seen in dogs that survived the early mortality phase were cancers, primarily those associated with the respiratory tract.

References: For a general description of study and summary of significant results, with extensive bibliography, see: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 9352, pp: 195-196.

Experimental Groups:

Study 105.06
Life-Span Health Risks: Single-Inhalation Exposure of Yttrium-90 (in an Insoluble Matrix) in Young Adult Beagles

Group Id	Initial Burden (MBq/kg)	Number of Dogs	Median Post-Exposure Survival (y)
01	control	12	13.0
02	3.885	12	12.5
03	7.77	12	11.7
04	11.1	12	12.1
05	14.43	12	10.3
06	23.68	12	0.6
07	27.75	12	0.3
08	44.4	4	0.3
09	55.5	5	0.2
10	79.3	4	0.2
11	118.4	4	0.1
	Total	101	

105.07 Life-Span Health Risks: Single-Inhalation Exposure of Yttrium-91 (in an Insoluble Matrix) in Young Adult Beagles

Institution: Inhalation Toxicology Research Institute

Scientists: Boecker, Bruce B; active
Cuddihy, Richard G; retired
Griffith, William C; active
Hahn, Fletcher F; active
Hobbs, Charles H; active
Kanapilly, George M; deceased
Jones, Robert K; retired
McClellan, Roger O; currently at Chemical Industry Institute of Toxicology (CIIT)
Mauderly, Joe L; active
Pickrell, John A; currently at Kansas State University
Scott, Bobby R; active

Purpose: The major issues were the life-span health risks produced by chronic beta-particle irradiation of the respiratory tract and dose protraction associated with this insoluble form of internally deposited beta-emitter.

Status: Dogs were placed on experiment from 1970 to 1971 and held for life time observation until death of last dog in 1986. Analysis of this experiment is incomplete.

Treatment: Single inhalation of yttrium adsorbed to a polydisperse, insoluble, fused aluminosilicate vector aerosol (FAP) with mean activity median aerodynamic diameter (AMAD) 1.2 to 2.4 μm with a geometric standard deviation (GSD) of about 2.

Endpoints: Dogs were given semi-annual medical examinations including radiographic surveys and complete blood work-ups throughout life. Dogs were euthanized when moribund or to prevent unnecessary pain. The necropsy protocol included histopathological observation of all body tissues, with special emphasis on the respiratory tract and tissues or organs that had been clinically dysfunctional.

Dosimetry, based on individual dog, included: whole-body retention, lung clearance, and tissue distribution, and organ- and time-specific dose calculations. Medical reviews by a clinician and pathologist determined the primary cause of death, the immediate cause of death, and any major contributing diseases. Incidental diseases, with emphasis on neoplasia, were also determined.

Animal: 108 Beagle dogs (54 females, 54 males), 12 to 14 mo old, in 11 groups.

Results: Dogs with initial burdens of 130 μCi/kg or greater died of radiation pneumonitis and pulmonary fibrosis within 1 y of exposure. Late-occurring effects seen in dogs that survived the early mortality period were cancers, primarily those associated with the respiratory tract.

References: For a general description of study and summary of significant results, with extensive bibliography, see: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 9352, pp: 197-198.

Experimental Groups:

Study 105.07
Life-Span Health Risks: Single-Inhalation Exposure of Yttrium-91 (in an Insoluble Matrix) in Young Adult Beagles

Group Id	Initial Burden (MBq/kg)	Number of Dogs	Median Post-Exposure Survival (y)
01	control	12	13.6
02	0.592	12	13.0
03	1.147	12	13.0
04	1.702	12	11.5
05	2.96	12	7.7
06	3.885	12	3.2
07	4.81	12	0.6
08	6.29	12	0.5
09	7.77	4	0.4
10	9.99	4	0.5
11	11.47	4	0.4
	Total	108	

105.08 Life-Span Health Risks: Single-Inhalation Exposure of Strontium-90 (in an Insoluble Matrix) in Young Adult Beagles

Institution: Inhalation Toxicology Research Institute

Scientists: Boecker, Bruce B; active
Griffith, William C; active
Hahn, Fletcher F; active
Hobbs, Charles H; active
McClellan, Roger O; currently at Chemical Industry Institute of Toxicology (CIIT)
Mauderly, Joe L; active
Muggenburg, Bruce A; active
Pickrell, John A; currently at Kansas State University
Scott, Bobby R; active
Snipes, M. Burt B; active

Purpose: The major issues were the health risks produced by chronic beta-particle irradiation of the respiratory tract and dose protraction associated with this insoluble form of internally deposited beta-emitter.

Status: Dogs were placed on experiment from 1970 to 1974 and held for life time observation until death of last dog in 1991. Analysis of this experiment is incomplete.

Treatment: Single inhalation of strontium adsorbed to a polydisperse, insoluble, fused aluminosilicate vector aerosol (FAP) with mean activity median aerodynamic diameter (AMAD) 1.5 to 2.8 μm with a geometric standard deviation (GSD) of about 2.

Endpoints: Dogs were given semi-annual medical examinations including radiographic surveys and complete blood work-ups throughout life. Dogs were euthanized when moribund or to prevent unnecessary pain. The necropsy protocol included histopathological observation of all body tissues, with special emphasis on the respiratory tract and tissues or organs that had been clinically dysfunctional.

Dosimetry, based on individual dog, included: whole-body retention, lung clearance, and tissue distribution, and organ- and time-specific dose calculations. Medical reviews by a clinician and pathologist determined the primary cause of death, the immediate cause of death, and any major contributing diseases. Incidental diseases, with emphasis on neoplasia, were also determined.

Animal: 124 Beagle dogs (62 females, 62 males), 11 to 15 mo old, in 9 groups.

Results: Dogs with initial burdens of 2.072 MBq/kg or greater died of radiation pneumonitis and pulmonary fibrosis within 1 y of exposure. Late-occurring effects seen in dogs that survived the early mortality period were cancers, primarily those associated with the respiratory tract.

References: For a general description of study and summary of significant results, with extensive bibliography, see: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 9352, pp: 199-200.

Experimental Groups:

Study 105.08
Life-Span Health Risks: Single-Inhalation Exposure of Strontium-90 (in an Insoluble Matrix) in Young Adult Beagles

Group Id	Initial Burden (kBq/kg)	Number of Dogs	Median Post-Exposure Survival (y)
01	control	18	12.4
02	8.88	12	11.6
03	40.7	12	10.3
04	181.3	18	6.5
05	318.2	12	6.5
06	703	16	2.8
07	1,406	12	0.9
08	2,072	12	0.8
09	2,738	12	0.6
	Total	124	

105.09 Life-Span Health Risks: Single-Inhalation Exposure of Cerium-144 (in an Insoluble Matrix) in Immature (3 Month-Old) Beagles

Institution: Inhalation Toxicology Research Institute

Scientists: Boecker, Bruce B; active
Griffith, William C; active
Hahn, Fletcher F; active
Hobbs, Charles H; active
McClellan, Roger O; currently at Chemical Industry Institute of Toxicology (CIIT)
Mauderly, Joe L; active
Muggenburg, Bruce A; active
Scott, Bobby R; active

Purpose: The major issues were the effects of age on the health risks produced by chronic beta-particle irradiation of the respiratory tract and dose protraction associated with this insoluble form of internally deposited beta-emitter in very young animals.

Status: Dogs were placed on experiment from 1972 to 1976 and held for life time observation until death of last dog in 1993. Analysis of this experiment is incomplete.

Treatment: Single inhalation of cerium adsorbed to an insoluble fused aluminosilicate vector aerosol (FAP). Treatment protocol identical to similar study in Young Adult Beagles (105.04).

Endpoints: Dogs were given semi-annual medical examinations including radiographic surveys and complete blood work-ups throughout life. Dogs were euthanized when moribund or to prevent unnecessary pain. The necropsy protocol included histopathological observation of all body tissues, with special emphasis on the respiratory tract and tissues or organs that had been clinically dysfunctional.

Dosimetry, based on individual dog, included: whole-body retention, lung clearance, and tissue distribution, and organ- and time-specific dose calculations. Medical reviews by a clinician and pathologist determined the primary cause of death, the immediate cause of death, and any major contributing diseases. Incidental diseases, with emphasis on neoplasia, were also determined.

Animal: 54 Beagle dogs (22 females, 32 males); 3 mo old, in 11 groups.

Results:

References: For a general description of study and summary of significant results, with extensive bibliography, see: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 9352, pp: 201-202.

Experimental Groups:

Study 105.09
Life-Span Health Risks: Single-Inhalation Exposure of Cerium-144 (in an Insoluble Matrix) in Immature (3 Month-Old) Beagles

Group Id	Initial Burden (kBq/kg)	Number of Dogs	Median Post-Exposure Survival (y)
01	control	5	
02	0.333	5	
03	2.22	5	
04	7.03	5	
05	51.8	5	
06	185	5	
07	444	5	9.1
08	1,082	5	7.7
09	1,406	5	4.8
10	2,590	5	1.9
11	3,774	4	0.3
	Total	54	

105.10 Life-Span Health Risks: Single-Inhalation Exposure of Cerium-144 (in an Insoluble Matrix) in Aged (8- to 10-Year-Old) Beagles

Institution: Inhalation Toxicology Research Institute

Scientists: Boecker, Bruce B; active
Griffith, William C; active
Hahn, Fletcher F; active
Hobbs, Charles H; active
Jones, Robert K; retired
McClellan, Roger O; currently at Chemical Industry Institute of Toxicology (CIIT)

Mauderly, Joe L; active
Muggenburg, Bruce A; active
Pickrell, John A; currently at Kansas State University
Scott, Bobby R; active

Purpose: The major issues were the effects of age on the health risks produced by chronic beta-particle irradiation of the respiratory tract and dose protraction associated with this insoluble form of internally deposited beta-emitter in aged animals.

Status: Dogs were placed on experiment from 1972 to 1975 and held for life time observation until death of last dog in 1988. Analysis of this experiment is incomplete.

Treatment: Single inhalation of cerium adsorbed to an insoluble fused aluminosilicate vector aerosol (FAP). Treatment protocol identical to similar study in Young Adult Beagles (105.04).

Endpoints: Dogs were given semi-annual medical examinations including radiographic surveys and complete blood work-ups throughout life. Dogs were euthanized when moribund or to prevent unnecessary pain. The necropsy protocol included histopathological observation of all body tissues, with special emphasis on the respiratory tract and tissues or organs that had been clinically dysfunctional.

Dosimetry, based on individual dog, included: whole-body retention, lung clearance, and tissue distribution, and organ- and time-specific dose calculations. Medical reviews by a clinician and pathologist determined the primary cause of death, the immediate cause of death, and any major contributing diseases. Incidental diseases, with emphasis on neoplasia, were also determined.

Animal: 54 Beagle dogs (30 females, 24 males), 8 to 10 y old, in 5 groups.

Results: Dogs with initial burdens of 962 kBq/kg or greater died of radiation pneumonitis and pulmonary fibrosis within 2 y of exposure. Late-occurring effects seen in dogs that survived the early mortality phase were cancers, primarily those associated with the respiratory tract.

References: For a general description of study and summary of significant results, with extensive bibliography, see: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 9352, pp: 203-204.

Experimental Groups:

Study 105.10
Life-Span Health Risks: Single-Inhalation Exposure of Cerium-144 (in an Insoluble Matrix) in Aged (8- to 10-Year-Old) Beagles

Group Id	Initial Burden (MBq/kg)	Number of Dogs	Median Post-Exposure Survival (y)
01	control	12	3.7
02	0.2923	12	4.5
03	0.518	12	3.4
04	0.962	12	1.2
05	1.998	6	0.7
	Total	54	

105.11 Life-Span Health Risks: Repeated Inhalation Exposure of Cerium-144 (in an Insoluble Matrix) in Young Adult Beagles

Institution: Inhalation Toxicology Research Institute

Scientists: Boecker, Bruce B; active
Griffith, William C; active
Hahn, Fletcher F; active
McClellan, Roger O; currently at Chemical Industry Institute of Toxicology (CIIT)
Mauderly, Joe L; active
Muggenburg, Bruce A; active
Pickrell, John A; currently at Kansas State University

Purpose: The major issues were the health risks produced by chronic beta-particle irradiation of the respiratory tract and dose protraction by repeated inhalation exposure of an insoluble form of internally deposited beta-emitter.

Status: Dogs were placed on experiment in 1973 and held for life time observation until death of last dog in 1988. Analysis of this experiment is incomplete.

Treatment: Thirteen inhalations, at 56-d intervals, of cerium adsorbed in an insoluble fused aluminosilicate vector aerosol (FAP). Aerosol preparation and administration protocol identical to similar single exposure study (105.04).

Endpoints: Dogs were given semi-annual medical examinations including radiographic surveys and complete blood work-ups throughout life. Dogs were euthanized when moribund or to prevent unnecessary pain. The necropsy protocol included histopathological observation of all body tissues, with special emphasis on the respiratory tract and tissues or organs that had been clinically dysfunctional.

Dosimetry, based on individual dog, included: whole-body retention, lung clearance, and tissue distribution, and organ- and time-specific dose calculations. Medical reviews by a clinician and pathologist determined the primary cause of death, the immediate cause of death, and any major contributing diseases. Incidental diseases, with emphasis on neoplasia, were also determined.

Animal: 36 Beagle dogs (18 females, 18 males), 14 to 17 mo old at initial exposure, in 4 groups

Results:

References: For a general description of study and summary of significant results, with extensive bibliography, see: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 9352, pp: 205.

Experimental Groups:

Study 105.11
Life-Span Health Risks: Repeated Inhalation Exposure of Cerium-144 (in an Insoluble Matrix) in Young Adult Beagles

Group Id	Initial Burden (kBg/kg)	Number of Dogs	Median Post-Exposure Survival (y)
01	control	9	11.8
02	92.5	9	6.3
03	166.5	9	6.2
04	333	9	6.5
	Total	36	

105.12 Life-Span Health Risks: Single-Inhalation Exposure of Plutonium-238 Oxide ("Large" Particle Size, 3.0 μm AMAD) in Young Adult Beagles

Institution: Inhalation Toxicology Research Institute

Scientists: Boecker, Bruce B; active
Gillett, Nancy A; currently at Sierra Biomedical Inc.
Griffith, William C; active
Guilmette, Raymond, A; active
Hahn, Fletcher F; active
McClellan, Roger O; currently at Chemical Industry Institute of Toxicology (CIIT)
Mauderly, Joe L; active
Mewhinney, James A; currently at U.S. DOE
Muggenburg, Bruce A; active
Pickrell, John A; currently at Kansas State University
Raabe, Otto G; currently at Davis
Scott, Bobby R; active

Purpose: The 5 single-inhalation young-adult experiments (105.12 through 105.16) with inhaled monodisperse plutonium oxide were designed, as a group, to explore the influence of alpha-particle dose distribution within the lungs. The major issues were the health effects produced by chronic alpha-particle irradiation of the respiratory tract and non-uniformity of dose to lung.

Status: Dogs were placed on experiment from 1973 to 1976 and held for life time observation until death of last dog in 1990. "Core" manuscript published, records transfer to NRA in May, 1996.

Treatment: Single inhalation of monodisperse plutonium oxide aerosol, mean activity median aerodynamic diameter (AMAD) 3.0 μm (actual diameter 1 μm).

Endpoints: Dogs were given semi-annual medical examinations including radiographic surveys and complete blood work-ups throughout life. Dogs were euthanized when moribund or to prevent unnecessary pain. The necropsy protocol included histopathological observation of all body tissues, with special emphasis on the respiratory tract and tissues or organs that had been clinically dysfunctional.

Dosimetry, based on individual dog, included: whole-body retention, lung clearance, and tissue distribution, and organ- and time-specific dose calculations. Medical reviews by a clinician and pathologist determined the primary cause of death, the immediate cause of death, and any major contributing diseases. Incidental diseases, with emphasis on neoplasia, were also determined.

Animal: 84 Beagle dogs (42 females, 42 males), 12 to 14 mo old, in 7 groups.

Results: Deaths from radiation pneumonitis occurred 1.5 to 5.4 y after exposure in the highest level exposures. Tumors of the lung, skeleton and liver occurred beginning 3 y after exposure.

References: Muggenburg, B.A., R.A. Guilmette, J.A. Mewhinney, N.A. Gillett, J.L. Mauderly, W.C. Griffith, J.H. Diel, B.R. Scott, F.F. Hahn, and B.B. Boecker. Toxicity of inhaled plutonium dioxide in beagle dogs. *Radiation Research* **145**:361-381, 1996.

Experimental Groups:

Study 105.12
Life-Span Health Risks: Single-Inhalation Exposure of Plutonium-238 Oxide ("Large" Particle Size, 3.0 μm AMAD) in Young Adult Beagles

Group Id	Initial Lung Burden (kBq/kg)			Number of Dogs	Post-Exposure Survival (y)		
	Min	Median	Max		Min	Median	Max
01	control			12	2.2	12.5	16.1
02	0.15	0.47	0.77	12	5.4	12.1	15.9
03	0.84	1.4	1.7	12	4.1	10.2	13.6
04	2.4	3.0	3.8	12	5.2	9.9	11.1
05	4.1	7.0	9.4	12	3.1	5.6	9.7
06	10	13	16	12	3.3	4.3	5.3
07	20	25	43	12	1.7	3.5	4.6
			Total	84			

105.13 Life-Span Health Risks: Single-Inhalation Exposure of Plutonium-238 Oxide ("Medium" Particle Size, 1.5 μm AMAD) in Young Adult Beagles

Institution: Inhalation Toxicology Research Institute

Scientists: Boecker, Bruce B; active
Gillett, Nancy A; currently at Sierra Biomedical Inc.
Griffith, William C; active
Guilmette, Raymond, A; active
Hahn, Fletcher F; active
McClellan, Roger O; currently at Chemical Industry Institute of Toxicology (CIIT)
Mauderly, Joe L; active
Mewhinney, James A; currently at U.S. DOE
Muggenburg, Bruce A; active
Pickrell, John A; currently at Kansas State University
Raabe, Otto G; currently at Davis
Scott, Bobby R; active

Purpose: The 5 single-inhalation young-adult experiments (105.12 through 105.16) with inhaled monodisperse plutonium oxide were designed, as a group, to explore the influence of alpha-particle dose distribution within the lungs. The major issues were the health risks produced by chronic alpha-particle irradiation of the respiratory tract and non-uniformity of dose to lung.

Status: Dogs were placed on experiment from 1974 to 1976 and held for life time observation until death of last dog in 1995. "Core" manuscript published, records transfer to NRA in May, 1996.

Treatment: Single inhalation of monodisperse plutonium oxide aerosol, mean activity median aerodynamic diameter (AMAD) 1.5 μm (actual diameter 0.44 μm).

Endpoints: Dogs were given semi-annual medical examinations including radiographic surveys and complete blood work-ups throughout life. Dogs were euthanized when moribund or to prevent unnecessary pain. The necropsy protocol included histopathological observation of all body tissues, with special emphasis on the respiratory tract and tissues or organs that had been clinically dysfunctional.

Dosimetry, based on individual dog, included: whole-body retention, lung clearance, and tissue distribution, and organ- and time-specific dose calculations. Medical reviews by a clinician and pathologist determined the primary cause of death, the immediate cause of death, and any major contributing diseases. Incidental diseases, with emphasis on neoplasia, were also determined.

Animal: 84 Beagle dogs (42 females, 42 males), 12 to 15 mo old, in 7 groups.

Results: Deaths from radiation pneumonitis occurred 1.5 to 5.4 y after exposure in the highest level exposures. Tumors of the lung, skeleton and liver occurred beginning at 3 y after exposure.

References: Muggenburg, B.A., R.A. Guilmette, J.A. Mewhinney, N.A. Gillett, J.L. Mauderly, W.C. Griffith, J.H. Diel, B.R. Scott, F.F. Hahn, and B.B. Boecker. Toxicity of inhaled plutonium dioxide in beagle dogs. *Radiation Research* **145**:361-381, 1996.

Experimental Groups:

Study 105.13
Life-Span Health Risks: Single-Inhalation Exposure of Plutonium-238 Oxide ("Medium" Particle Size, 1.5 µm AMAD) in Young Adult Beagles

Group Id	Initial Lung Burden (kBq/kg)			Number of Dogs	Post-Exposure Survival (y)		
	Min	Median	Max		Min	Median	Max
01	control			12	2.2	12.5	16.1
02	0.10	0.36	0.69	12	10.1	12.3	15.6
03	0.77	1.1	1.6	12	7.1	10.8	13.8
04	1.9	2.8	4.1	12	5.8	8.7	11.8
05	4.4	6.0	8.4	12	4.0	5.2	6.6
06	8.6	11	15	12	3.2	4.3	6.4
07	15	24	45	12	1.5	3.6	4.2
			Total	84			

105.14 Life-Span Health Risks: Single-Inhalation Exposure of Plutonium-239 Oxide ("Small" Particle Size, 0.75 µm AMAD) in Young Adult Beagles

Institution: Inhalation Toxicology Research Institute

Scientists: Boecker, Bruce B; active
Griffith, William C; active
Guilmette, Raymond, A; active
Hahn, Fletcher F; active
Jones, Susan E; active
McClellan, Roger O; currently at Chemical Industry Institute of Toxicology (CIIT)
Mauderly, Joe L; active
Muggenburg, Bruce A; active
Pickrell, John A; currently at Kansas State University
Scott, Bobby R; active

Purpose: The 5 single-inhalation young-adult experiments (105.12 through 105.16) with inhaled monodisperse plutonium oxide were designed, as a group, to explore the influence of alpha-particle dose distribution within the lungs. The major issues were the health risks produced by chronic alpha-particle irradiation of the respiratory tract and non-uniformity of dose to lung.

Status: Dogs were placed on experiment from 1977 to 1979 and held for life time observation until death of last dog in 1994. Analysis of this experiment is incomplete.

Treatment: Single inhalation of monodisperse plutonium oxide aerosol, mean activity median aerodynamic diameter (AMAD) 0.75 μm (actual diameter 0.18 μm).

Endpoints: Dogs were given semi-annual medical examinations including radiographic surveys and complete blood work-ups throughout life. Dogs were euthanized when moribund or to prevent unnecessary pain. The necropsy protocol included histopathological observation of all body tissues, with special emphasis on the respiratory tract and tissues or organs that had been clinically dysfunctional.

Dosimetry, based on individual dog, included: whole-body retention, lung clearance, and tissue distribution, and organ- and time-specific dose calculations. Medical reviews by a clinician and pathologist determined the primary cause of death, the immediate cause of death, and any major contributing diseases. Incidental diseases, with emphasis on neoplasia, were also determined.

Animal: 60 Beagle dogs (30 females, 30 males), 12 to 15 mo old, in 5 groups.

Results: Deaths from radiation pneumonitis and pulmonary fibrosis occurred in the highest exposure levels. The late occurring effects were primarily lung cancers.

References: For a general description of study and summary of significant results, with extensive bibliography, see: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 9352, pp: 211-212.

Experimental Groups:

Study 105.14
Life-Span Health Risks: Single-Inhalation Exposure of Plutonium-239 Oxide ("Small" Particle Size, 0.75 μm AMAD) in Young Adult Beagles

Group Id	Quantity Injected (kBq/kg)	Number of Dogs	Median Post-Exposure Survival (y)
01	control	12	
02	0.518	12	
03	1.517	12	8.8
04	2.294	12	5.8
05	5.92	12	4.1
	Total	60	

105.15 Life-Span Health Risks: Single-Inhalation Exposure of Plutonium-239 Oxide ("Medium" Particle Size, 1.5 µm AMAD) in Young Adult Beagles

Institution: Inhalation Toxicology Research Institute

Scientists: Boecker, Bruce B; active
Griffith, William C; active
Guilmette, Raymond, A; active
Hahn, Fletcher F; active
Jones, Susan E; active
McClellan, Roger O; currently at Chemical Industry Institute of Toxicology (CIIT)
Mauderly, Joe L; active
Muggenburg, Bruce A; active
Pickrell, John A; currently at Kansas State University
Scott, Bobby R; active

Purpose: The 5 single-inhalation young-adult experiments (105.12 through 105.16) with inhaled monodisperse plutonium oxide were designed, as a group, to explore the influence of alpha-particle dose distribution within the lungs. The major issues were the health risks produced by chronic alpha-particle irradiation of the respiratory tract and non-uniformity of dose to lung.

Status: Dogs were placed on experiment from 1977 to 1979 and held for life time observation until death of last dog in 1995. Analysis of this experiment is incomplete.

Treatment: Single inhalation of monodisperse plutonium oxide aerosol mean activity median aerodynamic diameter (AMAD) 1.5 µm (actual diameter 0.44 µm).

Endpoints: Dogs were given semi-annual medical examinations including radiographic surveys and complete blood work-ups throughout life. Dogs were euthanized when moribund or to prevent unnecessary pain. The necropsy protocol included histopathological observation of all body tissues, with special emphasis on the respiratory tract and tissues or organs that had been clinically dysfunctional.

Dosimetry, based on individual dog, included: whole-body retention, lung clearance, and tissue distribution, and organ- and time-specific dose calculations. Medical reviews by a clinician and pathologist determined the primary cause of death, the immediate cause of death, and any major contributing diseases. Incidental diseases, with emphasis on neoplasia, were also determined.

Animal: 108 Beagle dogs (54 females, 54 males), 12 to 15 mo old, in 9 groups.

Results: Deaths from radiation pneumonitis and pulmonary fibrosis occurred in the highest exposure levels. The late occurring effects were primarily lung cancers.

References: For a general description of study and summary of significant results, with extensive bibliography, see: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 9352, pp: 213-214.

Experimental Groups:

Study 105.15
Life-Span Health Risks: Single-Inhalation Exposure of Plutonium-239 Oxide ("Medium" Particle Size, 1.5 μm AMAD) in Young Adult Beagles

Group Id	Quantity Injected (kBq/kg)	Number of Dogs	Median Post-Exposure Survival (y)
01	control	12	
02	0.1073	12	
03	0.3626	12	
04	0.777	12	
05	1.85	12	7.5
06	4.07	12	4.9
07	6.66	12	4.8
08	11.84	12	2.1
09	29.23	12	0.9
	Total	108	

105.16 Life-Span Health Risks: Single-Inhalation Exposure of Plutonium-239 Oxide ("Large" Particle Size, 3.0 μm AMAD) in Young Adult Beagles

Institution: Inhalation Toxicology Research Institute

Scientists: Boecker, Bruce B; active
Griffith, William C; active
Guilmette, Raymond, A; active
Hahn, Fletcher F; active
Jones, Susan E; active
McClellan, Roger O; currently at Chemical Industry Institute of Toxicology (CIIT)
Mauderly, Joe L; active
Muggenburg, Bruce A; active
Pickrell, John A; currently at Kansas State University
Scott, Bobby R; active

Purpose: The 5 single-inhalation young-adult experiments (105.12 through 105.16) with inhaled monodisperse plutonium oxide were designed, as a group, to explore the influence of alpha-particle dose distribution within the lungs. The major issues were the health risks produced by chronic alpha-particle irradiation of the respiratory tract and non-uniformity of dose to lung.

Status: Dogs were placed on experiment from 1977 to 1979 and held for life time observation until death of last dog in 1994. Analysis of this experiment is incomplete.

Treatment: Single inhalation of monodisperse plutonium oxide aerosol mean activity median aerodynamic diameter (AMAD) 3.0 μm (actual diameter 0.96 μm).

Endpoints: Dogs were given semi-annual medical examinations including radiographic surveys and complete blood work-ups throughout life. Dogs were euthanized when moribund or to prevent unnecessary pain. The necropsy protocol included histopathological observation of all body tissues, with special emphasis on the respiratory tract and tissues or organs that had been clinically dysfunctional.

Dosimetry, based on individual dog, included: whole-body retention, lung clearance, and tissue distribution, and organ- and time-specific dose calculations. Medical reviews by a clinician and pathologist determined the primary cause of death, the immediate cause of death, and any major contributing diseases. Incidental diseases, with emphasis on neoplasia, were also determined.

Animal: 84 Beagle dogs (42 females, 42 males), 12 to 15 mo old, in 7 groups.

Results: Deaths from radiation pneumonitis and pulmonary fibrosis occurred in the highest exposure levels. The late occurring effects were primarily lung cancers.

References: For a general description of study and summary of significant results, with extensive bibliography, see: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 9352, pp: 215-216.

Experimental Groups:

Study 105.16
Life-Span Health Risks: Single-Inhalation Exposure of Plutonium-239 Oxide ("Large" Particle Size, 3.0 µm AMAD) in Young Adult Beagles

Group Id	Quantity Injected (kBq/kg)	Number of Dogs	Median Post-Exposure Survival (y)
01	control	11	
02	0.703	12	
03	1.443	12	
04	4.07	12	6.2
05	9.25	12	3.7
06	18.13	12	2.0
07	37	12	1.2
	Total	83	

105.17 Life-Span Health Risks: Repeated Inhalation Exposure of Plutonium-239 Oxide in Young Adult Beagles

Institution: Inhalation Toxicology Research Institute

Scientists: Diel, Joseph H; active
Griffith, William C; active
Guilmette, Raymond, A; active
Hahn, Fletcher F; active
Lundgren, David L; active
Muggenburg, Bruce A; active

Purpose: The major issues were the life-span health risks produced by chronic alpha-particle irradiation of the respiratory tract, non-uniformity of dose to lung, and dose protraction by repeated inhalation exposure of an insoluble form of alpha-emitter.

Status: Dogs were given first exposure from 1977 to 1978 and held for life time observation until death of last dog in 1994. Analysis of this experiment is incomplete.

