From the Field to the Laboratory and Back: The What ifs, Wows and Who Cares of Radiation Biology

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Abstract:

My scientific journey started at the University of Utah chasing fallout. It was on everything, in everything, and was distributed throughout the ecosystem. This resulted in radiation doses to humans and caused me great concern. From this concern I asked the question, "Are there health effects from these radiation doses and levels of radioactive contamination?" I have invested my scientific career trying to address this basic question. While conducting research I got acquainted with many of the **What ifs** of radiation biology. The major **What if** in my research was, "What if we have underestimated the radiation risk for internally deposited radioactive material?" While conducting research to address this important question, many other **What ifs** came up related to dose, dose-rate and dose distribution. I also encountered a large number of **Wows**. One of the first was when I went from conducting environmental fallout studies to research in a controlled laboratory. The activity in fallout was expressed as pCi/Liter, whereas it was necessary to inject laboratory animals with μCi/g body weight to induce measurable biological changes, chromosome aberrations and cancer. **Wow**, that is 7-9 orders of magnitude above the activity levels found in the environment. Other **Wows** have made it necessary for the field of radiation biology to make important paradigm shifts. For example, one shift involved changing from "hit theory" to total tissue responses as the result of bystander effects. Finally, **Who Cares?** While working at DOE headquarters and serving on many scientific committees, I found that science does not drive regulatory and funding decisions. Public perception and politics seem to be major driving forces. If scientific data suggested that risk had been underestimated, everyone cared. When science suggested that risk had been overestimated, no one cared. This result dependent **Who Cares?** was demonstrated as we tried to generate interactions by holding meetings with individuals involved in basic low dose research, regulators and the news media. As the scientists presented their "exciting data" that suggested that risk was overestimated, many of the regulators simply said, "We cannot use such data." The news paper people said, "It is not possible to get such information by my editors." In spite of these

difficulties, research results from basic science must be made available and considered by the public, as well as by those that make regulatory recommendations. Public outreach of the data is critical and must continue to be a future focus to properly address the question of "**Who Cares**?". My journey in science, like many of yours, has been a mixture of chasing money, beatings and the joys of unique and interesting research results. Perhaps we can through our experiences improve research environments, funding and use of the valuable information that is generated. Scientists that study at all levels of biological organization, from the environment to the laboratory and human epidemiology must share expertise and data to address the **What ifs, Wows** and **Who cares** of radiation biology.

Introduction

It is a great honor for me to present the 36th L.S. Taylor Lecture. As a member of the NCRP for 30 years, I have worked actively with the organization that Dr. Taylor founded. I didn't know Dr. Taylor on a first name basis, but talked with him during my early days in the NCRP and always listened closely and respected everything he had to say. I want to thank the NCRP, especially Dr. Thomas Tenforde, for the support he has given me. Without his long hours, hard work and leadership, the NCRP would have been in serious trouble. I also want to thank Dr. William Morgan for letting me work at PNNL over the past two years. It has made it possible for me to keep my finger on the pulse of the field of Radiation Biology. Thanks to Dr. Noelle F. Metting for letting me work on the DOE Low Dose Research Program for the past 13 years. Finally, I must thank Dr. Roger O. McClellan for his support during my early days in the field and for the "kind" introduction. We had a wonderful research environment at Lovelace ITRI, where my only real job was to conduct research. Roger was really helpful making sure I set up the experiments carefully, evaluated the data and tried to understand what the data was telling me, not what was expected from the data. We had many vigorous and exciting discussions on every bit of data produced at ITRI. If you had your guns loaded, he would listen, but if not, you would get yourself so badly beaten down that you could have crawled out from under his door.

Early Life

My experience with radiation and radioactive materials came very early in life. As a young boy in my home town of St. George, Utah, we would often wake up in the early morning and watch

the sky light up, then count to see how long it would take to feel the earth tremble. Another atomic bomb (one of 103 that were tested above ground) had been set off at the Nevada test site. It was exciting to think of all the power involved. In St. George, we also had a truck with loud speakers mounted on the top that would drive around town and announce the local events, basket ball games, celebrations etc. In 1953, when I was 15 years old, they announced that a fallout cloud from the Nevada test site (Harry) was over town and that we should all go indoors. No-way. Not when I was in the middle of a basketball game! We had little concern at that time about fallout or health effects of radiation. Later, while working in a service station, I remember having the AEC pull cars into our station that had gone through a fallout cloud. I had to wash them. **What if** fallout could cause cancer or genetic problems? If it was not good to have fallout on the cars, why did they want us to wash it all off and keep it in the sump in our service stations? I am reminded of those sumps today when I see many current clean-up projects where we still just move radioactive materials around and often concentrate them.

I attended Dixie Junior College in St. George. My first concern about the potential health impact of fallout was when Dr. Arthur F. Bruhn, the president of Dixie, developed leukemia and died. Many in town blamed the fallout for his death and many books have been written on both sides of this concern.

The Fallout Days

I attended the University of Utah and got a BS degree in Physical Biology. I was majoring in teaching biology in high school, but in spite of coming from a family of teachers, didn't think that teaching was for me. As I was trying to determine what to do with a biology degree, Dr. Robert C. Pendleton got a grant from the AEC to study Radiation Ecology associated with the fallout from the Nevada test site. He was following fallout through the food chain and into people. I got a job and worked with him for almost 3 years. This resulted in my Masters of Science with a thesis "Comparative Radiation Ecology of Six Utah Dairy Farms". In my studies, I characterized six dairy farms very carefully and followed radioactive ^{131}I, ^{137}Cs and ^{90}Sr from the environment into people. Two of the farms were located in the Salt Lake Valley and the other four were in the mountains east of Salt Lake at an average elevation of 6,500 feet, where the rainfall was higher than in Salt Lake. **Wow!!** Fallout was everywhere. It was on everything and in everything. Figure 1 shows the amount of ^{137}Cs in the milk from my six farms

as well as the time the nuclear tests were conducted in Nevada. This figure illustrates two important points. First, there was a lot of variation in the level of fallout in the milk between farms. Second, since many of the Nevada tests during this time occurred after the milk sampling, the figure suggested that much of the fallout that we were detecting early in the milk was from world-wide fallout and not from Nevada. We also evaluated the amount of ^{137}Cs in the food and in the farmers to determine the activity and dose accumulated in the human population. Figure 2 shows some of these results and shows that I (Tony Brooks) was among those with the highest levels of ^{137}Cs. **Wow!!** I had "high" body burden ^{137}Cs. I was the top predator on the food chain eating a lot of venison and drinking milk directly from the farms we were studying.

I remember well the first scientific presentation that I gave. It was at the American Association for the Advancement of Science (AAAS) meeting. Dr. Pendleton was to report on the data we had collected on levels of ^{131}I in the milk in Utah from the Nevada test site and the movement of that material through the food chain to people (Pendleton et al. 1963). Dr. Pendleton liked to report his findings directly to the local newspapers, which by this time had generated a lot of interest in the fallout and its potential for health consequences. Only a few days before the meeting, Dr. Pendleton became ill, so he suggested that I go and give the presentation. I was excited, but also very worried. We were finding levels of ^{131}I in the milk as high as 100,000 pCi/liter of milk. But **Who cared** about fallout in milk? It seemed that everyone did. There was a big crowd at the meeting, reporters and a lot of public interest. After my talk, I still remember the first question asked. How much is a pCi? I gave every scientific definition in the book (it is a unit of activity, 2.2 disintegrations/minute,10^{-12} Ci) the questioner kept saying, "No, no, how much is a pCi?" He did not want a scientific definition. What he really wanted to know was "Will it hurt me? Will I die of cancer? Will my children have mutations?" Of course as a young graduate student, I didn't really know the answer to his question. This question at my first scientific meeting made me resolve to be involved in understanding the potential health impact of fallout.

What if the radiation exposure from fallout, which concentrates in certain organs, is more hazardous than external radiation exposure? This question raised my level of concern for the

potential health effects of internally deposited radioactive materials. It was very instrumental in my future studies as I, and the scientific community, have tried to address these concerns.

Fifty plus years later, the only difference in the question is the units we use. Now we ask how much is a Bq? The answer to this question is critical in order for the public to understand radiation hazards. I heard the same question recently January 25-26, 2012 in Rome Italy at a STORE meeting associated the radioactive releases associated with the Fukushima accident.

Chromosome Aberrations and PhD

To address health concerns associated with radiation, it was important to detect radiation-induced biological changes after radiation exposure. My first real research on health effects of radiation was at Cornell University as part of my PhD program. There I measured the frequency of chromosome aberrations to detect biological changes induced by radiation. At that time, and still today, the gold standard for bio-dosimetry is the induced frequency of chromosome aberrations. Using this biological change it is possible to estimate dose when physical dosimetry is not present. I used Chinese hamsters, since they have only 2n=22 chromosomes, a long life span and are close to wild type. I wanted to conduct my studies in whole animals (*in vivo*) to understand dose and time relationships for damage induced in both genetic and somatic tissues. At that time, the health risks associated with mutations and cancer were thought to be similar, so I included both in my study. Figure 3 shows one of the studies that I conducted that demonstrated that there was a higher level of chromatid damage in the testes than was present in the bone marrow following acute exposures to 1.0 Gy from ^{60}Co. It also demonstrated that there was a marked change in the frequency, as a function of time after the single exposure, suggesting differences in repair and removal of the damaged cells from the tissues (Brooks and Lengemann 1967). With this tool in hand, I was ready to start to address some of my concerns about the biological damage induced by internally deposited radioactive material.

