A Commentary on: "A History of the United States Department of Energy (DOE) Low Dose Radiation Research Program: 1998-2008"

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Brooks, A. L. An Overview of: "A History of the United States Department of Energy (DOE) Low Dose Radiation Research Program: 1998-2008"

Abstract:

This commentary provides a very brief overview of the book "A History of the United States Department of Energy (DOE) Low Dose Radiation Research Program: 1998-2008" available on the internet at http://lowdose.energy.gov. The History itself summarizes and evaluates the research progress, publications and impact of the U.S. Department of Energy Low Dose Radiation Research Program over its first 10 years. The aims of this History were to summarize the impact of the Program's research on the current thinking and low dose paradigms associated with the radiation biology field, to help stimulate research on the potential adverse and/or protective health effects of low doses of ionizing radiation, and to generate a summary of the data generated in the Program and a scientific background for anyone interested in conducting future research on the effects of low-dose or low dose-rate radiation exposure. The History's exhaustive list of publications coupled with discussions of major observations provide a significant resource for future research in the low dose and dose-rate region. However, because of space limitations only a limited number of critical references are mentioned. At the end of Chapters 4 through 10, a series of bullets are listed which highlight major advancements in the field of radiation biology.

Chapter 1

Goals of the Low Dose Program

Chapter 1 documents the first ten years of the U.S. Department of Energy (DOE) Low Dose Radiation Research Program providing information about the development of the Program, the funding, and the critical personnel involved in its development.

The goal of the Low Dose Program was to provide a critical scientific basis for setting radiation regulatory standards. By the time the Program was initiated, several well-accepted radiation paradigms already existed, many were based on assumptions dating back to the 1940's. By 2008, the Program's research had demonstrated that some of these paradigms need to be challenged. For example, it was assumed that the cell was the important biological unit for determining radiation response, and that energy deposited in an individual cell was responsible for the biological effect observed in that cell. This was called the "hit" theory. Results from Program research using microbeams and other techniques demonstrated that this is not the case, and that "bystander" cells, which have no energy initially deposited in them, also can respond to radiation exposure with a wide variety of different changes. A second assumption now in question is that all radiation results in detrimental effects in living systems. It is now recognized that at low doses and low dose rates some of these biological changes seem to be damaging, and others protective.

Chapter 2

State of the Knowledge Radiation Effects

Chapter 2 provides a brief review of the more than seventy years of radiobiological research that was conducted before the Low Dose Program started. Early research was focused on the immediate effects of high dose radiation exposure (termed "acute effects"). This early research defined the radiation damage to organs and tissues that resulted in early deaths from the *acute radiation syndrome*.

Concerns about radiation-induced cancer and genetic effects led to extensive research in Japan to follow the A-bomb survivors to determine the role of radiation dose on inducing "late effects". In addition to the human studies, several carefully controlled animal studies using a range of different species were also conducted where large numbers of animals were exposed to graded doses of radiation from either external sources or internal deposition of radioactive material. The animal exposures ranged from doses of zero through doses that resulted in acute lethality.

Chapter 2 of the History also provides a quick review of the cellular and sub-cellular studies conducted before the Program was started. Very early studies on *Drosophila* and other test organisms are discussed, originally suggesting that there was a linear dose response for the induction of mutations over a wide range of doses with little evidence of DNA repair. Subsequent extensive research was also conducted in many animal models, demonstrating repair of radiation-induced DNA damage as well as the induction and repair of chromosome aberrations (*1*). Chromosome aberrations continue to provide a useful biomarker of radiation exposure and dose.

Chapter 3

Scientific Need, development and early directions

Chapter 3 relates the genesis of the Low Dose Program itself, within Department of Energy. Staff within the Office if Science, Office of Biological and Environmental Research (BER) drafted and developed the scientific directions for the Program. Drs. Marvin Frazier and Ari Patrinos were instrumental in getting the program started and funded. Dr. David Thomassen became the first Program Manager. In 1997, both Dr. Frazier and Dr. Thomassen were heavily involved in planning the first scientific meeting held to get input on the needs and scientific direction from the scientific community. Leading radiation biology scientists were chosen to form a subcommittee of the BER Advisory Committee (BERAC), a standing committee to provide advice to DOE. This committee provided suggestions which formed the basis of the first call for proposals by the DOE Low Dose Program. In the year 2000, Dr. Noelle Metting became Program Manager.

