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Jacob D. Paz
J&L Environmental Service Inc.

TO:

Chairman Diaz

FOR SIGNATURE OF : ** GRN ** CRC NO: 03-0723

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Proposed Yucca Mountain Repository

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Dr. Jacob D. Paz
J&L Environmental Service Inc.
1200 S. Redwood St. # 89
Las Vegas, NV 89133
702-326-5857

The Honorable Chairman Neil Diaz
U.S. Nuclear Regulatory Commission
Washington, D.C. 20555-0001

October 31, 2003

Dear Chairman Diaz:

The NRC is providing oversight of the proposed Yucca Mountain Repository and will soon be asked to consider licensing the facility. We have been reviewing the scientific literature and Department of Energy documents related to Yucca Mountain and have identified possible problems in the estimation of health effects due to the combined affects of both radiation and hazardous chemicals. We invite you to work with us to develop a scientific methodology to evaluate the health risks associated with complex mixtures and the associated bystander cell effect. The bystander effect has recently been identified as a potential health problem in DOE and EPA studies, as well as the scientific literature. By establishing cooperative work, NRC will be in a better position to evaluate the license application for the Yucca Mountain Repository.

If encourage that the NRC to establishing a Cooperative collaboration, with one of the Universities or one of the National Laboratories which I have established research which collaboration. I am enclosing three publications for your staff to review:

1. Motthersill C., and Seymour C., Prevalence of Radiation-Induced Bystander Effects for Environmental Risk Assessment.
2. Draft Document Research Program Biological Effects of Low Dose and Dose Radiation Prepared for the DOE Office of Biological and Environmental Research.
3. Bystander Cells May Play Important Role In Determining Carcinogenicity, Official Says. Chemical Regulation Report No.11 March 17, 2003.

If you have any questions please feel free to communicate with me by phone or by mail.

Yours truly,,

Dr. Jacob Paz

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REPORTER

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Monday, March 17, 2003
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Conference Report
Society of Toxicology

Risk Assessment
Bystander Cells May Play Important Role In Determining Carcinogenicity, Official Says

SALT LAKE CITY–So-called bystander cells, which are adjacent to cells that are exposed to radiation or chemicals, may play an important role in determining whether an agent causes cancer, an Environmental Protection Agency scientist said March 11.

Julian Preston, head of the environmental carcinogenisis division of EPA's National Health and Environmental Effects Laboratory, said that based on assumptions about radiation, assessments of the carcinogenic risks of chemicals traditionally have focused on the genetic damage that can occur in cells directly exposed to gene-mutating agents.

However, research suggests that bystander cells near those that are directly exposed–but which are not exposed themselves–may also be important, Preston said in remarks at the Society of Toxicology's annual meeting.

That increases the number of cells affected by an exposure and increases the impact chemicals may have, he said. The implication is that cancer-causing chemicals may be more potent than previously recognized, Preston said. The more potent a carcinogen is, the more risk it may pose.

The information on bystander cells comes from studies on radiation, Preston said. Due to new technologies that allow a single radioactive particle to pass through a cell, researchers have recognized that the damaged cell appears to signal to other cells, increasing the effects of the damage, he said. The phenomenon is so clear in radiation research that it is presumed to apply to chemicals, he said.

Other biological processes that may affect carcinogenesis may also need more analysis, Preston said. These include the ability of radiation or chemicals to cause genomic instability that can result in mutations that lead to cancer, he said. This too could increase the potency of a carcinogen, Preston said.

By contrast, some studies have shown that small doses of radiation may trigger protective biological responses that reduce the risk of cancer, Preston said. The information, he stressed, has been observed at the cellular level. Whether these cellular changes translate into tumors is not clear, Preston said.

РАДИАЦИОННАЯ БИОЛОГИЯ. РАДИОЭКОЛОГИЯ, 2002, том 42, № 6, с. 585–587

СЕКЦИЯ 1. ЗАКОНОМЕРНОСТИ РАДИАЦИОННОГО МУТАГЕНЕЗА

УДК [614.7:539.1.04]:575+616.006

RELEVANCE OF RADIATION-INDUCED BYSTANDER EFFECTS FOR ENVIRONMENTAL RISK ASSESSMENT

© 2002 г. C. Mothersill*, C. Seymour

Radiation and Environmental Science Centre, Dublin Institute of Technology, Ireland

A novel mechanism involving a medium borne signalling factor has been identified following irradiation of populations of cells to doses ranging from 5 mGy-5 Gy γ-rays or to as little as 1 alpha particle traversal in a culture containing hundreds of cells. The factor can be released into culture medium and can induce responses in unexposed cultures. It has been called a "radiation-induced bystander factor". The effect is obviously relevant to risk assessment as it happens at very low doses. It could also offer new avenues for development of drugs aimed not at cell destruction but at restoring the tissues own control and coordination of response following DNA damage. The effect is clearly induced by radiation and probably by other substances. While these effects are now accepted to happen both in vitro and in vivo, their relevance and function is unknown. The investigation and modelling of the mechanism and the variation in level and type of effect in relation to genetic background and clinical history are key questions which need to be addressed in the field. The key driving hypothesis of the work being done by our laboratory is that radiation-induced bystander effects (RIBE) reflect emergent control in complex tissues and communicating cell systems, which can be harnessed for therapeutic gain.

Key words: *bystander effects, radiation effects, environmental risk assessment.*

GENERAL BACKGROUND CONCERNING RADIATION-INDUCED BYSTANDER EFFECTS

Our group has been heavily involved in the study of mechanisms by which radiation damages cells and in particular in the investigation of signals induced by exposure (reviewed in [1]). These signals appear to coordinate cellular responses even in cells not directly exposed or traversed by radiation.

Work on these effects has led to a paradigm shift in radiobiology over the last 5–10 years. Prior to this it was held that DNA double strand breaks and cellular survival/damage were inextricably linked and that radiation damage could be defined as a function of DNA double strand breaks. This is now being challenged because of an increasing number of studies which demonstrate indirect (ie non-DNA related) effects and coordinated tissue responses. These appear to saturate at low doses and lead to a breakdown of the dose response relationship which dominates at high doses. The low dose mechanisms may mitigate or exacerbate the direct effects of the dose and dominate the results at doses below 0.5 Gy. Current conventional models of radiation dose response do not accommodate these new findings and as long as the mechanisms remain unclear, modelling low dose effects is difficult and uncertainty is high.

While there is obvious interest in radiation protection in this field, there are likely to be applications in biotechnology and medicine. A novel mechanism for coordination of tissue responses is clearly being induced by radiation and probably by other substances. This offers new avenues for development of drugs aimed not at cell destruction but at restoring the tissues own control and coordination of response following DNA damage.