Health Effects of Internal Emitters (ITRI)

I was able to get a post-doctoral position at Lovelace Inhalation Toxicology Research Institute (ITRI) where Dr. Roger O. McClellan had just taken over as the new director. One of the first studies I conducted at ITRI was directed toward the impact of ^{90}Sr-^{90}Y on chromosome aberrations in the bone marrow of the Chinese hamster. This concern was related to the fact the

Strontium would be deposited and stay in bone and expose bone and bone marrow for a long period of time. ^{90}Sr would decay to ^{90}Y and ^{90}Y has a very short half life. This suggested the potential for the same cells to be "hit" by two beta particles over a fairly short time period. **What if** the two hits to the same cell are much more effective than two beta particles delivered to the same cell with a longer repair time between "hits"? We had been detecting ^{90}Sr-^{90}Y in the milk from fallout at the levels of a few pCi/liter, and I injected the Chinese hamsters with a 1-3 uCi/g body weight. **Wow!!** This was 7- 9 orders of magnitude higher level of radioactivity than existed in the environment! It really takes a lot of disintegrations to give a significant biological dose or produce changes in the frequency of chromosome aberrations in the bone marrow (Brooks and McClellan 1968). At the University of California in Davis they fed ^{90}Sr-^{90}Y to dogs from the time the mother was expecting, over their whole life. These lifespan studies, like many of the Beagle studies, yielded very useful data. The radiation dose and dose distribution were both well defined, biological changes followed with time using each dog as a clinical subject and the cause of death was carefully documented. Such careful studies were very important in showing that ^{90}Sr-^{90}Y were much less effective than whole body acute radiation exposure in producing biological damage and risk for bone cancer. This work by Dr. Otto Raabe (2010) is illustrated in Figure 4. It demonstrates that over a very wide range of dose rates and times there is no increase in bone cancer incidence following exposure to ^{90}Sr-^{90}Y. The data were evaluated in the low dose region and it was demonstrated that the frequency of bone cancer in the exposed animals was below that in the controls. Only after the dose rate and time were large (10Gy) did bone cancer frequency increase (Raabe 2011).

There were many lifespan studies conducted in dogs. These used radio-nuclides with different LET, half-lives and energies. One of these used inhalation as a route of entry for ^{90}Sr in a fused clay matrix. Inhalation resulted in a very large dose to the lung and heart. These data are shown in Figure 5 and illustrate that there is a marked change in the mechanism of action as the radiation dose decreased. At very high levels of activity that resulted in huge doses to the lungs, the animals died of radiation pneumonitis at early times (about 200-500 days after the inhalation). Those animals that were resistant to acute death following these doses and lived more than 500 days had a very high frequency of lung and other cancers. As the inhaled activity and dose continued to decrease, there was no decrease in either life shortening or cancer incidence. Additional studies were conducted following inhalation of other radio-nuclides (^{144}Ce,

^{91}Y and ^{90}Y) in fused clay particles. These radio-nuclides have a wide range of different half-lives. These studies all the same dose-response pattern (Brooks et al. 2008). These early data suggested that at doses below 20 Gy there was no life shortening or increase in cancer frequency (Brooks et al. 2009). Thus, extensive repair of radiation induced damage was apparent and that the Dose-Dose-Rate-Effectiveness Factor (DDREF) was very large when the dose was high and the dose-rate very low. **Wow!!** It takes a lot radioactive material deposited in the lung and bone to increase the risk for cancer in these organs.

A heightened concern about the potential health impact of Plutonium developed, since it is present in both nuclear weapons and power production. This radioactive material has a very long physical and biological half live, emits a high-LET alpha particle, and is retained for a very long time in the lung, liver and bone, producing dose to those target organs. Alpha particle exposures were known to be more hazardous than low-LET radiation. **What if** as was suggested at that time, that ^{239}Pu was the most hazardous substance known to man? I went to work to define the level of chromosome aberrations detected in the liver following deposition of ^{239}Pu. I compared this level of damage to that produced by other alpha emitters, the beta gamma emitting ^{144}Ce-^{144}Pr and both acute and chronic exposure to ^{60}Co. These were difficult studies. It was necessary to first, determine the retention and distribution of the radioactive material, second to use this information to calculate the radiation dose and dose-rate and finally, to relate dose and dose-rate to the amount of damage detected in the liver. The liver of the Chinese hamster was a very good organ for these studies since the Chinese hamster has only 2n=22 chromosomes, both ^{239}Pu and ^{144}Ce accumulate and are retained in the liver, and the liver cells divide very infrequently under normal conditions. Therefore the same cells can be exposed at a low dose-rate over a long period of time and can be stimulated to rapid cell division by partial-hepatectomy. The experimental design was to inject graded levels of radioactive material, subject the animals to a partial-hepatectomy at different times after injection to stimulate cell proliferation, calculate the radiation dose to the liver and measure the frequency of chromosome type aberrations in the liver cells at the first cell division after the stimulus. This proved to be a very useful technique. This research resulted in Figure 6. This figure shows that ^{239}Pu is not the most hazardous substance known to man. It is, in fact, very similar to all other alpha emitting radioactive materials and is between 15-20 times as effective in producing chromosome damage as low-LET radiation delivered at a low dose rate. The research also confirmed that high acute

doses of low-LET radiation are more effective in producing chromosome aberrations than chronic exposures (Brooks 1975).

The "hot particle hypothesis" was soon to follow (Tamplin and Cochran 1974). **What if** a single plutonium particle deposited in the lung can cause cancer? If this was so, then the current standards for Plutonium had underestimated risk by a very large amount (100,000 times). This was a very important question, and several research projects were started to address it. At ITRI, the aerosol science group developed a method of generating radioactive particles of $^{239}PuO_2$ and $^{238}PuO_2$ and characterizing the size and size distribution of the particles and separating them according to size. Dogs were exposed to a variety of aerosols using either $^{238}PuO_2$ or $^{239}PuO_2$ of different sizes to change the dose-distribution following inhalation (Muggenburg et al. 1996). I designed a study to test the "hot particle hypothesis" where I injected a constant activity of $^{239}PuO_2$ into the jugular sinus of Chinese hamsters using well-defined particles of a known size. With this protocol, the same total activity would have a lot of small particles or a few large particles. Over 90% of the injected particles were taken up by the liver and resulted in the same average radiation dose to the liver with very different dose distributions. We also injected Chinese hamsters with ionic Plutonium, so that the dose to the liver was the same from the dose from the particles but the distribution of Plutonium in the liver was uniform. We could thus directly determine the influence of dose distribution on two major biological endpoints, chromosome aberrations and liver cancer. According to the "hot particle hypothesis", since the dose to the cells close to the large particles was very much higher than the average dose from the uniform distribution of the activity, the particles were postulated to result in a much higher level of cancer. My hypothesis at the time was that the particles would be much less effective than the uniform distribution. I was of the opinion that the damage would be much less following particle exposure since only a small number of the cells in the liver would be "hit" by an alpha particle, many of the "hit" cells would be killed and the liver would have very few chromosome aberrations. Figure 7 shows the frequency of chromosome aberrations plotted as a function of average radiation dose (Brooks et al. 1974). **Wow!!** There was no difference in the frequency of chromosome aberrations as a function of particle size or dose distribution. The tissue thus responded as a unit and not as single cells. Of course, these studies were done before we realized that there were bystander effects and that organs respond as a function of total dose and not as a function of dose-distribution. The induction of liver cancer was equally surprising, since there

was no change in cancer frequency as a function of particle size (Figure 8). The citrate form of the plutonium was the most effective in production of cancer (Brooks et al. 1983). These types of data suggested that perhaps the "hit" theory may need to be re-evaluated. Such information supports studies which suggest that it takes a tissue to make a tumor (Barcellos Hoff 2005, Barcellos Hoff and Brooks 2001). These studies, with many others, showed that the "hot particle hypothesis" was not correct, that the highest frequency of liver cancer was in the animals with a uniform distribution of radioactive Plutonium, and that the current standards and risks for Plutonium were appropriate.