Chapter 4

Early Observations and New Technology

The DOE Low Dose Radiation Research Program was founded on the presumption that it would be possible to use techniques and technology developed as part of the Human Genome Project (e.g., changes in gene expression (*2*)) to measure, characterize, and understand biological responses produced by exposures to low doses of radiation. Modern biological data were

critically needed, because epidemiology studies are limited in their ability to define the shape of dose-response relationships in the low dose region and to measure changes in the low dose range especially when the dose is delivered at a low dose-rate. Thus, it was important to understand the mechanisms of interaction of radiation with biological systems in the region which in the past had not been possible. By applying new tools and techniques developed both in the physical and biological sciences it became possible to measure biological changes in much lower dose ranges than in the past. Chapter 4 reviews how new tools such as the radiation microbeam (*3*, *4*) were applied to make measurements in the low dose region.

CH 4 Major Points: Application of New Technology

- Microbeams: The DOE Low Dose Radiation Research Program played a critical role in the development of microbeams to provide technology for exposing specifically-chosen individual cells within a culture to defined doses of radiation. Various microbeam systems were developed, utilizing alpha particles, electron guns, or focused variable-energy X-ray beams, to simulate environmental radiations sources.
- Molecular sequencing techniques developed by the U.S. Human Genome Program made it possible to measure different patterns of radiation-induced gene expression in large numbers of genes that changed as a function of radiation dose and dose-rate. It was determined that radiation differentially regulated unique genes following low dose exposures in a pattern that was different than observed after high doses suggesting different mechanisms of action.

- New DNA repair detection technology using γH2AX foci made it possible to determine the number and location of nuclear traversals from microbeam irradiation. New imaging techniques were further developed that made it possible to detect multiple damage sites in DNA.
- Improved methods to detect cell-killing further defined the fine structure in the dose response relationships, enabling the demonstration of non-linear responses in the low dose region.
- Improved identification and detection of apoptosis made it possible the identification of low dose radiation-induced selective cell killing of transformed cells by apoptosis.
- Emerging developments in proteomics, secretomics, and metabolomics became important tools for detecting metabolic and biological changes as a function of radiation dose.

Chapter 5

Paradigm Shifts in Low Dose Radiation Biology and Application of Data

Chapter 5 covers critical new biology that was possible to observe using the new tools and more sensitive techniques described in Chapter 4. With these technologies and techniques it became possible to make several important biological observations and discover new phenomena describing how biological systems respond to low doses of radiation. The major early discoveries were related to three unique biological responses: bystander effects (*5*), adaptive responses (*6*), and genomic instability (*7*). The characterization and validation of these responses for the low dose region was an important early accomplishment of the Program.

"Bystander effects" (or radiation induced cell/cell communication) first seen in planar-alpha-irradiated cell cultures (8), were clearly validated using the microbeams. These instruments made it possible to deposit energy in defined cells and to measure the responses both in the cells with energy deposition in them as well as in the "non-hit" cells. Research demonstrated that it was not necessary to have energy deposited in a cell to get a biological response. Thus, the whole culture, tissue, or organ was responding to the radiation exposure. This observation had marked impact on the "hit theory" which suggested that the cells with the energy deposition were the only cells responding to the exposure.

"Adaptive responses" had also been discovered well before the start of the Program (*9*). There are two types of adaptive responses. The first was observed by giving a small priming dose prior to a large challenge dose. The pre-exposure decreased the response to the challenge dose. The second, generated by data that demonstrated that a very small dose of ionizing radiation decreased the background level of many biological responses. This could impact standard setting. Extensive research in the program was conducted to determine the magnitude, time course and potential protective effects of the "adaptive response".

"Genomic instability" was another important development in science that was impacted by the program. This phenomena showed that radiation can alter the genome in a way that after several cell divisions, the cells lose their control of the genome and become unstable (*10*). This suggested that the single hit, single mutation, single cancer hypothesis may not be the only mechanism for radiation induced cancer.