Treatment: Twenty inhalations at 6-mo intervals of monodisperse plutonium oxide aerosol, mean activity median aerodynamic diameter (AMAD) 0.75 μm.

Endpoints: Dogs were given semi-annual medical examinations including radiographic surveys and complete blood work-ups throughout life. Dogs were euthanized when moribund or to prevent unnecessary pain. The necropsy protocol included histopathological observation of all body tissues, with special emphasis on the respiratory tract and tissues or organs that had been clinically dysfunctional.

Dosimetry, based on individual dog, included: whole-body retention, lung clearance, and tissue distribution, and organ- and time-specific dose calculations. Medical reviews by a clinician and pathologist determined the primary cause of death, the immediate cause of death, and any major contributing diseases. Incidental diseases, with emphasis on neoplasia, were also determined.

Animal: 72 Beagle dogs (36 female, 36 male), 12 to 15 mo old, in 4 groups.

Results:

References: For a general description of study and summary of significant results, with extensive bibliography, see: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 9352, pp: 217.

Experimental Groups:

Study 105.17
Life-Span Health Risks: Repeated Inhalation Exposure of Plutonium-239 Oxide in Young Adult Beagles

Group Id	Mean Deposition per Exposure (kBq/kg)	Number of Exposures	Number of Dogs	Median Survival after First Exposure (y)
01	control	0	12	
02	0.0592	20	24	
03	0.555	20	12	
04	0.703	1	24	
		Total	72	

105.18 Life-Span Health Risks: Single-Inhalation Exposure of Plutonium-239 Oxide in Immature (3-Month-Old) Beagles

Institution: Inhalation Toxicology Research Institute

Scientists: Berry, Mary A; active
Boecker, Bruce B; active
Griffith, William C; active
Guilmette, Raymond, A; active
Hahn, Fletcher F; active
McClellan, Roger O; currently at Chemical Industry Institute of Toxicology (CIIT)
Mauderly, Joe L; active
Muggenburg, Bruce A; active

Purpose: The major issues were the effect of age of administration on the health risks produced by an insoluble form of an internally deposited alpha-emitter. These very young dogs may be compared with old (105.19) and young adult (105.15) beagles exposed to similar aerosols.

Status: Dogs were placed on experiment from 1979 to 1983 and held for life time observation until death of last dog which is projected to occur in 1998. Analysis of this experiment is incomplete.

Treatment: Single inhalation of monodisperse plutonium oxide aerosol, mean activity median aerodynamic diameter (AMAD) 1.5 μm.

Endpoints: Dogs were given semi-annual medical examinations including radiographic surveys and complete blood work-ups throughout life. Dogs were euthanized when moribund or to prevent unnecessary pain. The necropsy protocol included histopathological observation of all body tissues, with special emphasis on the respiratory tract and tissues or organs that had been clinically dysfunctional.

Dosimetry, based on individual dog, included: whole-body retention, lung clearance, and tissue distribution, and organ- and time-specific dose calculations. Medical reviews by a clinician and pathologist determined the primary cause of death, the immediate cause of death, and any major contributing diseases. Incidental diseases, with emphasis on neoplasia, were also determined.

Animal: 108 Beagle dogs (54 females, 54 males), 2.6 to 3.6 mo old, in 9 groups.

Results:

References: For a general description of study and summary of significant results, with extensive bibliography, see: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 9352, pp: 218-219.

Experimental Groups:

Study 105.18
Life-Span Health Risks: Single-Inhalation Exposure of Plutonium-239 Oxide in Immature (3-Month-Old) Beagles

Group Id	Initial Burden (kBq/kg)	Number of Dogs	Median Post-Exposure Survival (y)
01	control	12	
02	0.0148	12	
03	0.0925	12	
04	0.481	12	
05	0.888	12	
06	1.961	12	
07	5.589	12	
08	7.4	12	
09	20.35	12	4.4
	Total	108	

105.19 Life-Span Health Risks: Single-Inhalation Exposure of Plutonium-239 Oxide in Aged (7-to 10-Year-Old) Beagles

Institution: Inhalation Toxicology Research Institute

Scientists: Boecker, Bruce B; active
Griffith, William C; active
Guilmette, Raymond, A; active
Hahn, Fletcher F; active
McClellan, Roger O; currently at Chemical Industry Institute of Toxicology (CIIT)
Muggenburg, Bruce A; active

Purpose: The major issues were the effect of age of administration on the health risks produced by an insoluble form of an internally deposited alpha-emitter. These old dogs may be compared with very young (105.18) and young adult (105.15) beagles exposed to similar aerosols.

Status: Dogs were placed on experiment from 1979 to 1982 and held for life time observation until death of last dog in 1988. Analysis of this experiment is incomplete.

Treatment: Single inhalation of monodisperse plutonium oxide aerosol, mean activity median aerodynamic diameter (AMAD) 1.5 μm.

Endpoints: Dogs were given semi-annual medical examinations including radiographic surveys and complete blood work-ups throughout life. Dogs were euthanized when moribund or to prevent unnecessary pain. The necropsy protocol included histopathological observation of all body tissues, with special emphasis on the respiratory tract and tissues or organs that had been clinically dysfunctional.

Dosimetry, based on individual dog, included: whole-body retention, lung clearance, and tissue distribution, and organ- and time-specific dose calculations. Medical reviews by a clinician and pathologist determined the primary cause of death, the immediate cause of death, and any major contributing diseases. Incidental diseases, with emphasis on neoplasia, were also determined.

Animal: 60 Beagle dogs (30 females, 30 males), 7 to 10 y old, in 5 groups.

References: For a general description of study and summary of significant results, with extensive bibliography, see: R.C. Thompson, *Life-Span Effects of Ionizing Radiation in the Beagle Dog*, 1989, Pacific Northwest National Laboratory, Richland, WA 9352, pp: 220-221.

Experimental Groups:

Study 105.19
Life-Span Health Risks: Single-Inhalation Exposure of Plutonium-239 Oxide in Aged (7- to 10-Year-Old) Beagles

Group Id	Initial Burden (kBq/kg)	Number of Dogs	Median Post-Exposure Survival (y)
01	control	12	5.0
02	1.11	12	5.0
03	3.33	12	2.9
04	5.92	12	1.4
05	13.69	12	0.8
	Total	60	

105.20 Effects of Repeated Inhalation Exposures to Plutonium-239 Dioxide in C57Bl/6J Mice

Institution: Inhalation Toxicology Research Institute

Scientists: Lundgren, David L; active
Gillett, Nancy A; relocated
Griffith, William C; active
Hahn, Fletcher F; active
McClellan, Roger O; relocated

Purpose: This is one of a series of six studies designed to test the hypothesis that at similar cumulative doses to the lungs, repeated inhalation exposures to aerosols are not more carcinogenic that a single inhalation exposure. The studies compared the effects of cerium-144 dioxide, a beta-emitter, with those of plutonium-239 dioxide, an alpha-emitter, in three species: mice, hamsters, and rats.

Status: This study is complete and published; reprints are on file at the NRA, however, computer data files are not currently available.

Treatment: Young adult mice exposed once or repeatedly to achieve or to re-establish desired alpha-emitter lung burdens.

Endpoints: Lung burdens and retention determined by serial sacrifices and tissue and whole-body counting or radiochemistry. Life-span observation, necropsy and histopathology to determine cause of death and tumorigenesis.

Animal: Female C57BL/6J (Jackson Laboratory) mice, 84 d old at start of study.

Results: Protraction of alpha dose increased its carcinogenicity.

References: Lundgren, D.L., N.A. Gillett, F.F. Hahn, W.C. Griffith, and R.O. McClellan. Effects of protraction of the alpha dose to the lungs of mice by repeated inhalation exposure to aerosols of plutonium-239 dioxide. *Radiation Research* **111**:210-224, 1987.

ITRI Annual Reports: 1975-76, pp. 297-300; 1976-77, pp. 182-185; 1977-78, pp. 171-175.

Experimental Groups:

Study 105.20
Effects of Repeated Inhalation Exposures to Plutonium-239 Dioxide in C57Bl/6J Mice

Exposure Regimen	Group Id	Aerosol	Desired Initial or Re-established Lung Burden (kBq)	Alpha Dose to Lung at Death (Gy ± SD)	Number of ♀ Mice	Median Survival After Initial Exposure (d ± SE)
All 84 d old controls	01 02 03	Sham, stable Yb, or $^{169}Yb_2O_3$	0	0	480	764 ± 7
Single exposure at 84 d of age	04	$^{239}PuO_2$	20	1.2 ± 0.7	146	767 ± 2
	05		90	2.8 ± 0.7	74	713 ± 20
	06		460	14 ± 6.8	155	725 ± 18
	07		2300	64 ± 11	74	240 ± 8
Repeated exposures every 60 d between 84 and 460 d of age	08	$^{239}PuO_2$	20	2.7 ± 1.0	279	743 ± 3
	09		90	18 ± 4	125	716 ± 11
	10		460	53 ± 16	287	361 ± 5
Single exposure at 460 d of age	11	Sham	0	0	100	353 ± 8
	12	$^{169}Yb_2O_3$				
	13	$^{239}PuO_2$	90	7.5 ± 2.5	65	401 ± 20
	14		460	34 ± 16	130	299 ± 16
	15		2300	73 ± 31	62	71 ± 2
				Total	1977	

105.21 Effects of Repeated Inhalation Exposures to Cerium-144 Dioxide in C57Bl/6J Mice

Institution: Inhalation Toxicology Research Institute

Scientists: Lundgren, David L; active
Diel, Joseph H; active
Hahn, Fletcher F; active
Newton, George J; active

Purpose: This is one of a series of six studies designed to test the hypothesis that at similar cumulative doses to the lungs, repeated inhalation exposures to aerosols are not more carcinogenic that a single inhalation exposure. The studies compared the effects of cerium-144 dioxide, a beta-emitter, with those of plutonium-239 dioxide, an alpha-emitter, in three species: mice, hamsters, and rats.

Status: This study is complete and published; reprints are on file at the NRA, however, computer data files are not currently available.

Treatment: Seventy-, 260-, and 450-day-old mice were exposed once to Ce-144 dioxide to achieve desired initial lung burdens of 7.4, 37, or 170 kBq. Other groups of 70-day-old mice were exposed at 60 d intervals for one year to Ce-144 dioxide to re-establish desired lung burdens of 7.4, 37, or 170 kBq of Ce-144. Control mice were unexposed or sham exposed once or repeatedly or exposed to stable Ce dioxide once or repeatedly.

Endpoints: Lung burdens and retention determined by serial sacrifices and tissue and whole-body counting. Life-span observation, necropsy and histopathology to determine cause of death and tumorigenesis.

Animal: Conventionally reared C57BL/6J female mice (Jackson Laboratories) 8 to 10 w old.

Results: Carcinogenic effects related to total beta dose and not to dose rate.

References:

Lundgren, D.L., R.O. McClellan, F.F. Hahn, G.J. Newton, and J.H. Diel. Repeated inhalation exposure of mice to cerium-144 dioxide. I. Retention and Dosimetry. *Radiation Research* **82**:106-122, 1980.

Hahn, F.F., D.L. Lundgren and R.O. McClellan. Repeated inhalation exposure of mice to cerium-144 dioxide. II. Biologic effects. *Radiation Research* **82**:123-137, 1980.

Lundgren, D.L., F.F. Hahn and R.O. McClellan. Influence of age at the time of inhalation exposure to aerosols of cerium-144 dioxide on cerium-144 retention, dosimetry and toxicity in mice. *Health Phys* **38**: 643-655, 1980.

ITRI Annual Reports: 1972-73, pp.295-300; 1973-74, pp. 307-313; 1974-75, pp. 230-235.

Experimental Groups:

Study 105.21
Effects of Repeated Inhalation Exposures to Cerium-144 Dioxide in C57Bl/6J Mice

Exposure Regimen	Group Id	Aerosol	Desired Initial or Re-established Lung Burden (kBq)	Estimated Dose to Lung at Death (Gy ± SD)	Number of ♀ Mice	Median Survival After Initial Exposure (d ± SE)
All 70 d old controls	01 02 03	None Sham Stable CeO_2	0	0	826	784 ± 6
Repeated exposure at 70, 130, 190, 250, 310, 380, and 430 d of age	04	$^{144}CeO_2$	7.4	63 ± 26	163	748 ± 12
	05	$^{144}CeO_2$	37	320 ± 98	162	496 ± 19
	06	$^{144}CeO_2$	170	340 ± 110	161	123 ± 2
Single exposure at 70 d of age	07	$^{144}CeO_2$	7.4	9.9 ± 2.2	76	775 ± 39
	08	$^{144}CeO_2$	37	52 ± 12	320	734 ± 4
	09	$^{144}CeO_2$	170	290 ± 55	409	139 ± 3
Single exposure at 260 d of age	10	Stable CeO_2	0	0	84	535 ± 45
	11	$^{144}CeO_2$	37	44 ± 10	69	570 ± 38
	12	$^{144}CeO_2$	170	210 ± 63	74	345 ± 41
Single exposure at 450 d of age	13	Stable CeO_2	0	0	80	430 ± 22
	14	$^{144}CeO_2$	37	61 ± 25	76	400 ± 21
	15	$^{144}CeO_2$	170	310 ± 63	132	253 ± 6
				Total	2632	

105.22 Effects of Repeated Inhalation Exposures to Plutonium-239 Dioxide in Syrian Hamsters

Institution: Inhalation Toxicology Research Institute

Scientists: Lundgren, David L.; Active
Hahn, Fletcher F.; Active
Rebar, Alan H.; Active
McClellan, Roger O.; Relocated

Purpose: This is one of a series of six studies designed to test the hypothesis that at similar cumulative doses to the lungs, repeated inhalation exposures to aerosols are not more carcinogenic that a single inhalation exposure. The studies compared the effects of cerium-144 dioxide, a beta-emitter, with those of plutonium-239 dioxide, an alpha-emitter, in three species: mice, hamsters, and rats.

Status: This study is complete and published; reprints are on file at the NRA, however, computer data files are not currently available.

Treatment: Young adult Syrian hamsters were exposed once or repeatedly by inhalation to achieve or to re-establish desired lung burdens of the alpha emitter Pu-239 dioxide.

Endpoints: Survival times and histopathology.

Animal: 927 12-week-old male Syrian hamsters [Sch:(SYR)] (ARS Sprague-Dawely) in 15 groups.

Results: Syrian hamsters are relatively resistant to the carcinogenic effects of alpha radiation of the lung from inhaled Pu-239 dioxide. Only two lung neoplasms occurred in 646 hamsters exposed to Pu-239 dioxide.

Reference: D. L. Lundgren, F. F. Hahn, A. H. Rebar and R. O. McClellan. Effects of Single or Repeated Inhalation Exposure of Syrian Hamsters to Aerosols of $^{239}PuO_2$. *International Journal Radiation Biology* **43:** 1-18, 1983.

Experimental Groups:

Study 105.22
Effects of Repeated Inhalation Exposures to Plutonium-239 Dioxide in Syrian Hamsters

Exposure Regimen	Group Id	Aerosol	Desired Initial or Re-established Lung Burden (Bq)	Alpha Dose to Lungs at Death (Gy ± SD)	Number of Hamsters	Median Survival Time After Initial Exposure (d ± SE)
Repeatedly exposed at 84, 140, 204, 321, 384, and 448 days of age	01	Stable Yb_2O_3	0	0	61	490 ± 3
	02	$^{169}Yb_2O_3$	1800	0	63	456 ± 3
	03	$^{239}PuO_2$	74	2.2 ± 1.2	121	482 ± 6
	04	$^{239}PuO_2$	370	11 ± 4.3	126	499 ± 10
	05	$^{239}PuO_2$	1800	39 ± 15	111.	203 ± 4
Single exposure at 84 days of age	06	Unexposed	0	0	35	506 ± 9
	07	Stable Yb_2O_3	0	0	30	453 ± 8
	08	$^{169}Yb_2O_3$	1800	0	32	459 ± 8
	09	$^{239}PuO_2$	74	0.4 ± 0.2	55	441 ± 7
	10	$^{239}PuO_2$	370	4.5 ± 2.5	54	453 ± 10
	11	$^{239}PuO_2$	1800	15.0 ± 9.6	54	470 ± 8
Single exposure at 320 days of age	12	Stable Yb_2O_3	0	0	28	210 ± 8
	13	$^{169}Yb_2O_3$	1800	0	32	279 ± 7
	14	$^{239}PuO_2$	370	2.3 ± 1.2	64	230 ± 12
	15	$^{239}PuO_2$	1800	8.8 ± 4.8	61	221 ± 6
				Total	927	

105.23 Effects of Repeated Inhalation Exposures to Cerium-144 Dioxide in Syrian Hamsters

Institution: Inhalation Toxicology Research Institute

Scientists: Lundgren, David L.; Active
Hahn, Fletcher F.; Active
McClellan, Roger O.; Relocated

Purpose: This is one of a series of six studies designed to test the hypothesis that at similar cumulative doses to the lungs, repeated inhalation exposures to aerosols are not more carcinogenic that a single inhalation exposure. The studies compared the effects of cerium-144 dioxide, a beta-emitter, with those of plutonium-239 dioxide, an alpha-emitter, in three species: mice, hamsters, and rats.

Status: This study is complete and published; reprints are on file at the NRA, however, computer data files are not currently available.

Treatment: Young adult Syrian hamsters were exposed once or repeatedly by inhalation to achieve or to re-establish desired lung burdens of the beta emitter cerium-144 dioxide.

Endpoints: Survival times and histopathology.

Animal: 750 12-week-old male Syrian hamsters [Sch:(SYR)] (ARS Sprague-Dawely) in 15 groups.

Results: Carcinogenic effects were related to the total beta dose and not the dose rate. Syrian hamsters are relatively resistant to the carcinogenic effects of beta radiation of the lung from inhaled cerium-144 dioxide. Eighteen lung neoplasms occurred in 528 hamsters exposed to cerium-144.

Reference: D. L. Lundgren, F. F. Hahn, and R. O. McClellan. Effects of Single and Repeated Inhalation Exposure of Syrian Hamsters to Aerosols of cerium-144 dioxide. *Radiation Research* **90:** 374-394, 1982.

Experimental Groups:

Study 105.23
Effects of Repeated Inhalation Exposures to Cerium-144 Dioxide in Syrian Hamsters

Exposure Regimen	Group Id	Aerosol	Desired Initial or Re-established Lung Burden (kBq)	Dose to Lungs at Death (Gy ± SD)	Number of Hamsters	Median Survival Time After Initial Exposure (d ± SE)
Repeatedly exposed at 84, 154, 211, 264, 323, 390, and 456 days of age	01	Stable CeO_2	0	0	81	443 ± 7
	02	$^{144}CeO_2$	15	28 ± 7.2	75	501 ± 7
	03	$^{144}CeO_2$	74	100 ± 40	67	418 ± 15
	04	$^{144}CeO_2$	370	290 ± 720	75	175 ± 6
Single exposure at 84 days of age	05	Unexposed	0	0	42	467 ± 3
	06	Stable CeO_2	0	0	30	
	07	$^{144}CeO_2$	15	10 ± 3.7	33	524 ± 7
	08	$^{144}CeO_2$	74	49 ± 32	63	460 ± 3
	09	$^{144}CeO_2$	370	190 ± 40	30	321 ± 7
Single exposure at 220 days of age	10	Stable CeO_2	0	0	34	275 ± 8
	11	$^{144}CeO_2$	74	41 ± 15	56	307 ± 7
	12	$^{144}CeO_2$	370	190 ± 59	32	352 ± 10
Single exposure at 360 days of age	13	Stable CeO_2	0	0	35	266 ± 9
	14	$^{144}CeO_2$	74	66 ± 29	60	265 ± 6
	15	$^{144}CeO_2$	370	140 ± 41	37	170 ± 9
				Total	750	

105.24 Effects of Repeated Inhalation Exposures to Plutonium-239 Dioxide in F344 Rats

Institution: Inhalation Toxicology Research Institute

Scientists: Lundgren, David L; active
Diel, Joseph H; active
Griffith, William C; active
Haley, Patrick J; relocated
Hahn, Fletcher F; active
Scott, Bobby R; active.

Purpose: This is one of a series of six studies designed to test the hypothesis that at similar cumulative doses to the lungs, repeated inhalation exposures to aerosols are not more carcinogenic that a single inhalation exposure. The studies compared the effects of cerium-144 dioxide, a beta-emitter, with those of plutonium-239 dioxide, an alpha-emitter, in three species: mice, hamsters, and rats.

Status: This study is complete, reprints and data files transferred to the NRA in May, 1996.

Treatment: Young adult rats exposed once or repeatedly to achieve or to re-establish desired lung burdens of Pu-239 dioxide, an alpha-emitter.

Endpoints: Lung burdens and retention determined by serial sacrifices and tissue and whole-body counting or radiochemistry. Life-span observation, necropsy and histopathology to determine cause of death and tumorigenesis.

Animal: 1276 laboratory-reared, specific pathogen free F344/Crl-ITRI rats (approximately equal numbers of each sex) were exposed and held for life time observation. Additional animals were exposed and sacrificed to obtain dosimetry information.

Results: Carcinogenic effects related to total alpha dose and not to dose rate at doses less than 5 Gy. Protraction of alpha dose more carcinogenic at total doses of more than 5 Gy.

References: D.L. Lundgren, P.J. Haley, F.F. Hahn, J.H. Diel, W.C. Griffith, and B.R. Scott. Pulmonary carcinogenicity of repeated inhalation exposure of rats to aerosols of plutonium-239 dioxide. *Radiation Research* **142**:39-53, 1995.

ITRI Annual Reports: 1983-84, pp. 247-250; 1986-87, pp. 323-330.

Experimental Groups:

Study 105.24
Effects of Repeated Inhalation Exposures to Plutonium-239 Dioxide in F344 Rats

Exposure Regimen	Group Id	Aerosol	Desired Initial or Re-established Lung Burden (Bq)	Estimated Dose to Lung at Death (Gy ± SD)	Number of Rats	Median Survival After Initial Exposure (d)
Single exposure of 84 d old rats	01	Sham	0	0	41 ♂	786
					41 ♀	807
	02	$^{239}PuO_2$	30	0.061 ± 0.032	74 ♂	768
					72 ♀	800
	03	$^{239}PuO_2$	90	0.95 ± 0.46	81 ♂	766
					85 ♀	806
	04	$^{239}PuO_2$	280	3.7 ± 1.6	96 ♂	747
					59 ♀	773
	05	$^{239}PuO_2$	850	12 ± 2.4	4 ♂	665
					12 ♀	600
Single exposure of 450 d old rats	06	Sham	0	0	36 ♂	429
					40 ♀	526
	07	$^{239}PuO_2$	280	0.88 ± 0.62	77 ♂	412
					83 ♀	480
	08	$^{239}PuO_2$	850	6.7 ± 2.0	18 ♂	432
					14 ♀	548
Repeatedly exposed every 60 d between 84 and 450 d of age	09	Sham	0	0	51 ♂	752
					51 ♀	815
	10	$^{239}PuO_2$	26	0.90 ± 0.39	81 ♂	784
					86 ♀	797
	11	$^{239}PuO_2$	80	4.4 ± 1.8	64 ♂	737
					55 ♀	769
	12	$^{239}PuO_2$	259	10 ± 2.1	45 ♂	776
					49 ♀	794
				Totals	**668 ♂ 647 ♀**	

105.25 Effects of Repeated Inhalation Exposures to Cerium-144 Dioxide in F344 Rats

Institution: Inhalation Toxicology Research Institute

Scientists: Lundgren, David L; active
Diel, Joseph H; active
Hahn, Fletcher F; active
Snipes, M. Burton, active

Purpose: This is one of a series of six studies designed to test the hypothesis that at similar cumulative doses to the lungs, repeated inhalation exposures to aerosols are not more carcinogenic that a single inhalation exposure. The studies compared the effects of cerium-144 dioxide, a beta-emitter, with those of plutonium-239 dioxide, an alpha-emitter, in three species: mice, hamsters, and rats.

Status: This study is complete, reprints and data files transferred to the NRA in May, 1996.

Treatment: Young adult rats exposed once or repeatedly to achieve or to re-establish desired beta-emitter lung burdens.

Endpoints: Lung burdens and retention determined by serial sacrifices and tissue and whole-body counting. Life-span observation, necropsy and histopathology to determine cause of death and tumorigenesis.

Animal: Equal numbers of laboratory-reared, male and female, F344/Cr1-ITRI gnotobiotic rats aged 83 to 85 d at start of study.

Results: Carcinogenic effects related to total beta dose and not to dose rate.

References:

Lundgren, D.L., F.F. Hahn, J.H. Diel, and M.B. Snipes. Repeated irradiation exposure of rats to aerosols of cerium-144 dioxide. I. Lung, liver and skeletal dosimetry. *Radiation Research* **132**:312-324, 1992.

Lundgren, D.L., F.F. Hahn, and J.H. Diel. Repeated irradiation exposure of rats to aerosols of cerium-144 dioxide II. Effects on survival and lung, liver, and skeletal neoplasia. *Radiation Research* **132**:312-324, 1992.

ITRI Annual Reports: 1976-77, pp.172-175; 1978-79, pp. 187-19; 1979-80, pp. 95-98; 1980-81, pp. 130-133.

Experimental Groups:

Study 105.25
Effects of Repeated Inhalation Exposures to Cerium-144 Dioxide in F344 Rats

Exposure Regimen	Group Id	Aerosol	Desired Initial or Re-established Lung Burden (kBq)	Estimated Dose to Lung at Death (Gy ± SD)	Number of Rats	Median Survival After Initial Exposure (d ± SE)
Single exposure of 94 d old rats	01 02 03	None Sham Stable CeO_2	0	0	73 ♂	788 ± 19
					82 ♀	832 ± 20
	04	$^{144}CeO_2$	1.9	0.26 ± 0.25	20 ♂	763 ± 13
					21 ♀	832 ± 20
	05	$^{144}CeO_2$	9.2	1.2 ± 0.4	54 ♂	712 ± 65
					58 ♀	755 ± 61
	06	$^{144}CeO_2$	46	6.8 ± 1.7	19 ♂	747 ± 9
					21 ♀	795 ± 25
	07	$^{144}CeO_2$	230	46 ± 12	58 ♂	716 ± 23
					63 ♀	793 ± 7
Single exposure of 500 d old rats	08	Stable CeO_2	0	0	19 ♂	378 ± 33
					18 ♀	396 ± 73
	09	$^{144}CeO_2$	46	8.5 ± 5.0	19 ♂	377 ± 17
					18 ♀	452 ± 59
	10	$^{144}CeO_2$	230	36 ± 18	19 ♂	442 ± 38
					19 ♀	411 ± 45
Repeatedly exposed every 60 d between 94 and 460 d of age	11 12	Sham Stable CeO_2	0	0	56 ♂	791 ± 11
					61 ♀	823 ± 24
	13	$^{144}CeO_2$	1.9	2.1 ± 0.4	20 ♂	713 ± 30
					19 ♀	803 ± 44
	14	$^{144}CeO_2$	9.2	9.5 ± 1.8	20 ♂	799 ± 52
					27 ♀	838 ± 43
	15	$^{144}CeO_2$	46	50 ± 5.8	37 ♂	787 ± 24
					38 ♀	840 ± 15
	16	$^{144}CeO_2$	230	250 ± 51	18 ♂	539 ± 28
					21 ♀	582 ± 21
				Totals	**432 ♂ 466 ♀**	

105.26 Toxic Effects of Single-Inhalation Exposure of Curium-244 Sesquioxide in F344 Rats

Institution: Inhalation Toxicology Research Institute

Scientists: Lundgren, David L; active
Carlton, William W; active
Gillett, Nancy A; relocated
Griffith, William C; active
Guilmette, Ray A; active
Hahn, Fletcher, F; active

Purpose: In previous studies of the toxic effects of inhaled curium compounds, a direct measurement of the initial lung burden for each animal was not available. The purpose of this study was to obtain information on the alpha-particle dose-response relationships of curium-244 in rats exposed by inhalation to a well characterized aerosol of curium-244 sesquioxide in which the initial lung burden of each animal is determined, thus permitting more accurate dosimetry for each rat. The results will be compared with that of inhaled plutonium-239 dioxide.

Status: This study is complete and published, computer files transferred to the NRA in May, 1996.

Treatment: The curium, which contained curium-243 as a gamma label, was obtained by removal of the Pu daughters from a stock material by solvent extraction and prepared as a monodisperse aerosol with activity median aerodynamic diameter of 1 micrometer. Electron diffraction crystallography indicated the material is curium sesquioxide with 2 crystal types, monoclinic and body centered cubic. Groups of rats were exposed to the aerosol within 24 h of its preparation.

Endpoints: Survival times and patterns, and histopathology.

Animal: 1263 laboratory-reared, 12 w old, specific pathogen-free F344/Crl/ITRI rats, of both sexes, in 8 groups.

Results: Curium-244 sesquioxide was about 50% less carcinogenic than plutonium-239 dioxide at similar total alpha doses to lungs. The results support the hypothesis that more uniformly distributed doses of alpha radiation are more carcinogenic in the lungs than less uniformly distributed doses. There was a significant increase in the crude incidence of lung neoplasms at graded dose levels that ranged from 0.74 to 27 Gy to the lungs. The risk of death with a lung neoplasm did not increase significantly with decreasing dose to the lung.

References: Lundgren, D.L, F.F. Hahn, W.W. Carlton, W.C. Griffith, R.A. Guilmette, and N.A. Gillett. Dosimetry and biological effects of inhaled monodisperse aerosols of curium-244 sesquioxide in F344 rats. Submitted to *Radiation Research* in 1996.