Many of the newly recognised effects are similar to systemic stress or immune responses, in that there is no simple relationship between exposure and effect and the outcome is not obviously dependent on dose or number of cells hit by radiation. Mitochondria appear to be important to the coordination and regulation of these effects. So far, research by our group and others has suggested that radiation causes hit cells to produce signals, which can be received by cells close to or distant from the targeted cell [2–6]. The recipient cells transduce the signals and appear to coordinate an appropriate response. Responses recorded to date include initiation of apoptosis [7, 8], differentiation [9] or proliferation [10]. These coordinated responses can be protective as for example, an apoptotic response can remove an abnormal cell from the population, but the response can also involve fixation of mutations, induction of genomic instability or cellular transformation as premalignant responses [11–16]. The nature of the signal(s) is (are) unknown although the properties are becoming clearer. Much of the phenomenological data are suggestive of a very small (less than 400 dalton) peptide molecule but it is also possible to argue for long-lived radicals leading to peroxide or aldehyde release from cells (D. Spitz, Univ. Iowa, p.comm. April 2002). The mechanisms by which the cells coordinate their responses are also unknown but signalling which leads to increased ROS and modulation of biochemical

* Adresse for correspondence: Radiation and Environmental Science Centre, Dublin Institute of Technology, Kevin Str., Dublin 8, Ireland and Saint Luke's Institute of Cancer Research, Rathgar, Dublin 6, Ireland; Phone: +353 1 4 027 509; fax +353 1 6 620 884; e-mail: cmothersill@rsc.iol.ie.

pathways in mitochondria (particularly HMP shunt) have been demonstrated [17–19].

In vitro models to study these effects involve irradiation using low doses of high LET radiation (protons or alpha particles) where not all cells in the field are hit by a radiation traversal. Effects are looked for in "un-hit" cells. [4, 6, 20]. Our laboratory has developed a simple medium transfer protocol which enables low dose, low LET radiation effects, to be studied. Our previous work which is reviewed in [1] has shown that medium from irradiated cells and from the distant progeny of irradiated cells contains a "factor" which can significantly alter survival of cells which were never irradiated and were never in contact with irradiated cells. Inhibitors of the production of the factor (or response to it), include the MAO inhibitor *L-deprenyl* and lactate [3]. Current work in the laboratory aimed at dissecting out the relative importance of signal production and cellular response, suggests that these are independently modulated and that cell lines which do not produce a signal may respond to one.

One of the most interesting areas in this field, is the link between bystander effects and induction and perpetuation of genomic instability. Radiation-induced genomic instability is characterised by the appearance in cell populations, of progeny with higher than normal levels of NON-CLONAL cytogenetic abnormalities and cell death. The instability is persistent but effects occur at a stable rate in the post irradiation survivors for many generations. Affected progeny populations do not either die out or dominate – an apparent paradox, which is difficult to reconcile with current the "world view" of competitive natural selection of favourable genes. The mechanism of perpetuation is now thought to be epigenetic and to involve an excess generation of reactive oxygen species (ROS). This is "signalled" to neighbours and perpetuated in progeny via mechanisms similar to the bystander mechanisms discussed earlier. The transmissible factors are very likely to be related to "bystander factors" [21–22].

HISTORICAL PERSPECTIVE

There is considerable evidence going back to 1954 that cells exposed to doses of radiation can produce a factor (or factors) which affects the survival and function of unexposed cells which were not in the field. These effects are sometimes referred to as "abscopal effects" or "clastogenic effects" The effects have been detected in numerous cell lines, and after both densely ionising and sparsely ionising exposures. The recent upsurge of interest in these effects has led to the development of a number of new experimental approaches. These include very low dose alpha particle fluences, where not every cell is traversed by a track, microbeam irradiation of single cells or parts of a cell in a field, or transfer of medium, (irradiated cell conditioned medium or ICCM) harvested from irradiated cells, to cultures of unirradiated cells. There is recent experimental evidence using animals that these effects can be reliably detected in vivo [22]. While the effects have become known in the radiobiology literature as "bystander effects" they are similar to a cytokine mediated effect and clearly may but do not always require gap junction mediated transfer of the factor from cell to cell. The response of cells to the bystander signal can include induction of apoptosis, or delayed effects such as genomic instability delayed death, or delayed mutations. Elevated levels of proteins associated with the above effects and with a generalised stress response have also been detected. While the effect has been widely detected, it is not always present in a cell line. Medium transfer between responding and non responding cell lines has clearly shown that signal production by an irradiated cell and response to that signal by a recipient cell can be distinguished as separate processes. Both processes appear to be p53 independent, although there is evidence that the response in fibroblast cells may require a functional p53 pathway.

GENETIC BASIS FOR BYSTANDER EFFECTS

Our group and others have previously demonstrated a clear genetic basis for the production of these types of effects following irradiation in bone marrow and urothelium from pure inbred mouse strains and also as individual variation in response in primary cultures of human urothelium from a large number of patients. To summarise a large amount of data, media harvested from irradiated cultures of tissue from human and mouse bladder, contains a signal or factor which can induce protein expression and cell death in unirradiated, allogenic explants or reduce the cloning efficiency of a human epithelial cell line. The induced effects are transmissible to progeny. The magnitude of the effect varies from patient to patient and is less in biopsies from males and male smokers.. The data for urothelium are consistent with the hypothesis that the bystander signal can induce effective radiation damage response pathways in normal cells but that death signal production at least is affected by smoking and in tumour tissues.

Clear issues of relevance to radiation protection arise from this. It is most important:

- to determine whether this effect holds for other tissues;
- to determine the effect of chronic and acute exposures;
- to determine the effect of environmental chemicals and smoking on signal production and response;
- to understand the basis of individual variation and identify susceptibility genes;
- to understand the mechanisms and possible points for intervention.

WIDER RELEVANCE

While knowledge about radiation-induced genomic instability and bystander effects has been growing in the radiation field for over 15 years, it has only recently become apparent that chemicals in the natural environment can also induce the state of genomic instability in cells and hence low dose chemical toxicity probably also involves bystander effects [23, 24]. This widens the relevance of

these indirect damage mechanisms to include environmental toxins other than radiation and makes it important to understand the mechanisms involved. These mechanisms have only recently been studied in a mechanistic way, and our laboratory is a major contributor to the field.

The induction of lethal mutations/delayed reproductive death by cadmium chloride and nickel chloride in HF19 cells revealed that both cadmium chloride and nickel chloride were able to induce this phenotype for up to 25 population doublings post-exposure. However there was a type of reproductive recovery observed at 30 population doublings especially in cultures that had been initiated with cadmium chloride. The reason for this reproductive recovery is unknown. Lethal mutations possibly act to remove unrepaired damage from the genome. Chromosomal instability persists for up to 50 population doublings post-exposure but reproductive recovery from lethal mutations is evident, therefore the lethal mutations have failed to purge the genome completely of unrepaired damage. It was postulated by Mothersill et al. [23] that lethal mutations may represent an active safety mechanism that is disabled early in carcinogenesis. The cessation of the lethal mutation effect in this study may reflect cellular transformation or that a gene, which modulated cell death may have been deleted by chromosomal damage.

In conclusion, bystander effects may require us to rethink the basis upon which we base our risk estimates. Clearly, genetic predisposition is crucial and may even be more important than dose.

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02.09.2002

Значимость радиационно-индуцированных эффектов наблюдателя для оценки экологического риска

К. Матерсал, К. Сеймур

Радиационный и экологический научный центр, Технологический институт, Дублин, Ирландия

Установлен новый механизм, включающий участие сигнального фактора, порождаемого питательной средой при облучении популяций клеток γ-излучением в дозах от 5 мГр до 5 Гр или малым количеством α-частиц (1 частица проходила через образец культуры, содержащий сотни клеток). Этот фактор может выделяться в питательную среду и индуцировать ответ в необлученных культурах. Он был назван "радиационно-индуцированным фактором наблюдателя". Очевидно, этот эффект важен для оценки риска при очень низких дозах. Он может также предложить новые пути для разработки лекарств, нацеленных не на разрушение клеток, а на восстановление в тканях контроля и координации ответа на повреждение ДНК. Этот эффект явно индуцирован излучением и, вероятно, другими веществами. Хотя сейчас признано, что эти эффекты происходят как in vivo, так и in vitro, их значимость и функции неизвестны. Исследование и моделирование механизма и вариации уровня и типа эффекта в связи с генетическим фоном и клинической историей – вот ключевые вопросы, которые ждут ответа в этой области. Ключевая гипотеза этой работы, проведенной в нашей лаборатории, заключается в том, что радиационно-индуцированный эффект наблюдателя (RIBE) отражает исходящее управление в сложных тканях и коммуникирующих клеточных системах, что может быть использовано в терапевтических целях.