It has now been established that these observations, bystander effects, adaptive response, and genomic instability are very tightly linked and may represent different manifestations of

similar biological processes. They are all influenced by the genetic background of the biological system in which they are measured. Additional research is need to better understand the mechanisms involved in these and the impact they could have on estimates of human health risks.

CH 5 Major Points: Bystander effects

- Cells that have energy deposited in them communicate with neighboring cells, which are not "hit".
- Bystander effects have been measured both *in vitro* and *in vivo* and demonstrate that tissues respond to radiation exposure as a whole and not as single cells.
- There are two different types of bystander effects; those that require direct cell-cell and cell/matrix contact and those that result from release of substances into the culture media or blood.
- The bystander effects are dependent on the physiological and oxidative status of the cells and tissues.
- The type of damage in bystander cells is different from that induced in cells with energy deposited in them.
- Bystander responses are non-linear with dose and suggest that the response in bystander cells may increase or decrease the radiation related cancer risk.

CH 5 Major Points Adaptive Responses

- The cellular and molecular responses following exposure to low doses of radiation are different from those induced by high doses, suggesting different mechanisms of action.
- Radiation-induced adaptive responses are very general biological phenomenon and have been carefully documented for many important biological endpoints including the induction of DNA damage, mutations, micronuclei, chromosome aberrations, cell killing, apoptosis, genomic instability, and cell transformation.
- Adaptive response have been demonstrated both *in vitro* and *in vivo*.
- Protective adaptive responses suggests that the use of the LNT biophysical models may overestimate risk.

CH 5 Major Points: Genomic Instability

- Many cancers display genomic instability.
- Radiation exposure can induce genomic instability both *in vitro* and *in vivo*.
- At high doses, radiation-induced genomic instability is a frequent event. This suggests that it is not a process involving a single gene or small numbers of genes but requires a larger target (the nucleus) for its induction.
- The amount of reactive oxygen species (ROS status) and mitochondrial metabolism of the irradiated cell play critical roles in the loss of genomic stability.

Chapter 6

Mechanisms of Action

When the DOE Low Dose Radiation Research Program issued its first call for proposals in 1999, many scientists suggested that they could not measure biological changes in the dose range of interest, <0.1 Gy (10 rads). Dr. Marvin Frazier, the Program's scientific director, replied that in that case, they need not apply for funding. This was good advice, and many new techniques and technologies were developed and applied by Program-supported scientists that made it possible to detect previously undetectable radiation-induced biological changes in the low dose region.

Chapter 6 discusses the mechanisms of action for the observed low dose biological phenomena, absolutely essential before the observations could be used to inform regulatory standards. To quote from the BEIR VII report (*11*), "…until the molecular mechanisms responsible for genomic instability and its relationship to carcinogenesis are understood, extrapolation of the limited dose-response data for genomic instability to radiation-induced cancers in the low-dose range <100 mGy is not warranted." Similar statements were in the report for adaptive response and bystander effects.

At the time of the BEIR VII report, the lack of mechanistic data suggested that the new science could not be used in risk estimates. However, since then, the Program has generated additional mechanistic data on each of these responses (*12)*. This chapter summarizes the mechanistic data and provides a source of information that can help direct future research. To put all these data together using a systems approach (*13*) will require additional research and funding, but it is essential to be able to use the information produced to date to understand risk,

the mechanisms involved and the impact of low dose and dose-rate exposures on the shape of the dose-response relationships in the low dose region.

CH 6 Major Points: Mechanisms of Action

- Biological systems can detect and respond to very low doses of radiation.
- Direct damage to DNA increases as a linear function of radiation dose but the processing of the DNA damage and the signaling that results from it results in many non-linear processes.
- Low doses of radiation modify the ROS free radical status of the cells. Such modifications are suggestive of radiation protective effects seen in adaptive and protective responses. Higher doses increase the ROS status of the cells to produce responses that are known to damage cells and increase cancer risks.
- In the low dose region, direct radiation effects and the signaling pathways modify cellular responses in ways thought to be protective. These include cell transformation, mutations, chromosome aberrations, telomere function, and cell cycle delay. High doses alter these same endpoints in a way that would be predicted to be harmful.
- Radiation can induce hypersensitivity for cell killing in the low dose region. As the dose increases there is an induced radiation resistance. Hypersensitivity may be protective by eliminating damaged cells, while induced resistance could be detrimental by protecting damaged cells and allowing them to remain in the population. Additional research is needed.