ITRI Annual Reports: 1980-81, pp. 186-189; 1981-82, pp. 357-360; 1982-83, pp. 278-282; 1985-86, pp. 263-266, 1991-92, pp. 123-126.

Experimental Groups:

Study 105.26
Toxic Effects of Single-Inhalation Exposure of Curium-244 Sesquioxide in F344 Rats

Group Id	Initial Lung Burden (kBq/kg)	Number of Rats		Median Survival Time (d)	
		♀	♂	♀	♂
01	Sham	79	79	826	799
02	0.037 - 0.740	66	120	822	785
03	0.740 - 1.85	134	120	807	800
04	1.85 - 5.55	102	74	805	767
05	5.55 - 16.65	65	62	763	738
06	16.65 - 55.5	80	74	722	670
07	55.5 - 129.5	34	46	539	507
08	129.5 -629	70	58	63	62
	Total	630	633		

105.27 Biological Effects of Alpha-Particle Dose Nonhomogeneity from Inhaled Plutonium-239 Dioxide in the Lungs of F344 Rats

Institution: Inhalation Toxicology Research Institute

Scientists: Lundgren, David L.; active
Guilmette, Raymond, A; active
Griffith, William C.; active
Hahn, Fletcher F.; active
Haley, Patrick J.; relocated
Diel, Joseph H.; active
Muggenburg, Bruce A.; active
Boecker, Bruce B.; active

Purpose: The purpose of this study was to compare the biological responses to inhaled plutonium-239 of two different particle sizes, activity median aerodynamic diameter (AMAD) of 1.08 μm or 2.41 μm, that resulted in different patterns in the alpha-particle radiation dose to the lungs in rats.

Status: This study is in-progress; materials are in active use at ITRI.

Treatment: Rats were exposed once briefly by inhalation to either one of two different monodisperse aerosols of plutonium-239 dioxide; 1.08 and 2.41 μm AMAD. Initial lung burdens were determined by whole-body counting and retention was determined by radiochemistry.

Endpoints: Survival times and histopathology.

Animal: 639 12-week-old male and female F344/Crl-ITRI rats in 6 groups.

Results: The fractions of the lung irradiated ranged from 0.08 to 1.0 among the rats exposed to 2.41 μm AMAD particles whereas the entire lungs of all rats exposed to the 1.08 μm AMAD particles were irradiated. The biological responses of the rats to the two particle sizes were consistent with that expected from rats exposed to plutonium-239 dioxide and were not significantly different from each other. This study

adds additional support to the hypothesis that "hot particles" resulting in a more heterogeneous distribution of the radiation dose to the lungs are not more carcinogenic than similar doses distributed more homogeneously.

Reference: ITRI Annual Reports: 1978-79, pp. 150-153; 1979-80, pp. 149-152; 1980-81, pp. 178-180.

Experimental Groups:

Study 105.27
Biological Effects of Alpha-Particle Dose Nonhomogeneity from Inhaled Plutonium-239 Dioxide in the Lungs of F344 Rats.

Group Id	Range of Lifetime Doses to Lungs (Gy)	Number Exposed		Median Survival Time (d)	
		♀	♂	♀	♂
01	Unexposed	48	65	923	817
1.08 μm AMAD particles					
02	>0.32-1.0	1	9	919	776
03	>1.0-3.2	43	41	855	765
04	>3.2-7.9	39	35	850	749
05	>7.9	8	9	710	737
2.41 μm AMAD particles					
06	<0.32	14	1	887	581
07	>0.32-1.0	18	12	760	801
08	>1.0-3.2	35	43	849	800
09	>3.2-7.9	18	59	941	777
10	>7.9	2	9	666	654
	Total	226	283		

105.28 Survival and Liver-Tumor Induction: Thorotrast or Plutonium-239 Injected in Chinese Hamsters

Institution: Inhalation Toxicology Research Institute

Scientists: Guilmette, Ray A; active
Gillett,Nancy A; currently at Sierra Biomedical, Inc.
Hahn, Fletcher F; active
Eidson, A F; relocated
Brooks, Antone, L; currently at PNNL

Purpose: The estimation of risk to the liver from deposited alpha-emitting radionuclides is based on epidemiologic data accumulated from patients injected with Thorotrast as an x-ray contrast medium. Injected Thorotrast, a colloidal suspension of small (~10 nm diameter) Th-232 dioxide particles with a complex decay scheme, is very nonuniformly deposited in the liver, and results in highly nonuniform irradiation of the tissues. In contrast, comparable levels of other hepatrotyropic alpha emitters would involve a much smaller mass and deposit much more uniformly in liver.

This study will provide information useful in comparing the carcinogenicity of a low-mass, uniformly distributed alpha emitter (Pu-239 dioxide) with that of a high-mass, heterogeneously distributed alpha emitter, Thorotrast, in Chinese hamsters.

Status: This study is complete and published, computer files available through ITRI.

Treatment: Chinese hamsters were injected intravenously in the jugular vein with either Th-232 dioxide colloid or Pu-239 citrate. Two control groups were used, one injected with the peptizing agent, yellow dextrin, which is part of the Thorotrast suspension; the second with sodium citrate.

Endpoints: Three endpoints are being evaluated in different animals: (1) survival; (2) the production of liver lesions in animals held for life span; and (3) the generation of chromosome abnormalities in liver cells from serial sacrifice animals.

Animal: The life-span study consisted of 450 Chinese hamsters, 90-120 d of age, of both sexes, in 6 groups.

Results: The relative risk for liver lesions increased in a dose-related manner for Thorotrast. The relative risk for Pu or Thorotrast were similar. The risk coefficients for each dose group were similar, regardless whether a liberal or conservative approach for grading lesions was used.

References: R.A. Guilmette, N.A. Gillett, A.F. Eidson, W.C. Griffith, and A.L. Brooks. The influence of nonuniform alpha irradiation of Chinese hamster liver on chromosome damage and induction of cancer. Proceedings of the Workshop on Risks from Radium and Thorotrast, Bethesda MD 3-5 October 1988. *Brit. Inst. Radiol.* Report 21, 142-148, 1989.

ITRI Annual Reports: 1984-85, pp. 265-269; 1985-86, pp. 267-270; 1986-87, pp. 336-340.

Experimental Groups:

Study 105.28
Survival and Liver-Tumor Induction:
Thorotrast or Plutonium-239 Injected in Chinese Hamsters

Group Id	Exposure Type	Number Exposed	Injected Dose ($Bq\ g^{-1}$)	Median Survival Time (d ± SE)	
				♀	♂
01	Citrate Controls	58	0	975 ± 20	1018 ± 24
02	Dextrin Controls	51	0	966 ± 18	1100 ± 27
03	^{239}Pu Citrate	97	7.4	970 ± 34	961 ± 41
04	Thorotrast	100	0.3	981 ± 43	1035 ± 21
05	Thorotrast	100	1.5	856 ± 48	1023 ± 20
06	Thorotrast	54	7.4	463 ± 64	407 ± 107
Total		460			

105.29 Toxic Effects of Single Inhalation Exposure to Yttrium-90 (in an Insoluble Matrix) in CFW Mice

Institution: Inhalation Toxicology Research Institute

Scientists: Lundgren, David L; active
Hahn, Fletcher F; active
McClellan, Roger O; relocated

Purpose: This purpose of this study was to determine the toxicity of a short-half-lived beta-emitting radionuclide yttrium-90 (half life = 2.7 d) to compare with data from mice that had inhaled a longer-half-lived beta-emitting radionuclide cerium-144 (half life = 285 d) in relatively insoluble forms and to provide data for comparison with the results of similar studies in beagle dogs.

Status: This study is complete and published; reprints are on file at the NRA, however, computer data files are not currently available.

Treatment: Mice were exposed once briefly by inhalation to an aerosol of yttrium-90 in relatively insoluble fused aluminosilicate aerosols (FAP). Initial lung burdens were determined by whole-body counting.

Endpoints: Survival times and histopathology.

Animal: 2286 7-9 wk-old CFW random-bred male mice (Carworth Farms, New York City, NY) in 10 groups.

Results: Initial lung burdens (ILBs) of > 800 kBq (>30 Gy to lungs) resulted in radiation pneumonitis and significant life shortening. The incidence of all lung neoplasms and other lesions mice exposed to yttrium-90 FAP were similar to those in control mice, except pulmonary adenomas, that were found more frequently in groups of mice with ILBs of 37-370 and 380-780 kBq (11 ± 3.8 23 ± 4.0 Gy to lungs; respectively). The early occurring biological effects observed in mice were similar to those observed in beagle dogs exposed to yttrium-90.

References: Lundgren, D. L., F. F. Hahn, and R. O. McClellan. Toxicity of Yttrium-90 in Relatively Insoluble Fused Aluminosilicate Particles when Inhaled by Mice. *Radiation Research* **88:** 510-523, 1981.

Experimental Groups:

Study 105.29
Toxic Effects of Single Inhalation Exposure to Yttrium-90 (in an Insoluble Matrix) in CFW Mice

Group Id	Initial Lung Burden Range (kBq)	Number Exposed	Initial Lung Burden Range (MBq kg^{-1} body weight)	Dose to Lungs (Gy ± SD)	Median Survival Time (d ± SE)
01	Unexposed	42	0	0	680 ± 9
02	Sham exposed	340	0	0	606 ± 8
03	Stable Y-FAP	381	0	0	564 ± 17
04	37 - 370	849	1.1 - 12	11 ± 3.8	563 ± 5
05	380 - 780	330	13 - 25	23 ± 4.0	563 ± 4
06	790 - 1100	74	26 - 37	38 ± 4.4	66 ± 2
07	1200 - 1500	89	38 - 50	60 ± 4.0	41 ± 0.5
08	1550 - 1850	110	51 - 62	72 ± 3.4	28 ± 0.5
09	1900 - 2100	47	63 - 74	88 ± 6.0	21 ± 0.7
10	2200 - 5200	24	75 - 174	140 ± 22	12 ± 0.2
	Total	2286			

105.30 Effects of Single-Inhalation Exposure to Relatively Low Levels of Cerium-144 Dioxide in F344 Rats

Institution: Inhalation Toxicology Research Institute

Scientists: Lundgren, David L; active
Hahn, Fletcher, F; active
Hubbs, Ann F; relocated
Cuddihy, Richard, G; retired
Griffith, William C; active
Nikula, Kristen J; active
Newton, George J; active.

Purpose: Information about the human health effects of inhaled radionuclides comes primarily from exposures to radon. However, radon irradiates the upper airways, whereas insoluble radionuclides irradiate cells of the small airways and alveoli. Arrays of animal toxicity studies may be used to assess risk to these tissues. Most animal studies are inappropriate for estimating cancer risk factors for people because relatively high doses resulted in life shortening. This study of rats exposed to non-life-shortening doses of irradiation to the lung will help estimate risk to people from an inhaled beta-emitter. This study is designed to be compared with a study of low thoracic and whole body exposure to X-rays (105.30).

Status: This study is complete, manuscript submitted; computer files transferred to the NRA in May, 1996

Treatment: Rats were entered into the study in a series of 12 blocks between December 1984 and September 1985. Each block contained a similar number of controls and rats exposed to 1 of 3 different activity levels of Ce-144 inhaled as Ce-144 dioxide.

Endpoints: Survival times and patterns, lung histopathology.

Animal: 2751, (1430 female, 1430 male), laboratory-reared, 12 w old, specific pathogen-free F344/N-ITRI rats, in 8 groups.

Results: Relatively low levels of beta radiation to lung (<40Gy) are not more carcinogenic than higher doses. Excess numbers of rats with lung neoplasms per 10 kGy at relatively low beta doses (<40 Gy) was approximately 50. The linear risk of lung neoplasms in rat was constant at a value of approximately 47 excess lung neoplasms per 10,000 rat Gy over a range of 3.6 to 37 Gy.

References: D.L. Lundgren, F.F. Hahn, W.C. Griffith, A.F. Hubbs, K.J. Nikula, C.J. Newton, R.G. Cuddihy, and B.B. Boecker. Pulmonary carcinogenicity of relatively low doses of beta-particle radiation from inhaled cerium-144 dioxide in rats. Submitted to *Radiation Research* in 1996.

ITRI Annual Reports: 1983-84, pp.251-257; 1984-85, pp. 216-219; 1985-86, pp. 257-262; 1986-87, pp. 308-312; 1985-86, pp. 263-266.

Experimental Groups:

Study 105.30
Effects of Single-Inhalation Exposure to
Relatively Low Levels of Cerium-144 Dioxide in F344 Rats

Group Id	Relative Dose Level	Number of Rats	Sex	Initial Lung Burden (kBq ± SD)	Median Survival	
					(d)	(95% CI)
01	Sham	523	♂	0	606	597-612
		541	♀	0	744	730-763
02	Low	520	♂	21 ± 7.6	592	584-599
		539	♀	16 ± 6.0	757	742-765
03	Medium	122	♂	66 ± 24	596	579-609
		125	♀	55 ± 25	728	742-765
04	High	193	♂	205 ± 64	591	568-623
		188	♀	156 ± 47	720	669-760
Total		2751				

105.31 Effects of Thoracic and Whole-Body Exposure to Relatively Low Levels of X-Irradiation in F344 Rats

Institution: Inhalation Toxicology Research Institute

Scientists: Lundgren, David L; active
Griffith, William W; active
Hahn, Fletcher, F; active
Boecker, Bruce B; active

Purpose: This study involved fractionated x-irradiation of the thorax in one group and the single or fractionated exposure of the whole body of two other groups of rats. Results will be compared with effects of relatively low, beta-radiation doses to lungs of rats exposed by inhalation to aerosols of Ce-144 dioxide.

Status: This study is in-progress; materials are in active use at ITRI.

Treatment: Rats were entered into the study in a series of 12 blocks (containing about 1/12 the total number per group) between July, 1987 and August, 1990. Groups of rats were exposed either to fractionated doses of X-rays to the thorax or to the whole body on 10 successive workdays (M-F) or to a single, whole-body exposure. The X-ray therapy machine was operated at an equivalent energy of 135 keV to produce 0.221 Gy/min at 1 meter.

Endpoints: Survival times and patterns, lung histopathology.

Animal: 4164 laboratory-reared, specific pathogen-free F344/N-ITRI rats in 8 groups.

Results: As anticipated, the higher radiation doses reduced survival time. Lung tumor incidence was significantly increased at all doses, with an increasing frequency of squamous cell carcinomas at the lower doses in contrast to the decreasing frequency seen with inhaled beta-emitting radionuclides.

References: ITRI Annual Reports: 1983-84, pp. 251-257; 1986-87, pp. 313-317; 1987-88, pp. 241-244; 1988-89, pp. 213-214; 1989-90, pp. 129-132; 1990-91, pp. 89-93; 1991-92, pp. 121-122; 1992-93, pp. 64-65.

Experimental Groups:

Study 105.31
Effects of Thoracic and Whole-Body Exposure to Relatively Low Levels of X-Irradiation in F344 Rats

Group Id	Dose (Gy)	Exposure Type	Number Rats Exposed		Median Survival (d ± SE)	
			♀	♂	♀	♂
01	0	Sham	504	504	735 ± 6	621 ± 5
02	3.5	Fractionated thoracic	503	502	719 ± 9	606 ± 6
03	3.5	Fractionated whole-body	146	144	641 ± 16	588 ± 19
04	5.8	Fractionated thoracic	251	249	738 ± 11	594 ± 5
05	5.8	Fractionated whole-body	253	250	557 ± 11	532 ± 12
06	5.8	Single whole-body	250	250	514 ± 10	501 ± 6
07	11	Fractionated thoracic	120	118	668 ± 13	604 ± 10
08	38	Fractionated thoracic	60	60	622 ± 31	523 ± 11
		Total	2087	2077		

105.32 Effects of Combined Single-Inhalation Exposure to Plutonium-239 Dioxide and Subsequent Whole-Body X-Irradiation of F344 Rats

Institution: Inhalation Toxicology Research Institute

Scientists: Lundgren, David L; active
Boecker, Bruce B; active
Hahn, Fletcher, F; active
Griffith, William W; active
Hoover, M.D.; active

Purpose: Characterize the lifetime effects of combined exposure of rats to external x-radiation and internally deposited plutonium, as well as to each agent alone.

Status: This study is in-progress; materials are in active use at ITRI.

Treatment: Rats were exposed to a split dose of whole-body, 135 keV, X irradiation at about 23 R/min at 1 m on d 30 and 60 after single inhalation exposure to Pu-239 dioxide.

Endpoints: Lung burdens and retention determined by serial sacrifices and tissue and whole-body counting or radiochemistry. Life-span observation, necropsy and histopathology to determine cause of death and tumorigenesis.

Animal: 3201 laboratory-reared, F344/N-ITRI rats (1606 female, 1595 male), 11 to 13 w old.

Results: No significant life-shortening occurred among the rats exposed only to plutonium compared with the respective sham-inhalation-exposed rats. Within each X-ray exposure group, there was also no life shortening related to the plutonium exposures. In contrast, a dose-response relationship for life shortening occurred among the rats exposed to whole-body X irradiation with shorter survival times of female rats than male rats. The question of additive or synergistic effects awaits completion of histopathology and analysis.

References: ITRI Annual Reports: 1986-87 pp. 318-322; 1987-88, pp..251-255; 1991-92, pp. 115-117; 1992-93, pp. 61-63.

Experimental Groups:

Study 105.32
Effects of Combined Single-Inhalation Exposure to Plutonium-239 Dioxide and Subsequent Whole-Body X-Irradiation of F344 Rats

Group Id	Initial Lung Burden (Bq)	X-ray (Gy)	Number Rats Exposed		Median Survival (d ± SE)	
			♀	♂	♀	♂
01	Sham	Sham	160	160	719 ± 13	617 ± 12
02	56	Sham	191	192	750 ± 13	618 ± 9
03	170	Sham	182	182	749 ± 14	607 ± 11
04	Sham	3.84	156	158	594 ± 10	557 ± 10
05	56	3.84	192	192	620 ± 7	565 ± 10
06	170	3.84	191	188	593 ± 13	549 ± 7
07	Sham	11.5	160	160	485 ± 13	431 ± 11
08	56	11.5	191	191	473 ± 14	451 ± 9
09	170	11.5	183	172	492 ± 12	449 ± 10
		Total	1606	1595		

105.33 Effects of Combined Single-Inhalation Exposure to Beryllium Metal and Plutonium-239 Dioxide Aerosols in F344 Rats

Institution: Inhalation Toxicology Research Institute

Scientists: Finch, Gregory L; active
Hoover, Mark D; active
Hahn, Fletcher F; active
Griffith, William C; active
Carlton, William W; active
Mewhinney, James A; relocated
Rebar, A; Purdue University

Purpose: The purpose of this study is to investigate the potential interactions between Pu and Be in the production of lung tumors in rats exposed by inhalation to particles of Pu-239 dioxide, Be metal, or these agents in combination.

Status: Phase I completed, data analysis in progress. Phase II in progress.

Treatment: Phase I - Groups of 60 rats received Pu-239 dioxide (activity median aerodynamic diameter = 0.7 μm, sigma g = 1.7, exposure duration 5 to 25 min, Pu-239 concentration = 630 Bq/l), followed immediately by exposure to Be metal (mass median aerodynamic diameter = 1.4 μm, sigma g = 1.9, exposure duration = 8 to 50 min, Be air concentration = 200 to 1200 mg/cubic m), or the appropriate air control. Pu-239 dioxide particles were labeled with Yb-169 to permit periodic external radioactivity counting.

Phase II - similar to Phase I, except that the Be metal exposure occurs 1 d after the Pu-239 dioxide exposure.

Endpoints: Survival times and patterns, lung histopathology, lung clearance and dosimetry of plutonium and beryllium, molecular analysis of tumors.

Animal: Phase I (1987-1989) - 2848 laboratory-reared F344/N-ITRI rats, 12 ± 1 w old, of both sexes. Phase II - 2598 specific pathogen-free CDFr(F344)/CrlBR rats, 12 ± 1 w old, of both sexes. were acquired from an outside source, Charles River Laboratory.

Results: Beryllium exposure significantly retarded Pu clearance at lung burdens as low as 1.0 µg. Acute pneumonitis caused deaths within 3 w at the highest lung burden. In Phase I, the losers lung burden of Be used (50µg) produced lung tumors in approximately 2/3 of exposed rats.

References:

Finch, G.L., P.J. Haley, M.D. Hover, M.B. Snipes, and R. G. Cuddihy. Responses of rat lungs to low lung burdens of inhaled beryllium metal. *Inhalation Toxicology*, 6:205-224, 1994.

Finch, G.L., P.J. Haley, M.D. Hoover, and R.G. Cuddihy. Responses of rat lungs following inhalation of beryllium metal particles to achieve relatively low lung burdens. *Ann. Occup. Hyg.* **38** Supplement 1, 419-424, 1994.

Finch, G.L., M.D. Hoover, F.F. Hahn, K.J. Nikula, S.A. Belinsky, P.J. Haley, and W.C. Griffith. Animal models of beryllium-induced lung disease. *Environ. Health Perspect.* In press 1995

ITRI Annual Reports: 1994-95, pp.77-79.

Experimental Groups:

Study 105.33

Effects of Combined Single-Inhalation Exposure to

Beryllium Metal and Plutonium-239 Dioxide Aerosols in F344 Rats

Experimental design to study the combined effects of Plutonium-239 dioxide and Beryllium metal in rats

Initial Lung Burden Be Metal (µg)	Number of Rats by Experimental Group						
	Initial Lung Burden $^{239}PuO_2$ (Bq)						
	0		60	170	230	460	Total
0	208	270	240	240	288	156	1402
0.3		288					288
1.0		288			288		576
3.0		288					288
10		288			288		576
50	240	156	240	240			886
150	240		240	240			720
450	240		240	240			720
Total	2516		960	960	864	156	5456
Phase II indicated by shading							

NRA database representation of study the combined effects of Plutonium-239 dioxide and Beryllium metal in rats

Group Id	Initial Lung Burden		Number of Rats
	Be Metal (µg)	$^{293}PuO_2$ (Bq)	
Phase I (1987-1989) - higher beryllium burdens			
01	0	0	208
02	0	60	240
03	0	170	240
04	50	0	240
05	50	60	240
06	50	170	240
07	150	0	240
08	150	60	240
09	150	170	240
10	450	0	240
11	450	60	240
12	450	170	240
		Total	2848
Phase II (1991 -) - lower beryllium burdens			
13	0	0	270
14	0	230	288
15	0	460	156
16	0.3	0	288
17	1.0	0	288
18	1.0	230	288
19	3.0	0	288
20	10	0	288
21	10	230	288
22	50	0	156
		Total	2598

105.34 Effects of Chronic Inhalation Exposure to Cigarette Smoke and Single Acute Inhalation Exposure to Plutonium-239 Dioxide in F344 Rats

Institution: Inhalation Toxicology Research Institute

Scientists: Lundgren, David L; active
Griffith, William W; active
Hoover, M.D.; active
Finch, Gregory L.; active
Barr, Edward B; active
Nikula, Kristen J; active

Bechold, William E; active
Chen, Bean; relocated

Purpose: Characterize the lifetime effects of combined exposure of rats to chronically inhaled cigarette smoke and internally deposited plutonium, as well as to each agent alone.

Status: Exposures completed in 1994, data analysis in progress.

Treatment: Beginning at 6 wk of age, groups of rats were exposed by the whole-body mode (6 h/d, 5 d/wk) to either filtered air of mainstream cigarette smoke for 6 wk. At 12 wk, they were removed from the chamber and exposed to either filtered air or Pu-239 dioxide aerosol. One wk later, they were returned to the chamber for continued exposure to filtered air or cigarette smoke for up to 30 m. Cigarette smoke was diluted to concentrations of either 100 or 250 mg total particulate matter (TPM)/cubic m.

Endpoints: Survival times and patterns, lung histopathology, radiation dosimetry, and molecular analysis of tumors.

Animal: 2165 specific pathogen-free CDF®(F344)/CrlBR rats, of both sexes, in 16 groups.

Results: Preliminary findings indicate synergistic interactions in lung tumor formation between cigarette smoke and alpha-particles and, compared to controls a significant increase in lung tumors caused by cigarette smoke exposure alone. Cigarette smoke reduces plutonium clearance from the lung.

References:

Finch, G.L., K.J. Nikula, B.T. Chen, E.B. Barr, I.-Y. Chang, and C.H. Hobbs. Effect of chronic cigarette smoke exposure on lung clearance of tracer particles inhaled in rats. *Fundamental and Applied Toxicology* 24:76-85, 1995.

Finch, G.L., B.T. Chen, E.B. Barr, I,-Y. Chang, and K.J. Nikula. Effects of cigarette smoke exposure on F344 rat lung clearance of insoluble particles. In *Toxic and Carcinogenic Effects of Solid Particles in the Respiratory Tract*, U. Mohr, D.L. Dugworth, J.L. Mauderly, and G. Oberdörster, eds, International Life Sciences Institute (ILSI) Press, Washington D.C., 1994.

ITRI Annual Reports: 1991-92, pp. 110-111; 1992-93, pp. 53-55; 1993-94, pp. 71-73; 1994-95, pp. 77-79.

Experimental Groups:

Study 105.34
Effects of Chronic Inhalation Exposure to Cigarette Smoke and Single Acute Inhalation Exposure to Plutonium-239 Dioxide in F344 Rats

Group Id	^{239}Pu Initial Lung Burden (Bq)	Cigarette Smoke TPM (mg m^{-3})	Designation	Number of Rats
01	Sham	Sham	life	237
02	Sham	Sham	sacrifice	114
03	Sham	100	life	353
04	Sham	100	sacrifice	115
05	Sham	250	life	163
06	Sham	250	sacrifice	115
07	400	Sham	life	234
08	400	Sham	sacrifice	108
09	400	100	life	346
10	400	100	sacrifice	110
11	400	250	life	163
12	400	250	sacrifice	107
			Total	2165

105.35 Effects of Chronic Inhalation Exposure to Cigarette Smoke and Either Thoracic Exposure to X-rays or Single-Acute Inhalation Exposure to Plutonium-239 Dioxide in Rats and Mice

Institution: Inhalation Toxicology Research Institute

Scientists: Finch, Gregory L; active
Barr, Edward B; active
Bechtold, William E; active
Belinsky, Steven A; active
Griffith, William C; active
Hahn, Fletcher F; active
Hobbs, Charles H; active
Hoover, Mark D; active
Lundgren, David L; active
Nikula, Kristen J; active

Purpose: Determine the lifetime effects of combined exposures of both rats and mice to chronically inhaled cigarette smoke combined with internally deposited plutonium-239 dioxide (hybrid rats, mice) or thoracic X-irradiation (F344 rats, mice).

Status: In progress, study initiated October 1995.

Treatment: Beginning at 6 wk of age, groups of animals are exposed by the whole-body mode (6 h/d, 5d/wk) to either diluted, mainstream cigarette smoke or filtered air. Radiation exposure occurs at 12 wk of age in the form of either (I) single acute inhalation exposure to Pu-239 dioxide with a desired initial lung burden (ILB) of 200 Bq in mice and 400 Bq in rats, or (ii) thoracic exposure to X-rays divided into 10 fractionated doses administered over two wk for a total exposure of 1800 R. For plutonium-exposed animals, smoke exposure resumes at 13 wk of age. For X-ray-exposed animals, smoke exposure continues during X-ray exposure. Smoke is administered at a concentration of 250 mg total particulate matter/cubic m.

Endpoints: Survival times and patterns, lung histopathology, Pu-239 lung clearance and dosimetry, molecular analysis of tumors.

Animals: 1. CDF(F344)/CrlBR rats; 2. Brown Norway x F344/N F1 hybrid rats; 3. B6C3F1 mice, all acquired from Charles River Laboratory.

Results: No results yet available.

References:

Experimental Groups:

Study 105.35
Effects of Chronic Inhalation Exposure to Cigarette Smoke and Either Thoracic Exposure to X-rays or Single-Acute Inhalation Exposure to Plutonium-239 Dioxide in Rats and Mice

Group Id	Species and Strain	X-Ray (R)	Desired ^{239}Pu Initial Lung Burden (Bq)	Cigarette Smoke TPM (mg m^{-3})	Designation	Number of Animals
01	F344 rat	Sham	Sham	Sham	life	270
02					sacrifice	30
03				250	life	270
04					sacrifice	30
05	B6C3F1 mouse	Sham	Sham	Sham	life	342
06					sacrifice	30
07				250	life	342
08					sacrifice	30
09	F344 rat	1800	Sham	Sham	life	222
10					sacrifice	30
11				250	life	222
12					sacrifice	30
13	B6C3F1 mouse	1800	Sham	Sham	life	162
14					sacrifice	30
15				250	life	162
16					sacrifice	30
17	FBNF1 hybrid rat	Sham	400	Sham	life	48
18					sacrifice	6
19				250	life	48
20					sacrifice	6
21	B6C3F1 mouse	Sham	200	Sham	life	156
22					sacrifice	42
23				250	life	156
24					sacrifice	42
					Total	2736

105.36 Effects of Combined Single-Inhalation Exposure to Plutonium-239 Dioxide Aerosol and Multiple Injections of a Chemical Carcinogen (NNK) in F344 Rats

Institution: Inhalation Toxicology Research Institute

Scientists: Lundgren, David L; active
Belinsky, Steven A; active
Griffith, William W; active
Hoover, M.D.; active.

Purpose: Characterize the lifetime effects of combined exposure of rats to 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and internally deposited plutonium, as well as to each agent alone. This study will provide information on whether combined exposure to these two agents is additive, synergistic, or antagonistic.