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Conference Report
Society of Toxicology

Risk Assessment
Bystander Cells May Play Important Role In Determining Carcinogenicity, Official Says

SALT LAKE CITY--So-called bystander cells, which are adjacent to cells that are exposed to radiation or chemicals, may play an important role in determining whether an agent causes cancer, an Environmental Protection Agency scientist said March 11.

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By contrast, some studies have shown that small doses of radiation may trigger protective biological responses that reduce the risk of cancer, Preston said. The information, he stressed, has been observed at the cellular level. Whether these cellular changes translate into tumors is not clear, Preston said.

Computer Models

Rory Conolly, of CIIT Centers for Health Research, a nonprofit research organization based in Research Triangle Park, N.C., said computer models can be used to develop hypotheses to explain whether any dose of a chemical could cause cancer (linear assumption) or whether there may be doses that do not.

DRAFT DOCUMENT

RESEARCH PROGRAM PLAN

BIOLOGICAL EFFECTS OF

LOW DOSE AND DOSE RATE RADIATION

Prepared for:

The Office of Biological and Environmental Research

By

The Low Dose Radiation Research Program Plan Subcommittee
of the Biological and Environmental Research Advisory Committee

Low Dose Radiation Research Program Plan

II. TABLE OF CONTENTS

LOW DOSE RADIATION RESEARCH PROGRAM PLAN

III. EXECUTIVE SUMMARY

Each and every cell in the human body is constantly engaged in a life and death struggle to survive "in spite of itself." Normal physiological processes needed for cell survival generate toxic oxidative products that are damaging, even mutagenic, and potentially carcinogenic. Yet cells and people survive because of the cell's remarkable capacity to repair the majority, if not all, of this oxidative damage. We don't know, however, the relationship between this normal oxidative damage and the high frequency of cancers that exist in all human populations. Is cancer a price we pay for the very biological processes that keep us alive?

We are also constantly exposed to low levels of natural background radiation from cosmic radiation and from naturally occurring radioactive materials in air, soils, water, and even living things. Research has taught us that while even low levels of radiation induce biological damage, the damage is very similar to the oxidative damage induced by normal cellular processes. Thus a critical, yet unanswered, question in radiobiology is **whether the biological damage induced by low doses and low dose rates of radiation is repaired by the same cellular processes and with the same efficiency as normal oxidative damage that is a way of life for every living cell.**

This Program Plan will outline a research strategy to determine if low dose and low dose-rate radiation presents a health risk to people that is the same as or greater than the health risk resulting from the oxidative by-products of normal physiological processes. This information is a key determinant in decisions that are made to protect people from adverse health risks from exposure to radiation.

Extensive research on the health effects of radiation using standard epidemiological and toxicological approaches has been used for decades to characterize responses of populations and individuals to high radiation doses, and to set exposure standards to protect both the public and the workforce. These standards were set by using modeling approaches to extrapolate from the cancers observed following exposure to high doses of radiation to predicted <u>but unmeasureable</u> changes in cancer frequency at low radiation doses. The use of models was necessary because of our inability to detect

changes in cancer incidence following low doses of radiation. Historically, the predominant approach has been the Linear-no-Threshold model which assumes that each unit of radiation, no matter how small, can cause cancer. As a result, radiation-induced cancers are predicted from low doses of radiation for which it has not been possible to directly demonstrate cancer induction.

Most of the projected radiation exposures associated with human activity over the next 100 years will be to low dose and low dose-rate radiation from medical tests, waste clean-up, and environmental isolation of materials associated with nuclear weapons and nuclear power production. The major type of radiation exposures will be low Linear Energy Transfer (LET) ionizing radiation (primarily X- and gamma-radiation) from fission products. The DOE Low Dose Radiation Research Program will thus concentrate on studies of low-LET exposures delivered at low total doses and low dose-rates.

The overriding goal of this program is to ensure that human health is adequately and appropriately protected. It currently costs billions of dollars to protect workers and the public from exposure to man-made radiation, often at exposure levels lower than the natural background levels of radiation. If it could be demonstrated that there is no increased risk associated with these exposures, these resources could be directed toward more critical societal issues.

The research program will build on advances in modern molecular biology and instrumentation, not available during the previous 50 years of radiation biology research, to address the effects of very low levels of exposure to ionizing radiation. It will concentrate on understanding the relationships that exist between normal endogenous processes that deal with oxidative damage and processes responsible for the detection and repair of low levels of radiation-induced damage. Research will focus on understanding cellular processes responsible for recognizing and repairing normal oxidative damage and radiation-induced damage. If the damage and repair induced by low dose radiation is the same as for normal oxidative damage, it is possible that there are thresholds of damage that the body can handle. In contrast, if the damage from ionizing radiation is different from normal oxidative damage, then its repair, and the hazard associated with it, may be unique. To understand the relationship between normal oxidative damage and radiation-induced damage, studies will be conducted at very low, doses and dose-rates and the

perturbation of the normal physiological processes will be characterized at all levels of biological organization - from genes to cells to tissues to organisms. Research needs are identified in five interrelated areas:

1. ***Low dose radiation vs. endogenous oxidative damage - the same or different?***
   A key element of this research program will be to understand the similarities and differences between endogenous oxidative damage, damage induced by low levels of ionizing radiation, and the health risks from both.
2. ***Understanding biological responses to radiation and endogenous damage.***
   Molecular, cellular, and tissue responses modify the processing of radiation induced damage and/or determine whether or not damaged cells are eliminated, inhibited, or expressed as cancers. These responses impact cancer risks from radiation.
3. ***Thresholds for low dose radiation - fact or fiction?***
   We don't know if there are radiation doses or energies below which there is no significant biological change or below which the damage induced can be effectively dealt with by normal cellular processes. If there are, then there should be no regulatory concern for exposures below these thresholds since there will be no increase in risk.
4. ***Genetic factors that affect individual susceptibility to low dose radiation.***
   Do genetic differences exist making some individuals more sensitive to radiation-induced damage? Such genetic differences could result in sensitive individuals or sub-populations that are at increased risk for radiation-induced cancer.
5. ***Communication of research results.***
   This research program will only be a success if the science it generates is useful to policy makers, standard setters, and the public. Research results must be effectively communicated so that current thinking reflects sound science.

Research conducted in this program will help determine health risks from exposures to low levels of radiation, information that is critical to adequately and appropriately protect people and to make the most effective use of our national resources.