DOE and Regulations

In the early days of radiation biology, scientists from the national laboratories would go to Washington DC for 2-3 years as technical representatives to provide scientific input to headquarters. Dr. Roger O. McClellan, suggested that I might benefit from such an experience, so I went. This provided me with a good overview of the research that was being conducted on the health effects of internally deposited radioactive material and chronic exposures to external radiation sources, since I was involved in reviewing all the lifespan dog studies. It also gave me an inside view as to how funding was distributed. Before I went to Washington, I thought that science was the most important part of the research programs, but found that many forces outside science influence funding. I was impressed with how hard my boss, Dr. Nick Carter, and most of the individuals in the funding agency, worked. Dr. Carter really knew the investigators, the research being conducted and the program down to the last dollar. **Wow!!** These were a hard working group of individuals!! After I learned all the acronyms that the bureaucrats used on a daily basis, I started to fit in. However, when Dr. Carter gave me an assignment to cut 2 million dollars out of the dog program, I had a very hard time. I worked for weeks on each program and tried to save the very best science. I provided Dr. Carter the input then waited for something to happen. Nothing did. Finally, I asked Nick about the funding changes. He said that the ancillary beta-gamma studies and the program to remove radioactive materials from the body were about the right size for the budget cut, so he cut them.

It seemed to me that often at DOE headquarters I found myself talking out of both sides of my mouth. One side would say, "We know more about the health effects of ionizing radiation than any other environmental contamination." The other side would say, "We really need to have

additional research to define the effects and human health risks associated with ionizing radiation." However, through my experience at DOE, I gained a greater understanding of the relationships between scientific information, public perception, funding and regulations.

Toxicology and ITRI

When I returned to ITRI, Jimmy Carter was the President of the United States. Fear of nuclear power continued to increase and concerns about health impacts of other forms of energy production were not well defined. **What if** the health risks associated with producing power from other technologies was higher than that using nuclear power? To address this important question, each of the National Laboratories was to select a technology and evaluate the health risk. At ITRI, we were working on pollution from transportation with a focus on diesel exhaust. We also evaluated the risks associated with fluidized bed coal combustion. Since I was working on the induction of genetic changes and cancer, I applied the skills from our cell and molecular biology group to these important problems. We evaluated many endpoints, including cell killing, mutation induction, sister chromatid exchanges, chromosome aberrations and the induction of cancer in experimental animals. Using cell and molecular tests we determined that extracts from aerosols produced by these technologies were highly mutagenic in bacterial cell systems. The extracts also resulted in well-defined and marked increases in mutations in mammalian cells, sister chromatid exchanges and chromosome aberrations both *in vivo* and *in vitro*. These extracts had interactions with the DNA and resulted in significant increases in all the endpoints used. We also demonstrated that many of the extracts were very carcinogenic.

One of the major problems we had in comparing the risk from chemicals to that of radiation was the fact that radiation is a very good cell killer which is why we use it in cancer radiotherapy. Many chemicals are very good mutagens but produce limited cell killing. Thus, to compare the mutagenic activity for radiation to that from chemicals we reported mutation frequency as mutants per surviving cell. Because of the cell killing, plates that were subjected to radiation would have few total cells and even fewer mutant colonies. The plates treated with the chemical mutagens and extracts from non-nuclear energy production and would have limited cell killing and be covered with mutant colonies. We had similar problems comparing the carcinogenic activity of radiation and the chemicals. If the radiation dose was low, we were not able to demonstrate an increase in cancer in the small groups we were evaluating. If the radiation was

too high, the animals all died. Thus, we had a very limited dose range where we could evaluate the risk of radiation- induced cancer. In many groups of animals treated with chemicals, the frequency of cancer was very high, especially with the positive control chemical carcinogens. These studies on health impact from environmental pollutants associated with energy production resulted in many open literature publications. The bottom line was that nuclear energy had much less environmental and health impact than other forms of energy production. **Wow!!** Compared to many environmental chemicals, radiation is a rather poor mutagen and carcinogen. **Who Cared?** Nobody seemed to.

PNNL and Radon

When Dr. McClellan was scheduled to leave ITRI, I got worried about future funding in the field of radiation biology at ITRI, so I looked around. Thanks to Dr. William J. Bair got a job at the Pacific Northwest National Laboratory (PNNL). They had a very large radiation biology and radon program underway, where I fit in. Radon was of concern because it was responsible for more than half the natural background dose and an increase in lung cancer had been observed in Uranium miners. **What if** radon in homes was producing a significant increase in lung cancer? PNNL conducted extensive studies on the biological effects of radon on lung cancer. When I joined the laboratory PNNL had a very large data base on the production of lung cancer in rats. They had also done many studies on radon-induced lung cancer in other species. I had a long talk with Dr. Fred Cross about his data, and asked why there were lots of lung cancers in the population of exposed rats, but he had not observed any cancers in the trachea (Cross et al. 1992). PNNL also demonstrated that some species, like the Syrian hamster, were very resistant to radon-induced lung cancer, while the rats had a high frequency of lung cancer. Dr. Cross suggested that there may be differences in the doses delivered as a function of location in the respiratory tract, with the trachea having small doses and the deep lung having much larger doses. It was suggested that dose differences between species may have also resulted in differences in cancer frequency. Since dose is impossible to measure following radon exposure, we had to depend on models for dose calculation. I initiated research on chromosome damage and the induction of micronuclei as biomarkers to determine the differences in dose as a function of location in the respiratory tract, as well as measuring differences in dose to the deep lung in different species. It was determined that the frequency of chromosome damage as a function of

location in the respiratory tract was similar, so that the dose and initial damage was the same in the different tissues (Brooks et al. 1994). It had to be a difference in the processing of the damage that resulted in the very large difference in the cancer frequency between the deep lung and the trachea. We also noted that there were no major differences between species in the frequency of chromosome damage in the deep lung following radon inhalation. Chinese and Syrian hamster had the higher frequency of micronuclei induced while the Wistar rat had the highest frequency of lung cancer (Khan et al. 1995). **Wow!! T**he frequency of chromosome damage measured either as aberrations or micronuclei was a useful measure of radiation dose delivered, but chromosome damage did not reflect cancer risk (Brooks et al 2003). These data were useful in correlating radiation dose to radon exposure in WLM.

The BEIR VI committee, "Health Effects of Exposure to Radon" related the animal data to human experience and derived risk estimates for radon in homes (NAS/NRC 1999). This committee used the Uranium miner data as its primary source of information and extrapolated and estimated the risk from the low doses in the home using the LNTH. The logic behind this extrapolation was that when a single alpha particle "hit" a cell the energy deposited and dose to that cell was on the average rather constant. As the dose is decreased, the dose/hit cell was large and rather constant and only the number of cells "hit" changed. At that time, this was a very reasonable assumption. The bottom line from the BEIR VI report was, "Nonetheless, this indicates a public-health problem and makes indoor radon the second leading cause of lung cancer after cigarette-smoking."(NAS/NRC 1999). BEIR VI also stated that "It can be noted that the deaths from radon-attributable lung cancer in smokers could most efficiently be reduced through tobacco-control measures, in that most of the radon-related deaths among smokers would not have occurred if the victims had not smoked." (NAS/NRC 1999). It seems that this second statement has been ignored and the only laws and procedures for radon mitigation have been initiated. The magnitude of the impact of radon mitigation and controlling cigarette smoking is illustrated in Figure 9. This shows that the lung cancer frequency in the United States (data from 1995) would drop on the average of 16,800 if mitigation of the radon were to occur in the homes of smokers. Mitigation of radon in homes of never smokers would potentially save 1, 970 lung cancer deaths which is a factor of about 10 lower. If the cigarette smoking was to be eliminated, the estimated number of lives saved each year would be 120,470 or a factor of more than 60 times as many lung cancers as seen from mitigation of radon in homes of non-smokers.

Wow!! Radon in homes is not really the second leading cause of lung cancer! It is the combined effect of radon and smoking that makes radon a potential public-health problem in homes. Remediation in homes of non-smokers has little impact on public health. **Who cares?** The EPA initiated a very large program making it mandatory to measure and remediate homes for radon before they can be sold.

Washington State and DOE Low Dose Radiation Research Program

Radiation risk continued to be a major scientific concern especially in the low dose region. In 1997, I had three grants, one from NASA, one from NIH and one from DOE. I took my grants and moved to Washington State University, where the overheads were lower and the money would buy more technical help. At this time, it was well recognized that the standards were set based on the Linear No-Threshold Hypothesis (LNTH) model and that there was limited data in the low dose and dose-rate range to validate this model. Senator Pete Domenici of New Mexico was aware of this problem and its importance. His support for a research program, focused on responses in the low dose region, was evident in a quote from Senator Domenici at Harvard University October 31, 1997. "In this year's Energy and Water Appropriation Act, we initiated a ten year program (13 million/year) to understand how radiation affects genomes and cells so that we can really understand how radiation affects living organisms. For the first time, we will develop radiation protection standards that are based on actual risk." This formed the basic philosophy for the DOE Low Dose Radiation Research Program, which was to combine developments in both technology and biology to evaluate changes in the low dose region. Senator Domenici continued to provide support at the Gordon Research Conference August 6, 1998 where he said, "I feel very strongly that we need the best possible standards for radiation risks, based on the best science we can produce".