Status: This study is in-progress; materials are in active use at ITRI

Treatment: Subcutaneous injections of NNK (3/w for 20 w) began when the rats were 6 w old, and Pu-239 dioxide exposures were given at 12 w of age.

Endpoints: Survival times and patterns, lung histopathology and time to tumor occurrence.

Animal: 740 specific pathogen-free male CDF®(F344)/CrlBR (Charles River Laboratory) rats in 7 groups.

Results: No significant difference in survival times among groups of rats exposed to plutonium with or without exposure to NNK. The median survival of NNK treated rats (with or without plutonium) was decreased by 8 to 15% relative to controls. The tentative conclusion is that exposure to NNK in combination with inhaled plutonium acts in, at best, an additive manner in inducing lung cancer in rats.

References: ITRI Annual Reports: 1991-92, pp. 118-120; 1992-93, pp. 56-57; 1993-1994 pp. 74-76; 1994-95, pp. 80-83.

Experimental Groups:

Study 105.36
Effects of Combined Single-Inhalation Exposure to Plutonium-239 Dioxide Aerosol and Multiple Injections of a Chemical Carcinogen (NNK) in F344 Rats

Group Id	^{239}Pu Initial Burden (Bq)	NNK (mg/kg)	Number of ♂ Rats	Median Survival Time (d)
01	Sham	Sham	100	722
02	480 ± 70	Sham	140	650
03	Sham	0.3	110	667
04	470 ± 68	0.3	150	658
05	Sham	1.0	80	624
06	460 ± 76	1.0	120	615
07	None	50	40	281
		Total	740	

106 Ernst O. Lawrence Berkeley Laboratory (LBL)

106.01 Colony Control Rhesus Monkeys

Institution: Lawrence Berkeley Laboratory, Berkeley, CA

Scientists: Patricia W Durbin; active

Purpose: Provide control metabolic and distribution information.

Status: These monkeys were maintained at LBL between 1954 and 1970, and serve as controls for studies 106.01 and 106.02. Data from this study is stored at the NRA as a sequestered collection, pending release by the principle investigator.

Treatment: No radionuclide was injected; excreta collection, necropsy, and sample preparation identical to 106.01 and 106.02.

Dosimetry: Various beta particle detectors were employed over the 30 course of this study, ranging from a Geiger-Muller tube with a background of about 60 cpm to continuous gas flow or coincidence shielded detectors with a background around 1.5 cpm. Photon detectors included a well scintillator, a dual-crystal system, and a large crystal whole body counter in an iron-shielded room.

Endpoints: Excreta was collected and analyzed to estimate radionuclide kinetics. Animals were periodically whole-body counted. At necropsy, all bones and tissues were collected and exhaustively analyzed.

Animal: 54 Rhesus monkeys, (Macaca mulatta).

Results:

References: A comprehensive peer-reviewed summary document is in preparation. LBL technical reports *Collected original data on distribution of 90-strontium in bones of monkeys*, LBL-28649, March 1993, and *Collected original data on distribution of 90-strontium in plasma, whole body, and excreta of monkeys*, LBL-28652, March 1993, are stored at the NRA.

Experimental Groups:

Study 106.01
Colony Control Rhesus Monkeys

Group Id	Treatment	Number of Monkeys
01	Control	54

106.02 Distribution and Kinetics: Strontium-90 in Rhesus Monkeys

Institution: Lawrence Berkeley Laboratory, Berkeley CA

Scientists: Patricia W Durbin; active

Purpose: This project is part of the ongoing effort to provide accurate internal dosimetry to protect human beings from the harmful effects of internally deposited radionuclides. Strontium-90 is the most biologically important component of world-wide fallout from detonation of fusion weapons in the atmosphere; it is environmentally mobile, and metabolically analogous to calcium.

Status: Studies of strontium-90 metabolism were conducted at LBL between 1954 and 1970. Similar studies were conducted at the University of Rochester (UR) between 1954 and 1963; information from the UR studies was transferred to LBL. Data from this study is stored at the NRA as a sequestered collection, pending release by the principle investigator.

Treatment: Animals were injected with 1 to 5 ml of strontium citrate solution containing from 1.5 to 3.7 MBq/ml of strontium-90. Most of the injections were intravenous, although some were intramusclear or intraperitoneal. Ten monkeys were fed the strontium. Eighteen infants received the strontium from a female by placental transfer, milk, or both. Treated animals and followed for periods ranging from 1 to 7000 d.

Dosimetry: Various beta particle detectors were employed over the 30 course of this study, ranging from a Geiger-Muller tube with a background of about 60 cpm to continuous gas flow or coincidence shielded detectors with a background around 1.5 cpm. Photon detectors included a well scintillator, a dual-crystal system, and a large crystal whole body counter in an iron-shielded room.

Endpoints: Excreta was collected and analyzed to estimate Sr kinetics. Animals were periodically whole-body counted for Sr-90 bremsstrahlung activity. Some were injected with the short half-life gamma emitting tracer Sr-85. At necropsy, all bones and tissues were collected and exhaustively analyzed.

Animal: Strontium was given to 90 Rhesus monkeys, (Macaca mulatta).

Results:

References: A comprehensive peer-reviewed summary document is in preparation. LBL technical reports *Collected original data on distribution of 90-strontium in bones of monkeys*, LBL-28649, March 1993, and *Collected original data on distribution of 90-strontium in plasma, whole body, and excreta of monkeys*, LBL-28652, March 1993, are stored at the NRA.

Experimental Groups:

Study 106.02
Distribution and Kinetics of Strontium-90 in Rhesus Monkeys

Group Id	Age at injection	Number of Monkeys
01	Maternal transfer to Infant	18
02	Immature	14
03	Adolescent	19
04	Adult	39
	Total	90

106.03 Distribution and Kinetics: Actinides in Monkeys

Institution: Lawrence Berkeley Laboratory, Berkeley CA

Scientists: Patricia W Durbin; active

Purpose: Determine the initial distribution and define retention of selected actinides in primates.

Status: Monkeys were injected with americium between 1960 and 1982, or with plutonium between 1973 and 1979. All long term animals were killed in 1980. Detailed information and descriptions of methods are on file at the NRA as a sequestered collection pending release by the principle investigator.

Treatment: Most animals were given intravenous or intramuscular injections of about 11 kBq/kg, a quantity sufficient for easy detection in excreta and tissues, but which was not expected to alter metabolism significantly. (The initial series of americium animals received 16-32 kBq/kg, therefore 4 monkeys were given 0.3 kBq/kg in 1982 to evaluate possible radiation damage and take advantage of improved detection techniques.)

Dosimetry: Plutonium was analyzed by detection of uranium 234 X-rays.

Endpoints: Materials balance, distribution in body at death.

Animal: Macaque monkeys (3 species, both sexes, various ages) were employed in this study. Neptunium was given to 1, plutonium to 28, and americium to 30.

Results: Neptunium - Retention (4 d, 1 animal), 40% excretion via urine.

Plutonium - Retention (1 w) and distribution (2 y) were, respectively, 28 and 14% in bones and teeth, 60 and 11% in liver, 6 and 1% in other soft tissues. Clearance half time was about .5 y in liver and 3 y in bone. Initial Pu concentration was about 4.5 times greater on trabecular bone surfaces than in red marrow.

References: Comprehensive peer-reviewed summary documents are in preparation. LBL technical reports containing collected original data on distribution of these actinides in bone, plasma, whole body, and excreta of monkeys are stored at the NRA.

Experimental Groups:

Study 106.03
Distribution and Kinetics of Actinides in Monkeys

Group Id	Nuclide	Age at Injection	Number of Macaques		
			Rhesus	Cynomolgus	Stumptail
01	^{237}Np	Adult		1	
02	^{237}Pu	Adult		1	
03	^{238}Pu	Immature	4	1	
04	^{238}Pu	Adult	6	14	2
05	^{241}Am	Immature		3	
06	^{241}Am	Adult	2	25	
		Total	12	45	2

107 Oak Ridge National Laboratory (ORNL)

107.01 Survival and Carcinogenesis: Low-Dose Gamma-Irradiation of Female BALB/cBd and RFM/Bd Mice

Institution: Oak Ridge National Laboratory, Oak Ridge TN

Scientists: Ullrich, Robert L; relocated to University of Texas
Storer, John B; retired
Fry, R J Michael; retired
Upton, Art C; retired

Status: Exposure of animals in 1977, analysis complete; information transferred to the NRA in 1991.

Purpose: To study carcinogenesis and survival in two strains of mice exposed at different dose rates.

Treatment: BALB/cBd and RFM/Bd female mice were exposed to a 74 TBq cesium-137 source to obtain 0, 0.5, or 2.0 Gy at 4.0 Gy/min.

Dosimetry:

Endpoints: Survival, carcinogenesis

Animal: BALB/cBd and RFM/Bd female mice, age 10 w

Results:

References: J.B. Storer, T.J. Mitchell, and R.J.M. Fry. Extrapolation of the relative risk of radiogenic neoplasms across mouse strains and to man. *Radiation Research* **114**, pp. 331-353, 1988.

Experimental Groups:

Study 107.01
Survival and Carcinogenesis:
Low-Dose Gamma-Irradiation of Female BALB/cBd and RFM/Bd Mice

Group Id	Dose (Gy)	Number of ♀ Mice	Strain
01	0	833	BALB/cBd
02	0.5	834	
03	2.0	809	
04	0	745	RFM/Bd
05	0.5	748	
06	2.0	759	
Total		4728	

107.02 Survival and Carcinogenesis: Low-Dose Gamma-Irradiation of C3Hf/Bd and C57BL/6Bd Mice

Institution: Oak Ridge National Laboratory, Oak Ridge TN

Scientists: Ullrich, Robert L; relocated to University of Texas
Storer, John B; retired
Fry, R J Michael; retired
Upton, Art C; retired

Purpose: To study carcinogenesis and survival in two strains of mice exposed at different dose rates.

Status: Exposure of animals in 1987, analysis complete; information transferred to the NRA in 1991.

Treatment: C3Hf/Bd and C57BL/6Bd male and female mice were exposed to a 74 TBq cesium-137 source to obtain 0, 0.5, 1.0 or 2.0 Gy at 4.0 Gy/min.

Dosimetry:

Endpoints: Survival, carcinogenesis

Animal: C3Hf/Bd and C57BL/6Bd male and female mice, age 10 w

Results:

References: J.B. Storer, T.J. Mitchell, and R.J.M. Fry. Extrapolation of the relative risk of radiogenic neoplasms across mouse strains and to man. *Radiation Research* **114**:331-353, 1988.

Experimental Groups:

Study 107.02
Survival and Carcinogenesis:
Low-Dose Gamma-Irradiation of C3Hf/Bd and C57BL/6Bd Mice

Group Id	Dose (Gy)	Number of Mice		Strain
		Female	Male	
01, 02	0	495	502	C57BL/6
03, 04	0.5	253	254	
05, 06	1.0	251	260	
07, 08	2.0	255	259	
09, 10	0	503	502	C3Hf/Bd
11, 12	0.5	251	244	
13, 14	1.0	250	249	
15, 16	2.0	258	252	
Total		2516	2522	

107.03 Survival and Carcinogenesis: Low-Dose Gamma-Irradiation of RFM Mice

Institution: Oak Ridge National Laboratory, Oak Ridge TN

Scientists: Ullrich, Robert L; relocated to University of Texas
Storer, John B; retired
Upton, Art C; retired

Purpose: To study carcinogenesis and survival in mice exposed at different dose rates.

Status: Exposure of animals prior to 1979, analysis complete; information transferred to the NRA in 1991.

Treatment: Specific-pathogen-free RFM f/Un mice (10 + or - 0.5 w old) were exposed in rotating individual plastic tubes to a 74 TBq Cs-137 source at a distance of 45 cm and a dose rate of 0.45 Gy/min.

Dosimetry:

Endpoints: Survival, carcinogenesis. Cages were checked twice daily (5 d/w) for dead or moribund animals; these were removed and autopsied and tissues taken for histologic examination. Using this routine an average of 97% of the animals in this study were subjected to autopsy. Methods of examination and criteria for diagnosis of the various forms of tissue neoplasms in the RFM mouse have been described by Clapp (An Atlas of the RF Mouse Pathology: Disease Descriptions and Incidences, TID-26373). As noted by Clapp, the reticulum cell sarcoma classification includes several forms based on cellular appearance. No attempt was made in this study to quantitatively examine these subtypes or their variation with dose.

Animal: Specific-pathogen-free RFM f/Un mice (10 + or - 0.5 w old)

Results:

References:

Ullrich, R. L. and J.B. Storer. Influence of gamma irradiation on the development of neoplastic disease in mice I. Reticular tissue tumors. *Radiation Research* **80**:303-316, 1979.

Ullrich, R. L. and J.B. Storer. Influence of gamma irradiation on the development of neoplastic disease in mice II. Solid tumors. *Radiation Research* **80**:317-324, 1979.

Ullrich, R. L. and J.B. Storer. Influence of gamma irradiation on the development of neoplastic disease in mice III. Dose-rate effects. *Radiation Research* **80**:325-342, 1979.

Detailed information on the animals, their maintenance, and the irradiation factors and procedures will be found in:

A.C. Upton et. al. Quantative experimental study of low-level radiation carcinogenesis. in *Radiation-Induced Cancer*, pp 425-438, International Atomic Energy Agency, Vienna, 1969.

L.J. Serrano. Defined mice in a radiobiological experiment. in *Defining the Laboratory Animal*, pp 13-43. National Academy of Sciences, Washington DC, 1971.

Experimental Groups:

Study 107.03
Survival and Carcinogenesis:
Low-Dose Gamma-Irradiation of RFM Mice

Group Id	Dose (Gy)	Number of Mice		
		Serial Sacrifice	Life Span	
		Female	Female	Male
18, 08, 01	0	457	4013	430
09, 02	0.1		2827	256
10, 03	0.25		964	94
11, 04	0.50		1143	247
12	0.75		246	
13, 05	1		1100	230
14, 06	1.5		1043	199
15	2		333	
19, 16, 07	3	517	4133	571
17	4		396	
Total		974	16198	2017

108 CETT/CRHL Colorado State University (CSU)

108.01 Effects of Single-Exposure Gamma-Irradiation: Baseline Study in Immature Beagles

Institution: Colorado State University (CSU), Fort Collins CO

Scientists: Stephen Benjamin; active

Purpose: The overall objectives of the study are to examine the long-term effects on the beagle dog of a single whole body exposure given at different periods of development and, using these effects as criteria, to determine the relative radiosensitivity at these periods. The study, in fact, represents part of an overall study designed to permit inference of both the short-term and long-term risk to human beings exposed to diagnostic radiation during pre-natal life.

Status: This study was initiated in 1964; it is complete, animal numbers for colony characterization purposes only available at NRA; no other detailed information

Study 108.01, known at CSU as "Long-Term Study, Segment I", was a baseline, or pilot , supporting study to characterize prenatal development and short-term prenatal radiosensivity.

Treatment: Bilateral exposure to cobalt-60 gamma radiation; constant exposure time of 10 min; all but abdomen shielded in pregnant bitches.

Dosimetry: Mid-line in-air exposure was measured using thermoluminsecent dosimeters and thimble chambers at selected distances from the AECL Gamma Beam 150 C 185 Tbq cobalt-60 source and recorded in roentgens (R). Doses were cross checked by computations based on source strength decay and position in the room. The range of exposure rates was between 70 R/min to 850 mR/min. The mid-line in-air exposures were converted to mid-line in-tissue exposures based on dosimetric studies in various sized phantoms or cadavers.

Endpoints: Extensive assessment of: (1) growth, development, and aging, (2) hyperplastic and neoplastic disorders, (3) degenerative changes, morbidity and mortality, and (4) reproduction.

Animal: Colony raised beagle dogs of both sexes. (Experimental animals were taken from the fourth and succeeding generation of animals produced within the barrier-maintained colony.)

Results:

References:

Experimental Groups: not available

108.02 Effects of Single-Exposure Gamma-Irradiation: Age Sensitivity Study in Immature (Fetal to 2-Day-Old) Beagles

Institution: Colorado State University (CSU), Fort Collins CO

Scientists: Stephen Benjamin; active

Purpose: The overall objectives of the study are to examine the long-term effects on the beagle dog of a single whole body exposure given at different periods of development and, using these effects as criteria, to determine the relative radiosensitivity at these periods. The study, in fact, represents part of an overall study designed to permit inference of both the short-term and long-term risk to human beings exposed to diagnostic radiation during pre-natal life.

Study 108.02, known at CSU as "Long-Term Study, Segment II", had dual objectives: (1) to determine the relative radiosensivity and (2) to examine delayed effects within a few y following exposure. Ages at exposure were: 8, 28, or 55 d post coitus, or 2 d post partum; exposures from 180 R to 435 R bracketed the LD-50.

Status: This study was initiated in 1964; it is complete, animal numbers for colony characterization purposes only available at NRA; no other detailed information

Treatment: Bilateral exposure to cobalt-60 gamma radiation; constant exposure time of 10 min; all but abdomen shielded in pregnant bitches.

Dosimetry: Mid-line in-air exposure was measured using thermoluminsecent dosimeters and thimble chambers at selected distances from the AECL Gamma Beam 150 C 185 TBq cobalt-60 source and recorded in roentgens (R). Doses were cross checked by computations based on source strength decay and position in the room. The range of exposure rates was between 70 R/min to 850 mR/min. The mid-line in-air exposures were converted to mid-line in-tissue exposures based on dosimetric studies in various sized phantoms or cadavers.

Endpoints: Survival, modest assessment of: (1) growth, development, and aging, (2) hyperplastic and neoplastic disorders, and (3) degenerative changes, morbidity and mortality.

Animal: Colony raised beagle dogs of both sexes. (Experimental animals were taken from the fourth and succeeding generation of animals produced within the barrier-maintained colony.)

Results:

References:

Experimental Groups:

Study 108.02
Effects of Single-Exposure Gamma-Irradiation: Age Sensitivity Study in Immature (Fetal to 2-Day-Old) Beagles

Group Id	Age at Exposure	Exposure Range (R)	Number of Dogs
01	control	0	64
02	8 d postcoitus	180-270	61
03	28 d postcoitus	125-270	65
04	55 d postcoitus	220-330	59
05	2 d postpartum	330-435	81
		Total	330

108.03 Life-Span Health Risks: Single-Exposure Gamma-Irradiation in Immature (Fetal to 1-Year-Old) Beagles

Institution: Colorado State University (CSU), Fort Collins CO

Scientists: Stephen Benjamin; active

Purpose: The overall objectives of the study are to examine the long-term effects on the beagle dog of a single whole body exposure given at different periods of development and, using these effects as criteria, to determine the relative radiosensitivity at these periods. The study, in fact, represents part of an overall study designed to permit inference of both the short-term and long-term risk to human beings exposed to diagnostic radiation during pre-natal life.

Study 108.03, known at CSU as "Long-Term Study, Segment III", is the principle experiment of the CSU program to characterize prenatal development and short-term prenatal radiosensitivity of the Beagle.

Status: Animals were exposed between 1967 and 1972, and the last dog died in 1989. The study is complete and results have been published. Detailed information is available through the NRA.

Treatment: Bilateral exposure to cobalt-60 gamma radiation; constant exposure time of 10 min; all but abdomen shielded in pregnant bitches. Dogs were given exposures at 8 (preimplantation), 28 (embryonic), or 55 (fetal) d postcoitus (dpc) or at 2 (neonatal), 70 (juvenile), or 365 (young adult) d postpartum (dpp). There were 360 sham-irradiated controls. Exposures were 0, 20 or 100 R (group averages absorbed dose of 0, 16, or 83 cGy) at 8, 28, or 55 d post coitus or 2, 70 or 365 d postpartum. Each level included sacrifice animals on schedule at 5, 8, 11, or 14 y of age.

Dosimetry: Mid-line in-air exposure was measured using thermoluminsecent dosimeters and thimble chambers at selected distances from the AECL Gamma Beam 150 C 185 TBq cobalt-60 source and recorded in roentgens (R). Doses were cross checked by computations based on source strength decay and position in the room. The range of exposure rates was between 70 R/min to 850 mR/min. The mid-line in-air exposures were converted to mid-line in-tissue exposures based on dosimetric studies in various sized phantoms or cadavers.

Endpoints: Extensive assessment of: (1) growth, development, and aging, (2) hyperplastic and neoplastic disorders, (3) degenerative changes, morbidity and mortality, and (4) reproduction.

All dogs were given regular clinical examinations on at least an annual basis and more frequently if there was illness. Clinical, hematologic, and blood chemical data were collected at least annually. All dogs that died or were euthanized were given a complete gross and microscopic necropsy examination. For each dog, a determination was made as to the primary cause of death, as well as for any major or principal diseases that may have contributed to the dog's death. Also, any lesions suspected of being neoplasms were evaluated. All of the above information was recorded in a computerized data base. This report addresses primarily questions concerning life-shortening and mortality related to both neoplastic and non-neoplastic disease. Fatal and non-fatal thyroid disease, both neoplastic and non-neoplastic in nature, is also addressed.

Animal: 1680 Colony-raised beagle dogs of both sexes in 32 groups. (Experimental animals were taken from the fourth and succeeding generation of animals produced within the barrier-maintained colony.)

Results: **Prenatal and early postnatal mortality:** Increased embryonic mortality, decrease in the percentage of females pups, and increased in neonatal mortality with excess mortality in females. **Life-shortening:** no significant overall effect, but mean age to death for fetally-irradiated females was reduced. Mean life-span in both male and female beagles that were irradiated at 55 dpc and that died because of neoplasia was significantly reduced. **Cause of Death in order of frequency:** neoplasia, inflammatory diseases, chronic renal disease, hypothyroidism, cardiac failure, idiopathic convulsive seizures, thrombosis and infarction, intervertebral disk degeneration, and diabetes mellitus. **Cause of Death**

related to irradiation: neoplasia, chronic renal disease, and diabetes mellitus (possibly genetic trait of this colony). Neoplasia pattern was consistent with epidemiologic studies in humans.

References:

R.E. Albert, S.A.Benjamin and R. Shukla. Life span and cancer mortality in the Beagle dog and humans. *Mechanisms of Ageing and Development* **74** 149-159, 1994.

G.M. Angleton, S.A. Benjamin, and A.C. Lee. Health effects of low-level irradiation during development: experimental design and prenatal and early neonatal mortality in beagles exposed to cobalt-60 gamma rays. *Radiation Research* **115** 70-83, 1988.

S.A. Benjamin, W.J. Saunders, G.M. Angleton and A.C. Lee.Radiation carcinogenesis in dogs during prenatal and postnatal development. *Radiation Research Supplement* **2** 86-103, 1991.

S.A. Benjamin, A.C. Lee, G.M. Angleton, W.J. Saunders, G.K. Miller, J.S. Williams, R.D. Brewster, and R.I. Long. Neoplasms in young dogs after perinatal irradiation. *J Natl Cancer Inst* **77**: 563-57., 1986.

Experimental Groups:

Study 108.03

Life-Span Health Risks: Single-Exposure Gamma-Irradiation in Immature (Fetal to 1-Year-old) Beagles

Group Id	Age at Exposure	Exposure (R)	Absorbed Dose (mGy)	Designation	Number of Dogs
01	8 d post coitus	0	0	life span	46
02	8 d post coitus	0	0	sacrifice	14
03	28 d post coitus	0	0	life span	46
04	28 d post coitus	0	0	sacrifice	14
05	55 d post coitus	0	0	life span	46
06	55 d post coitus	0	0	sacrifice	14
07	2 d postpartum	0	0	life span	46
08	2 d postpartum	0	0	sacrifice	14
09	70 d postpartum	0	0	life span	46
10	70 d postpartum	0	0	sacrifice	14
11	365 d postpartum	0	0	life span	46
12	365 d postpartum	0	0	sacrifice	14
13	8 d post coitus	20	160	life span	98
14	8 d post coitus	20	160	sacrifice	22
15	28 d post coitus	20	160	life span	98
16	28 d post coitus	20	160	sacrifice	22
17	55 d post coitus	20	160	life span	97
18	55 d post coitus	20	160	sacrifice	23
19	2 d postpartum	20	160	life span	98
20	2 d postpartum	20	160	sacrifice	22
21	8 d post coitus	100	830	life span	98
22	8 d post coitus	100	830	sacrifice	22
23	28 d post coitus	100	830	life span	98
24	28 d post coitus	100	830	sacrifice	22
25	55 d post coitus	100	830	life span	96
26	55 d post coitus	100	830	sacrifice	24
27	2 d post partum	100	830	life span	97
28	2 d post partum	100	830	sacrifice	23
29	70 d post partum	100	830	life span	96
30	70 d post partum	100	830	sacrifice	24
31	365 d post partum	100	830	life span	191
32	365 d post partum	100	830	sacrifice	49
				Total	1680

109 Brookhaven National Laboratory (BNL)

109.01 Leukemogenesis: Exposure to Low Doses of X- or Gamma-Irradiation in CBA/Ca or C57/BL Male Mice

Institution: Brookhaven National Laboratory (BNL), Upton NY

Scientists: Cronkite, Eugene P; active

Purpose: The purpose of this study is to ascertain the parameter "alpha" of the linear quadratic dose response curve and to ascertain the dose effect curve for the induction of leukemia and other neoplasms. Different strains of mice were irradiated with single, repeated doses and with a wide range of dose rates to determine: 1) the incidence of leukemia at low average dose and dose rates, 2) the presence of preleukemic cells in the mice as a function of total dose and dose rate; 3) the number of preleukemic cells initiated by radiation; 4) the relative degree of "repair" following single, repeated, and continuous exposure; and 5) if there remains a fraction of the effects of low LET radiation that is nonrepairable, or comparable to the "single hit" damage and effects seen with high LET radiation.

Status: The exposures started in 1982 and were completed in 1987. Data available: gross autopsy and histological diagnosis in electronic form. Materials available: lab books, paraffin blocks, stained tissue sections.

Treatment: 250 kVp X-rays (0.5 mm Cu & 1.0 mm Al filter) or Cs-137 source. Some groups were exposed to X-rays at 250 kVp with 0.5 mm of Cu and 1.0 mm of Al filtration. Other groups were exposed to gamma rays from a Cs-137 source. The mode and fractionation is described in detail in each group identification record.

Dosimetry: Victoreen r-meters, checked by TLDs.

Endpoints: survival time, incidence of neoplasia, and CFU-S assay of bone marrow.

Animal: The mice were C57B1/6 and CBA/Ca males, bred and maintained at BNL. Stock was originally obtained from Jackson Lab.

Results:

References:

Experimental Groups:

Study 109.01

Leukemogenesis: Exposure to Low Doses of X- or Gamma-Irradiation in CBA/Ca or C57/BL Male Mice

C57BL/6 Mice

Group Id	Radiation Source	Exposure Rate (R/min)	Exposure Regimen	Exposure (R)	Age at first Exposure (mo)	Number of Mice
01	Shelf Control					333
02	X	175	3 X 8 d interval	525	2	70
03		525	single			70
04		5.25	5/wk X 20 wk			120
05	Gamma	5.25 in 22 h	5/wk X 20 wk			135
					Total	728

CBA/Ca Mice

Group Id	Radiation Source	Exposure Rate (R/min)	Exposure Regimen	Exposure (R)	Age at first Exposure (mo)	Number of Mice
06	Shelf Controls					319
07	X	0.5	3/wk X 33 wk	50	4	141
08		1		100	4	140
09		2		200	4	140
10		3		300	4	140[4]
11		2			4	151
12		1			4	150
13		100	single		4	100
14					5	77
15					9	131
16				200	4	99
17					9	129
18				100	4	101
19					9	130
20				50	4	95
21					9	120
22	Satellite control CBA/Ca (33 or 50 w in gamma exposure facility)					130
23	Gamma	1.2 in 22 h	5/w	300	4	120
24	Gamma	1.2 in 22 h				120
					Total	2533

109.02 Leukemogenesis Neutron Exposure of CBA/Ca Male Mice

Institution: Brookhaven National Laboratory (BNL), Upton NY

Scientists: Bond, Victor, P; active

Purpose: Mice will be exposed to several relatively small doses from four different "monoenergetic" fast neutron beams at the RARAF facility, to obtain quantitative microdosimetric data and the incidence of acute myeloblastic leukemia (AML). The objective is not additional RBE values, but rather to develop, for leukemia, a new relationship termed the "hit size effectiveness function" (HSEF). This S-shaped function provides the probability of malignant cell change and leukemia vs. the amount of energy transfer or "hit size" per cell. With this function on can, in principle, with low-level exposure (LLE) to radiation, provide directly the risk of cancer for an individual exposed to radiation of any one quality or admixture.

Status: In progress

110 University of Rochester (UR)

The landmark radiobiology studies conducted at the University of Rochester (UR) between 1943 and 1965 contributed significantly to our knowledge of the toxic effects of atomic age materials. These studies are not only interesting in themselves, they provide essential background for the understanding of the motivation and methodology of subsequent studies in other laboratories. Many of the scientists whose work is described elsewhere in this document received their training at Rochester.

In 1992, Dr. J. Newell Stannard, retired UR dean of graduate studies, and former chief of the section on radiation toxicology and the section on radioactive inhalation of the UR Atomic Energy Project, visited UR in search of detailed experimental records, tissue preparations, and other materials to transfer to the NRA. He was too late. After the termination of the AEC contract, there was little incentive for campus authorities to expend funds for the preservation of these materials. Eventually, the project buildings were razed to make room for expansion of the medical school, and the radiobiology research records were discarded.