IV. INTRODUCTION

Estimates of cancer risks following exposure to ionizing radiation are based on epidemiological studies of exposed human populations, principally the Japanese A-bomb survivors. While analyses of these populations provide relatively reliable estimates of risks for high dose and high dose rate exposures, it is the effects of low doses and low dose rates that present the greatest health concerns for radiation workers and the general population today. The risks of cancer and mutations produced by very low doses remain a critical unresolved issue because they cannot be directly measured in exposed populations. Conceptually, we are forced to estimate risks for low-doses and for doses received as chronic protracted exposures or low dose fractionated exposures by applying various dose response models to available high dose data.

Currently, overall estimates of low dose risks are based on empirical linear fits of existing human data from relatively high dose exposures that have been adjusted for low-dose and low dose-rate exposures. This approach has generally been adopted by those responsible for assessing radiation risks.[4,9] However, others have argued that this approach is inappropriate, greatly overestimating cancer risks. Among those who believe that current protection standards overestimate risks, many argue that a threshold for radiation-induced cancer exists. This is a critical issue because of the potential societal and economic impact of decisions upon which these estimates of risk are based. Epidemiological data by themselves are not capable of resolving the critical questions at hand; moreover, conventional radiation biology experimental approaches have gone as far as they can toward addressing low dose issues.

Through recent advances in cell and molecular biology and concomitant advances in chemical and biological technology, scientists have now created an extraordinary opportunity to definitively resolve this critical low dose issue. Research to decode the genome, to understand structure-function relationships for genes and proteins, and to apply molecular biology to medical problems has resulted in the development of new scientific resources and technologies. These can be modified and applied to basic problems in radiation biology. In association with the development of instrumentation, there has been an explosion of knowledge in the fields of molecular and cellular biology. For example, it is now possible to identify the genetic basis of many diseases, to clone

and amplify individual genes, to grow a wide range of critical cell types associated with cancer, and to develop transgenic animal models. All these techniques help us understand and modify the expression and action of many genes. With new molecular techniques and the proper application of instrumentation, it will be possible to increase understanding of normal processes that repair oxidative and radiation-induced damage at the molecular, cellular and tissue levels, to evaluate molecular processes that modify the expression of these changes during cancer development, and to determine the role of low levels of radiation in these processes.

Over the last several years it has become clear that oxidative free radicals produced by normal cellular metabolism are involved in the production of endogenous DNA damage. The types of damages produced by these free radicals overlap with the majority of molecular damage produced by ionizing radiation. Cellular DNA repair mechanisms, that are highly conserved across species, evolved to remove these endogenous oxidative DNA damages and thus preserve genomic integrity. It is precisely because free radical-induced DNA damages are efficiently repaired that cells have low rates of spontaneous mutation. This raises two critical questions. **Does low level ionizing radiation induce damage that can be efficiently repaired by the same or similar repair systems as endogenous damage? If so, does this result in a threshold for adverse effects induced by low doses of radiation?**

There is ample evidence that DNA repair competence can influence radiation effects, including radiation-induced cancer. There is also accumulating evidence that even low doses of radiation can elicit numerous molecular responses that have the potential to influence the consequences of those exposures. Thus, a convincing, but unproven, case can be made supporting the view that a threshold may exist at low doses of radiation. With the continuing development of sophisticated molecular biological approaches, together with new and evolving chemical and biophysical techniques, it is now possible to readdress the low-dose issue, including the likelihood of a threshold.

Coupled with advances in biological research, new technologies will have to be advanced, including new approaches to measure cellular damage following very low dose exposures and to determine molecular responses to that damage at the level of single genes or for small changes in gene expression. Much of this technology development will

be facilitated by interactions with other ongoing programs such as the human genome and structural biology programs.

Recent epidemiological and genetic studies suggest there may be a large number of genetic polymorphisms. The potential of these polymorphisms to change the risk for cancer as a result of interactions with environmental factors, including low doses of radiation, is yet to be established and is a major thrust of this program. If the frequencies of polymorphisms that impact susceptibility to radiation-induced cancer are relatively high, they could significantly impact risk estimates at low doses for the population in general. It is now possible to identify, map, and clone the genes involved in radiation damage response functions, define the polymorphic frequencies of these genes in the population and determine their importance for susceptibility. This will provide the opportunity to directly determine their impact on cancer risk estimates after exposure to radiation. This effort will also be facilitated by interactions with the human genome program.

V. PROGRAM OUTLINE

A. Low Dose Radiation vs. Endogenous Oxidative Damage - The Same or Different?

1) **Key Question: Is the DNA damage produced by low dose ionizing radiation qualitatively and/or quantitatively different from normal oxidative damage?**

2) **Description**

Over the last several years it has become clear that oxidative free radicals produced by normal cellular metabolism are involved in the production of endogenous DNA damage. The types of damages produced by these free radicals overlap with the majority of molecular damage produced by low LET ionizing radiation. The majority of damage produced by low LET ionizing radiation is due to the radiolysis of water in the vicinity of the DNA molecule, leading to free radical-induced DNA damages, similar to that produced by endogenous free radicals. These free radicals damage the DNA sugars and bases producing single strand DNA breaks, base loss, and a large number of modified DNA bases. A much smaller number of double strand DNA breaks are produced by

direct ionization of DNA or, possibly, by the processing of multiple single lesions produced in close proximity. Protein-DNA cross-links are also formed, but in very low amounts.

In spite of the fact that the frequency of double strand breaks is much lower than that of other types of damage, double strand breaks may be the major determinant that distinguishes normal oxidative damage from low dose radiation induced damage to DNA.[19,20] In mammalian cells, the double strand break is considered to be the primary lesion involved in cellular lethality and, perhaps more significantly in terms of cancer risk, the lesion that is more difficult for cells to accurately repair. Clustered DNA damage that, at least at high radiation doses, appears to be unique to ionizing radiation may be particularly difficult to repair. Free radical-induced lesions present on a single strand of DNA have not generally been implicated in cell death and carcinogenesis because they are readily repaired by the cell's base excision repair. Although the impact of unrepaired DNA damage to vital genes cannot be ignored, it is likely that subsequent misprocessing leading to misrepaired DNA damage is largely responsible for chromosomal aberrations, genomic instability, and, ultimately, cancer.

3) Decision Making Value

We marvel at the differences in "metabolism" that exist between people not stopping to think that comparable differences in normal oxidative damage may exist between us. We live at high elevations like Denver or Salt Lake City (90 mrad/year), at sea level (23 mrad/year), and everywhere in between without realizing that there are 4-fold differences in natural cosmic background radiation that are simply dependent on elevation. "For significant sub-populations, the range of annual cosmic-ray dose equivalent exceeds an order of magnitude, i.e., from 150 to 5000 μSv (15 to 500 mrem)."[10] In addition, the lung dose from radon in homes that contributes most of the natural radiation dose, varies between regions of the United States by more than an order of magnitude.[11] Research is needed to understand and quantify real, not calculated, differences or similarities in DNA damage induced by normal oxidative processes versus low doses or low dose rates of ionizing radiation in efforts to efficiently and effectively protect people from unnecessary and avoidable health risks. The problem facing scientists and policy makers today is that all the information for radiation-induced DNA damage is

from information obtained at high doses; doses at which cells are traversed by multiple ionization tracks. There are simply no data at the low doses normally considered relevant to public health issues where a cell may only be traversed by a single electron track over a long period of time, e.g., one year. It is not difficult to imagine that the spectrum of damage at such low doses may be substantially different from that observed at high doses. Because the background of spontaneous damage from normal oxidative processes is fairly high, the question arises as to whether low levels of ionizing radiation actually make a significant addition to the background level of damage.[19] Thus, it is fundamental to the entire low dose issue to determine whether the amount and kinds of DNA damage produced at low doses of radiation are different from those normally produced within cells.