The staff of the Office of Biological and Environmental Research (OBER) in the Department of Energy drafted and developed the scientific directions that they thought the program should follow. Dr. Marvin Frazier assigned Dr. David Thomassen to be the Program Manager for the new Low Dose Program. I applied for the position of "Lead Scientist" of the Program and was successful. In this position I worked closely with Dr. Noelle F. Metting who has been the DOE Low Dose Research Program manager for almost 15 years. This was the focus of my activities until my retirement. I really enjoyed this job and often told my wife that if I could

have designed a job for me at this stage of my life it would be the one that I had. This provided an opportunity to follow all the research that was being conducted, review the new proposals and be involved in the yearly contractors meeting to evaluate the progress being made in the program research. It was really great because I didn't have to be involved in any of the funding decisions.

The big concern of the research Program was, **what if** the LNTH overestimated risk and resulted in very conservative regulations? The Program recruited the best radiation scientists available to address this question. Low dose was defined as 0.1 Gy and each proposal had to conduct research in this dose range to qualify for funding. Early in the Program, many of the scientists said that they didn't think they could see any biological changes following such a low dose of radiation. Dr. Frazier just told them, "Then don't apply for funding". The Program generated lots of good proposals from the scientific community and research was off and running. In the early days of the Program, communication of the results to regulators, other scientists and the public was an important component of the Program. I received a grant to help develop and run a web site which is still operational as http://lowdose.pnl.gov. This site has important information for anyone who is interested in research on the health effects of low doses of radiation. It was exciting to follow and communicate the combination of new technologies and advancements in biology which made it possible to measure molecular and cellular changes induced by low doses of radiation.

Early research suggested that exposure to low doses of alpha particles produced a higher frequency of Sister Chromatid Exchanges than the calculated number of alpha hits to the cells. This suggested that cell communication was producing damage in cells that had no energy deposited in them (Nagasawa and Little 1992). The development of microbeams was an important part of the early work in the program. With this technology it was possible to define which cells were "hit" and which cells did not have energy deposited in them and define potential "bystander" effects. One of the first microbeams to be successful was developed at PNNL. We used it to estimate the radiation dose delivered by alpha particles to the deep lung from radon inhalation. Chromosome aberrations and micronuclei were used as biomarkers of dose to compare the biological response of single cells hit with known numbers of alpha particles to the responses following exposure to radon and ^{239}Pu (Nelson et al. 1996). Recently developed microbeams and other technology exposed individual cells and measured the response of the "hit"

cells and the response of neighboring cells. The results of these studies demonstrated the presence of "bystander effects (Ponnaiya et al. 2004). These effects demonstrate that a cell traversed by an alpha particle or "hit" by a focused low- LET microbeam communicate with neighboring cells and can produce changes in "non-hit" cells. These changes have been shown to be both "harmful" and "protective" and are most marked following exposure to high-LET radiation (Little 2006). Bystander effects impact the current use of "hit-theory" in defining radiation risk, since the radiation target is much larger than the individual cell. The research demonstrates that cells communicate within each tissue, making the assumption of independence of action of individual cells used in the BEIR VII biophysical model inappropriate. Since non-hit cells show biological responses, it may not be appropriate to calculate radiation dose to individual cells or cell types in tissues (NAS/NRC 2006). Bystander effects also make it more difficult to define the biological target for the interaction of radiation with cells and the induction of cancer. The data suggest that tissues and organs respond as a whole and that the biological response is related to the dose to the whole organ/tissue, which is the metric used by BEIR VII in all the human studies, rather than to the dose to individual cells (Barcellos-Hoff and Brooks 2001). As the research progressed, the combination of modern biology with low doses was very exciting. One of the first papers on the changes in gene expression as a function of radiation dose was done at Lawarence Livermore Laboratory. Techniques were developed so that changes in gene expression could be detected in thousands of genes at the same time. This research is shown in Figure 10 where it is very obvious that the genes activated following high doses were different than those activated following low dose exposures (Yin et al 2003). These results have been duplicated in many different laboratories. Research on gene transcription has been extended to many other OMICS (proteomics, metabolomics, phosoproteomics, epigenomics, etc) and again for each of the different techniques the responses to low doses are different than the response to high doses. These data suggest that the mechanisms of action are different at low doses than those after high doses. Many of these molecular studies have been combined with studies on biological endpoints to evaluate how these low dose responses could potentially influence risk.

It was determined before the Low Dose Program started that exposure to low doses of radiation given before a high dose resulted in a decrease in the expected response from the high dose (Wolff 1998). This was called the adaptive response and suggested that low doses of radiation may be protective and activate protective mechanisms. It has been well established that biological systems can detect and respond to very low doses of ionizing radiation. As molecular and cellular technology has

improved, the magnitude and importance of these responses has been carefully defined. It has been demonstrated that many of the responses associated with low doses of radiation decrease the biological response below the normal background level. This has been demonstrated for many biological endpoints such as induction of mutations (Sykes et al. 2006), cell transformation (Azzam et al. 1996; Redpath 2004) and has even been suggested for the induction of cancer in mice (Mitchel 2006). There remains a great deal of discussion and conflict as to the meaning of these *in vitro* results in terms of risk. The focus of the DOE Program move from single cell systems to more complex systems. This has made it possible to evaluate the results in more realistic systems.

In 2005 and 2006, two major reports released from scientific bodies reached very different conclusions. The US National Academy of Sciences released the BEIR VII report that supported the LNTH (NAS/NRC 2006). The French Academy of Sciences report suggested that LNTH was conservative and resulted in an overestimation of risk in the low dose region (Tubiana et al. 2005). The magnitude of the response for all of these phenomena has been shown to be dependent on the genetic background of the cells, tissues and organisms in which they are being measured (Coleman et al. 2005; Ponnaiya et al. 1997; Azzam and Little 2004; Little 2006).

What if the mechanisms of action for low doses of radiation are different than those following high doses? **Wow!!** Many mechanisms of action for these observations have been published and evaluated and include changes in gene expression as a function of radiation dose (Yin et al. 2003), protective changes in the ROS status of the cells (Spitz et al. 2004, Azzam et al. 2001), selective apoptosis which eliminates transformed cells (Bauer 2007 and Portess et al. 2007) and control of the cellular and molecular responses by tissue-matrix interactions which seem to be protective (Barcellos-Hoff and Costes 2006; Barcellos-Hoff and Brooks 2001). All these data indicate that the mechanisms of action for the biological responses induced by low doses of ionizing radiation are different from those induced by high doses and that the responses estimated from linear extrapolation from high doses would overestimate the real risk associated with these low dose and dose-rate exposures. Two useful recent reviews of these data are Dauer et al. 2010 and Feinendegen et al. 2011.

Genomic instability suggests that, in addition to rare mutational events, frequent radiation-induced changes following exposure may play an important role in cancer induction. Radiation-induced

genomic instability is seen at a high frequency in cells many cell divisions after the radiation exposure. The instability results in increased frequency of mutations, chromosome aberrations, and cell killing. Radiation-induced genomic instability seems to be one of the early stages in the carcinogenesis process and has been seen both *in vitro* (Morgan et al. 1996) and *in vivo* Ponniaya et al. 1997). These observations challenge the relative importance that initial mutations play in radiation-induced cancer (Kadhim et al. 2004.)

The magnitude of the response for all of these low dose biological phenomena has been shown to be dependent on the genetic background of the cells, tissues and organisms in which they are being measured (Coleman et al. 2005; Ponnaiya et al. 1997; Azzam and Little 2004.; Little 2006.). A better definition of the range of inter-individual genetic sensitivity is needed. However, currently it is not possible to identify either radiation resistant or radiation sensitive individuals, or to use this information in a regulatory framework (NCRP 2011).

Retirement and Back to the Field

I retired and for two years worked to write a History of the DOE Low Dose Radiation Research Program (1998-2008) currently being processed to be posted on the Low Dose Web Site, http//lowdose.pnl.gov and is to be published as a government document. I have also been working part time as a contractor for PNNL and EPRI. This has provided me a great opportunity to continue to stay up on current events like Fukushima and scientific advances in the field of radiation biology. It was of interest to relate the levels of ^{137}Cs used to produce biological changes in the dog studies to the levels observed in the environment following fallout and nuclear accidents like Chernobyl and Fukushima. In Figure 11 the activity in Bq/Kg or Bq/L in biological materials or Bq/m^2 in soil are presented. Each line is a factor 10 above the previous line. This shows that there are many (4-5) orders of magnitude between the levels in the environment and those used in the dog studies to produce biological damage. Such relationships need to be communicated more effectively to the public to help them address the question. How much is a Bq? With such information they can make decisions on health risks of internally deposited radioactive material and appreciate the safety factors associated with regulatory limits.

Summary

It is of interest to review what I have called my **What ifs**. These were based on important scientific hypotheses in the field of radiation biology. I invested my life searching for answers to these questions.