In addition to open literature publication, the Rochester studies were reported extensively in limited distribution technical reports, know as the UR series of government documents. Many of these reports cover details of studies, such as tabulation of hundreds of animals, which were not suitable for open literature summary papers. A complete collection of these is available at the NRA along with a collection of all open literature publications.

Dr. Stannard prepared a summary of 51 significant studies of internal emitters which, for convenience, have been compiled under a few headings below. The original study number given by Dr Stannard is indicated as [##] for reference purposes.

110.01 Studies on the Metabolism of Polonium in Relation to Other Toxic Radionuclides

Institution: University of Rochester (UR), Rochester NY

Scientists: A very large number of scientists participated over more than 30 years in these studies. Rather than attempting to list them all, a few prominent names are given as an aid to literature review. Scientists associated with polonium research at Rochester included William Bale, Robert Fink and later, John Hursh, Newell Stannard, and George Casarett.

Purpose: To develop a global understanding of the risks of polonium-210 based on physicochemical, metabolic, tissue distribution, toxicological and pathological studies and to compare these risks with those of Sr-90, Ra-226 and Pu-239

Treatment: *Physicochemical and metabolic studies*

a) Po solutions added to biological molecules [25];
b) Single exposure of IV, oral, subcutaneous or volatilized (inhaled) polonium chloride (37-1110 kBq/animal) at neutral pH. Observations for 308 d in a pilot experiment[1];
c) Short term study comparing Po given by gavage, IV injections in tail vein as a single dose; sacrifice on a defined schedule over a period of 70 d [26];
d) Long term study after IV injection of polonium-210. Observations over a period of 500 d [27];
e) Multiple (monthly IV injections over the entire life span) vs single IV dose; observations over life span, about 900 d [28];

f) Instillation into the trachea through a surgical incision in the trachea with observations up to a period of 60 d [30];
g) Instillation into the trachea of a colloidal Po-210 solution with observations up to a period of 60 d [31];
h) Inhalation in an inhalation chamber with observations up to a period of 60 d [32];
i) Nose only exposure in an inhalation chamber with observations up to a period of 30 d [33];
j) Injection of Po-210 to different species including man (study performed 1943-1955) [34];
k) Oral or IV administration of Ra-226 chloride (0.481- 37 MBq/animal) with observations of excreta up to 280 d and of tissues to 300 d to serve as comparison with the behavior of actinides [2];

Radioautographic analysis of tissue distribution

l) Intratracheal instillation or inhalation of unaggregated Po or Po colloids to rabbits; observations up to a period of 30 d [35];
m) Inhalation of Po aerosols in an inhalation chamber; observations up to a period of 30 d [36];
n) Oral or IV administration of Po-210 to the rat, injection into a stomach pouch or intestinal loop in the cat with autoradiography of tissues for a period up to 20 d [29].

Dosimetry:
a) Analysis of administered solution.
b-y) Some supplementary information on the basis of measuring recovery of Po in tissues.
h,i) Determination of aerosol size and activity and of amounts retained in body
t) Determination of Bremsstrahlung of Sr-90 to measure body burden in addition to radiochemical analysis of tissues

Endpoints:
a) Solubility behavior, binding of Po to biological molecules;
b-k) Body, tissue content, redistribution among tissues, urinary and fecal excretion as a function of time.
i) Additionally emphasis on measurements of deposition in upper/lower respiratory tract and lung clearance;
l-n) Autoradiography of lung and other tissues;

Animal:
a) *In vitro* study;
b-k) Rats mostly of the Wistar strain
m-n) Rats mostly of the Wistar strain
l) Albino rabbits;
j) Additionally other species including man;
m) Additionally cats.

Results: The studies helped to obtain comparative data on metabolism, toxic effects and risks from Po-210 in comparison with those from other, already better known, radionuclides (Ra-226) at a time when an assessment of such risks was critically needed in the atomic energy project. With respect to metabolism, it was found among others that (e) a significant difference in metabolism exists between animals receiving a single dose and those where the body burden was maintained. (j) Substantial differences in metabolism exist between species.

References:
Fink, R.M. *Biological studies with polonium, radium, and plutonium*. National Nuclear Energy Series, div. VI, vol 3. New York-Toronto-London: McGraw-Hill, 1950.

Stannard, J.N. and G.W. Casarett, eds. Metabolism and biological effects of an alpha particle emitter, polonium-210. *Radiation Research* Supplement 5, 1964.

d) *The Long Term Retention and Distribution of Polonium- 210 in the Rat*, UR-393, 6/16/55 (27)

j) *Species Differences in the Metabolism of Polonium-210*, UR-487, 5/16/57

l) *Analytical and Autoradiographic Methods for Polonium- 210*, UR-305, 11/4/55

m) *Autoradiographic Observations Following the Inhalation of Polonium-210 in Rats*, UR-557, TID-4500. (15th Ed.), 10/14/59

Autoradiographic Study of Lung Clearance and Distribution of Polonium-210 After Intratracheal Injection, UR-540, TID-4500, (14th Ed.), 2/18/59.

Autoradiographic Study of Effects of Route of Administration on Distribution of Polonium-210, UR-447, 5/28/56

Analytical and Autoradiographic Methods for Polonium- 210, UR-305, 11/4/55

110.02 Studies on the Toxicity of Polonium in Relation to Other Toxic Radionuclides

Institution: University of Rochester (UR), Rochester NY

Scientists: A very large number of scientists participated over more than 30 years in these studies. Rather than attempting to list them all, a few prominent names are given as an aid to literature review. Scientists associated with polonium research at Rochester included William Bale, Robert Fink and later, John Hursh, Newell Stannard, and George Casarett.

Purpose: To develop a global understanding of the risks of polonium-210 based on physicochemical, metabolic, tissue distribution, toxicological and pathological studies and to compare these risks with those of Sr-90, Ra-226 and Pu-239

Treatment: *Toxicological studies*

a) Acutely toxic doses of Po given by oral, IV or IP administration; observations over a period of 200 d [37];
b) Single doses or monthly injections of Po-210 or Sr-89 with life span follow up to 149 w [39]
c) Single IV injection of Po-210, Ra-226 or Pu-239 (neutral solutions) for a comparative pilot study of acute and subchronic toxicity [3];
d) Single IV injection of Po-210, Ra-226 or Pu-239 (neutral solutions) for a comparative life span study of toxicity [4];
e) Comparative evaluation of earlier studies on life span shortening after application of Po-210, Ra-226 and Pu-239 [38]
f) Feeding daily carrier-free Sr-90 (in equilibrium with Y-90) to rats or monkeys during a period of 10-30 d [24]

Pathological-physiological studies

g) Polonium given by gavage to produce an absorbed dose of 925 kBq/kg, comparison with an IV application of 962 kBq/kg; observations performed up to 122 d [43];
h) Single IV injection of Po-210 (37, 185, 370 or 740 kBq/kg; total 209 rats) with serial sacrifice for the study of acute toxic consequence [40];
i) Single IV injection of Po-210 (37, 185, 370 or 740 kBq/kg) with blood samples taken at necropsy and observations continuing up to 22 months; special measurements performed for 740 kBq/kg group [41];
j) Multiple IV injections of Po-210 (0.85 -55 kBq /kg as five groups, total 483 animals) with some animals studied up to 22 months [42];
k) Single IV injection of 370 kBq/kg; observations on continued for 1 year [44];
l) Injection of an about 50% lethal dose of Po-210 (270 kBq); measurement of reticulo-endothelial functions (uptake, clearance) of injected, P-32 labelled chromic phosphate in spleen and liver for up to 23 d.

Dosimetry: Analysis of administered solution.
- b-l) Some supplementary information on the basis of measuring recovery of Po in tissues;
- f) Determination of Bremsstrahlung of Sr-90 to measure body burden in addition to radiochemical analysis of tissues.

Endpoints:
- a) Mortality, life span, tissue content at time of death ;
- b) Growth rate, survival time, computation of life-span shortening as a fraction of dose, comparison between sexes, comparison with the effects of Sr-89;
- c,d,e) Life span, survival ratio, pathology, some hematology;
- f) General health and osteosarcoma incidence, gross and microscopic pathology;
- i) Analysis of blood samples at necropsy for all formed elements plus hemoglobin concentration;
- g,h,j) Study of neoplastic and non-neoplastic changes in all important tissues and organs;
- k) Measurement of blood pressure, cataractogenesis with the slit lamp, kidney function;
- l) Uptake of chromic P-32 phosphate by spleen and liver, half times of blood clearance, mean organ weights;

Animal:
- a-l) Rats mostly of the Wistar strain
- f, h) Long Evans rats;
- b, e) Additionally CF1 mice;
- f) Additionally, Rhesus monkeys, (Macaca mulatta), which were transferred to LBL (see study 106.02) after the closure of the facilities in 1963.

Results: With regard to toxicity of polonium-210, the studies yielded an acute LD50 (about 270 kBq/rat) and a determination of the shortening of survival in relation to dose and route of application. (e)The results confirmed that alpha-emitters produce a much higher fraction of irreparable injury that radionuclides emitting low LET radiation. (a) Despite considerable differences in tissue distribution related to the route of entry, acute toxicity was about the same regardless of the way of application. This could be interpreted that acute toxic effects are determined by the Po content of the entire body, or that the non-aggregated material whose distribution is less dependent on the route of entry determines toxicity. (b) A maintained body burden of Po-210 did not result in greater injury than a single application since the injury was not reparable for either mode. (g) Pathological changes differed between animals receiving Po-210 orally and those receiving it by IV injection. However, effects of mortality were similar and depended primarily on Po body burden. (I) Pathological changes also differed between animals which had received the same dose as a single IV injection from those where the body burden was maintained by multiple injections. (h) Widespread neoplasms were seen after an IV injection of 185-370 Bq/kg and hypertension was indicated by pathological changes in kidney. At higher doses survival was too short for these changes to develop. (j) Rats treated with 370 kBq/kg showed increased blood pressure, hair depigmentation, cataract formation and a reduction in kidney function.

References:

Fink, R.M. *Biological studies with polonium, radium, and plutonium*. National Nuclear Energy Series, div. VI, vol 3. New York-Toronto-London: McGraw-Hill, 1950.

Stannard, J.N. and G.W. Casarett, eds. Metabolism and biological effects of an alpha particle emitter, polonium-210. *Radiation Research* Supplement 5, 1964.

a) *The Acute Toxicity and Retention of Orally Administered Polonium-210 in the Rat*, UR-392, 4/27/55. *The Acute Toxicity and Retention of Intratracheally Administered Polonium-210 in the Rat*, UR-431, 3/28/56.

R.J. Della Rosa and J.N. Stannard. *The Acute Toxicity and Retention of Intraperitoneally Administered Polonium-210 in the Rat*, UR-519, 2/28/58

b) *The Effects of a Maintained Body Burden of Polonium in Rats. I. Pilot Distribution and Excretion Experiment*, UR-329, 4/27/54.

The Effects of a Maintained Body Burden of Polonium in the Rat II. Plan of Long Term Experiment; Distribution, Excretion and Retention Data, UR-376, 1/4/55.

The Effects of a Maintained Body Burden of Polonium in the Rat. III. Mortality, Life Span, and Growth, UR-395, 6/16/55

f, h) Sproul, J.A., H.A. Blair, and R.C. Baxter. Some late physiological changes in rats after polonium-210 alpha particle irradiation. *Radiation Research*, Supplement , 1964.

g) *The Acute Toxicity and Retention of Orally Administered Polonium-210 in the Rat*, UR-392, 4/27/55

j) *The Effects of a Maintained Body Burden of Polonium in Rats. I. Pilot Distribution and Excretion Experiment*, UR-329, 4/27/54

The Effects of a Maintained Body Burden of Polonium in the Rat II. Plan of Long Term Experiment; Distribution, Excretion and Retention Data, UR-376, 1/4/55.

The Effects of a Maintained Body Burden of Polonium in the Rat. III. Mortality, Life Span, and Growth, UR-395, 6/16/55

110.03 Metabolism and Toxicity of Uranium

Institution: University of Rochester (UR), Rochester NY

Scientists: A very large number of scientists participated over more than 30 years in these studies. Rather than attempting to list them all, a few prominent names are given as an aid to literature review. Scientists generally associated with uranium research at Rochester included Harold Hodge, C. Voegtlin, and A. Tannenbaum, and those associated with individual studies included: f,g) L.J. Leach; k)T.V. Barnett, R.G. Metcalf.

Purpose: To develop a global approach to an understanding of the metabolism of uranium compounds under different conditions, of the toxicity of such compounds for different routes of application such as oral, parenteral, lung, skin and eye, to clarify the pathogenic mechanisms, especially for kidney and bone, and to develop guidelines for human exposure.

Treatment:

a) Single IV injection of various uranium compounds to determine tissue distribution and excretion [11];

b) IP injection of uranyl nitrate with studies of binding to bone structures, bone distribution and bone metabolism (via P-32) as a function of age[18];

c) IP injection of uranyl nitrate tetrahydrate as a baseline for a series of studies where uranium was added to the diet for periods of up to 2 y [14];

d) Feeding of different uranium compounds at concentrations of 0.5, 2 and 20% of diet [7];

e) IP or IF administration of different uranium compounds to several hundred rats studied over a period of 2 w [6];

f) Exposure of animals to uranium dust (0.05-20 mg/cubic meter) in inhalation chambers with an observation period, in general, of 30 d [10]

g) Chronic inhalation exposure in an aerosol chamber 6 h/d for 5 d/w for a maximum of 5 y. This was the largest, most extensive and most long-lasting of the Rochester internal emitter experiments [15];

h) Intratracheal insufflation thru a surgical incisions with observations for up to 40 d [16];

i) Topical application of uranium compounds (including uranium tetrafluoride to the skin) with observation periods up to 30 d [8];

j) Exposure of eyes of rabbits to various uranium compounds; also acute and chronic exposure of eyes of rabbits, guinea pigs and rats to uranium tetrafluoride [9]

k) Multiple inhalation, feeding, parenteral administration and application to skin of various uranium compounds [5];

l) Application via different routes of different uranium compounds to study acute toxicity, especially in kidney, with observation periods up to 8 days [13];
m) Single or repeated IV injections of uranyl nitrate hexahydrate with observations on clinical chemistry and metabolism up to a period of 40 d [17]
n) Single IP injection of soluble uranium (1/15 or 1/10 of lethal dose) followed by challenging doses to determine whether rats develop a tolerance towards uranium [12];

Dosimetry: a-e) Analysis of injection solution; spectrochemical analysis of U in tissues and excreta;
d) Analysis of uranium added to food;
f,g) Analysis and characterization of aerosols, analysis of tissues and excreta;
h) Analysis of injection solution; spectrochemical analysis of U in tissues and excreta;
i,j) Analysis of applied solution;
k-n) Analysis of injected solution

Endpoints: a) Determination of excretion over periods to 1,000 h (~42 d), tissue distribution
b) Incorporation of P-32 in function of age, effect of diet; autoradiography of deposition in bone, physico-chemical properties of U in bone, *in vitro* adsorption of U on bone, ion-exchange, ion-competition, surface chemistry, non-isotopic processes in rat femur;
c) Body weight, growth retardation, reproductive function, survival, testes changes, hematology, urinary excretion and urine chemistry, general tissue pathology;
d) Mortality
e) Mortality at 30 d, 1 y and 2 y; gross pathology and hematology, food consumption, body weight;
f) A large spectrum of parameters including survival, pathology, general health criteria, kidney function;
g) A large spectrum of parameters including survival, pathology, general health criteria, kidney function;
h) Chemical changes, lung clearance, U blood and tissue levels, mortality, body weight, urine volume and composition;
I) Mortality, body weight, uranium content of blood, local irritation, clinical changes, blood chemistry for time periods up to 30 d;
j) Inflammation, oedema, exudation and ulceration, especially of the cornea. Mortality, time for complete recovery. In the chronic study, also vascularization and cloudiness of the cornea;
k) Gross microscopy and pathology;
l) Pathological and clinical chemical tests for toxic effects on kidney;
m) Measurement of carbohydrate metabolism for a period up to 40 d.
n) Body weight, mortality, excretion and retention in kidney of U, excretion of citric acid and other biological functions in liver and kidney over a period of 78 d.

Animal: a-e) Wistar rat;
f) Rabbits, cats, rats, guinea pigs, mice and dogs
g) Wistar rats and some dogs;
h) Rabbits;
I) New Zealand rabbits (and other strains?), guinea pigs, Wistar rats, several strains of mice;
j) Rabbits (New Zealand?), guinea pigs, Wistar rats
k) Wistar rats, C3H mice;
l) Various animals, not specified;
m) Wistar rats, albino rabbits, dogs
n) Wistar rats

Results: The studies which at that time were crucial for the development of the atomic energy project yielded information on uptake, distribution and excretion of uranium compounds in the body, the mechanisms of binding to bone as a function of calcium exchange, behavior and clearance in lung, topical toxicity to skin and eye, toxic action on kidney.

References: A large amount of information can be found in the reports from the UR and, in particular, in the book *Radioactivity and Health - A History*, by J.N. Stannard, especially in Chapters 2 and 9. Several volumes of the National Nuclear Energy Series (i.e. Div. VI, pts I, II, III, IV and Div IV, vol 23) deal with uranium research at UR.

Morrow, P.E., F.R. Gibb, and L.J. Leach. The clearance of uranium dioxide dust from the lungs following single and multiple inhalation exposures. *Health Physics* **12**:1217-23, 1966.

Leach, L.J., E.A. Maynard, H.C. Hodge, J.K. Scott, C.L. Yuile, G.E. Sylvester, and H.B. Wilson. A five-year inhalation study with natural uranium dioxide dust - I Retention and biologic effect in the monkey, dog and rat. *Health Physics* **18**:599-612, 1970.

Leach, L.J., C.L. Yuile, H.C. Hodge, G.E. Sylvester, and H.B. Wilson. A five-year inhalation study with natural uranium dioxide dust - II Postexposure retention and biologic effects in the monkey, dog and rat. *Health Physics* **25**:239-58, 1973.

110.04 Metabolism and Toxicity of Thorium

Institution: University of Rochester (UR), Rochester NY

Scientists: A very large number of scientists participated over more than 30 years in these studies. Rather than attempting to list them all, a few prominent names are given as an aid to literature review. Scientists generally associated with thorium research at Rochester included Harold Hodge and E.A. Maynard; associated with specific projects were: d) L.J. Leach; e) W.L. Downs, J.K Scott.

Purpose: To develop an integrated understanding of the risks of thorium on the basis of metabolic and toxicological studies.

Treatment:
- a) IV injection, gavage and intratracheal injection carrier-free radiothorium (ionium-UX1) sulfate [19];
- b) Injection of the citrated form of carrier-free thorium-234 (UX-1) in tracer quantities by IV, IP, intramuscular, and intratracheal routes [21];
- c) Inhalation of a thorium-234 chloride aerosol in a single short term exposure [22]
- d) Inhalation over 210 w and a chronic 1 y inhalation of thorium dioxide in high concentrations To investigate **chemical** (not radiological) toxicity [23];
- e) Ingestion, inhalation, or IP injection of thorium nitrate tetrahydrate [20]

Dosimetry:
- a) Analysis of injection fluids, recovery of ashed whole bones.
- b) Radiochemical analysis and whole body counting
- c) Counting in a NaI well scintillation counter plus separation of blood constituents for counting.
- d) Chemical analysis for thorium.
- e) Analysis of administered solutions

Endpoints:
- a) Urinary and fecal excretion and tissue content, over a period of up to 42 d.
- b) Blood disappearance rate, tissue content, kinetics of excretion. Study covered a period up to 100d
- c) Urinary and fecal excretion, tissue distribution, blood content as a function of time - early and late (80 d).
- d) Mortality, body weight, urine and blood constituents, histological changes.
- e) Acute toxicity (mortality, body weight, general health) over a 4 month period. There was a small amount of work with dogs for comparison

Animal:
- a-e) Wistar rats
- a) Additionally, rabbits and guinea pigs.
- e) Additionally, a few dogs

Results: The research on thorium yielded important results on the behavior of soluble and insoluble thorium compounds. It showed among others (d) that natural thorium compounds used are essentially inert in terms of chemical toxicity.

References:

d) Hodge, H.C., E.A. Maynard, and L.J. Leach. *The Chemical Toxicity of Thorium Dioxide Following Inhalation by Laboratory Animals* UR-562, 1/6/60

e) Downs, W.L., J.K Scott, E.A. Maynard, H.C. Hodge. *Studies on the Toxicity of Thorium Nitrate* UR-561, 3-35, Pec. 16, 1959.

110.05 Survival, Growth, and Pathology of Animals Exposed to Whole-Body X-Irradiation in Divided Doses over Long Periods of Time

Institution: University of Rochester (UR), Rochester NY

Scientists: Andrew H. Dowdy
Robert D. Boche
Francis W. Bishop
Roger G. Metcalf (part c)
J. Newell Stannard

Purpose: To develop methods for chronic X-irradiation of different species, follow the effects on growth and survival and study resulting organ and tissue injury.

Treatment: A 1,000 keV G.E. industrial X-ray unit or a Picker 250 keV industrial unit was used to irradiate rats, dogs, rabbits and monkeys. Rats were exposed at 0.1, 0.5, 1.0, and 2.0 R/d. Animals were irradiated 6 d/w with exposure times from 8 to 18 minutes.

Dosimetry: Victoreen R-Meter at various points inside animal holders. Depth dose patterns were determined for a phantom dog.

Endpoints:
a) Dosimetric measurements in phantoms [46];
b) Survival time and growth rats in rats (as well as in some other species) [48];
c) Autopsy and microscopic pathology endpoints included pulmonary infection, liver necrosis, nephritis, periarteritis, ulcer, edema, granuloma, hemorrhage, hyper- and hypoplasia, atrophy, sarcoma, carcinoma, leukemia, adenoma, and benign tumors [49].

Animal: Wistar-derived rats (400 total, 50-100 per group) as well as some dogs, rabbits and monkeys.

Results:
b) A statistically significant increase in mortality rate was found only at 10 R/d. The data suggests small effects at lower dose rates. The increase in average death rate per X-ray exposure was approximately linear with the amount of radiation given per treatment. Growth (body weight changes) was relatively unaffected, except at 10 R/d.
c) Testis injury was detected only at 10 R/d. Data suggest an increase in leukemia and mammary fibroadenoma at doses less than 10 R/d.

References:

a) Chapter 9 of National Nuclear Energy Series VI-2 *Biological Effects of External Radiation*, 1954, "Observations on Animals Exposed to Whole-Body E Radiation in Divided Doses over Long Periods: Introduction and Techniques", pp 207-221. University of Rochester report MDDC-254 (II-188-5979).

b) Chapter 10 of National Nuclear Energy Series VI-2, *Biological Effects of External Radiation*, 1954, "Effects of Exposure to X Radiation on Growth and Survival, pp 222-252. MDDC-204 (II-188-5936).

c) Chapter 12 of National Nuclear Energy Series VI-2, *Biological Effects of External Radiation*, 1954, "Pathology in Animals Subjected to Repeated Daily Exposure to X-rays, pp 268-338. UR-88, July 1951.

110.06 Genetic Effects of Chronic X-Irradiation Exposures in Mice

Institution: University of Rochester (UR), Rochester NY

Scientists: Donald R. Charles
Joseph A Tihen
Arther Otis
Eileen M. Otis
Arnold B. Grobman

Purpose: To measure the incidence of genetic effects n the offspring of irradiated male mice.

Status: Study initiated in about 1943, final technical reports produced in 1958. All material at the University of Rochester has been discarded; collected publications and government documents available through the NRA

Treatment: Male DBA mice were exposed daily for adult life time at 0, 0.1, 0.5, 1.0, or 10.0 R/d. These animals were mated with C-57 Black females, and offspring were studied [47].

Dosimetry: The method of dosimetry is not given, but it is assumed that it was a Victoreen R-Meter and short (8 to 18 minute) exposures since that technique was used in other University of Rochester experiments at that time. Irradiation was performed with a Picker 250 kVp industrial unit at a distance of 68 inches with half value layers of 1.1 to 1.5 mm of copper. Each mouse was contained in a small cage of quarter-inch 16 gauge mesh hardware cloth during exposure.

Endpoints: Fecundity and survival time of control and irradiated males was measured. Other endpoints were: 1) sperm counts, 2) sex ratio of F1 offspring, 3) F1 mortality between birth and weaning, 4) F1 mortality between weaning and necropsy, 5) F1 muscle strength and response time to ether anaesthesia, 6) F1 body weight, body length, and tail length, 7) number of Peyers patches in the small intestine of F1 offspring, 8) F1 coat color and other morphologic changes, 9)Extensive necropsy of F1 offspring, 10) total mice in 4 litters from F1 bred females.

Animal: Male DBA mice were irradiated and mated with C-57 Black female mice. Over 12,000 offspring were examined. F1 females were mated with Swiss-Brag hybrid albino male mice to measure total number of offspring produced in four litters. The total number of animals bred in the entire study was 400,000.

Results: Survival times were lower and there was a reduction in fecundity in mice exposed to 10 R/d. At 10 R/d all mice eventually became sterile. No difference in F1 sex ratios could be determined at weaning (data for sex ratios at birth have been lost). The incidence of rare morphological anomalies, visible tested mutations, and F1 litter size taken together were definitely increased by radiation at the rate of at least 0.000116 per R of paternal exposure. In nearly every category the apparent mutation effect in the 0.1 R/d group was greater than predicted by a straight line regression. Based on total mutations, the doubling dose was about 50 R.

References: Charles, D.R., J.A. Tihen, E.M. Otis and A.B. Grobman. *Genetic Effects of Chronic X-Irradiation Exposure in Mice*, UR-565, pp 1-354, 1960. (Contains extensive tabulation of data.)

Charles, D.R. Radiation-Induced Mutations in Mammals, *Radiol.* **55**:579-581, 1950.

Experimental Groups:

Study 110.06
Genetic Effects of Chronic X-Irradiation Exposures in Mice

Group Id	Exposure (R/d)	Average Lifetime Dose (R)	Number of ♂ Mice
01	Control		51
02	0.1	13	58
03	0.5	69	29
04	1.0	134	16
05	10.0	238	33
		Total	187

110.07 Equivalent Ages in Mouse and Human Embryos

Institution: University of Rochester (UR), Rochester NY

Scientists: Eileen M. Otis
Arthur Otis
Robert Brent

Purpose: To correlate the equivalent ages of mouse and human embryos so that estimates of prenatal effects in mice can be extrapolated to humans.

Treatment: Mouse embryos were collected at various times after conception and examined for development of structures and organ systems [50].

Dosimetry: N/A

Endpoints: Number of somites, crown-rump length, ossification times, and more than 130 developmental structures.

Animal: 163 embryos were the offspring of Bragg Albino or Carworth Farm CFCW mice. These lines were originally constructed from crosses of C-57 females with DBA males. Data on early mouse development (< 7 d) was obtained form other published studies, as were the human data.

Results: Although this was a short term study, the data are important in correlating the equivalency of embryo ages between mice and humans. Careful consideration was given to estimating the actual time of conception in mice and its possible error. The work is based on an analysis of 163 embryos. Data on early mouse development (< 7 d) was obtained from published studies, as were the human data.

References:

Otis, E.M. and R. Brent. *Equivalent Ages in Mouse and Human Embryos*, UR-194, pp 1-38, 1952.

Otis, E.M. and R. Brent. Equivalent Ages in Mouse and Human Embryos, *Anatomical Record* **120**:33-63, 1954.

110.08 Clinical, Pathological, and Hematological Effects of Chronic Neutron Irradiation

Institution: University of Rochester (UR) Rochester NY and Biomedical Research Foundation, Newark, Del

Scientists: J.O. Ely
M.H. Ross
R.G. Metcalf
F.A. Inda
Mary-Lou Ingram
T.B. Barnett
G.W. Casarett

Purpose: To study effects of neutrons on rats, rabbits and dogs.

Treatment: Rats were exposed 6 d/w for 1 y to the neutron beam from the Delaware cyclotron. (9.5 MeV deuterons on Be producing a maximum neutron energy of 13.5 MeV) [51].

Dosimetry: Victoreen R-Meter expressed in "n" units.

Endpoints: Body weight, mortality, cataracts, coat color, tumors, microscopic pathology, and hematology.

Animal: 250 rats, also some dogs and rabbits.

Results: Extensive pathological data are available in tabular form.

References:
E. McDonald. Chapter 16 of National Nuclear Energy Series VI-2, *Biological Effects of External Radiation*, 1954, "Fast-Neutron-Irradiation Procedure", pp 403-418.

J.O. Ely. Chapter 17 of National Nuclear Energy Series VI-2, *Biological Effects of External Radiation*, 1954, "Clinical, Pathological , and Hematological Effects of Chronic Neutron Irradiation", pp 419-497.

M.B. Ingram and W.B. Mason, University of Rochester Report UR-92, January 16, 1950.
Report AECD-2595.

111 Atomic Energy of Canada Ltd. Chalk River (AECL)

111.01 Mammary Tumor Development: Low Dose Rate Tritium-, Chronic and Acute, X- or Cobalt-60 Gamma-Irradiation of Female Rats

Institution: Chalk River Laboratories, AECL, Chalk River, Canada ONT

Scientists: David K. Myers; retired
John R. Johnson; presently at PNNL
J.S. Jackson; active
D.W. Dunford; active
N.J. Gragtmans; presently at Warren Lambert/Park Davis, Mississauga, Ontario
A.R. Jones; retired

Purpose: Investigate the relative biological effectiveness (RBE) of tritium beta rays compared to chronic X irradiation for acceleration of the appearance of mammary tumors.

Status: Animals were exposed in 1980 - 1981. Study complete, report published, archived tissues being analyzed by AECL.