If the DNA damage produced by low doses of ionizing radiation is qualitatively similar to the damage produced by normal physiological processes then we can, as outlined below, determine if our normal damage defense mechanisms protect us from this additional damage. This could lead to a conclusion that the linear-no-threshold model is inappropriate for estimating health risks from low dose radiation. On the other hand, if low dose ionizing radiation produces unique types of damage not produced by normal oxidative processes and not removed by our damage defense mechanisms, then the linear-no-threshold model may be shown to be the most appropriate tools for estimating risk.

4) Recommendations and Costs.

Research is needed to understand and quantify real, <u>not calculated</u>, differences or similarities in DNA damage induced by normal oxidative processes versus low doses or low dose rates of ionizing radiation. This information is the foundation for the many aspects of the Low Dose Radiation Research Program. Although always needed, it was not previously attainable because critical resources and technologies were not available. Today, technologies and resources such as those developed as part of the human genome program, e.g., coupled capillary electrophoresis and mass spectrometry systems and DNA sequence information, have the potential to detect and characterize small differences in damage induced by normal oxidative processes and low doses of radiation.[7]

Research is needed in two closely related and interdependent areas: technology development and basic research.

A significant investment in technology development will be required to expand current capabilities for identifying and quantifying small amounts of oxidative or radiation-induced damage. Radically new technologies are likely not needed but current technologies will need to be modified. Methodologies having high sensitivity as well as high signal-to-noise ratios will be critical in this effort. A focused technology development effort consisting of two cycles of three-year grants should yield broadly useful and available methods for measuring small amounts and differences of oxidative damage in cells. An annual investment of approximately $4 million will be required for each of the first three years with approximately $1.5 million required for each of the next three years.

Similarly, a significant research effort will be required to characterize and quantify normal oxidative damage in cells and the incremental increases induced by low doses of ionizing radiation. Partnerships should be encouraged between laboratories involved in characterization and quantification of radiation and oxidative damage and groups with expertise in or developing new technology to facilitate progress in both areas simultaneously. An annual research investment of approximately $1.5 million will be required for each of the first three years increasing to approximately $3 million for the next three years as new technologies are developed and become more widely available. A critical goal of the research component of this program is to quantify levels of damage induced by normal oxidative processes and the incremental increases due to low dose radiation. Qualitative descriptions of differences and/or similarities between the types of damage induced under both conditions are useful in the design and interpretation of experiments in other parts of the low dose radiation research program. However, to be most useful in risk models and for regulators these differences or similarities must be quantified.

Funding area	Annual cost	
	Years 1-3	Years 4-6
Damage detection technology	$4.2 million	$1.6 million
Damage detection research	$1.6 million	$3.2 million

B. Understanding biological responses to radiation and endogenous damage.

1) Key Question: Do molecular, cellular, or tissue responses to radiation modify the processing of radiation induced damage and/or determine if damaged cells are eliminated, inhibited, or expressed as cancer?

2) Description

Knowing the types of damage produced by low dose ionizing radiation and the differences and/or similarities of that damage to normal oxidative damage are key first steps in understanding potential health risks from low dose radiation. Only by understanding these difference and/or similarities can we determine if and how low doses of ionizing radiation affect cells, tissues, and people. However, it is the biological effects of this radiation-induced damage, not the damage itself, that determines the health risks to people. Thus, several questions need to be answered before we can accurately evaluate the health risks from exposure to low doses of ionizing radiation: **Do the same things happen in cells, tissues, and people exposed to high and low doses of ionizing radiation? Do they happen the same way?** In the end, the goal of the research described in this section of the Low Dose Radiation Research Plan is to determine if health risk is directly proportional to radiation dose regardless of the dose. Understanding the mechanisms of and the dose-effect relationships for the biological effects of low doses of ionizing radiation will provide the scientific basis in support of or against the existence of a threshold for adverse effects induced by low doses of ionizing radiation.

Cellular pathways for recognizing damage, for signaling information on damage throughout the cell and to other cells, and for responding to damage are key elements in damage repair and processing. While there has been a significant amount of research defining radiation-induced genes and radiation-induced stress responses in mammalian cells, the relative contribution of a particular inductive response to the cellular consequences, e.g., survival, apoptosis, cancer, has been examined in detail for only a few genes such as p53 or PKC. At low doses of radiation no relationships between radiation-induced responses and other oxidative stresses have yet been defined. Most

radiation-induced gene changes reported to date are transient events, occurring at a specific time following exposure and then decreasing some time thereafter. The kinetics of these responses appear to vary with radiation dose, radiation quality, and cell type but systematic studies on specific radiation-induced responses have not been carried out. It must be determined which genes and proteins are specifically induced in response to low doses of ionizing radiation, how these relate to other oxidative stresses, and, importantly, how the induced proteins affect endpoints relevant to radiation-induced cancer.

In mammalian cells, the principal DNA repair pathways involved in the repair of ionizing radiation induced DNA damage are base excision repair and non-homologous end-rejoining. Base excision repair, which evolved to protect cells against endogenous damage, removes radiation-induced single DNA lesions, base damages, single strand breaks, and sites of base loss. Together these types of damage have been estimated to account for about 70% of radiation-induced DNA damage.[19] This simple DNA repair pathway is well understood and is highly homologous between bacteria and humans with many of the proteins involved exhibiting up to 40% identity. This pathway is relatively error free in most instances. Interestingly, a confounder specific to ionizing radiation is that multiple single lesions in DNA formed in close proximity to one another are recognized by the enzymes of the base excision repair pathway but their processing can result in a double strand break.

In contrast to the types of DNA damage described above, double strand breaks in mammalian cells are generally repaired by non-homologous end-rejoining. This type of repair does not require that the ends of the two recombining molecules have any sequence homology, i.e., ends of broken DNA molecules that don't belong together or that have pieces missing can actually be joined by this process. Although less well characterized than excision repair, this pathway is extremely important with respect to radiation effects. This is because radiation-induced double strand breaks, while lower in frequency than most other types of radiation-induced damage, are the major threat to the integrity of the genome because of the problems associated with their repair. Isolated mammalian cells and mice defective in components of this pathway are hypersensitive to the cytotoxic effects of ionizing radiation. Recent studies of cancer prone human populations have served to underscore the potential importance of this pathway.

Because of the nature of the damage, the non-homologous end-rejoining pathway may be more error prone. Thus, processing of DNA double strand breaks leads to mutations, chromosomal aberrations, and, perhaps, genomic instability (see below).[5] These consequences can also reveal important information relevant to the low dose question. For example, newer chromosome painting techniques have revealed that an unexpectedly large proportion of radiation-induced chromosome aberrations is due to exchanges requiring multiple breaks and involving multiple chromosomes.[14] Less sensitive techniques had previously indicated that such rearrangements appeared to be simple exchange events between chromosomes. These newer results present a clear challenge to current theories including key aspects that underpin the linear no threshold dose response.