What if the fallout in southern Utah was responsible for a cancer epidemic? The scientific data generated associated with these questions and my answer is a very strong NO. Utah has the lowest cancer rate in the nation. My home town, St. George, is in Washington County, which has the second lowest cancer rate in Utah. Yes, there was an exposure to fallout estimated to be between 30 and 50 mSv. This is a very small dose and BEIR VII risk estimates suggest that the excess cancers in a population of about 20,000 people in Washington County would be very low. Still the public perception in Utah is that each and every cancer in Southern Utah was caused by the fallout.

What if internally deposited radioactive material is more hazardous than external exposures? The data demonstrate that low dose rate and non-uniform distribution of that dose from internally deposited radioactive material is less hazardous than single acute whole body exposures. There is a large dose-rate effectiveness factor to reduce the risk from the low dose generated by fallout.

What if ^{239}Pu is the most hazardous substance known to man and that inhalation of $^{239}PuO_2$ particles results in a very large risk for lung cancer? The data demonstrated that the answer to both questions is NO!!

What if the health risks associated with producing power from other technologies is higher than that using nuclear power? After extensive research on health effects from energy technologies, it was concluded that using nuclear power to generate electricity was a very safe alternative. Yes!! Nuclear power is much safer than any of the technologies that involve burning coal and this research was conducted before the added concerns about power production from coal and greenhouse gases and global warming.

What if radon in homes results in a serious public health problem by causing a significant increase in lung cancer? Radon in homes alone resulted in a minimal risk, cigarette smoking produces a very large risk and the combination of radon and cigarette smoke increased that risk. If you have radon in your home, don't smoke!!

What if the mechanisms of action are different following exposure to low doses than those produced by high doses? The huge database on the biological effects of radiation at all levels of biological organization; molecular, cellular, tissue, organ, animal and human data demonstrate that Yes!! the mechanisms of action for biological responses are different at low doses than those from high doses.

Finally, **What if** the LNTH overestimated risk and has resulted in very conservative regulations that are overprotective? This remains an important research question. As I have evaluated the data, it demonstrated that cells can detect and respond to very low doses of radiation, that this response seems to be protective and that the LNTH is conservative. In my opinion, attempts to further lower the standards must be carefully justified and based on scientific data. Thus, the LNTH hypothesis does not reflect the actual risk in the low dose region, but provides a useful tool to control exposures. The LNTH is easy to use, the exposure levels can be achieved by those using radioactive materials and it is adequately conservative.

However, when collective dose is combined with a linear dose-response coefficient to predict risk in large populations exposed to low doses, the number generated will overestimate real risk. The mechanisms of action following these low doses are different and the dose-response is lower than predicted by the LNTH.

Often in conducting research the data does not match the scientists' preconceived ideas. These observations lead to unanticipated **Wows!!** and when followed up, may result in changes in paradigms. There are many very good scientists doing research on the health effects of radiation and each one of them have their own set of **Wows!!** It is essential that scientists communicate these, to those who make policy, as well as to the public. This is the only way to influence the fear and the perception of risk associated with exposures to low doses of radiation.

The fear of radiation is still real. Is it as great as it was 50+ years ago when I first started to be a scientist? I know that my fear has changed drastically over the years. I now compare radiation

risks to other well-known risks in our lives. The persistence of radio-phobia however, still suggests that all this new information on the risks from radiation has had minimal impact on the public. Scientists must, every chance we get, focus on communication of our scientific results both through the open literature and in regulatory and public settings.

I want to thank you all again for this opportunity to review my research and to voice my opinions on a wide variety of subjects. I know that some of you will not agree with me, but that is what science is all about. We each generate data, look at the information, apply it according to our own background and needs, and often reach different conclusions. This presentation has provided me with a chance to do this, which I greatly appreciate. I hope that we can all examine the **What if's, Wows** and **Who Cares** of our own research and communicate our data and experience to others lest it be lost. Perhaps through our experiences we can improve research environments, funding and effective use of the valuable information generated.

Literature Cited

Amundson, SA, Fornace AJ Jr. Gene expression profiles for monitoring radiation exposure. Radiat Protection and Dosimetry 97(1): 11-16; 2001.

Azzam, E.I. and Little, J.B. Radiation-induced bystander effect: Evidence and significance. Human and Experimental Toxicology 23(2): 61-65; 2004.

Azzam EI, de Toledo SM, Raaphorst GP, Mitchel RE. Low-dose ionizing radiation decreases the frequency of neoplastic transformation to a level below the spontaneous rate in C3H 10T1/2 cells. Radiat Res 146(4): 369-373; 1996.

Barcellos-Hoff MH. Integrative radiation carcinogenesis: Interactions between cell and tissue responses to DNA damage. Seminars in Cancer Biology 15(2): 138-148; 2005.

Barcellos-Hoff MH, Brooks AL. Extracellular signaling through the microenvironment: A hypothesis relating carcinogenesis, bystander effects and genomic instability. Radiation Research 156(5 Pt 2): 618-627; 2001.

Barcellos-Hoff MH, Costes SV. A systems biology approach to multi-cellular and multi-generational radiation responses. Mutation Res 597(1-2): 32-38; 2006.

Bauer G. Low dose radiation and intercellular induction of apoptosis: Potential implications for the control of oncogenesis. International J. of Radiation Biology 83(11-12): 873-888; 2007.

Brooks AL. Chromosome damage in liver cells from low dose rate alpha, beta and gamma irradiation: derivation of RBE. Science 190: 1090-1092; 1975.

Brooks AL, Lengermann FW. Comparison of radiation-induced chromatid aberrations in the testes and bone marrow of the Chinese hamster. Radiat Res 32:587-595; 1967.

Brooks AL, McClellan RO. Cytogenic effects of strontium-90 on the bone marrow of the Chinese hamster. Nature 219:761-763; 1968.

Brooks AL, Retheford JC, McClellan R0. Effect of $^{239}PuO_2$; particle number and size on the frequency and distribution of chromosome aberrations in the liver of the Chinese hamster. Radiat. Res. 59:693-709; 1974.

Brooks AL, Benjamin SA, Hahn FF, Brownstein DG, Griffith MW, McClellan RO. The induction of liver tumors by ^{239}Pu citrate or $^{239}PuO_2$ particles in the Chinese hamster. Radiat. Res. 96:135-151; 1983.

Brooks AL, Khan MA, Duncan A, Buschbom RL, Jostes RF, Cross FT. Effectiveness of radon relative to acute ^{60}Co gamma-rays for induction of micronuclei *in vitro* and *in vivo.* Int. J. Radiat. Biol. 66: 801-808;1994.

Brooks AL, Lei XC, Rithidech K. Changes in biomarkers from space radiation may reflect dose not risk. Advances in Space Research 31(6): 1505-1512; 2003.

Brooks AL, Eberline PE, Couch LA, Boecker BB. The role of dose-rate on risk from internally-deposited radionuclides and the potential need to separate dose-rate effectiveness factor (DREF) from the dose and dose-rate effectiveness factor (DDREF). Health Phys 97(5): 458-469; 2009.

Coleman MA, Yin E, Peterson LE, Nelson D, Sorensen K, Tucker JD, Wyrobek AJ. Low-dose irradiation alters the transcript profiles of human lymphoblasoid cells including genes associated with cytogenetic radioadaptive response. Radiat Res 164(4 Pt 1): 369-382; 2005.

Cross FT, Dagle GE, Gies RA, Smith LG, Buschbom RL. Experimental animal studies on radon and cigarette smoke, In: *Indoor radon and lung cancer: Reality or Myth* Edt Fredrick T. Cross, Twenty-Ninth Hanford Symposium on Health and Environment. Battelle Press, Columbus, Richland 1992.

Dauer L.T., Brooks, A.L. Hoel, D.G., Morgan W.F., Stram, D., Tran, P. Review and evaluation of updated research on the health effects associated with low-dose ionizing radiation. Radiat. Protection Dosimetry 140: 103-136; 2010.

Feinendegen LE, Brooks AL, Morgan WF. Biological consequences and health risks of low-level exposure to ionizing radiation. Health Phys 100: 247-260; 2011.

Kadhim, MA, Moore, SR, and Goodwin, EH Interrelationships amongst radiation-induced genomic instability, bystander effects, and the adaptive response. *Mutation Research* **568(1):** 21-32; 2004.

Khan MA, Cross FT, Bushbom RL, Brooks AL. Inhaled radon-induced genotoxicity in Wistar rat, Syrian hamster and Chinese hamster deep-lung fibroblasts *in vivo*. Mutat. Res. 334: 131-137; 1995.

Little JB. Cellular radiation effects and the bystander response. Mutat Res 597(1-2): 113-118; 2006.

Muggenburg BA, Guilmette RA, Mewhinney JA, Gillett NA, Mauderly JL, Griffith WC, Diel JH, Scott BR, Hahn FF, Boecker BB. Toxicity of inhaled plutonium dioxide in beagle dogs. Radiat Res. 145: 361-381; 1996.

Morgan WF, Day JP, Kaplan MI, McGee EM, Limoli CL, Genomic instability induced by ionizing radiation. Radiat Res 146: 247-258;1996.