Treatment: Intraperitoneal injections of tritiated water ranging in concentrations from 45 to 370 Mbq/100 g body weight were administered to four groups of rats, followed by 4 additional injections at 2-d intervals and half of the initial concentrations (the biological half-life of HTO was taken as 2 d).

Four groups chronically exposed rats were irradiated over 10 d to a total dose of 0.29, 0.57, 1.1, and 2.0 Gy. Irradiation was continuous except for four 1-h interruptions for animal care. Another two groups received 0.57 or 1.78 Gy of X irradiation over a 1-h (acute) period. Two groups were exposed to cobalt-60 gamma rays (but were not analyzed until completion of study **111.02**).

Dosimetry: Tritium levels in the injection solution and urine samples was measured by liquid scintillation to obtain retention curve information for dose estimation. Doses were estimated based on average tritium levels in the initial 8-d of urine, plus integration under a three component retention curve. Serial sacrifice and analysis of tritium in tissue lipid and nonlipid fractions was used to refine the dose estimates for mammary glands.
The X-ray generator was operated at 200 kVp, an acrylic block was used to attenuate the beam for the low dose rate exposures without significant change in the energy spectrum. X-ray doses absorbed by the rats were measured using sensitized LIF thermoluminescent dosimeters.

Endpoints: Rats in each group were allowed to live until the cumulative number of animals with at least one mammary tumor exceeded 50% of those at risk. Mammary tumor development was monitored by palpation every 2-3 w; tumors were excised and classified histologically upon reaching 2.5 cm diameter. Mammary neoplasia was summarized on a tumor per 100 rat as well as rats with tumor basis.

Animal: Female, specific pathogen free, Sprague-Dawley rats (1611 in 13 groups) were exposed to tritiated water or irradiated with various doses of x or gamma rays at age 45 - 50 d.

Results: Tritium beta rays are about 1.1 to 1.3 times more effective in total tumor induction than chronic 200 kVp X-rays. Acute X irradiation appears to be slightly more effective than chronic X irradiation.

References: N.J. Gragtmans, D.K. Myers, J.R. Johnson, A.R. Jones, and L.D. Johnson.Occurrence of mammary tumors in rats after exposure to tritium beta rays and 200 kVp X-rays. *Radiation Research* **99**: 636-650, 1984.

Experimental Groups: **Study 111.01**
Mammary Tumor Development:
Low Dose Rate Tritium-, Chronic and Acute, X- or Cobalt-60 Gamma-Irradiation of Female Rats

Group Id	AECL Group	Type of Radiation	Dose (Gy)	Average Dose Rate (Gy/hr)	Number of Rats
01	CONT	Control	0	0	199
02	HTO05	Tritium	0.46	0.00192	110
03	HTO10		0.92	0.0038	113
04	HT019		1.8	0.0074	120
05	HTO44		3.8	0.016	119
06	CX029	Chronic X-ray	0.3	0.0012	120
07	CX057		0.6	0.0024	120
08	CX110		1.1	0.0046	120
09	CX200		2.0	0.0083	120
10	AX057	Acute X-ray	0.6	0.57	120
11	AX178		1.8	1.78	112
12	AG064	Acute Gamma	0.6	0.6	119
13	CG093	Chronic Gamma	0.9	0.002	119
				Total	1611

111.02 Mammary Tumor Development: Low Dose Rate, Acute X-, and Acute or Chronic Gamma-Irradiation of Female Rats

Institution: Chalk River Laboratories, AECL, Chalk River, Canada ONT

Scientists: David K. Myers; retired
John R. Johnson; presently at PNNL
J.S. Jackson; active
D.W. Dunford; active
N.J. Gragtmans; presently at Warren Lambert/Park Davis, Mississauga, Ontario
A.R. Jones; retired

Purpose: The excess number of mammary tumors in the single cobalt-60 gamma irradiation group of the previous study (**111.01**) was less than expected from the X-ray results, hence this follow-up study was undertaken to further investigate the relative biological effectiveness (RBE) of x irradiation compared with cobalt-60 gamma irradiation for acceleration of the appearance of mammary tumors.

Status: Animals were exposed in 1982 and 1983. Study complete, report published, archived tissues being analyzed by AECL.

Treatment: Four groups of rats were given X irradiation doses of 0.62, 1.2, 2,5, and 3.7 Gy. Another 4 groups of rats were exposed to unattenuated cobalt-60 gamma rays at a high dose rate of 26.3 Gy/hr. Four additional groups were exposed to attenuated gamma rays at a dose rate of 0.0075 Gy/hr. Two intermediate gamma ray groups were also exposed.

Dosimetry: X-ray machine was operated at 200 kVp, 17.5 mA, to produce 37.2 Gy/hr at 50 cm. The beam current was continuously adjusted to achieve desired reading on reference ion chamber. A factor of 0.0095 was used to convert R to Gy.

Cobalt-60 gamma doses were also measured with an ion chamber, using a factor of 0.00966 to convert from R to Gy. Low-dose gamma exposure was achieved by insertion of lead attenuators in the source assembly.

Endpoints: Rats in each group were allowed to live until the cumulative number of animals with at least one mammary tumor exceeded 50% of those at risk. Mammary tumor development was monitored by palpation every 2-3 w; tumors were excised and classified histologically upon reaching 2.5 cm diameter. Mammary neoplasia was summarized on a tumor per 100 rat as well as rats with tumor basis.

Animal: Female, specific pathogen free, Sprague-Dawley rats (960 in 15 groups) were irradiated with various doses of X- or gamma-rays.

Results: The incidence of adenocarcinomas and fibroadenomas at a given time after exposure increased linearly in proportion to total dose. However, no significant increase in adenocarcinomas was observed with chronic gamma irradiation up to 1.1 Gy, and the increase in fibroadenomas with chronic gamma irradiation at a dose rate of 0.0076 Gy/hr up to an accumulated dose of 3.3 Gy was small compared to that observed for acute exposures. The incidence of all mammary tumors increased almost linearly with the log of dose rate in the range 0.0076 to 26.3 Gy/hr for 3 Gy total dose. The effects of X-rays appeared to be less influenced by dose rate than those of gamma rays.

References: J.R. Johnson, N.J. Gragtmans, D.K. Myers, and A.R. Jones. Dose-rate effects for mammary tumor development in female Sprague-Dawley rats exposed to X and gamma radiation. *Radiation Research* **118**: 545-558, 1989.

Experimental Groups:

Study 111.02
Mammary Tumor Development: Low Dose Rate, Acute X-, and Acute or Chronic Gamma-Irradiation of Female Rats

Group Id	AECL Group	Type of Radiation	Dose (Gy)	Average Dose Rate (Gy/hr)	Number of Rats
01	CONT	Control	0	0	120
02	AX050	Acute X-rays	0.6	37.2	60
03	AX100		1.2	37.2	60
04	AX200		2.5	37.2	60
05	AX300		3.7	37.2	60
06	AG050	Acute Gamma	0.5	26.3	60
07	AG100		1.0	26.3	60
08	AG200		2.0	26.3	60
09	AG300		3.0	26.3	60
10	CG050	Chronic Gamma	0.6	0.0076	60
11	CG100		1.1	0.0076	60
12	CG200		2.3	0.0076	60
13	CG300		3.4	0.0076	60
14	IG001	Intermediate Gamma	3.0	2.04	60
15	IG002		3.0	0.167	60
				Total	960

111.03 Induction of Myeloid Leukemia: Intraperitoneal Tritium Application or X-Irradiation in CBA/H Mice

Institution: Chalk River Laboratories, AECL, Chalk River, Canada ONT

Scientists: David K. Myers; retired
John R. Johnson; presently at PNNL
J.S. Jackson; active
D.W. Dunford; active
N.J. Gragtmans; presently at Warren Lambert/Park Davis, Mississauga, Ontario
A.R. Jones; retired
D.H. Percy; Ontario Veterinary College, University of Guelph

Purpose: Investigate the relative biological effectiveness (RBE) of tritium exposure compared with X irradiation compared for the appearance of myeloid leukemia.

Status: Animals were exposed in 1986 and 1987. The study is complete, reports are published, archived tissues being held for additional analysis by AECL, detailed technical documentation is available through Atomic Energy Canada or the NRA.

Treatment: HTO was administered via single intraperitoneal injection of 90, 180, or 270 mBq of tritium per mouse to deliver an anticipated dose of 1, 2, or 3 Gy.

Mice were exposed in 6 replications. Two X-ray sources were used, a 300 kVep X-ray tube operated at 200 kVp (which failed in rep 2), and a 150 kVep tube with filtration to provide an average energy of 104 keV. The LET of the two X-ray sources are presumed to be essentially the same. Mice were exposed continuously (23.5 h/d) for 10 d. The initial dose rates of 0.24, 0.48, or 0.72 Gy/d were reduced by 45% every two d to parallel the change in tritium dose rate. Target doses were 1, 2, or 3 Gy.

Dosimetry: Actual HTO doses were estimated from periodic assays of tritium in urine over the first 2 w. The average dose to the cells was assumed to be 0.733 times the dose to body water. Group average doses were 0.85, 1.86, or 3.04 Gy.

X-ray doses were measured by TLDs placed subcutaneously in mice or in air. The average X-ray doses for all mice in 6 repetitions were 1.06, 1.98, or 2.64 Gy.

Endpoints: Myeloid leukemia was diagnosed from gross pathology, hematologic profiles, and histopathology of spleen and/or bone marrow, (or other tissue if these were not available).

Animal: Of the 5336 Male CBA/H mice entered into the study at age 100 d, 130 were lost due to various accidents, leaving a total of 5206 divided roughly equally into 7 groups.

Results: The lifetime incidence of leukemia in these mice increased from 0.13% in the control group to 6-8% in groups exposed to higher doses. The calculated RBE for tritium compared to X-rays ranged from 1.0 to 1.3.

References:
J.R. Johnson, D.K. Myers, J.S. Jackson, D.W. Dunford, N.J. Gragtmans, H.M. Wyatt, A.R. Jones, and D.H. Percy. Relative biological effectiveness of tritium for induction of myeloid leukemia in CBA/H mice. *Radiation Research* **144**: 82-89, 1995.

J.R. Johnson, D.K. Myers and N.J Gragtmans. An experiment designed to measure the RBE of tritium for the induction of myeloid leukemia in animals. *Radiation Protection Dosimetry* **16** 161-164, 1986.

Experimental Groups:

Study 111.03
Induction of Myeloid Leukemia: Intraperitoneal Tritium Application or X-Irradiation in CBA/H Mice

Group Id	AECL Group	Type of Radiation	Average Dose (Gy)	Average Age at Death (d)	Number of Mice
01	CONT	Control	0	767	747
02	X-1	Continuous X-rays	1.06	720	734
03	X-2		1.98	715	739
04	X-3		2.64	714	746
05	HTO-1	Tritium	0.85	737	732
06	HTO-2		1.86	728	754
07	HTO-3		3.04	714	754
				Total	5206

111.04 Health Effects of Inhaled Uranium Ore Dust

Institution: Chalk River (AECL), Canada ONT

Scientists: Ron E.J. Mitchel; active
J. S. Jackson; active

Purpose: Study the health effects on experimental animals exposed to different concentrations of airborne high grade uranium ore dust. Inter-organ transfer of uranium and the rate of clearance from the lung will also be studied. Since uranium miners have always been exposed to a mixture of external gamma radiation and internal radiation from radon decay products and ore dust, it has not been possible to separate the contribution of each component to the observed rate of lung cancer. This was of little consequnce as long as radon daughters were the predominant hazard, but this becomes an issue in Sackatchewan mines where some ore is 50% uranium and chemical toxicity may exceed radiological toxicity.

Status: Exposure apparatus constructed and evaluated; full-scale animal study in progress.

Treatment: Nose-only inhalation of ore dust 4.5 h/d, 5d/week for 65 weeks at two concentrations. Ore (44% uranium) was ground to < 5 μm diameter.

Dosimetry:

Endpoints: Induction of cancer of the lung and cellular effects.

Animal: Sprague-Dawley rats

Results: Inhaled lung burdens of natural uranium ore are transient and decrease with time after inhalation. Lymph node burdens (and therefore doses) are ultimately much lower that lung burdens; testicular burdens are relatively low and essentially vanish when inhalation ceases.

References:

Experimental Groups: not communicated

Japanese Radiobiological Archives of Animal Experiments (JRA)

List of Communicated Experiments

Prepared under the Auspices of

Japanese Late Effects Project Group (JLEG)

by

Tsutomu Sugahara and Shigefumi Okada

201 National Institute of Radiological Sciences, Chiba

201.01 Induction of Liver and Lung Tumors in C57BL/6J Male Mice Irradiated With Low Doses of High-LET Radiation

Institution: National Institute of Radiological Sciences, Chiba

Scientists: T. Furuse; active
H. Otsu; active
S. Kobayashi; retired
H. Ohara; active

Purpose: To determine the tumor incidence after whole body irradiation and estimate the RBEs for tumor induction from two energies of fast neutrons.

Status: 1985 -ongoing

Treatment: Single exposure to 2 MeV fast neutrons from a Van de Graaff accelerator at a dose rate of 0.067 Gy/min (gamma contamination 10%) or 13 MeV fast neutrons from a cyclotron at a dose rate of 0.33 Gy/min (gamma contamination<4%).

Dosimetry: Ionization chamber

Endpoints: Life-span study with macroscopic/microscopic pathological observation; tissues embedded in paraffin, stained with HE.

Animal: Male C57BL/6J mice of 28 days of age

Results: Life shortening was statistically significant between the control group and the groups irradiated with 3 Gy or more of gamma-rays, and between the control group and the groups irradiated with 1 Gy or more of the two kinds of fast neutrons. RBEs, calculated from the doses that brought a 25% reduction in the 50% - surviving periods, were 3.4 for the 2 MeV neutrons and 2.3 for the 13 MeV neutrons. Tumor incidence increased in the 1 Gy gamma-ray group, but life shortening was not seen. In the 7 Gy gamma-ray group, there were many thymic lymphomas, and life shortening was remarkable. In fact, total tumor as high as 65% and 72% were observed in the two 1 Gy - neutron irradiated groups. Dose dependent increases in liver tumor incidence were observed in the groups irradiated with 0.125, 0.25 and 0.5 Gy of the two types of neutrons. Lung tumors were observed in 25% of the 1 Gy 2 MeV - neutron group, and the same level of the tumor incidence was observed in the 2 Gy 13 MeV neutron group. Higher incidences than that of control group were observed in 0.25 and 0.5 Gy neutron groups.

References: Furuse, T., H. Otsu, Y. Noda, S. Kobayashi and H. Ohara. Induction of liver tumors and lung tumors in C57BL/6J male mice irradiated with low doses of high LET radiations, pp. 207-210. *In* T. Sugahara, L.A. Sagan and T. Aoyama [eds.], *Low Dose Irradiation and Biological Defense Mechanisms*. Elsevier Science Publ., The Netherlands, 1992.

Experimental Groups:

Study 201..01
Induction of Liver and Lung Tumors in C57BL/6J Male Mice Irradiated with Low Doses of High LET Radiations

Type of Radiation	Group Id	Dose (Gy)	No of mice
Control	1	0	171
Gamma-rays	2	1	84
	3	3	97
	4	5	120
	5	7	189
Fast Neutron (13 MeV)	6	0.125	41
	7	0.25	80
	8	0.5	52
	9	1.0	157
	10	2.0	127
	11	3.0	162
Fast Neutrons (2 MeV)	12	0.5	89
	13	1.0	133
	14	2.0	139
	15	3.0	148

201.02 Influence of Dose Rate on Tumorigenesis in C3H/He Male Mice Irradiated At a High Dose Rate or a Low Dose Rate.

Institution: National Institute of Radiological Sciences, Chiba

Scientists: H. Otsu; active
T. Furuse; active
Y. Noda; active
N. Yasuda; retired
A. Shiragai; active

Purpose: To compare the incidence of different types of neoplasias in mice irradiated at a high dose rate and at low dose rate, and to calculate the parameters of the dose-effect relationship and the dose rate effectiveness factor.

Status: 1988 -ongoing

Treatment: Continuous whole body exposure to Cs-137 gamma rays at a dose rate of 882 mGy/min and at dose rates of 0.298, 0.068, 0.016 mGy/min for 22 hours daily. accumulated dose of 1, 2 or 4 Gy.

Dosimetry: Ionization chamber

Endpoints: Life-span study with macroscopic/microscopic pathological observations; tissues embedded in paraffin, stained HE

Animal: Male C3H/He mice of 58 days of age

Results: Lung tumor and myeloid leukemia were statistically significant among the various types of neoplasms arising in this study, and their incidences showed an acceptable fit for the linear-quadratic model as a function of dose in both high and low dose rates groups. The equations for dose effect relationships for leukemia were Ir = 0.78 + 14.95D - 2.29DxD (r = 0.93) in the high dose rate group and Ilr = - 0.68 + 2.67D - 0.18DxD (r = 0.92) in the low dose rate (0.398 Gy/day) group, and equations for lung tumor were Ir = 1.98 + 0.79D - 0.098DxD (r = 0.80) and ILr = 2.05 + 0.67D - 0.045DxD (r = 0.85). The DDREF values were 4.90 (9.46/1.93) for leukemia, 1.11 (1.13/1.01) for lung tumor and 1.22 (3.80/3.10) for the ratio of life (RL) shortening. The differences in the DDREF values implied that there were differences in the influence of dose rate on tumorigenesis among various irradiated tissues.

References: Otsu, H., S. Kobayashi, T. Furuse, Y. Noda, A. Shiragai and F. Sato. Age and sex dependence in tumorigenesis in mice by continuous low dose rate gamma-ray whole body irradiation, pp. 211-216. *In Proceedings International Conference on Radiation Effects and Protection*, March 18-22. Mito, 1992.

Experimental groups: not communicated

201.03 Comparison Between Characteristics of Thymic Lymphomas Induced by Ionizing Radiation and a Chemical Carcinogen

Institution: National Institute of Radiological Sciences, Chiba

Scientists: Y. Shimada; active
M. Nishimura; active
H. Ishii; active
T. Ogiu; active

Purpose: To determine the difference between radiation-induced and chemically-induced tumors.

Status: 1995 -ongoing

Treatment: Single exposure to X-ray (200 kV, Model Shinai, Shimazu Co., Ltd., 0.25 Gy/min.) at dose 1.61 Gy for 4 times, total 6.5 Gy, with weekly interval, or 400 ppm ethylnitrosourea solution in distilled water in the drinking water for 6-10 weeks.

Dosimetry: Ionization chamber

Endpoints: Life-span study with macroscopic / microscopic pathological observations, embedded in paraffin, stained HE and with FACStar analysis stained with thymocyte cell-surface markers.

Animal: Female 5-week-old B6C3F1 mice

Results:

References:

Experimental groups:

Study 201.03
Comparison Between Characteristics of Thymic Lymphomas Induced by Ionizing Radiation and a Chemical Carcinogen

X-irradiation (Gy)	Group Id	Ethylnitrosourea (ppm in water)	No of mice
0	1	0	100
4 x 1.61 Gy (at weekly intervals)	2	0	50
0	3	400 ppm for 6 week	50
0	4	400 ppm for 10 week	50

201.04 Carcinogenic Susceptibility to Ionizing Radiation of Scid Mice and its Control Strain C.B-17 Mice

Institution: National Institute of Radiological Sciences, Chiba

Scientists: T. Ogiu; active
S. Kobayashi; retired
H. Ishii; active
M. Nishimura; active
Y. Shimada; active

Purpose: To determine the effect of scid mutation (defect of DNA damage-repair) on carcinogenesis by ionizing radiation.

Status: 1995 -ongoing

Treatment: Single exposure to gamma-ray (Cs-137 gamma-ray irradiator, Model RSG-50, Tokyo Shibaura Electric Co., Ltd., 0.6 Gy/min.) at dose 0, 1, 2 or 3 Gys in SPF animal facility.

Dosimetry: Ionization chamber

Endpoints: Life-span study with macroscopic / microscopic pathological observations, tissues embedded in paraffin, stained HE

Animal: 8-week-old female scid, C. B-17 and (C. B-17 x scid) F1 mice.

References: T. Ogiu. Severe combined immunodeficiency (scid) mice and radiosensitivity. *Hoshasen-Kagaku (Radiological Sciences)* **37**:287-293, 1994. (in Japanese).

Experimental groups:

Study 201.04

Carcinogenic Susceptibility to Ionizing Radiation of scid Mice and its Control Strain C.B-17 Mice

Experiment Strain	Group Id	Dose (Gy)	No ♀ Mice
scid mice (8-week-old)	1	0	100
	2	1	100
	3	2	100
	4	3	100
C.B-17 (8-week-old)	5	0	100
	6	1	100
	7	2	100
	8	3	100
(C.B-17 x scid) F1	9	0	100
	10	1	100
	11	2	100
	12	3	100

201.05 The Effect of Caloric Restriction on Radiation-Induced Myeloid Leukemogenesis

Institution: National Institute of Radiological Sciences, Division of Physiology and Pathology, Chiba

Scientists: K. Yoshida; active
T. Inoue; active
T. Sado; retired

Purpose: To examine whether the incidence of radiation-induced myeloid leukemia is reduced by caloric restriction.

Status: 1988 - 1994, 1994- ongoing

Treatment: X-irradiation; 3 Gy of whole body at a dose rate 0.614 Gy/min. with 200kV, 20mA, 0.5mm Al+0.5mm Cu filter.
Caloric restriction: The caloric-intake was adjusted by controlling the amount of carbohydrates and dextrose. Diets consisted of four different caloric-controlled regimens(60, 65, 70, and 95 kcal/wk/mouse, but with an equal amount of other nutrients such as proteins, lipids, vitamins and minerals.

Dosimetry: Monitor dosimeter(A1142, Clear Pulse Co.)

Endpoints: Life span study with macroscopic/ microscopic pathology, tissues embedded in paraffin, stained with HE. Mice displaying symptoms of advanced leukemia were sacrificed at the terminal stage for haematological/pathological examination.

Animal: Male C3H/He mice 10 weeks of age at time of irradiation:

Experimental groups:

Study 201.05
The Effect of Caloric Restriction on Radiation-Induced Myeloid Leukemogenesis
Experiment 1 (1988-1994)

Diet Groups (Calorie intake kcal/wk/mouse)	Group Id	Dose (Gy)	No Mice
Control diet groups, 95 kcal	1	0	165
	2	3	163
Restriction diet A groups*, 95 kcal (6-10wk), then 60, 65, 70 or 95 kcal	3	0	135
	4	3	131
Restriction diet B groups*, 65 kcal (6-10wk), then 60, 65, 70 or 95 kcal	5	0	70
	6	3	76

Experiment 2 (1994 -ongoing)

Diet Groups (Calorie intake kcal/wk/mouse)	Group Id	Dose (Gy)	No Mice
Control diet groups, 95 kcal	7	0	109
	8	3	111
Restriction diet C group*, 95 kcal (6-10wk), then 75 kcal	9	0	96
	10	3	102
Restriction diet D group*, 65 kcal (6-10wk), then 95 kcal	11	0	147
	12	3	150

*The body weight of mice in the restriction diet groups was maintained at 25-27 g by giving diets of 60-95 kcal

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201.06 Exacerbating Factors of Radiation-Induced Myeloid Leukemogenesis

Institution: National Institute of Radiological Sciences, Division of Physiology and Pathology, Chiba

Scientists: K. Yoshida; active
M. Seki; retired

Purpose: To investigate whether an inflammatory reaction can promote radiation-induced myeloid leukemogenesis and whether the incidence of radiation-induced myeloid leukemia differs between females and males.

Status: 1985-1990, terminated

Treatment: X-irradiation; 2.84 Gy of whole body exposure at a dose rate of 0.614Gy/min (200kV, 20mA, 0.5mm Al+0.5mm Cu filter). To provoke an inflammatory reaction, a piece of cellulose acetate membrane(CAM) was inserted into the peritoneal cavity of the mouse.

Dosimetry: Monitor dosimeter(A1142, Clear Pulse Co.)

Endpoints: Life span study with macroscopic/ microscopic pathology, tissues embedded in paraffin, stained with HE. Mice displaying symptons of advanced leukemia were sacrificed at the terminal stage for hematological/pathological examination.

Animal: C3H/He mice 8-10 weeks of age at time of irradiation, both sexes

Results: The incidence of spontaneous myeloid leukemia in non-irradiated female mice was slightly higher than in males, whereas that of radiation-induced myleoid leukemia in femal mice was significantly lower than in males. Insertion of CAM did not affect the incidence of myeloid leukemia in unirradiated mice, but produced a significant increase in incidence in irradiated mice of both sexes compared with that in irradiated-only mice.

References: Yoshida, K., K. Nemoto, M. Nishimura and M. Seki. Exacerbating factors of radiation-induced myeloid leukemogenesis. *Leukemia Res.* 17:437-440, 1993.

Experimental groups:

Study 201.06
Exacerbating Factors of Radiation-Induced Myeloid Leukemogenesis

Strain and Sex	Dose (Gy)	Group Id	CAM	No Mice
C3H/He (♂)	0	1	Not inserted	110
	0	2	Inserted	49
	2.84	3	Not inserted	109
	2.84	4	Inserted*	49
	2.84	5	Inserted†	104
C3H/He (♀)	0	6	Not inserted	49
	0	7	Inserted	49
	2.84	8	Not inserted	50
	2.84	9	Inserted*	50
	2.84	10	Inserted†	50

* Inserted 7 days before irradiation. † Inserted immediately after irradiation.

201.07 Radiation-Induced Myeloid Leukemia in C3H/He Mice and the Effect of Prednisolone Acetate on Leukemogenesis.

Institution: National Institute of Radiological Sciences, Division of Physiology and Pathology, Chiba

Scientists: M. Seki; retired
K. Yoshida; active

Purpose: To investigate the dose-response relationship for myeloid leukemia in C3H/He mice and to determine the effect of the synthetic glucocorticoid prednisolone acetate on radiation-induced leukemogenesis.

Status: 1980-1987, terminated

Treatment: X-irradiation; single whole body exposure at a dose rate of 0.614Gy/min (200kV, 20mA, 0.5mm Al+0.5mm Cu filter).
Administration of glucocorticoids; 1mg of prednisolone acetate or corticosterone bu subcutaneous injection to mice immediately prior irradiation

Dosimetry: Monitor dosimeter(A1142, Clear Pulse Co.)

Endpoints: Life span study with macroscopic/ microscopic pathology, tissues embedded in paraffin, stained with HE. Mice displaying symptons of advanced leukemia were sacrificed at the terminal stage for hematological/pathological examination.

Animal: Male C3H/He mice 8-10 weeks of age at the time of irradiation

Results: The induction of myeloid leukemia increased after doses from 0.47 to 2.84 Gy, and then decreased after a dose of 4.73 Gy. The administration of prednisolone acetate after irradiation resulted in a significant increase in the incidence of myeloid leukemia after a dose of 2.84 Gy.

References: Seki, M., K. Yoshida, M. Nishimura and K. Nemoto. Radiation-induced myeloid leukemia in C3H/He mice and the effect of prednisolone acetate on leukemogenesis. *Radiat. Res.* **127**:146-149, 1991.

Experimental groups:

Study 201.07
Radiation-Induced Myeloid Leukemia in C3H/He Mice and the Effect of Prednisolone Acetate on Leukemogenesis.

Group Id	Dose (Gy)	Administration of glucocorticoid	No ♂ Mice
1	0	none	110
2	0	prednisolone	100
3	0	corticosterone	110
4	0.47	none	133
5	0.47	prednisolone	100
6	1.42	none	110
7	1.42	prednisolone	108
8	2.84	none	109
9	2.84	prednisolone	109
10	2.84	corticosterone	107
11	4.73	none	110
12	4.73	prednisolone	105

201.08 Life-Span Study of the Carcinogenic Effects of Injected Pu-239 Citrate in Mice

Institution: National Institute of Radiological Sciences, Division Radiotoxicology, Chiba

Scientists: Y. Oghiso; active
Y.Yamada; active
H. Sato; active
H. Iida; active
J. Inaba; active

Purpose: To estimate human cancer risk from experimental data on the dose-responses and tumor spectra in mice after injection of Pu-239 citrate solution.

Status: 1990 -ongoing

Treatment: Single intraperitioneal injection of Pu-239 citrate solution of pH 6.8 to yield initial body burdens of 10 to 10.000 Bq per animal.

Dosimetry: Radiochemical analysis of injected and deposited activity in the whole skeleton of a group of mice sacrificed at 7, 30, 90, 180 and 270 days after injection in order to estimate mean absorbed skeletal dose by calculation.

Endpoints: Life-span study on spontaneously dead animals with macroscopic/ microscopic pathology of the whole organs with either neoplastic or non-neoplastic diseases

Animal: Female CB3H/He mice of age 80-100 days at injection

References: Oghiso Y., Y. Yamada and H. Iida. Differential induction of bone and hemaopoietic tumors in C3H mice after injection of ^{239}Pu citrate. *J. Radiat. Res.* **35**: 236-247, 1994

Experimental groups:

Study 201.08
Life-Span Study of the Carcinogenic Effects of Injected Pu-239 Citrate in Mice

Injected Dose (Bq)	Group Id	Estimated Skeletal Dose (Gy)	Total No of Injections	Total No of Examinations*
0	1	0	120	100
10.7	2	<0.1	50	47
119	3	<1.0	50	50
580 - 727	4	1.8 - 3.5	30	30
1102 - 1330	5	4.0 - 5.5	30	30
1540 - 1712	6	6.0 - 8.5	25	25
5160 - 6050	7	11.0 - 20.0	25	25
7600- 8609	8	21.0 - 30.0	25	25
10600 - 11600	9	37.0 - 45.0	25	25

* as of December 1994

In addition, 30 animals with initial body burden of 1000 Bq were used to assess Pu content in the skeleton of groups of 6 animals sacrificed at 7, 39, 90, 180 and 270 days after injection

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201.09 Life-Span Study of the Carcinogenic Effects of Inhaled Pu-239 Citrate in the Rat

Institution: National Institute of Radiological Sciences, Division Radiotoxicology, Chiba

Scientists: Y. Oghiso; active
Y.Yamada; active
N. Ishigure; active
H. Sato; active
S. Fukada; active
A. Koizumi; active
J. Inaba; active

Purpose: To estimate human cancer risk from experimental data on the dose-responses and histopathological characteristics of lung tumors in rats after inhalation exposures to high-fired P-239 dioxide aerosols.