- There is evidence that low doses of radiation produce selective apoptosis in cells that are transformed. Killing of transformed cells by low doses of radiation provides a potential mechanism of action for adaptive responses observed. Extensive research on the role of apoptosis in radiation risk demonstrates a potential protective role which requires more extensive research.
- Limited research on radiation-induced epigenetic effects suggest a mechanism to decrease cancer risk. This new area of research needs further definition.

Chapter 7

Modeling

Mathematical models are essential in the process of transferring basic biological data into a form that meets the needs of regulators. The current model used for risk assessment from radiation is the Linear-Non-Threshold model (LNT) (*11*, *14*, *15*). Chapter 7 describes non-linear models developed in the Program to include many levels of physical and biological organization.. The most important data that influence regulatory bodies in setting regulatory standards are those associated with human studies, both biological and epidemiological. Models that define the role of dosimetric, molecular (*16*), chromosomal (*17*), cellular (*18*), and mechanistic data need to be combined with human epidemiological models to define the shape of the dose-response relationship relationships in the low dose region. Non-linear human models

have been developed as part of the Program (*19*) and provide useful direction and information. . Complex processes must be expressed as models that are easy to understand and communicate.

CH 7 Major Points: Modeling

- Traditional LNT models were used to fit human epidemiology data and fit very well in the high dose range.
- LNT models are used and are essential in regulating radiation exposure. Research from the Program suggest that this model may overestimate the risk in the low dose region.
- Extensive data measured for many levels of biological organization has been generated and modeled by the Program.
- Some models incorporate the radiation induced decrease of responses below the background levels suggesting the potential for adaptive and protective effect in the low dose region.

Chapter 8

Taking a Systems Biology Approach to Risk

An important new approach that has been applied to understanding the biological responses in the low dose region is known as systems biology. Systems biology integrates the responses from the molecular to human population studies into complex models (*20*). These models determine how biological responses influence risk at each level of biological

organization. The ultimate goal is to develop a level of understanding of the mechanisms of action of low doses of radiation that makes it possible to predict responses and to use these responses to move up to the next level of complexity (*21*). When it is possible to predict responses it will also be possible to define the shape of the dose-response relationships and appropriately associate the risks with these low dose exposures.

CH 8 Major Points: Systems Biology

- Many biological changes and mechanisms associated with risk from ionizing radiation in the low dose region have been defined and systems biology provides an approach to integrating these into estimating risk.
- Simple "hit" models of DNA damage and response do not adequately describe the complex biology.
- Models need to be constructed at each level of biological organization and integrated to link responses across levels of biological organization.
- The very large data bases generated by the Program require a systems biology approach to integrate them into cancer risk assessment models. Additional research is needed to incorporate systems biology into cancer risk estimates.

Chapter 9

Program Communication and Monitoring

A major goal of the DOE Low Dose Radiation Research Program was to monitor and communicate the results of the research effectively, first to the scientific community involved in the research, then to policy makers to help government agencies use the information to set standards to control radiation exposure, and third, to stakeholders and the public to help them make informed choices associated with the risks from radiation. Without proper communication it is unlikely that new scientific understanding will be accepted (*22*). The public has a fear of radiation that makes it very difficult to communicate basic science which might suggest that the fear is not based on science (*23*). During formation of the Program the BERAC subcommittee outlined the key question related to communication, "How can the information derived from the low-dose initiative be best communicated to scientists, policy makers, stakeholders and to the public?"

CH 9 Major Points: Communication and Monitoring

- Communication of research results was and remains a priority of the Low Dose Program. This included communication between researchers, communication of the data to regulatory agencies, and communication and education of the findings to the public.
- An informal standing review committee composed of non-governmental stakeholders was set up to provide input for the Low Dose Program; a chief scientist was also supported to provide a vital link between the Program and the larger scientific community.