Mitchel REJ. Adaptive response in vitro and in vivo and its impact on low-dose radiation risk. In: Advances in Medical Physics: Biological Effects of Low Doses of Ionizing Radiation. Advances in Medical Physics Chapter 3: 264-270; 2006.

Nagasawa H, Little JB. Induction of sister chromatid exchanges by extremely low doses of alpha-particles. Cancer Res 55(22): 6394-6396; 1992.

Nelson JM, Brooks AL, Metting NF, Khan MA, Buschbom RL, Duncan A, Miick R, Braby, LA. Clastogenic effects of defined numbers of 3.2 MeV alpha particles on individual CHO-K1 cells. Radiat Res 145:568-574; 1996.

NAS/NRC National Academies of Sciences , National Research Council. BEIR VI. Health effects of exposure to radon;1999.

NAS/NRC National Academies of Sciences, National Research Council. BEIR VII. Health risks from exposure to low levels of ionizing radiation; 2006.

National Council for Radiation Protection and Measurements. The potential impact of individual genetic susceptibility and previous radiation exposure on radiation risk for astronauts. Bethesda MD. NCRP Report No. 167; 2011.

Pendleton RC, Mays CW, Lloyd RD, Brooks AL. Differential accumulation of I^{131} from local fallout in people and milk. Health Physics 9:1253-1262; 1963.

Ponnaiya B, Jenkins-Baker G, Brenner DJ, Hall EJ, Randers-Pehrson G, Geard CR. Biological responses in known bystander cells relative to known microbeam-irradiated cells. Radiat Res 162(4): 426-432; 2004.

Ponnaiya, B, Cornforth, MN, and Ullrich, RL. Induction of chromosomal instability in human mammary cells by neutrons and gamma rays. Radiat Res 147: 288-294; 1997.

Portess DI, Bauer G, Hill MA, O'Neill P. Low-dose irradiation of nontransformed cells stimulates the selective removal of precancerous cells via intercellular induction of apoptosis. Cancer Research 67(3): 1246-1253; 2007.

Raabe OG. Concerning the health effects of internally deposited radionuclides, Health Physics 98 (3): 515-536; 2010.

Raabe OG. Toward improved ionizing radiation safety standards. Health Phys 101(1): 84-93; 2011.

Redpath JL. Radiation-induced neoplastic transformation in vitro: Evidence for a protective effect at low doses of low-LET radiation. Cancer and Metastasis Reviews 23(3-4): 333-339; 2004.

Spitz DR, Azzam EI, Li JJ, Gius D. Metabolic oxidation/reduction reactions and cellular responses to ionizing radiation: A unifying concept in stress response biology. Cancer and Metastasis Reviews 23(3-4): 311-322; 2004.

Sykes PJ, Zeng G, Day TK, Hooker AM, Blyth BJ, Bhat M, Tilley WD. Non-linear chromosomal inversion response in prostate after low dose X-radiation exposure. Mutation Res 602: 65-73; 2006.

Tamplin A, Cochran TB. Radiation standards for hot particles. A report on the inadequacy of existing radiation protection standards related to internal exposure of man to insoluble particles of plutonium and other alpha-emitting hot particles. In National Resources Defense Council Report. Washington, D.C. 1974.

Tubiana M, Aurengo A, Averbeck D, Bonnin A, Le Guen B, Masse R, Monier R, Valleron AJ, de Vathaire F. Dose-effect relationships and estimation of the carcinogenic effects of low doses of ionization radiation. Paris: Academie National de Medicine, Institute de France-Academie des Sciences; 2005 (English translation).

Wolff, S. The adaptive response in radiation biology: evolving insights and implications. Environ Health Perspect 106: 277-283;1998.

Yin E, Nelson DO, Coleman MA, Peterson LE, Wyrobek AJ. Gene expression changes in mouse brain after exposure to low-dose ionizing radiation. Internat J of Radiat Biol 79(10): 759-775; 2003.

Figure Legends

Figure 1

^{137}Cs in milk from Utah dairy farms. Note that the above ground weapons tests in 1962 were after the first peak in ^{137}Cs activity in the milk. The first peak was related to worldwide fallout taken up by grazing early in the spring. Later peaks related to local fallout from the Nevada test site. There was a lot of between station and time variability in the levels of ^{137}Cs in milk.

Figure 2

Repeat counting of individuals living on the dairy farms in Utah. This demonstrated a trend of increase levels of ^{137}Cs as a function of time. It also illustrates that males were higher than females and that (Tony Brooks) had a level that was higher than most in the study.

Figure 3
The induction and repair of chromatid aberrations in the bone marrow and testes of Chinese hamsters as a function of time after an acute external whole body exposure of 1.0 Gy from a ^{60}Co source. The initial frequency of chromatid aberrations was higher in the testes than the bone marrow.

Figure 4
Induction of bone cancer in Beagles from ^{90}Sr following ingestion. There was no increase in bone cancer until very late times and very high dose rates. The control animals had a higher frequency of bone cancer than those exposed to total doses of less than 10 Gy (Raabe 2011).

Figure 5
The life shortening and cancer incidence in Beagle dogs following the inhalation of ^{90}Sr in fused clay particles. The mechanism of action change as a function of total dose with very high doses resulting in early deaths from lung failure, as dose decreased the frequency of lung cancer was very high and with further decrease to doses below 20 Gy there was no change in cancer frequency or life shortening.

Figure 6
Dose-response relationships for chromosome aberrations produced in the liver of Chinese hamsters following exposure to internally deposited radioactive material (^{241}Am, ^{239}Pu, ^{252}Cf Alpha emitters) (^{144}Ce-^{144}Pr beta-gamma emitter) or external doses from acute or protracted exposures to the gamma rays from ^{60}Co. ^{239}Pu had similar responses as the other alpha emitters.

Figure 7
Dose-response relationships for chromosome aberrations produced in the liver of the Chinese hamster as a function of dose-distribution from $^{239}PuO_2$ particles of different sizes or ^{339}Pu citrate. The dose-response was constant for all treatments regardless of dose distribution.

Figure 8
The induction of liver cancer in the Chinese hamster as a function of radiation dose-distribution. There was no change in liver cancer frequency as a function of particle size. The use of ^{239}Pu citrate produced liver cancer with a shorter latency than observed from the particles.

Figure 9
The interaction between cigarette smoking and radon exposure to produce increased lung cancer. The figure shows the impact of remediation of radon in homes and the impact on never smoking. Most of the radon induced cancers were related to cigarette smoking with remediation producing little benefit in homes on non-smokers.

Figure 10

Dose-response relationship for radiation induced changes in gene expression. The genes expressed change as a function of radiation with low dose and high dose genes apparent. This same pattern has been demonstrated for many cellular and molecular responses to radiation. (Yin et al. 2003)

Figure 11
^{137}Cs in the environment (Bq/m^2 or Bq/liter), regulatory limits (Bq/Kg) and levels of ^{137}Cs used in experimental dog studies (Bq/Kg) to produce health effects (life shortening and cancer). This demonstrates that it takes a very large amount (Bq/Kg) of ^{137}Cs to produce health effects and that there are many orders of magnitude between the levels observed in the environment and that used in experimental animals to cause health effects.