Status: 1990 -ongoing

Treatment: Single nose-only inhalation exposure to submicron and polydisperse aerosols of Pu-239 dioxide (AMAD 0.3-0.4 μm / GSD 2.0) heated to 1000 C to give an initial lung burden deposition of 50-3500 Bq.

Dosimetry: Cumulative calculated lung dose during the life-time from the exposure day (day 0) up to death by whole body counting of LX-rays with a specific energy of 17 keV.

Endpoints: Life-span study on spontaneously dead animals with macroscopic/ microscopic pathology of the lung and the other main organs with either neoplastic or non-neoplastic diseases

Animal: Female Wistar strain rats of age from 80 to 150 days at inhalation exposure

References: Oghiso Y., Y. Yamada, N. Ishigure, S. Fukuda, H. Iida, Y. Yamada, H. Sato, A. Koizumi and J. Inaba. High incidence of malignant lung carcinomas in rats after inhalation of $^{239}PuO_2$ aerosol. *J. Radiat. Res.* **35**: 222-235, 1994

Oghiso Y., Y. Yamada, H. Sato and J. Inaba. Differential induction of benign and malignant lung tumors in the rat after inhalation of plutonium dioxide. Proceedings of the 10th ICRR Meeting, Würzburg, Germany, 1955

Experimental groups:

Study 201.09
Life-Span Study of the Carcinogenic Effects of Inhaled Pu-239 Citrate in the Rat

Injected Dose (Bq)	Group Id	Estimated Lung Dose (Gy)	Total No of Exposures	Total No of Examinations*
0	1	0	150	78
<145	2	< 1.0	53	14
150 - 280	3	< 2.0	76	17
300 - 540	4	< 3.0	46	0
500 - 990	5	< 4.0	30	8
605 - 972	6	< 5.0	43	40
828 - 1080	7	< 6.0	31	31
970 - 1393	8	< 7.0	30	30
7600- 8609	9	21.0 - 30.0	31	31
1802 - 3065	10	10.3 - 20.3	10	10

* as of December 1994

In addition, 30 animals with of 1500-2800 Bq were used to assess Pu content in the lung by both follow-up of whole body count and radiochemistry. Another 100 control and 150 exposed animals with initial lung deposition of 1000 Bq or less will be added to the above groups from 1996 to 1997.

201.10 Late Effects of Radiation on Immune System in Mice

Institution: National Institute of Radiological Sciences, Division of Physiology and Pathology, Chiba

Scientists: T. Sado; retired
S. Kobayashi; retired
H. Kamisaku; active
H. Kurokawa; active
Y. Kataoka; active

Purpose: To determine the late effects of radiation on immune system with emphasis on the assessment of the radiation induced acceleration of aging of the immunologic functions.

Status: 1973-1977, terminated

Treatment: Whole-body single dose exposure to graded doses of X-rays (150, 200, 300, 400 R)

Dosimetry: Victoreen chamber

Endpoints: Assessments of the splenic anti-sheep red blood cell (SRBC) plaque forming cell (PFC) response, allogeneic skin graft survival, number of T and B cells in the spleens, proliferative response of spleen cells to T and B cell mitogens (PHA, LPS) and allogeneic stimulator cells (mixed lymphocyte reaction; MLR) at varying intervals after radiation exposure.

Animal: Male BC3F1 and B6C3F1 mice of varying ages

Results: No significant difference in the various immunologic functions between sublethally irradiated (150-400 R) and control groups at all time intervals examined in this study, indicating no evidence for acceleration of aging, or earlier decline of the immune competence of mice as a result of earlier exposure to sublethal doses of X-rays.

References: Sado, T., S. Kobayashi, H. Kamisaku, H. Kurokawa and Y. Kataoka. Immunological competence of aging mice exposed to X- or gamma-rays during young adulthood. *Late Biological Effects of Ionizing Radiation.* Vol.II. pp.115-125, IAEA, 1978.

Experimental groups: not communicated

201.11 Immediate and Long-Term Effects of Radiation on Immune System in Specific-Pathogen-Free Mice

Institution: National Institute of Radiological Sciences, Division of Physiology and Pathology, Chiba

Scientists: T. Sado; retired
H. Kamisaku; active
Y. Ikarashi; active
E. Kubo; active

Purpose: To determine the immediate and long-term effects of radiation on immune system with emphasis on the assessment of the time course of the initial suppression, subsequent recovery and aging of the immunologic functions.

Status: 1976-1988, terminated

Treatment: Whole-body single dose exposure to graded doses of γ-rays from Cs-137.

Dosimetry: Ionization chamber

Endpoints: Assessments of the number of T and B cells and T cell subsets in the spleens, splenic anti-sheep red blood cell (SRBC) plaque forming cell (PFC) response, cytotoxic (killer) T cell response of spleen cells to allogeneic target cells as a function of radiation dose etc.

Animal: Male mice of different strains (C3H/He, C57BL/6, B10, B10.BR, BALB/c, B6C3F1) and of varying ages

Results: B cells consists of a homogeneous radiosensitive population, whereas T cells consists of radiosensitive and highly radioresistant subpopulations ; D_0 values of the radiosensitive subpopulations were not significantly different among different T cell subsets but the proportion of the radioresistant subpopulation differs between the helper/inducer (Lyt 1+, L3T4+) T cell subset and the cytotoxic/suppressor (Lyt 2+) T cell subset ; there was a significant difference in the radiosensitivity of anti-SRB PFC response potential among different strains ; no evidence of accelerated aging, or earlier decline of immune response potential as a result of earlier exposure to sublethal doses (2.5-5.8 Gy) of γ-rays.

References: Sado, T., H. Kamisaku, Y. Ikarashi and E. Kubo. Immediate and long-term effects of radiation on immune system of specific-pathogen-free mice. *Int. J. Radiat. Biol,* **53**, 177-187, 1988.

Experimental groups: not commnicated

201.12 Radiation-Induced Immunosuppression and Friend Leukemia Virus (FLV-induced Leukemogenesis in FLV-Resistant B6C3F1 Mice

Institution: National Institute of Radiological Sciences, Division Radiotoxicology, Chiba

Scientists: T. Sado; retired
H. Kamisaku; active
S. Aizawa; active
M. Kitagawa; active

Purpose: To determine the relationship between the degree of immunosuppression induced by radiation and the ease with which the irradiated animals develop leukemias following inoculation with FLV.

Status: 1990-1994, terminated

Treatment: In one experiment, groups of mice were exposed to a single whole-body dose of X-rays (1.5, 3.0, 4.5, and 6.0 Gy); animals from each irradiation and control group were examined for various immunologic functions, i.e., counts of T and B cells and T cell subsets in the spleens, anti-SRBC PFC response, and proliferative response of spleen cells to T and B cell mitogens (PHA, ConA, LPS) 24 hours later, other groups of irradiated and control mice were inoculated with FLV and incidences of FLV-induced leukemia were determined ; in another experiment a group of mice were exposed to 4.5 Gy of X-rays; 1,2,3 and 4 weeks later, these mice were tested for their anti-SRBC PFC response potential or were inoculated with FLV and the incidence of leukemia was determined.

Dosimetry: Victoreen chamber

Endpoints: Assessment of the number of residual T and B cells and T cell subsets in the spleens, splenic anti-sheep red blood cell (SRBC) plaque forming cell (PFC) response, proliferative response of spleen cells to T and B cell mitogens (PHA, ConA, LPS), and incidence of FLV-induced leukemia as a function of radiation dose ; anti-SRBC PFC response and FLV-induced leukemogenesis as a function of time after exposure to 4.5 Gy of whole body irradiation.

Animal: Male B6C3F1 (FLV-resistant) and DBA/2 (FLV-sensitive) mice

Results: The development of FLV-induced leukemia was observed only when immune competence, expressed by relative response to control animals, was less than 0.2 for anti-SRBC PFC and cytotoxic T cell response to allogeneic cells, less than 0.5 for T and B cells and T cell subsets, and less than 0.6 for mitogen responsiveness ; the suppression of the immunologic functions to such levels occurs when B6C3F1 mice were exposed to more than 2 Gy one day before the test was performed or within 2 weeks following exposure to 4.5 Gy.

References: Sado T., H. Kamisaku, S. Aizawa and M. Kitagawa. Radiation-induced immunosuppression and Friends leukemia virus (FLV)-induced leukemogenesis in FLV resistant B6C3F1 mice (in preparation)

Experimental groups: not commnicated

201.13 Mechanism of Fractionated X-Irradiation Induced Thymic Lymphomagenesis in B10 Mice

Institution: National Institute of Radiological Sciences, Division Radiotoxicology, Chiba

Scientists: T. Sado; retired
H. Kamisaku; active
E. Kubo; active

Purpose: To analyze the cellular events that take place during fractionated X-irradiation (FX) induced thymic lymphomagenesis in B10 mice by using bone marrow transplantation between Thy 1 congenic donor-host combinations.

Status: 1985-1990, terminated

Treatment: Whole-body exposure of male B10 mice to fractionated X-irradiation (1.61 Gy x 4, beginning at the age of 33 ± 3 days after birth and with an interval of 8 days between fractions) ; these mice may be used as recipients of bone marrow from normal Thy 1 congenic donors or used as bone marrow donors to reconstitute lethally (9 Gy) irradiated Thy 1 congenic recipient mice.

Dosimetry: Victoreen chamber

Endpoints: 1) Incidence of thymic lymphomas.
2) Thy 1 typing of the developed tumors (thymic lymphomas).
3) Analysis of the kinetics of the repopulation of donor- and host-derived cells in the regenerating thymuses.

Animal: Male B10 (H-2^b, Thy 1.2) and B10.Thy 1.1 mice.

Results: Bone marrow transplantation (BMT) from normal Thy 1 congenic donors into FX-mice within one day after FX-treatment resulted in the suppression of the development of thymic lymphomas, the suppression being exponentially proportional to the increasing number of bone marrow cells injected; the suppression of the tumor development was shown to be due to a prevention of the development of prelymphoma (or preleukemic) cells (where prelymphoma cells are defined as initiated cells that require thymic environment to further develop into autonomously growing neoplastic cells that are no longer thymus dependent); BMT from FX-treated donors, which are deficient of pre T cell, into lethally (9 Gy) irradiated Thy 1 congenic recipients resulted in the development of high incidence of thymic lymphomas most of which (~76%) were *host*-derived; it was concluded that the primary cause of the FX-induced thymic lymphomagenesis was a shortage in supply of primitive T cell precursors (pre T cell) from the bone marrow to the depleted thymus, which caused differentiation arrest of the progeny of the regenerating intrathymic radioresistant T cell precursors, followed by development of

prelymphoma cells that eventually evolve into autonomous lymphoma cells within the thymus.

References: Sado T., H. Kamisaku and E. Kubo. one marrow-thymus interactions during thymic lymphomagenesis induced by fractionated radiation exposure in B10 mice : Analysis using bone marrow transplantation between Thy 1 congenic mice. *J. Radiat. Res.* **32**, Suppl. 2, 168-180, 1991.

Experimental groups: not communicated

202 Institute for Environmental Sciences (IES), Rokkasho-Mura, Aomori

202.01 Evaluation of Stress Responses and Defense Mechanisms Induced by Gamma-Irradiation At Low Doses in Mice

Institution: Institute for Environmental Sciences (IES), Rokkasho-mura, Aomori

Scientists: S. Sasagawa; active
M. Saito; active
T. Yanai; active

Purpose: To determine biochemical indices for stress responses and defense mechanisms and to evaluate induction of stress responses and defense mechanisms by radiation externally irradiated at low dose rates for consecutive days in mice.

Status: 1994 -ongoing

Treatments: Continuous exposure to the Cs-137 gamma sources at various dose rates at the Low-Dose Radiation Effects Research Facilities (LERF) of the IES.

Dosimetry: Ionization chamber

Endpoints: Induction of stress proteins including metallothione

Animal: B6C3F1 SPF mice aged 8 weeks, both sexes

Results: Ongoing research

Experimental Groups:

Study 202.01
Evaluation of Stress Responses and Defense Mechanisms Induced by Gamma-rradiation At Low Doses in Mice

Group Id	Total Dose (mGy)	Dose Rate (mGy/22hr/day)	No Mice*
1	0	0	20
2	240 ~ 4000	20	220

* Includes both sexes.

203 Hokkaido University, Department of Environmental Veterinary Medicine, Laboratory of Radiation Biology, Hokkaido

203.01 Tumor Induction in Offspring From Irradiated Parental Mice

Institution: Laboratory of Radiation Biology, Department of Environmental Veterinary Medicine, Graduate School of Veterinary Medicine, Hokkaido University, Hokkaido

Scientists: F. Sato; active
D. Endoh; active
T. Itakura; active
T. Iwasaki; active
N. Hashimoto; active
T. Imanishi; active

Purpose: To determine whether parental irradiation may induce tumors in the offspring.

Status: 1991 -ongoing

Treatment: Co-60 gamma rays 3 Gy to C57BL/6 male mated with unirradiated C57BL/6 female mice as controls

Dosimetry: Fricke's chemical dosimeter

Endpoints: Life span study with macroscopic / microscopic pathological observation

Animal: C57BL/6CrSlc mice, both sexes

Results: A paper written on the results is reviewed by the Editorial Board of International Journal of Radiation Biology.

References:

Experimental groups:

Study 203.01
Tumor Induction in Offspring From Irradiated Parental Mice

	Group Id	Dose (Gy)	No Mice
Irradiated groups			
Male parents	1	3	109
Female parents	2	0	109
F1 male from irradiated parent	3	0	134
F1 female from irradiated parents	4	0	106
Control groups			
Male parents	5	0	65
Female parents	6	0	65
F1 male from unirradiated parents	7	0	155
F1female from unirradiated parents	8	0	118

204 Tohoku University, Department of Radiation Research, Sendai

204.01 Induction of External Abnormalities in Offspring of Male Mice Irradiated with Cf-252 Neutrons

Institution: Department of Radiation Research, School of Medicine, Tohoku University, Sendai

Scientists: A. Kurishita; active
T. Ono; active
S. Okada; retired
Y. Mori; active
S. Sawada; active

Purpose: To study genetic effects of fission neutron irradiation.

Status: 1992, terminated

Treatment: ICR-MCH male mice were irradiated with 0.24 -1.9 Gy of fission neutron (Cf-252, 63% neutron and 37% gamma, 0.84 cGy/min). They were mated to females 71-120 days after irradiation. Pregnant females were autopsied on day 18 of gestation and external abnormalities in fetuses were examined.

Dosimetry: Fricke's ferrous sulfate.

Endpoints: Open eyelid, dwarfism, exencephaly, umbilical hernia, cleft palate, polydactyly, kinky tail, microphthalmia.

Animal: ICR-MCH mice at 10 weeks of age, males

Results: The frequencies of external abnormalities were 1.40% with 0.238 Gy, 2.23% with 0.475 Gy, 3.36% with 0.95 Gy and 3.26% with 1.9 Gy. The spontaneous level was 1.65%. The linear regression revealed an induction rate of 2.7 / gamete/ Gy in the dose range of 0 - 0.95 Gy.

References: Kurishita A., T. Ono, S. Okada, Y. Mori and S. Sawada, Induction of external abnormalities in offspring of male mice irradiated with ^{252}Cf neutron. *Mutation Res.* **268**, 323-328, 1992.

Experimental groups:

Study 204.01
Induction of External Abnormalities in Offspring of Male Mice Irradiated with Cf-252 Neutron

Group Id	Dose (mGy)	No. of Dams	No. of Live Fetus
1	0	100	1269
2	238	70	924
3	475	70	893
4	950	70	920
5	1900	70	950

205 The University of Tokyo, Faculty of Medicine, Department of Radiation Biophysics, Tokyo

205.01 Does the Capacity to Rejoin Radiation-induced DNA Breaks Decline in Senescent Mice?

Institution: Department of Radiation Biophysics, Faculty of Medicine, University of Tokyo, Tokyo

Scientists: T. Ono; active
S. Okada; retired

Purpose: To examine whether the capacity to repair radiation-induced DNA breaks declines in old mice.

Status: 1978, terminated

Treatment: Whole body irradiation with Cs-137 gamma-rays

Dosimetry: Fricke's ferrous sulfate dosimeter

Endpoints: Rejoining rates of gamma-ray induced DNA single-strand breaks in cerebellum, liver, and spleen

Animal: C57BL/6 and WHT/Ht mouse at 2, 14 and 22 months of age, male

Results: No significant age-related alteration of DNA rejoining rate were observed in all tissues examined.

References: Ono T. and S. Okada, Does capacity to rejoin radiation-induced DNA breaks decline in senescent mice? *Int. J. Radiat. Biol.* **33**, 403-407, 1978.

Experimental groups:

Study 205.01
Does the Capacity to Rejoin Radiation-induced DNA Breaks Decline in Senescent Mice?

Tissue	Age (month)	Dose (Gy)	Group Id	No Mice
Brain	2	0	1	5
		100	2	30
	22	0	3	3
		100	4	9
Liver	2	0	5	9
		400	6	12
	14	0	7	5
		400	8	6
	22	0	9	6
		400	10	11

206 The University of Tokyo, Faculty of Medicine, Department of Radiological Health, Tokyo

206.01 Carcinogenic Effects of Fetal and Postnatal Gamma-Irradiation in Female Mice

Institution: Department of Radiological Health, Faculty of Medicine, University of Tokyo, Tokyo

Scientists: T. Kusama; active
Y. Yoshizawa; active

Purpose: To investigate the carcinogenic effects of fetal and postnatal gamma irradiation on C57BL mice.

Status: 1979-1982, terminated

Treatment: Whole body irradiation with Cs-137 gamma-rays (0.2 Gy/min) with doses of 1 Gy (0.2 Gy/min) on day 15 of gestation; 1 Gy (0.2 Gy/min) 4 Gy (0.2 Gy/min) on the 30th postnatal day.

Dosimetry: Ionization chamber and TLDs

Endpoints: Life-span study (maximum life span : 1036 days)

Animal: C57BL/6J mice, female

Results: The incidences of tumors in the non-irradiated, prenatal 1Gy, postnatal 1Gy and postnatal 4Gy exposure groups were 75.5, 75.0, 79.2 and 83.6%, respectively. There were no ststistically significant differences among the groups in the observed incidences of tumors. However, the distributions of types of tumor differed among experimental groups. In the experimental study of carcinogenesis, especially in life span study, it is needed to adjust for competing risk in order to estimate accurate tumor incidence.

References: T. Kusama T. and Y. Yoshizawa. The carcinogenic effects of fetal and postnatal radiation in female mice. *J. Radiat. Res.* **23**:290-297, 1982.

Experimental Groups:

Study 206.01
Carcinogenic Effects of Fetal and Postnatal Gamma Irradiation in Female Mice

Treatment	GroupId	Dose (Gy)	No of mice
Control groups	1	0	116
Irradiated groups Prenatal irradiation	2	1	65
Postnatal irradiation	3	1	76
Postnatal irradiation	4	4	61

206.02 Dose Dependence of the Severity of Radiation-Induced Thymic Lymphoma in C57BL/6J Mice

Institution: Department of Radiological Health, Faculty of Medicine, University of Tokyo, Tokyo

Scientists: Y. Kikuchi; active
T. Kusama; active

Purpose: To investigate the dose dependence of the *severity* of radiation-induced thymic lymphoma to test the generally assumed postulate of radiation protection that the severity of radiation-induced cancer is independent of dose.

Status: 1993 -ongoing

Treatment: Four exposures to doses of 0.5, 1.5 and 2.0 Gy of Cs-137 gamma rays (0.2 Gy/min) at 8-day interval starting at 4 weeks of age.

Dosimetry: Ionization chamber and TLDs

Endpoints: Periodical sacrifice at days 75, 100, 150, 200 and 300 after first irradiation and observation of pathological and histological changes in each mouse and detection of the p53 protein in each specimen.

Animal: C57BL/6J mice, both sexes

Results: A clear dependence on dose of the severity of thymic lymphoma was observed. The latent periods of thymic lymphoma varied between 75 and 100 days after irradiation and showed no dose-dependency.

References:

Experimental groups:

Study 206.02
Dose Dependence of the Severity of Radiation-Induced Thymic Lymphoma in C57BL/6J Mice

Dose (Gy)	Group Id	No. of mice
Control	1	154
0.5 x 4 (8-day interval)	2	150
1.0 x 4 (8-day interval)	3	146
2.0 x 4 (8-day interval)	4	144

207 Research Institute of Environmental Medicine, Nagoya University, Nagoya

207.01 High Vulnerability of Developing Fetal Brain to Ionizing Radiation.

Institution: Research Institute of Environmental Medicine, Nagoya University, Nagoya

Scientists: Y. Kameyama; active
K. Hoshino; deceased
M. Inouye; active

Purpose: To investigate the mechanism that determines the high vulnerability of developing brain to low-dose radiation, especially the mechanism determining the sensitive phase for the induction of histogenetic disorders in the cerebral cortex.

Status: 1978-1994, terminated

Treatment: Single acute exposure to X-rays (200kVp, 15mA, 0.5mm Cu + 0.5mm Al filter, 0.24 Gy/min) in utero at doses of 0.03-0.48 Gy on day 10-15 of gestation.

Dosimetry: Ionization chamber

Endpoints: Histopathological and immunohistochemical examination of the fetal cerebral mantle at 1-24 hrs. after exposure.

Animal: Slc: ICR mice, both sexes

Results: The acute cell injury in the embryonic telencephalon caused by doses as low as 0.1 Gy did not recover up to 6 hours after exposure. The injured cells expressed apoptotic death beginning at 2 hours after exposure and peaking at 6-9 hours. Radiation-induced cell death in the cerebellar-external granular layer of newborn mice exposed to 0.24 Gy was suppressed completely by cycloheximide, a protein synthesis inhibitor. The high incidence of radiation-induced apoptosis of the telencephalic ventricular cells observed at the beginning of cortical neuron production could be attributed to the emergence of radiosensitive G_1 phase cells at this stage. One of the significant factors determining the period of high sensitivity for radiation-induced apoptosis could be a certain initial phase of chemical cytodifferentiation.

References:

Kameyama, Y. and K. Hoshino. Sensitive phases of CNS development, pp. 75-92. *In* H. Kriegel, W. Schmahl, G.B. Gerber and F.E. Stieve [eds.], *Radiation Risks to the Developing Organism*. Gustav Fischer Verlag, Stuttgart, 1986.

Hoshino, K. and Y. Kameyama. Developmental-stage-dependent radiosensitivity of neural cells in the ventricular zone of telencephalon in mouse and rat fetuses. *Teratology* **37**:257-262, 1988.

Kameyama, Y. and M. Inouye. Irradiation injury to the developing nervous system: Mechanisms of neuronal injury. *Neurotoxic.* **15**:75-80, 1994.

Experimental groups: not communicated

208 Shiga University of Medical Sciences, Department of Experimental Radiology, Shiga

208.01 Changes in Bone Mineral Content and Microscopic Changes in Morphology in Rat Tibia After Irradiation

Institution: Department of Experimental Radiobiology, Shiga University of Medical Science, Shiga

Scientists: H. Kimura; active
M. M. Nyaruba; active
I. Yamamoto; active
M. Ikebuchi; active
R. Morita; active
T. Aoyama; retired

Purpose: To study late effects in bone 1, 2, 4 and 6 months after irradiation in relation to changes in both, bone mineral content and morphology.

Status: 1991 -ongoing

Treatment: Left hind legs of aged female rats were either exposed to 60 Gy as a single dose or to 2.5 Gy X-rays daily fractions with an accumulated dose of 60 Gy.

Dosimetry: Ionization chamber installed in the X-ray machine Hitachi MBR-1520R

Endpoints: Changes in bone mineral content and microscopic pathological observation in morphology.

Animals: Older female Wistar rats of about 30 weeks age

Results: An increase in bone mineral content appeared only in the upper part of the tibia which includes metaphysis, epiphyseal plate and epiphysis. Dose fractionation clearly reduced the effect. Morphological changes in the spongiosa region were associated with an increase in bone mineral content.

References:
Kimura H., I. Yamamoto, M. Ikebuchi, R. Morita and T. Aoyama. Dose fractionation caused reduction of excess mineral deposition by X-rays in rat tibia. Proc. Int. *Conf. on low dose irradiation and biological defense mechanisms*, Kyoto, Japan, 12-16 July 1992.

Nyaruba M. M., I. Yamamoto, H. Miura, M. Ikebuchi, H. Kimura, T. Aoyama and R. Morita. Increase of bone mineral content in rat tibia after irradiation. *Osteoporosis Japan* :3 (2) 198(268)-201(271), 1995

Experimental Groups:

Study 208.01
Changes in Bone Mineral Content and Microscopic Changes in Morphology in Rat Tibia After Irradiation

Group Id	Dose X-rays (Gy) and application	No of ♀ Wistar Rats
1	5 (single)	8
2	7.5 (single)	8
3	10 (single)	8
4	0	5
5	20 (single)	5
6	20 (fractionated)	9
7	0	12
8	40 (single)	5
9	40 (fractionated)	6
10	0	20
11	60 (single)	82
12	60 (fractionated)	14

209 Nara Medical University, Kashihara, Nara

209.01 Accumulation and Biological Functions of Tumor Suppressor Gene P53 Product Induced by a Low Dose of Ionizing Radiation

Institution: Nara Medical University, Department of Biology, Nara

Scientists: T. Ohnishi; active
H. Matsumoto; active
X. Wang; active
A. Takahashi; active

Purpose: To determine the biological function, especially cancer suppression, of the p53 protein accumulated after a low-dose radiation exposure.

Status: 1993- ongoing

Treatments: Whole body irradiation with X-rays (250kVp, 15mA, 1mm Al filter) at a dose rate of 0.50 Gy/min.

Dosimetry: Ionization chamber

Endpoints: Determination of p53 protein expression of principal organs (small intestine, bone marrow, adrenal gland, brain, liver, spleen, hypophysis, skin and testis) at serial sacrifice at 0, 3, 6, 12, 24 or 36 hours after irradiation. The determination of mtation frequency and cancer incidence studies are being planned.

Animal: Six-week-old F344 rat and 4-week-old C57BL/6N mice, all males.

Results:

References:
Wang X., H. Matsumoto, A. Takahashi, T. Nakano, K. Okaichi, M. Ihara and T. Ohnishi. p53 accumulation in the organs of low-dose X-ray-irradiated mice. *Cancer Lett.*, in press.

Wang X., H. Matsumoto, K. Okaichi and T. Ohnishi. p53 Accumulation in Various organs of rats after whole-body exposure to low-dose X-ray irradiation. *Anti-cancer Res.*, in press.

Experimental Groups:

Study 209.01
Accumulation and Biological Functions of Tumor Suppressor Gene P53 Product Induced by Low Dose-ionizing Radiation

Group Id	Dose (mGy)	Time after irradiation (hours)	No of ♂ F344 Rats
1	0	0	3
2	100	0	3
3		3	3
4		6	3
5		12	3
6		24	3
7		36	3
8	250	0	3
9		3	3
10		6	3
11		12	3
12		24	3
13		36	3
14	500	0	3
15		3	3
16		6	3
17		12	3
18		24	3
19		36	3

Group Id	Dose (mGy)	Time After Irradiation (hrs)	No of ♂ C57BL/6N Mice
20	0	0	3
21	250	0	3
22		3	3
23		6	3
24		12	3
25		24	3
26		36	3
27	500	0	3
28		3	3
29		6	3
30		12	3
31		24	3
32		36	3
33	1000	0	3
34		3	3
35		6	3
36		12	3
37		24	3
38		36	3

210 Osaka University, Faculty of Medicine, Department of Radiation Biology, Osaka

210.01 Effect of Radiation Dose Rate on Survival and Cancer Incidence in Mice

Institution: Department of Radiation Biology, Faculty of Medicine, Osaka University, Osaka

Scientists: T. Nomura; active
H. Nakajima,active
T. Hongyo; active
K. Fukuda; active
E. Taniguchi; active
M. Kurooka; active
L. Y. Li; active
K. Suto,active
K. Mori,active

Purpose: To determine the influence of radiation dose rate on late effects in C57BL/6J and C3H/HeJ mice.

Status: 1988 -ongoing

Treatment: Exposure to Co-60 gamma-ray (1.7 or 0.5 Gy x 4) at different dose rate 0.0002, 0.001, 0.002, 0.01, 0.05, 0.57 Gy/min

Dosimetry: Radcon standardized with standard source

Endpoints: Cause of animal death with macroscopic/ microscopic pathological observation and molecular studies

Animals: C57BL/6J and C3H/HeJ mice of 6 weeks of age, both sexes

Results:

References:

Experimental Groups: Not communicated, total 2,500 male and female mice

210.02 Programmed Cell Deaths (Apoptosis) by Low Dose Radiation

Institution: Department of Radiation Biology, Faculty of Medicine, Osaka University, Osaka

Scientists: T. Nomura; active
H. Nakajima; active
T. Hongyo; active

Purpose: To determine the genes controlling the sensitivity to radiation induced programmed cell death at low doses.