The biological effects of radiation can be affected by responses at many levels - from molecules to tissues. Evidence that molecular, cell and tissue responses can influence radiation effects is challenging current radiobiological theory underpinning the linear no-threshold model. For example, over the last decade, a number of studies have demonstrated an apparent adaptive response in cells irradiated with small doses of ionizing radiation.[21] These cells exhibit an increased resistance to the induction of radiation effects from subsequent higher doses of ionizing radiation. Although the initial endpoint in these studies was chromosome aberrations, adaptive responses to mutation, cytotoxicity, and cancer induction have been observed in cultured cells and in mice. It is likely that radiation-induced adaptation involves changes in DNA repair, signal transduction and/or cell cycle kinetics. Most evidence indicates the adaptive response is related to oxidative stress and is associated with excision repair, although restriction enzymes that produce double strand breaks have also been shown to induce the adaptive response to ionizing radiation. Clearly, the adaptive response has the potential to impact adverse health risks and estimates of risk from low doses of radiation.

Even cells that are not irradiated can be affected by the irradiation of a neighboring cell. Recently, several laboratories have demonstrated changes in gene expression, increases in sister chromatid exchanges, and the induction of chromosomal instability in cells not directly irradiated but rather in proximity to irradiated cells.[8] Biological changes in cells not traversed by radiation have been called "bystander"

effects. The mechanisms involved to induce bystander effects are under investigation and will help understand the mode of action of radiation. To date, bystander effects have only been associated with high LET radiation. It is important for this program to determine if these effects can be induced by exposure to low LET radiation delivered at low total doses or dose-rates. Demonstration of a by-stander effect for low doses of low LET radiation could, potentially, suggest an increased risk from low doses of radiation above the risks already predicted by linear no-threshold models.

The induction of genomic instability is postulated to be the underlying event that leads to the cascade of genetic changes that results in the genetic diversity observed in most solid cancers. It has now been clearly demonstrated that radiation can induce changes in cells that result in an increase in mutations and chromosome aberrations and a decrease in the cloning efficiency of the progeny of irradiated cells many population doublings after irradiation. Genomic instability has been demonstrated in both *in vitro* systems[5] and *in vivo* using mice.[13] What appears to be unique about radiation-induced genomic instability is its high frequency suggesting that it is not produced as the result of a change in a single gene or even a group of genes. Since the target for induction of genomic instability is located in the cell nucleus the high frequency suggests the target size is likely to encompass a large fraction of the genome.[6]

Finally, tissues have also been shown to play a deciding role in the ultimate fate of cancer or precancerous cells. For example, the extracellular matrix (ECM), the mass of fibrous and globular proteins that surrounds cells, performs a critical role in dictating a tissue's organization and function.[1] Communication networks have been demonstrated between the nucleus, cells, and their microenvironment. Surprisingly, ECM can actually trip switches deep within the nucleus and spur the genes themselves into action. ECM has been shown to play a critical role in the reversion of breast cancer cells to normal cell function in culture and in dramatically reducing tumors in mice. The notion that cancer is the result of not just genetic change, but an interweaving of mutation and changes in developmental regulation and tissue structure will have a profound impact on how we view cancer induction, diagnosis, and prognosis. It will also impact the way that we estimate cancer risk, especially from low dose exposures from which only small

number of precancerous, and potentially inhibitable or reversible, changes might be expected.

3) Decision Making Value

There is both suggestive and direct evidence that biological changes and responses induced by high doses of radiation may not always be the same at low doses of radiation. Some of these changes and responses will likely have no effect on the ultimate health risk from low dose radiation but others could be critical determinants of health risks from low dose radiation exposure. These various changes and responses need to be sorted out so that they are most useful to those charged with estimating health risk from low dose radiation exposures. Understanding the mechanisms of and the dose-effect relationships for the biological effects of low doses of ionizing radiation will provide the scientific basis in support of or against the existence of a threshold for adverse effects induced by low doses of ionizing radiation. As previously noted, a problem facing scientists and policy makers today is that all the information for radiation-induced DNA damage and the responses to that damage is from information obtained at high doses. There are simply no data at the low doses normally considered relevant to public health issues. Thus, it is fundamental to the entire low dose issue to determine if things happen the same way in cells, tissues, and people exposed to high and low doses of ionizing radiation and if the same things even happen?

If the biological changes and responses induced by low doses of ionizing radiation are similar qualitatively and quantitatively to those induced by high doses of radiation, then the linear-no-threshold model may be most appropriate for estimating health risks from low dose radiation. On the other hand, some biological changes and responses may decrease or increase cancer risks at low radiation doses relative to risks at high doses. If such differences are demonstrated, then the linear-no-threshold model may be shown to overestimate (or even underestimate) cancer risk from low dose radiation.

4) Recommendations and Costs

Research is needed to understand and quantify real, not extrapolated or assumed, differences or similarities in biological changes and responses observed following exposures to low doses or low dose rates of ionizing radiation. This research covers the breadth of radiation and cancer biology from the initial recognition and

processing of radiation damage by a cell to the potential development of cancer. Not all research, no matter how important to our understanding of the mechanisms of cellular responses to low dose radiation or of cancer development, will necessarily be useful for estimating health risks from low dose radiation or in choosing low dose radiation risk models. However, understanding and quantifying key aspects of the biological changes and responses induced by low dose radiation is likely to have dramatic impacts on our ability to efficiently and effectively protect people from unnecessary and avoidable health risks.

Research will benefit from the rapidly increasing availability of DNA sequence data from humans and other model organisms including mouse, yeast, fruit fly, etc. Recently developed technologies for characterizing and quantifying gene expression should be exploited. In some cases, further improvements in these technologies will be needed, such as increases in the sensitivity for detecting and quantifying gene expression. Cytogenetic techniques that couple traditional cytogenetic approaches with advances in molecular biology and automation will likely be useful in efforts to determine how accurately low dose radiation damage is repaired. Advances in the use and development of model organisms and of advanced systems for studying "normal" cells in culture should also be exploited to study the more complex interactions of cells and tissues in determining the biological effects of low dose radiation.

Research is needed that addresses the following key questions:

Do cells recognize and respond to low doses of ionizing radiation the same way that they do to high doses of radiation? As previously discussed, much of the damage induced by radiation and normal oxidative processes is the same. Research should concentrate on damage that is unique to low doses of radiation and on differences or similarities between biological responses following high versus low doses of radiation. It must be determined which genes and proteins are specifically induced in response to low doses of ionizing radiation, how these relate to other oxidative stresses, and, importantly, how the induced genes and proteins affect endpoints relevant to radiation-induced cancer. It must also be determined if the ability and efficacy of cells to recognize and repair radiation damage is affected by the radiation dose.

Do cells repair DNA damage induced by low doses of ionizing radiation the same way that they do damage induced by high doses of radiation? Understanding the repair or misrepair of radiation induced damage is dependent on understanding the nature of damage induced by low and high doses of radiation outlined in **Section A** above. The repair of radiation-induced DNA damage is of fundamental importance to all aspects of a cell and/or an organism's responses to radiation exposure. The fidelity of the repair and damage processing systems will significantly affect the dose response curve for cancer induction, particularly at low doses. Ineffective repair or misrepair of radiation damage and subsequent processing of this unrepaired or misrepaired damage can significantly impact genomic integrity resulting in radiation-induced mutations, chromosomal aberrations, chromosomal stability, and cancer. Quite simply, if radiation-induced damage is faithfully repaired and processed, a threshold is expected. On the other hand, if repair and subsequent processing can lead to errors at low doses but not at high doses, an expectation of a threshold is not warranted.