- Annual investigator meetings provided the opportunity for all grantees and stakeholders to share valuable scientific information with others in the program.
- The Program Web Site (http://lowdose.energy.gov) has become a major recognized repository for information on the health effects of low doses of radiation, a site to store and access data published in the open literature, and an educational resource for the general public on radiation exposure, doses, and risk.

Chapter 10

Current and Potential Impact on Standards

In the late 1990s when the Program was first funded, there were many ongoing activities associated with radiation standards. The research associated with the Program had substantial input into some of these. From the start of the Program, it was important that the data be recognized and used as part of the process in determining the risk from exposure to low doses of ionizing radiation, and efforts have been made at every step to do this. From 2005-2008 a number of reports were published that have direct impact on radiation standards.

1. The National Academy of Sciences published the "Biological Effects of Ionizing Radiation" (BEIR VII) report (*11*).
2. The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (*24*). This report includes five scientific annexes.

3. Additional reports were issued by the International Commission on Radiation Protection and Units (ICRP) (*25*)

and the French National Academy of Sciences (*26*).

These reports all agreed that the risk per unit of dose delivered to an individual was low. However, they reached somewhat different conclusions as to how to use the data. The BEIR VII Report suggested that the risk was linearly related to dose and suggested a Dose Dose-Rate Effectiveness Factor (DDREF) of 1.5. Both the UNSCEAR and ICRP reports suggested that there was little need to change the risk coefficients and that they would continue to use LNT along with a DDREF factor of 2.0 for estimating risk in the low dose region. Finally, a report from the French National Academy of Sciences raised some serious questions about the validity of using the LNT for evaluating radiation risks. They suggested that the risk was overestimated in the low dose region using the LNT.

CH 10 Major Points: Impact on Standards

- BEIR VII reviewed the biological and epidemiological papers up to 2003 on the risk from low doses of radiation. The committee acknowledged the research from the Program, but because of lack of mechanistic understanding at the time, the low dose biology was not used..
- The French Academy of Science reviewed the data on the effects of low doses of radiation including data produced by the Program and recommended that the LNT

was not valid for estimating risk following low doses of ionizing radiation. They suggested that the use of LNT would overestimate the risk in the low dose region.

- International organizations, UNSCEAR and ICRP, both issued reports which acknowledged the research from the Program. Nevertheless, both of these organizations and reports continued to use the LNT with a DDREF if 2.0 to calculate risk from the human epidemiological data.
- Regulatory agencies (EPA and NRC) with the responsibilities for setting radiation standards reviewed the new data from the Program, evaluated the BEIR VII and French National Academy reports, and then accepted the more conservative recommendations for continued use of the LNT.
- The data from the Program is widely recognized as important and provides information on the scientific basis for low dose responses. Continued efforts are needed to insure that risk estimates and standards are based on the best scientific data available in the low dose region.
- To date data from the Program has had limited impact on standards used to control radiation exposure or the risk factors used to evaluate the shape or slope of the dose-response relationship in the low dose region.

Summary:

The book, "A History of the United States Department of Energy (DOE) Low Dose Radiation Research Program: 1998-2008" provides a complete set of references for the publications that were produced by the program. It reveals that this Program was the world leader in low dose research and through its leadership stimulated other countries to invest considerable time, money and scientific effort in this important problem. The History provides a summary of the results and the potential significance of these data, and highlights the critical need for future radiobiological research that can be used in combination with human epidemiological studies to better understand the risk to workers and the public from radiation exposures in the low dose region. This information is extremely valuable for understanding the use of radiation in medicine, nuclear power, and nuclear accidents.

Although the History has pointed out the critical need for additional research, the task of outlining future research needs must ultimately be done by expert scientific groups and committees. However, the research results outlined in the History do suggest that many old paradigms in the field of radiation biology must be carefully re-evaluated, and some perhaps discarded. It is also evident that there are several critical research gaps that must be filled so that radiation protection standards will be based on the best available science. The role of dose and dose-rate on the induction of inflammatory responses, ROS status of the cells and tissues, genetic background, epigenetic effects, immune system and protective responses in the low dose region all require additional research. These needs are already widely recognized by the world wide scientific community.

Finally, the History provides a useful review for scientists and others that are interested in studies on low-dose radiation effects. It is essential reading for anyone conducting research in the low-dose region of the dose-response curve.

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