Status: 1982 -ongoing

Treatment: Single exposure to X-rays (180kVp, 20mA, 0.5mm Cu, 1.0mm Al) at 0.01, 0.02, 0.05, 0.1, 0.25, 0.5 Gy

Dosimetry: Radcon standardized with Fricke dosimetry

Endpoints: Cell killing (apoptosis)

Animals: 50 Inbred strains, both sexes

Results:

References: Nomura, T., Kinuta, M., T., Nakajima, H. and Hatanaka, T. Programmed cell death in whole body and organ system by low dose radiation. *J. Radiat. Res.* **33**:Suppl., 109-123, 1992.

Experimental Groups: Not communicated, 500 mice in total

210.03 Radiation Carcinogenesis of Human Tissues Transplanted Into scid Mice

Institution: Department of Radiation Biology, Faculty of Medicine, Osaka University, Osaka

Scientists: T. Nomura; active
H. Nakajima; active
T. Hongyo; active
K. Fukuda; active
E. Taniguchi; active
M. Kurooka; active
L. Y. Li; active
K. Suto; active
K. Mori; active

Purpose: To determine the radiation carcinogenesis of transplanted human organs and tissues.

Status: 1987 -ongoing

Treatment: Exposure to Co-60 gamma-rays, X-rays (180kVp, 20mA, 0.5mm Cu, 1.0mm Al) and UVB

Dosimetry: Co-60 gamma-ray: Radcon standardized with standard source, X-rays: Radcon standardized with Fricke dosimetry

Endpoints: Mutation and cancer induction

Animals: C.B17/N-scid/scid, C57BL/6J/N-scid, C3H/HeJ/N-scid mice, both sexes

Results:

References:

Experimental Groups: Not communicated, 1,000 mice in total

210.04 Transgenerational Effects of Radiation in Mice and Humans

Institution: Department of Radiation Biology, Faculty of Medicine, Osaka University, Osaka

Scientists: T. Nomura; active
H. Nakajima; active
T. Hongyo; active
K. Fukuda; active
E. Taniguchi; active
M. Kurooka; active
L. Y. Li; active
K. Suto; active
K. Mori; active

Purpose: To determine the induction of mortality, malformations, and tumors after parental exposure to radiation.

Status: 1967 -ongoing

Treatment: Exposure to Co-60 gamma-rays and X-rays (180kVp, 20mA, 0.5mm Cu, 1.0mm Al)

Dosimetry: Co-60 gamma-ray: Radcon standardized with standard source, X-rays: Radcon standardized with Fricke dosimetry

Endpoints: Mortality, malformation, cancer, mutation

Animals: ICR, N5, LT mice both sexes

Results:

References:

Nomura, T. Changed urethane and radiation response of the mouse germ cell to tumor induction. In: *Tumors of Early Life in Man and Animals*. (Ed. Severi L.), pp. 873-891, Perugia Univ. Press, Perugia, 1978.

Nomura, T. Parental exposure to X-rays and chemicals induces heritable tumors and anomalies in mice. *Nature* **296:** 575-577, 1982.

Nomura, T. X-ray induced germ-line mutation leading to tumors: its manifestation in mice given urethane post-natally. *Mutation Res.* **121**: 59-65, 1983.

Nomura, T. Further studies on X-ray and chemically induced germ-line alterations causing tumors and malformations in mice. In: *Genetic Toxicology of Environmental Chemicals, Part B: Genetic Effects and Applied Mutagenesis* (Ed. Ramel, C.), pp. 13-20, Alan R. Liss, New York, 1986.

Nomura, T. Tumors and malformations in the offspring. In: Functional Teratogenesis (Eds. Fujii, T. and Adams, P. M.), pp. 175-185, Teikyo Univ. Press, Tokyo, 1987.

Nomura, T. X-ray and chemically induced germ-line mutation causing phenotypical anomalies in mice. *Mutation Res.* **198**: 309-320, 1988.

Nomura, T. Role of radiation-induced mutation in multigeneration carcinogenesis. In: *Perinatal and Multigeneration Carcinogenesis* (Eds. Napalkov, N. P., Rice, J. M., Tomatis, L. and Yamasaki, H.), IARC Scientific Publications No. 96, pp. 375-387, 1989.

Nomura, T., Gotoh, H., and Namba, T. An examination of respiratory distress and chromosomal abnormalities in the offspring of male mice treated with ethylnitrosourea. *Mutation Res.* **229**: 115-122, 1990.

Nomura, T. Of mice and men? *Nature* **345**:671, 1990.

Nomura, T. Multigeneration carcinogenesis. *Radiat. Environ. Biophys.* **30**: 201-203,

Nomura, T. Paternal exposure to radiation and offspring cancer in mice: reanalysis and new evidences. *J. Radiat. Res.* **32**: Suppl. 2, 64-72, 1991.

Nomura, T. In utero and transgeneration effects and biological defense mechanism in mice. In: *Low Dose Irradiation and Biological Defense Mechanism* (ed. Sugahara, T.), pp. 143-149, Elsevier, Amsterdam, 1992.

Nomura, T. Genetic effects of radiation and offspring cancer. In: *Low Dose Radiation and Living State* (ed. Huilgol, N. G.), pp. 40-56, Narosa Publ., Bombay (Springer-Verlag, Berlin), 1993.

Nomura, T. Leukaemia in children whose parents have been exposed to radiation. *Brit. Med. J.* **306:** 1412, 1993.

Experimental Groups: Not communicated, total 10,000 mice and 10,000 fetuses

210.05 *In Vivo* Somatic Mutations by Low Dose Radiation in Mice

Institution: Department of Radiation Biology, Faculty of Medicine, Osaka University, Osaka

Scientists: T. Nomura; ,active
H. Nakajima; active
T. Hongyo; active
T. Hatanaka; active
M. Kinuta; active
A. Nomura; active

Purpose: To determine the dose-response relationship of *in vitro* somatic mutations in the mouse embryo at low dose range.

Status: 1978 -ongoing

Treatment: X-Rays (180kVp, 20mA, 0.5mm Cu, 1.0mm Al), Co-60 gamma-rays, Cf-252 neutron and H-3 water

Dosimetry: X-Rays: Radcon standardized with Fricke dosimetry, Co-60 gamma-ray: Radcon standardized with standard source, neutron: twin ionization chamber

Endpoints: Coat colour mutation in PT-HTF1 mice

Animals: Male HT and female PT mice

Results:

References: Nomura, T. And Yamamoto O. *In vivo* somatic mutation in mice induced by tritiated water. In: Proceeding of the 3rd Japan-US *Workshop on Tritium Radiobiology and Health Physics* (Ed. Okada, S.), pp. 230-233, Inst. Plasma Physics, Nagoya Univ., Nagoya, 1989.

Experimental Groups: Not communicated, total 5,000 PT-HTF1 mice

211 Osaka Prefecture University, Research Institute of Advanced Science and Technology, Deptartment of Applied Biological Sciences, Osaka

211.01 Lack of Evidence for the Involvement of Type-C and Type-B Retroviruses in Radiation Leukemogenesis of NFS Mice

Institution: Department of Applied Biological Sciences, Research Institute for Advanced Science. & Technology, Osaka Prefecture University, Sakai

Scientists: M. Okumoto; active
R. Nishikawa; active
M. Iwai; active
Y. Iwai; active
Y. Takamori; active
O. Niwa; active
K. Yokoro; retired

Purpose: To examine the involvement of retroviruses in radiation leukemogenesis.

Status: 1986-1990, terminated

Treatments: Four doses of 1.7 Gy (0.5 Gy/min.) of X-rays (250kV, 0.3mm Cu, 0.5mm Al filter) at weekly intervals starting at 4 weeks of age

Dosimetry: Precision electrometer Model 500 with a #550-5 probe (Victoreen Inc. U.S.A.)

Endpoints: Lymphoma development was followed until 1 year after the last irradiation. Lymphoma DNAs were examined by Southern blot and dot blot hybridization

Animal: NFS/N mice, both sexes

Results: Radiation lymphomagenesis does not appear to involve the activation of endogenous type-C and type-B retroviruses.

References: Okumoto M., R. Nishikawa, M. Iwai, Y. Iwai, Y. Takamori, O. Niwa and K. Yokoro. Lack of evidence for the involvement of type-C and type-B retroviruses in radiation leukemogenesis of NFS mice. *Radiat. Res.* **121:** 267-273, 1990.

Experimental Groups:

Study 211.01
Lack of Evidence for the Involvement of Type-C and Type-B Retroviruses in Radiation Leukemogenesis of NFS Mice

Strain	Group Id	Dose (Gy)	No. of mice
NFS/N ♀	1	four fractions 1.7 Gy each	91
NFS/N ♂	2	four fractions 1.7 Gy each	72

211.02 Resistance of STS/A Mice to Lymphoma Induction by X-Irradiation

Institution: Department of Applied Biological Sciences, Research. Institute for Advanced Science. & Technology, Osaka Prefecture University, Sakai

Scientists: M. Okumoto; active
R. Nishikawa; active
S. Imai; active
J. Hilgers; active

Purpose: To analyze a strain difference of susceptibility to lymphoma induction by X-irradiation.

Status: 1987-1989, terminated

Treatment: Four doses of 1.7 Gy (0.5 Gy/min.) of X-rays (250kV, 0.3mm Cu, 0.5mm Al filter) at weekly intervals starting at 4 weeks of age

Dosimetry: Precision electrometer Model 500 with a #550-5 probe (Victoreen Inc. U.S.A.)

Endpoints: Lymphoma development was followed until 1 year after the last irradiation. Type of lymphomas were determined histopathologically and immunologically

Animal: BALB/cHeA, STS/A mice both sexes

Results: STS/A mice are extremely resistant to lymphoma induction by X-irradiation

References: Okumoto M., R. Nishikawa, S. Imai and J. Hilgers. Resistance of STS/A mice to lymphoma induction by X-irradiation. *J. Radiat. Res.* **30**:135-139, 1989.

Experimental Groups:

Study 211.02
Resistance of STS/A Mice to Lymphoma Induction by X-Irradiation

Strain		Group Id	Dose (Gy)	No. of mice
STS/A	♀	1	four fractions 1.7 Gy each	60
STS/A	♂	2	four fractions 1.7 Gy each	68
BALB/cHeA	♀	3	four fractions 1.7 Gy each	43
BALB/cHeA	♂	4	four fractions 1.7 Gy each	27

211.03 Genetic Analysis of Resistance to Radiation Lymphomagenesis with Recombinant Inbred Strains of Mouse

Institution: Department of Applied Biological Sciences, Research. Institute for Advanced Science. & Technology, Osaka Prefecture University, Sakai

Scientists: M. Okumoto; active
R. Nishikawa; active
S. Imai; active
J. Hilgers; active

Purpose: To analyze some genes that control the incidence of radiation-induced lymphomas.

Status: 1988-1995, terminated

Treatment: Four doses of 1.7 Gy (0.5 Gy/min.) of X-rays (250kV, 0.3mm Cu, 0.5mm Al filter) at weekly intervals starting at 4 weeks of age.

Dosimetry: Precision electrometer Model 500 with a #550-5 probe (Victoreen Inc. U.S.A.).

Endpoints: Lymphoma development was followed until 1 year after the last irradiation. The type of lymphomas was determined histopathologically and immunologically.

Animal: BALB/cHeA, STS/A, CXS recombinant inbred strains, both sexes

Results: Resistance to radiation lymphomagenesis is controlled by one major locus (Lyr) in a region with the b and Ifa loci on chromosome 4.

References: Okumoto M., R. Nishikawa, S. Imai and J. Hilgers. Genetic Analysis of resistance to radiation lymphomagenesis with recombinant inbred strains of mice. *Cancer Res.* **50**:3848-3850, 1990.

Experimental Groups:

Study 211.03

Genetic Analysis of Resistance to Radiation Lymphomagenesis with Recombinant Inbred Strains of Mouse

Strain	Group Id	Dose (Gy)	No. of mice
Recombinant inbred strain			
CXSG ♀	1	four fractions 1.7 Gy each	41
CXSA ♀	2	four fractions 1.7 Gy each	48
CXSI ♀	3	four fractions 1.7 Gy each	41
CXSC ♀	4	four fractions 1.7 Gy each	41
CXSL ♀	5	four fractions 1.7 Gy each	46
CXSF ♀	6	four fractions 1.7 Gy each	27
CXSK ♀	7	four fractions 1.7 Gy each	28
CXSB ♀	8	four fractions 1.7 Gy each	50
CXSN ♀	9	four fractions 1.7 Gy each	48
CXSJ ♀	10	four fractions 1.7 Gy each	39
CXSH ♀	11	four fractions 1.7 Gy each	44
CXSE ♀	12	four fractions 1.7 Gy each	18
Progenitor			
BALB/cHeA (C) ♀	13	four fractions 1.7 Gy each	43
STS/A (S) ♀	14	four fractions 1.7 Gy each	60
Cross			
(CXS)F1 ♀	15	four fractions 1.7 Gy each	35
(CXS)F1 x C ♀	16	four fractions 1.7 Gy each	31
(CXS)F1 x S ♀	17	four fractions 1.7 Gy each	45

211.04 Radiation-Induced Lymphomas in MSM, (BALB/cHeA x MSM)F1 and (BALB/cHeA x STS/A)F1 Hybrid Mice.

Institution: Department of Applied Biological Sciences, Research. Institute for Advanced Science. & Technology, Osaka Prefecture University, Sakai

Scientists: M. Okumoto; active
N. Mori; active
N. Miyashita; active
K. Moriwaki; active
S. Imai; active
S. Haga; active
S. Hiroishi; active
Y. Takamori; active
K. Esaki; active

Purpose: To examine a strain difference of susceptibility to lymphoma induction by X-irradiation in mice.

Status: 1990-1995, terminated

Treatment: Four doses of 1.7 Gy (0.5 Gy/min) of X-rays (250kV, 0.3mm Cu, 0.5mm Al filter) at weekly intervals starting at 4 weeks of age, whole-body irradiation.

Dosimetry: A precision electrometer Model 500 with a #550-5 probe (Victoreen Inc. U.S.A.).

Endpoints: Lymphoma development was followed until 1 year after the last irradiation. The type of lymphoma was determined histopathologically and immunologically.

Animal: MSM, STS/A, BALB/cHeA, (BALB/cHeA x MSM)F1, (BALB/cHeA x STS/A)F1 hybrid mice, both sexes

Results: MSM mice show extreme resistance to the induction of lymphomas following whole-body X-irradiation similar to STS/A mice. But (BALB/cHeA x MSM)F1 and (BALB/cHeA x STS/A)F1 mice show a high incidence of radiation-induced lymphomas.

References: Okumoto M., N. Mori, N. Miyashita, K. Moriwaki, S. Imai, S. Haga, S. Hiroishi, Y. Takamori and K. Esaki. Radiation-induced lymphomas in MSM, (BALB/cHeA x MSM)F1 and (BALB/cHeA x STS/A)F1 hybrid mice. *Exp. Anim.* 44(1):43-48, 1995.

Experimental Groups:

Study 211.04
Radiation-Induced Lymphomas in MSM, (BALB/cHeA x MSM)F1 and (BALB/cHeA x STS/A)F1 Hybrid Mice.

Strain		Group Id	Dose (Gy)	No. of Mice
MSM	♀	1	four fractions 1.7 Gy each	30
BALB/cHeA	♀	2	four fractions 1.7 Gy each	43
	♂	3	four fractions 1.7 Gy each	28
(BALB/cHeA x MSM)F1	♀	4	four fractions 1.7 Gy each	18
	♂	5	four fractions 2.5 Gy each	17
	♀	6	four fractions 2.5 Gy each	53
STS/A	♀	7	four fractions 1.7 Gy each	60
	♂	8	four fractions 1.7 Gy each	68
	♀	9	four fractions 2.5 Gy each	39
	♂	10	four fractions 2.5 Gy each	29
(BALB/cHeA x STS/A)F1	♀	11	four fractions 1.7 Gy each	35
	♀	12	four fractions 2.5 Gy each	56
	♂	13	four fractions 2.5 Gy each	24

212 Hiroshima University, Research Institute for Radiation Biology and Medicine, Hiroshima

212.01 Effects of Dose Rate and Energy Level on Cf-252 Tumorigenesis in B6C3F1 Mice

Institution: Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima

Scientists: H. Watanabe; active
M. Hoshi; active
S. Sawada; retired

Purpose: To determine the tumorigenic effects of fission neutrons at different dose rates and at lowering neutron energies by an iron block filter.

Status: 1991-1992, terminated

Treatment: External, whole body exposure to the Cf-252 source (71.4 Gbq). Fission neutron spectra ranged from 0.1 to 1.1 MeV with a peak at 0.7 MeV. Dose rate 8 mGy/min without iron filter, 0.5 mGy/min with 10 cm thick iron block. Total neutron dose 0.5 Gy.

Dosimetry: Ionization chambers (IC-17 and IC-17G; Far West Technology, Goleta, CA) and Fricke and thermoluminescence dosimeters

Endpoints: Tumorigenesis

Animal: Six-week-old female COBS B6C3F1 mice (C57BL/6NCrj x C3H/HeNCrj)

Results: A significant increase in tumorigenesis with the higher dose rate and no filtering influence of iron was evident, despite the decrease in neutron energy level.

References: Watanabe H., T. Okamoto, K. Yamada, Y. Ando, A. Ito, M. Hoshi and S. Sawada. Effects of dose rate and energy level on fission neutron (^{252}Cf) tumorigenesis in B6C3F1 mice. *J. Radiat. Res.* **34:** 235-239, 1993.

Experimental Groups:

Study 212.01
Effects of Dose Rate and Energy Level on Cf-252 Tumorigenesis in B6C3F1 Mice

Strain	Sex	Group Id	Fe filter	Dose rate (mGy/min)	Neutron dose (mGy)	Total dose (mGy)	No. of mice
B6C3F1	♀	1	+	0.5	500	560	30
B6C3F1	♀	2	-	0.5	500	750	30
B6C3F1	♀	3	-	8	500	750	30
B6C3F1	♀	4	-	0	0	0	30

212.02 Influence of Paternal Cf-252 Exposure in the F1 Offspring of Mice

Institution: Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima

Scientists: H. Watanabe; active
T. Takahashi; active
J.-Yi. Lee; active
A. Ito; active

Purpose: To investigate whether radiation-induced genetic damage can be passed to the offspring causing embryonic lethality and liver tumors in the F1 generation after paternal exposure of mice to Cf-252 neutrons.

Status: 1989 -ongoing

Treatment: External, whole body exposure to a Cf-252 source (71.4 GBq). Fission neutron spectra ranged from 0.1 to 1.1 MeV with a peak at 0.7 MeV. Dose rate 8 mGy/min. and doses of 0, 0,5, 1, 2 Gy.

Dosimetry: Iron chambers (IC-17 and IC-17G; Far West Technology, Goleta, CA) and Fricke and thermoluminescence dosimeters

Endpoints: Abnormal sperm, embryonal lethality, liver tumorigenesis

Animal: 7-week-old C3H/HeNCrj mice, male
9-week-old C57BL/6NCrj mice, female

Results:

1) Two weeks after irradiation, irradiated C3H male mice showed on increased incidence of sperm abnormalities, which led to embryo lethalities in a dose-dependent way when mated with unirradiated female mice.
2) Liver tumors in male offspring born to male mice irradiated with the 0.5Gy group significantly increased in 43.2% of the animals, in clear contrast to the unirradiated group value of 3.2%.
3) At 3 months after irradiation abnormal sperms and lethalities were not significantly increased.
4) The incidence of liver tumors in male offspring from the 0.5 Gy, 1 y and 2 y irradiated groups were 30%, 23% and 5%, respectively, but not significantly increased compared with that of control.

References:

Takahashi T., H. Watanabe, K. Dohi and A. Ito. ^{252}Cf relative biological effectiveness and inheritable effect of fission neutrons in mouse liver tumorigenesis. Cancer Res., 52, 1948-1953, 1992.

Watanabe H., T. Takahashi, J.-Yi Lee, M. Ohtaki, G. Roy, Y. Ando, K. Yamada, T. Gotoh, K. Kurisu, N. Fujimoto and A. Ito. Influence of paternal ^{252}Cf neutron exposure on abnormal sperm, embryonal lethality, and liver tumorigenesis in F_1 offspring of mice. *Jpn. J. Cancer Res.* **87:** 51-57, 1996

Experimental Groups:

Study 212.02

Influence of Paternal Cf-252 Exposure in the F1 Offspring of Mice

A. Body, liver, spleen, testis weight and ratio of abnormal sperms.

Strain	Neutron Dose (Gy)	Group Id	No of Mice	Observation
C3H/HeNCrj ♂	0	1	13	3 weeks after irradiation
	0.5	2	16	3 weeks after irradiation
	1	3	30	3 weeks after irradiation
	2	4	20	3 weeks after irradiation
C3H/HeNCrj ♂	0	5	27	3 months after irradiation
	0.5	6	25	3 months after irradiation
	1	7	18	3 months after irradiation
	2	8	30	3 months after irradiation

B. Lethality in embryos from irradiated male mice.

Strain	Father's radiation dose (Gy)	Group Id	Mating time	No of mother (Female 9-week-old) C57BL	No of embryo (18-day-old) B6C3F1
C3H/HeNCrj ♂ (7-week-old)	0	9	2 weeks after irradiation	14	96
	0.5	10		18	124
	1	11		19	121
	2	12		16	78
C3H/HeNCrj ♂ (7-week old)	0	13	3 months after irradiation	18	147
	0.5	14		7	54
	1	15		9	60
	2	16		18	154

C. Incidence of liver tumors in F1 offspring (B6C3F1).

Father's Radiation Dose (Gy)	Group Id	Sex of Offspring	Mating Time	No Mice
0	17	♂	2 weeks after irradiation	31
0.5	18	♂		44
1	19	♂		39
2	20	♂		0
0	21	♀	2 weeks after irradiation	30
0.5	22	♀		58
1	23	♀		35
2	24	♀		0
0	25	♂	3 months after irradiation	33
0.5	26	♂		20
1	27	♂		22
2	28	♂		19
0	29	♀	3 months after irradiation	-
0.5	30	♀		18
1	31	♀		24
2	32	♀		14

INDEX 1. Animal Species and Strains Used in the Experiments

Animal	Experiment No
Monkeys	
Baboons	02.09
Rhesus	11.03, 106.01, 106.02, 110.02, 110.05
Stumptail	106.02
Cynomolgus	106.02
Dogs	
Beagles	13.23, 17.01, 17.02, 17.03, 17.04, 17.05, 17.06, 17.07, 17.08, 17.09, 17.10, 101.01, 101.02, 101.03, 101.04, 101.5, 101.6, 101.7, 101.08, 101.09, 101,10, 101.11, 101.12, 101.13, 101.14, 102.01, 102.02 102.03, 102.04, 103.01, 103.02, 103.03, 103.04, 103.05, 103.06, 103.07, 104.01, 104.02, 104.03, 104.04, 104.05, 105.01, 105.02, 105.03, 105.04, 105.05, 105.06, 105.07, 105.08, 105.09, 105.10, 105.11, 105.12, 105.13, 105.14, 105. 15, 105.16, 105.17, 105.18, 105.19, 108.01, 108.02, 108.03, 110.03, 110.04, 110.05, 110.08
Cats	110.01, 110.03
Pigs	02.20, 02.21, 16.01, 18.01
Mice	
A/He	103.10, 103.11, 103.12, 103.13, 103.14, 103.16, 103.18
A/Jax	103.10, 103.11, 103.12, 103.16, 103.17, 103.18
AKR	05.06
B10 (.BR ...)	201.11, 201.13
$B6CF_1$	103.17, 103.20, 103.21, 103.22, 103.23, 103.24, 103.25, 103.26, 103.28, 103.29, 103.30, 105.35
$B6C3F_1$	201.03, 201.10, 201.11, 201.12, 202.01, 212.01
BALB/c[Cnb]	05.06, 05.08, 09.03, 09.04, 09.05 13.02, 103.10, 103.11, 103.12, 103.13, 103.16, 103.17, 103.18, 201.11
BALB/cBd	107.01
BALB/cHeA	211.02, 211.03, 211.04 (also hybrides)
BALB/c.C57BL/6 hybrids	103.10, 103.11
BCF_1	103.13, 103.16, 103.18,
BCF_2	103.16
BC3F1	
$\{C57BL/CnexC3H/Cne\}F_1$	03.01, 03.02, 03.04, 03.05, 201.10
C3H(f) (/He)	103.09, 103.10, 103.13, 103.14, 103.16, 103.18, 107.02, 110.03, 201.02, 201.05, 201.06, 201.07, 201.11, 210.01, 212.02
C3Hx102/F1	05.09
R=F1(C3Hx101	07.08
C57BL	05.06, 05.08, 07.08 13.02,13.04, 13.14
C57BL/6 (J) (N)	10.03, 103.10, 103.11, 103.12, 103.13, 103.14, 103.16, 103.17, 103.18, 105.20, 105.21 201.01, 201.11, 205.01, 212.02, 206.01, 206.02, 209.01, 210.01
C57BL/6CrSlc	203.01
C57BL/6Bd	107.02, 109.01
C57BL/Cne	09.01, 09.02, 09.04, 09.06, 09.07, 09.08, 09.09, 09.10

C57L	103.10, 103.11, 103.16, 103.18
CB3H/He	203.08
CBA	05.05, 05.06, 05.07, 05.08, 07.08
CBA/CA	01.01, 01.02, 01.03, 01.04, 01.05, 10.03, 10.05, 109.01, 109.02
CBA/H	07.01, 07.02, 07.03, 07.04, 07.05, 07.06, 07.07, 07.08, 07.09, 08.01, 13.18, 111.03
CBA/H/Cne	03.03
CBA/S	13.01, 13.02, 13.03, 13.05, 13.06, 13.07, 13.08, 13.09, 13.10, 13.11, 13.12, 13.13, 13.15, 13.16, 13.17, 13.18, 13.19, 13.20, 13.21, 13.22, 13.24
CD1	10.03
CF1	110.02
CXS	211.03
DBA/2	201.12
DBAxC57/BL	110.06, 110.07(derived Bragg albino, CFCW Carworth)
102/Ghg	05.06
Heiligenberg strain	12.01
HT	210.05
LAF1	103.08, 103.15, 103.16, 103.18, 103.19
LT	210.04
ICR-MCH	204.01, 210.04
MSM	211.04
N5	210.04
NFS/N	211.01
NMRI	05.01, 05.02, 05.03, 05.04, 05.05, 05.06, 05.07, 05.08, 13.01
PT	210.05
RFM/Bd	107.01
RFM f/un	107.03
SAS/4	10.01, 10.02, 10.03, 10.04
SCID	201.04
C.B-17 x SCID F_1	201.04, 210.03
C57BL/6J/N-SCID	210.03
C3H/HeJ/N-SCID	209.03
Slc: ICR	207.01
STS/A	211.02, 211.03, 211.04
XG/F	05.06
Swiss Albino	13.02
WHT/Ht	205.01
Various F1 hybrids	05.09, 13.02, 103.12
Various strains (not specified)	110.03
White footed field mouse (Peromyscus leucopus)	103.27

Rats

Brown Norway (BN/BIRIJ)	11.01, 11.02
CDF (F344)/CrlBR	105.24, 105.25, 105.26, 105.27, 105.30, 105.31, 105.32, 105.33, 105.34, 105.35, 105.36, 209.01
Brown Norway x F344/N F1	105.35
CFW	105.29
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Long Evans	110.02

INDEX 2. Chemical Substances Used in the Experiments

INDEX 3. Radiation Sources Used in the Experiments

External

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Other neutrons(accelerator)	
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high energy	09.05, 09.06, 201.01
Neutrons from ^{252}Cf	02.12, 02.17, 09.12, 204.01, 210.05, 212.01, 212.02

α-particles

from accelerator	02.12
from ^{244}Cm	10.01
β-rays	02.21, 07.09, 10.03, 11.02, 16.01

Radionuclides

$^{3}H_2O$	111.01, 111.03, 210.05
^{45}Ca	inh. 01.03, inj. 01.04
^{59}Fe	inh 02.06
^{89}Sr	oral 14.02; inj. 110.02
^{90}Sr	inj. 05.02, 13.01, 13.02, 13.05, 13.06, 13.07, 13.08, 13.09, 13.12, 13.13, 13.16,13.17, 13.19, 13.20, 13.23, 14.01, 101.05, 102.02, 102.03, 103.01, 103.02 oral 14.01, 14.02, 102.02, 106.01, 110.02 inh. 105.01, 105.08
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^{91}Y	inh. 105.03, 105.07
^{131}I	13.24, 14.02
^{137}Cs	inj. 13.22, 103.04, 105.05
^{141}Ce	inh. 02.07
^{144}Ce	inj. 02.06, 02.07, 103.03 inh. 02.07, 105.02, 105.04, 105.09, 105.10, 105.11, 105.21, 105.23, 105.25, 105.30
^{147}Pm	oral 14.02
^{169}Yb	inh. 104.06, 105.22
^{177}Lu	inj. 05.03, 05.04, 05.07,
^{210}Po	inj., oral, inh. 110.01, 110.02
^{222}Rn	inh. 01.06, 02.02 02.03 02.04 02.05, 02.06, 02.14, 11.04
^{224}Ra	inj. 05.01, 05.02, 05.05, 05.07, 07.01, 07.02, 07.03, 07.04, 101.14

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