Additional understanding of the molecular mechanisms involved and in the closely linked damage signaling pathways will provide information relevant to the faithful repair of specific lesions, the molecular responses of cells to specific lesions and the consequences of cellular processing of radiation-induced damage compared to that of endogenous damage. Many of these consequences can be assessed using rapidly developing molecular cytogenetic technology such as combinatorial fluorescence *in situ* hybridization (FISH). Because cytogenetic effects represent the synthesis of damage induction, repair and processing, these new technologies provide the opportunity to directly test certain key predictions of models of radiation effects at low doses. Substantially more information is also need on 1) the underlying repair processes; 2) the role of DNA sequence and chromatin structure in determining radiation response and target size for biological endpoints relevant to cancer; and 3) how and if the processing of damage induced by low doses of radiation leads to alterations in gene expression, changes in cell-cell or cell-matrix communication, mutations, chromosomal aberrations, and genomic instability.

Do low doses of radiation "protect" cells against subsequent low doses of ionizing radiation? If low doses of radiation regularly and predictably induce a protective

response in cells to subsequent low doses of radiation this could have a substantial impact on estimates of adverse health risk from low dose radiation. The generality and the extent of this apparent adaptive response in cells irradiated with small doses of ionizing radiation needs to be quantified.

Are the potentially damaging effects of low dose radiation amplified by interactions between cells? It is important for this program to determine if these so-called by-stander effects can be induced by exposure to low LET radiation delivered at low total doses or dose-rates. If such an effect is demonstrated and quantifiable, it could, potentially, increase estimates of risk from low dose radiation. This by-stander effect, in essence, "amplifies" the biological effects of a low dose exposure by effectively increasing the number of cells that experience adverse effects to a number greater than the number of cells directly exposed to radiation.

Is genetic instability, a key step in the development of cancer, induced or initiated by low doses of radiation? Current evidence suggests that DNA repair and processing of radiation damage can lead to instability in the progeny of irradiated cells and that susceptibility to instability is under genetic control. However, there is virtually no information on the underlying mechanisms and how the processing of damage leads to instability in the progeny of irradiated cells several generations later. Further, while there has been considerable speculation about the role of such instability in radiation-induced cancer, its role in this process remains to be determined.

Is the development of cancer induced by low (versus high) doses of radiation affected by normal tissues that surround the potential cancer cells? The ability of an irradiated cell to escape normal tissue regulatory processes or of a tissue to inhibit the further progression of precancerous cells may be differentially affected by high versus low doses of radiation. Exposure- and dose-response studies should be conducted to determine if the basic mechanisms of radiation action change as a function of total radiation dose and dose rate. High doses of ionizing radiation induce matrix and tissue disorganization, cell killing, changes in cell proliferation kinetics, induction of a multitude of genes and growth factors, and extensive chromosome and genetic damage. Many of these changes may be essential steps in radiation-induced cancer. It is important to determine if low doses of ionizing radiation can induce these biological changes. It

will also be important to determine if cancer can be induced by doses that are too low to produce such changes.

The research described in this section is long range, basic research that will require regular monitoring to ensure that it stays focused on questions and results that will be useful in estimating health risks from low doses of radiation. In general, research results that are quantifiable will be most useful. Anticipated progress will be incremental, depending on results from previous experiments and research efforts. Thus, it is anticipated that research in this component of the program will continue for the duration of the program. A series of three to four cycles of two to three year grants is anticipated, with the focus of each subsequent cycle dependent on the results of the previous cycle.

Funding area	Annual cost		
	Years 1-3	Years 4-7	Years 8-10
Biological responses to low dose radiation	$11.1 million	$11.1 million	$8.2 million

C. Thresholds for low dose radiation - fact or fiction?

1) Key Question: Are there radiation doses or energies below which there is no siginificant biological change or below which the damage induced is effectively dealt with by normal cellular processes?

2) Description

The goal of the research described in this section of the Low Dose Radiation Research Plan is to determine if there are radiation doses or energies below which there is no significant biological change or below which damage can be effectively dealt with by normal cellular processes. If there are, then there should be no regulatory concern for exposures below these thresholds since there will be no increase in risk. The previous two sections of the Low Dose Radiation Research Plan outlined a research strategy to determine if:

- endogenous oxidative damage and damage induced by low levels of ionizing radiation are the same or different.

- the same things happen in cells, tissues, and people exposed to high and low doses of ionizing radiation and if they happen the same way.

This information will be used by scientists to develop computational techniques, e.g., algorithms and advanced mathematical approaches, that can be used to determine health risks from low doses of ionizing radiation. The new information derived from cellular and molecular studies together with available data from epidemiologic and animal studies will be incorporated into these models.

The linear-no-threshold model of radiation induced cancer states that cancer risk increases as a linear function of dose. From such a model it follows that even the smallest dose of radiation is theoretically capable of producing at least some cancers. It therefore becomes important to establish the validity of this model at very low doses. At issue is whether there are thresholds below which no excess cancer or genetic damage is induced. This is the topic of the previous two sections of this program plan and is a difficult issue to approach experimentally because of the inability to actually measure cancers produced by very low doses.

Several types of thresholds have been suggested. There are statistical or practical dose thresholds below which no increase in cancer can be detected because of the severe statistical limitations imposed by the high background rate of cancer and the low frequency of radiation induced cancer. There are potential energy thresholds related to the physical characteristics of the radiation itself, especially for low LET radiation, where the amount of energy deposited in a biological system is not adequate to cause biological damage.[2] Finally, biological thresholds have been postulated to exist that depend on biological processes, such as those outlined in **Section B**, acting on radiation induced damage or responses. The goal here is to determine if biological or energy thresholds exist following very low doses of ionizing radiation and to incorporate that information into new computational algorithms or advanced mathematical approaches that can be used to determine health risks from low doses of ionizing radiation.

3) Decision Making Value

In the absence of clear or useful scientific data, standards for exposure to low doses of radiation in the workplace or the environment are currently based on default conservative assumptions. Extensive observational and epidemiological data is available

on the health effects of high levels of radiation exposure. Extrapolation of these data to low doses form the basis for current radiation standards. The research described in this Low Dose Radiation Research Plan will form the basis for a new scientific data set that will underpin future standards for and estimates of risk from exposure to low doses of ionizing radiation.

4) Recommendation and Cost

The principal focus of research in this component of the Low Dose Radiation Research Plan is to develop methods to synthesize or model new molecular level information on low dose radiation induced damage and biological responses to that damage into a low dose radiation risk model. The goal of this research program is to develop scientifically defensible tools and approaches for determining risk that are widely used, accepted, and understood. Research should include, but not be limited to development of computational techniques, e.g., algorithms and advanced mathematical approaches, for use in determining risk, that model new information from cellular and molecular studies together with available data from epidemiologic and animal studies.

A secondary, but essential component of this component of the Low Dose Radiation Research Plan, will be the design and conduct of additional biological experiments to address specific questions or predictions made by these new computational approaches. These biological experiments, though likely complementary to research conducted as part of **Section B** of the Low Dose Radiation Research Program, will be designed and conducted in collaboration with modelers.

It is anticipated that three to four cycles of two to three year grants will be funded as part of these studies. Focused biological studies will be funded in parallel with computational studies beginning after the first cycle of computational grants. Anticipated progress will be incremental, depending on results from previous experiments and research efforts. Thus, it is anticipated that research in this component of the program will continue for the duration of the program.