Figures

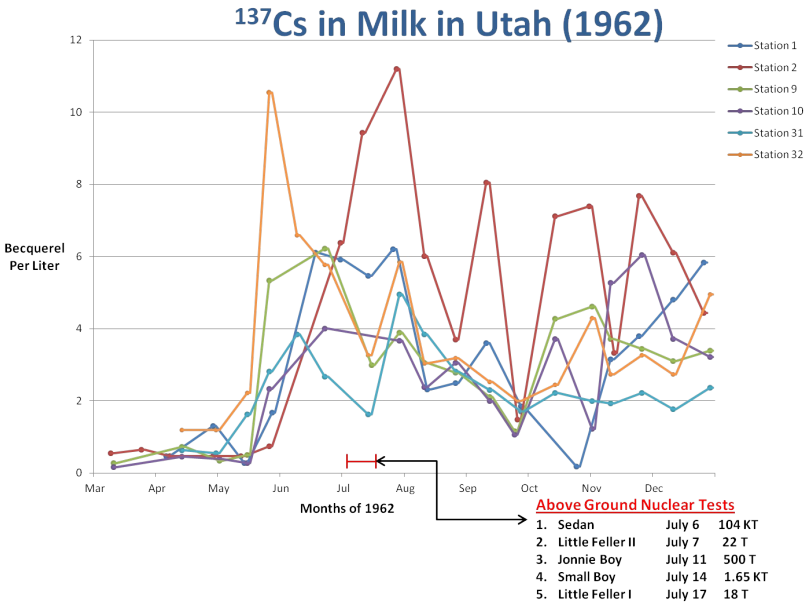

Figure 1

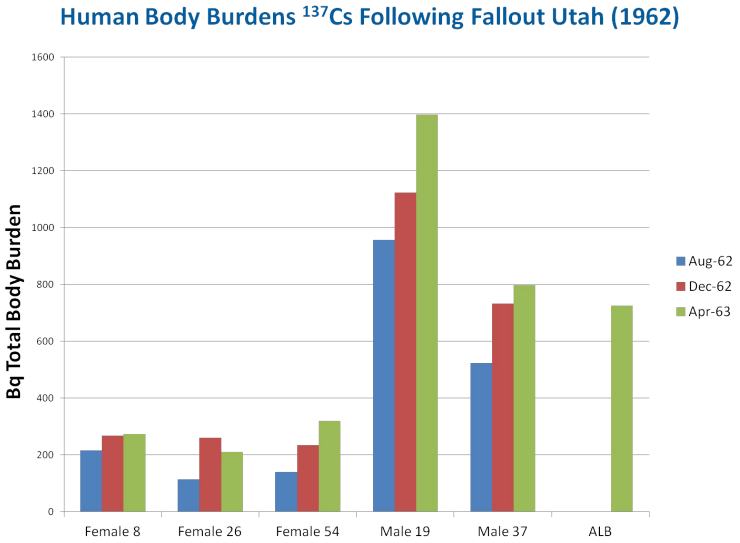

Figure 2

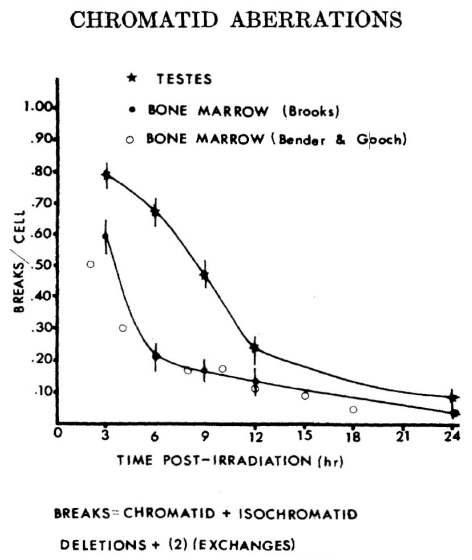
CHROMATID ABERRATIONS
TESTES
BONE MARROW (Brooks)
BONE MARROW (Bender & Gooch)
BREAKS / CELL
1.00
.90
.80
.70
.60
.50
.40
.30
.20
.10
0
3
6
9
12
15
18
21
24
TIME POST-IRRADIATION (hr)
BREAKS = CHROMATID + ISOCHROMATID
DELETIONS + (2) (EXCHANGES)

Figure 3

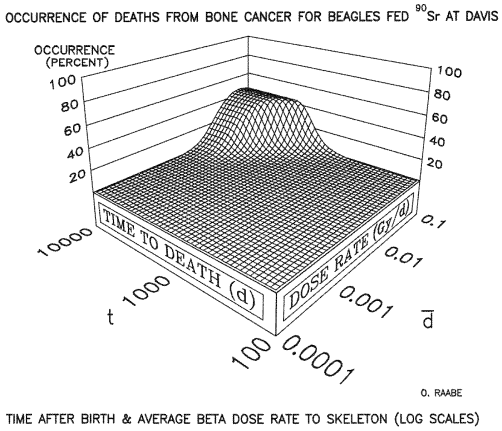
OCCURRENCE OF DEATHS FROM BONE CANCER FOR BEAGLES FED ^{90}Sr AT DAVIS
OCCURRENCE (PERCENT)
100
80
60
40
20
TIME TO DEATH (d)
10000
1000
100
t
DOSE RATE (Gy/d)
0.1
0.01
0.001
0.0001
d̄
O. RAABE
TIME AFTER BIRTH & AVERAGE BETA DOSE RATE TO SKELETON (LOG SCALES)

Figure 4

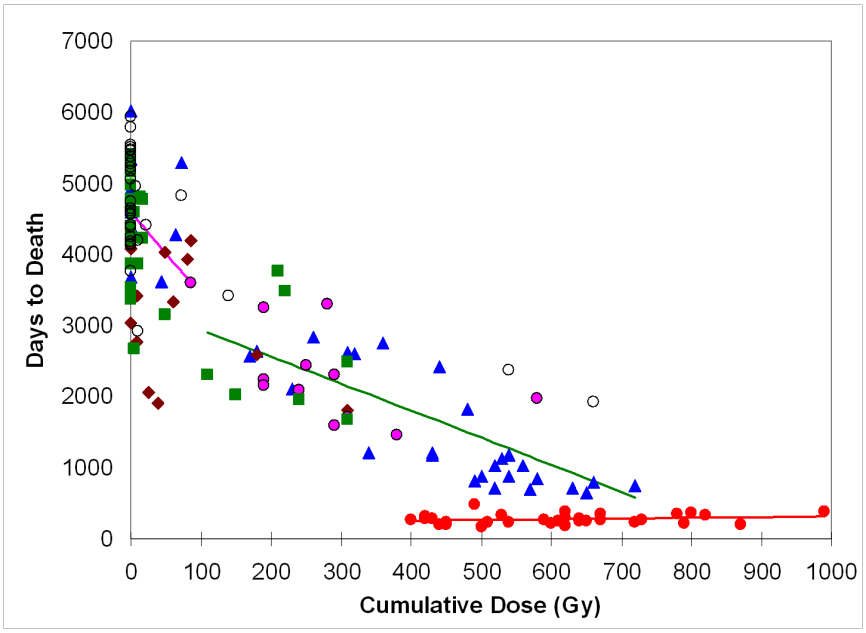

Figure 5

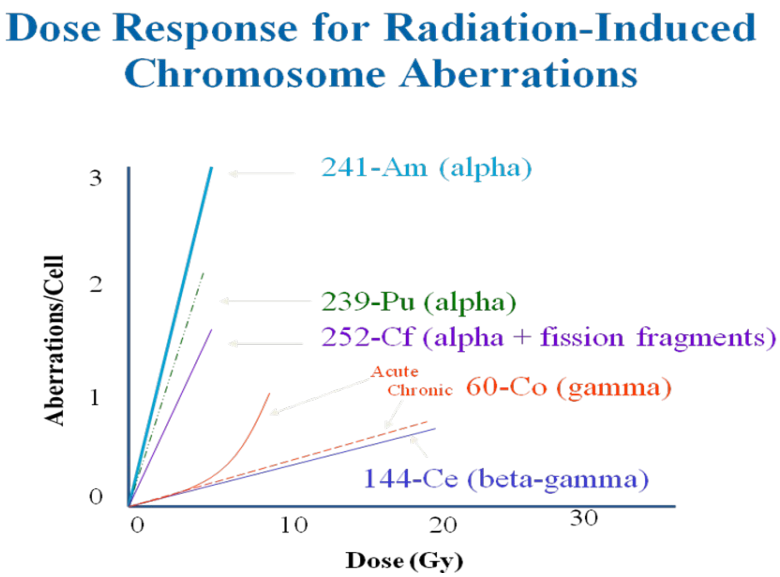

Figure 6

The Influence of ^{239}Pu Dose-Distribution on Chromosome Aberration Frequency

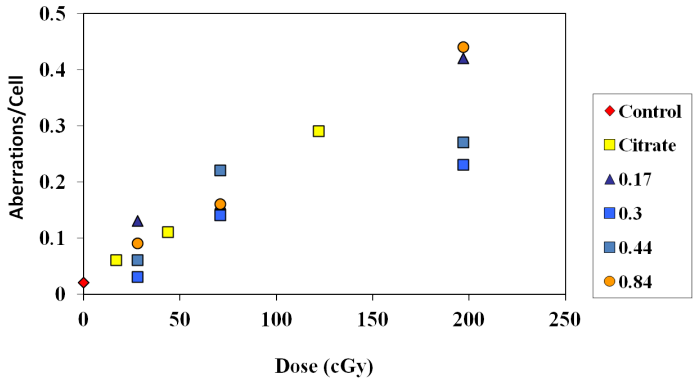

Figure 7

Cumulative Liver Tumor Incidence After $^{239}PuO_2$ or ^{239}Pu Citrate Exposure

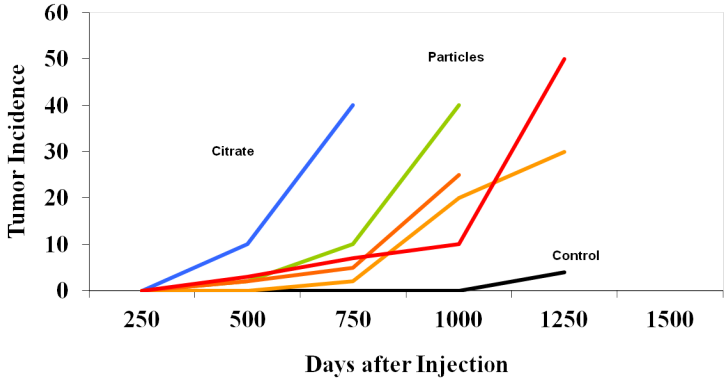

Figure 8

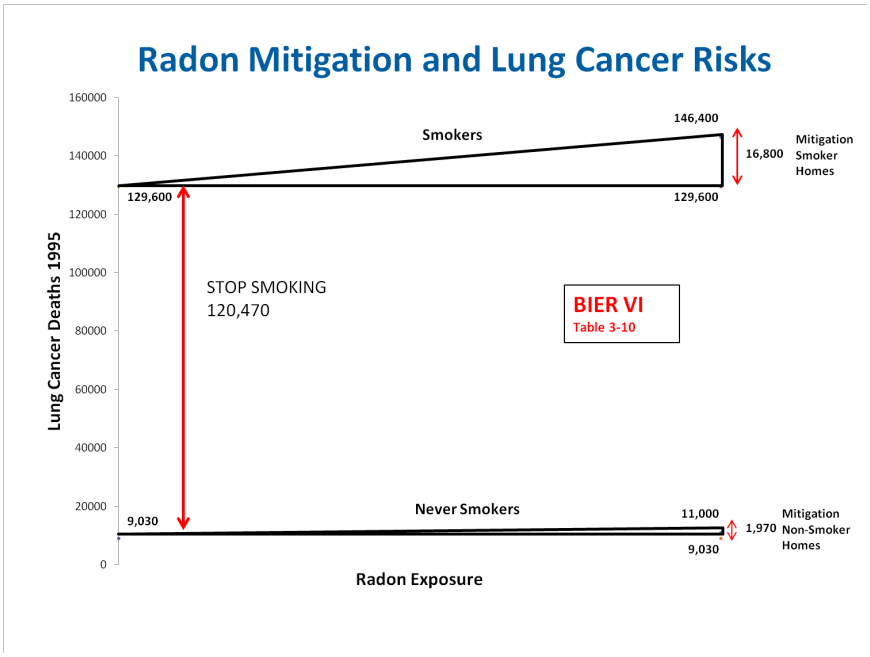

Figure 9

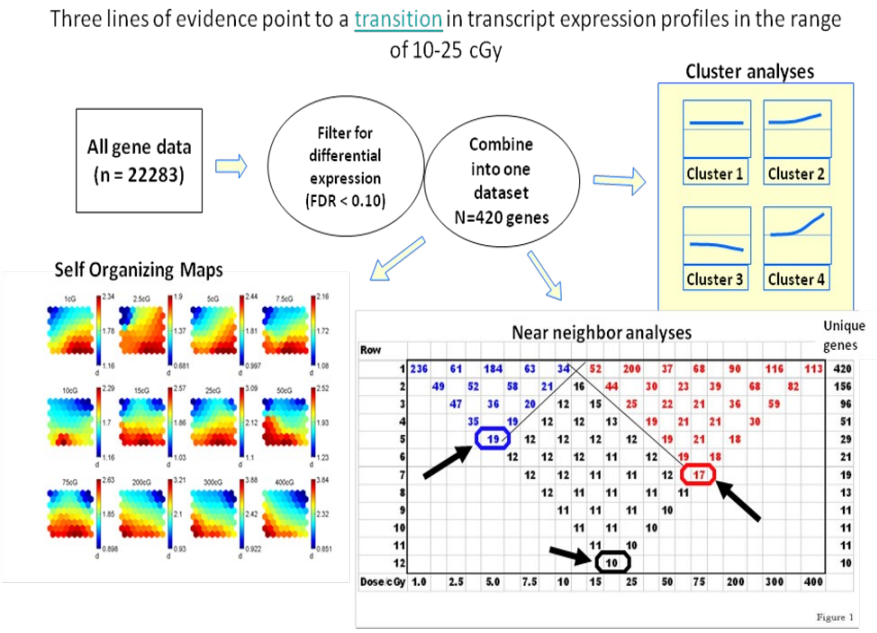

Figure 10

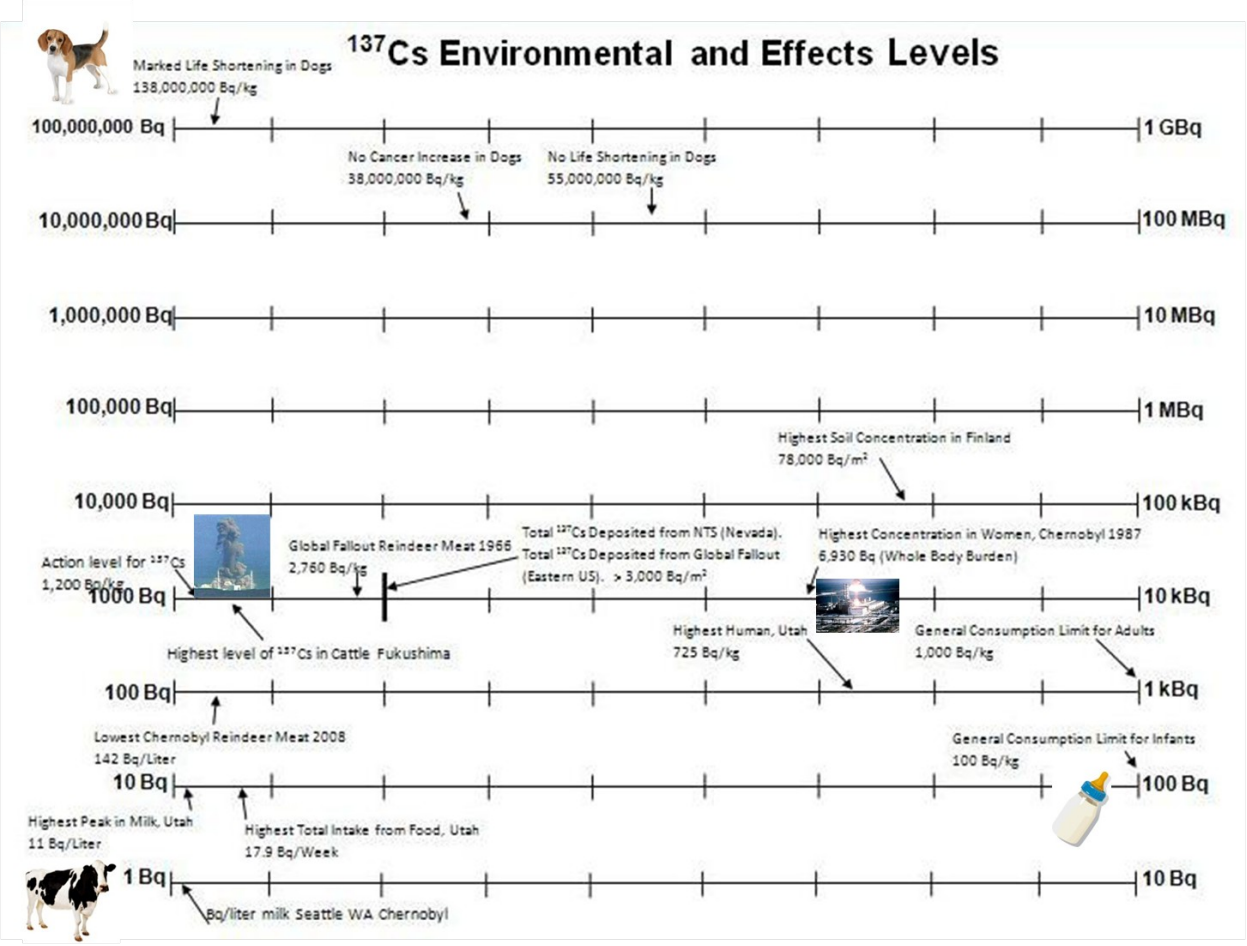
137Cs Environmental and Effects Levels
Marked Life Shortening in Dogs
138,000,000 Bq/kg
100,000,000 Bq
1 GBq
No Cancer Increase in Dogs
38,000,000 Bq/kg
No Life Shortening in Dogs
55,000,000 Bq/kg
10,000,000 Bq
100 MBq
1,000,000 Bq
10 MBq
100,000 Bq
1 MBq
Highest Soil Concentration in Finland
78,000 Bq/m²
10,000 Bq
100 kBq
Action level for 137Cs
1,200 Bq/kg
Global Fallout Reindeer Meat 1966
2,760 Bq/kg
Total 137Cs Deposited from NTS (Nevada).
Total 137Cs Deposited from Global Fallout
(Eastern US). > 3,000 Bq/m²
Highest Concentration in Women, Chernobyl 1987
6,930 Bq (Whole Body Burden)
1000 Bq
10 kBq
Highest level of 137Cs in Cattle Fukushima
Highest Human, Utah
725 Bq/kg
General Consumption Limit for Adults
1,000 Bq/kg
100 Bq
1 kBq
Lowest Chernobyl Reindeer Meat 2008
142 Bq/Liter
General Consumption Limit for Infants
100 Bq/kg
10 Bq
100 Bq
Highest Peak in Milk, Utah
11 Bq/Liter
Highest Total Intake from Food, Utah
17.9 Bq/Week
1 Bq
10 Bq
Bq/liter milk Seattle WA Chernobyl

Figure 11