Funding area	Annual cost		
	Years 1-3	Years 4-7	Years 8-10
Thresholds for low dose radiation	$1.8 million	$2.2 million	$2.8 million

D. Genetic factors that affect individual susceptibility to low dose radiation

1) **Key Question: Do genetic differences exist making some individuals more sensitive to radiation induced damage? Are these individuals or related subpopulations at increased risk for radiation induced cancer?**

2) **Description**

During the last decade there has been a progressive increase in understanding of the genetic contribution to complex diseases including cancer. Molecular studies examining the genetic component of susceptibility to cancer have identified a number of genes that confer susceptibility, and the number of such genes continues to increase. It is likely that there are also individual differences in susceptibility to radiation-induced cancer.

Recent developments have suggested a link between cellular responses to ionizing radiation and cancer susceptibility. Dose response kinetics for the induction of certain types of chromosome damage also correlate with cancer susceptibility although this correlation is only phenomenological. There is clear evidence in mice and humans for genetic control of susceptibility to radiation-induced genomic instability that may extend to cancer susceptibility as well. Further, gene products involved in the recognition and repair of DNA damage have been shown to be physically associated in cells whereas those same gene products are apparently disrupted in individuals with heritable diseases associated with genomic instability and cancer.[3,12] Functional associations linking cell cycle, apoptosis and double strand break repair have also been defined, offering additional gene pathways that may be involved in cancer susceptibility.[22]

Genes associated with several different cancer prone diseases have also been shown to be associated with some form of alteration in DNA repair. Cells deficient in the ATM gene (the recently isolated gene associated with the disease Ataxia Telangiectasia) have defective damage response mechanisms, are sensitive to ionizing radiation, and have increased levels of spontaneous and radiation-induced chromosome aberrations. A protein complex associated with non-homologous chromosomal end-rejoining is defective in patients with Nijmegen breakage syndrome.[3,18] Individuals with

either Ataxia Telangiectasia or Nijmegen breakage syndrome are cancer prone, radiation sensitive, and demonstrate increased levels of chromosomal instability. Interestingly, the BRCA1 and 2 genes, found to be defective in many patients predisposed to breast and ovarian cancer, also appear to be involved in DNA double strand break repair pathways.

Overall, few genes or genetic conditions have been identified as potential susceptibility genes for cancer or radiation sensitivity. Currently, there is insufficient information to determine the total number of potential susceptibility genes, to estimate the frequency of polymorphisms in these genes in the population, and to assess the impacts on radiation-induced health risk that they pose. Molecular technologies provide powerful new ways to analyze the mammalian genome and address these issues. As this area of research matures, more complex issues of genetic interactions, including gene modifiers and gene-gene interactions and their impact on radiation-induced cancer will be able to be addressed.

3) Decision Making Value

Studies focusing on genetic susceptibility to radiation-induced cancer will improve understanding of low dose risks and will create opportunities for new basic knowledge of potential wide-ranging importance. The extent to which these studies impact current and future risk policy depends on the frequency of susceptibility genes in the general population and the ability of those genes to significantly influence low dose risks. If there are enough people who are unable to properly respond to and process radiation damage, then any model of radiation risk to the general population suggesting a threshold would appear to be untenable. Such information will also create opportunities to specifically identify susceptible individuals as well as provide insight into approaches to modify such susceptibility.

Eventually we will have an understanding of all human genes and the possible role that some subset of these genes plays in determining individual susceptibility to radiation and to cancer. While attaining this level of understanding will be a major international achievement far beyond the scope of this research project, major challenges and uncertainties regarding the use of this information will remain. These challenges and uncertainties strike at the very heart of issues being actively discussed

today and include issues of individual rights, genetic privacy, workplace discrimination, and health insurance discrimination to name a few.

- If we had the capability today to identify all people with increased susceptibility to radiation induced damage what would we or could we do with that information? Would we keep them out of jobs or environments where they might receive even the smallest preventable radiation exposure? Would we tell them their risks and let them choose? Would we release this information to their employers? Their physicians? Their insurance companies? Their relatives? These are not and will not be easy decisions and are outside of the scope of this program.

Similarly, decisions will need to be made regarding the development of radiation exposure guidelines. The overriding goal of this research program is to provide information that can be used to ensure the adequate and appropriate protection of human health. What is adequate and appropriate? No risk at any cost? Acknowledged but acceptable minimal risk? Would we or should we protect all of society from radiation exposures that pose a health risk to the most sensitive among us? Again, difficult but unavoidable questions that will arise from research on the genetic susceptibility to low dose radiation that is an important part of this program.

4) Recommendations and Costs

The Low Dose Radiation Research Program should have three main goals in terms of genetic susceptibility to low dose radiation:

- identify genes involved in the recognition, repair, and processing of damage induced by ionizing radiation
- determine the frequencies of polymorphisms in these genes in the population
- determine the biological significance of these polymorphisms with respect to radiation induced cancer and radiation sensitivity.

Research in these three areas will strongly complement ongoing initiatives at the National Institutes of Health.

The National Human Genome Research Institute (NHGRI) is funding research to identify common variants in the coding regions of the majority of human genes identified during the next five years. The goal is to develop a catalog of all

common variants in all human genes. The NHGRI is also working to create a map of at least 100,000 single nucleotide polymorphisms, the most common polymorphisms in the human genome representing single base-pair differences between two copies of the same gene. These so-called SNPs will be a boon for mapping genes for complex diseases and traits such as cancer, cancer susceptibility, and susceptibility to low dose radiation.

The National Institute of Environmental Health Science (NIEHS) is funding research as part of the Environmental Genome Project to understand the impact and interaction of environmental exposures on human disease. The NIEHS project includes efforts to understand genetic susceptibility to environmental agents that will allow more precise identification of the environmental agents that cause disease and the true risks of exposures. Its principal focus is on chemicals. Thus, the focus on radiation in the Low Dose Radiation Research Program is highly complementary. Initially, the Environmental Genome Project will focus on categories of genes including: xenobiotic metabolism and detoxification genes; hormone metabolic genes; receptor genes; DNA repair genes; cell cycle genes; cell death control genes; genes mediating immune and inflammatory responses; genes mediating nutritional factors; genes involved in oxidative processes and, genes for signal transduction systems.

Efforts in the Low Dose Radiation Research Program should be coordinated with activities at the NHGRI and NIEHS in particular to prevent duplicative effort and to facilitate rapid progress. Coordination can include, but should not be limited to, joint planning, joint meetings of program staff and/or funded investigators, joint solicitations, or co-funding of research grants.

Identification of potential susceptibility genes and polymorphisms in those genes is only the first (and perhaps the easiest) step in the program to characterize and understand genetic susceptibility. Determining the biological significance of these genetic polymorphisms with respect to cancer and radiation sensitivity is the ultimate goal and the more difficult task. The international human genome project, structural biology research, and the NHGRI and NIEHS efforts described above play important roles in determining which polymorphisms are most likely to influence gene function. Population genetics and computational biology approaches will be required to estimate the potential impact on estimates of population and individual risk. Genetic epidemiology approaches

will also be needed to relate specific polymorphisms and combinations of polymorphisms with cancer risk. Inbred mouse strains and other model organisms with well-characterized differences in susceptibility to radiation-induced cancer are also important tools for identifying significant polymorphisms. Direct assessment of the biological significance of candidate "susceptibility genes" can also be undertaken using animal models such as knock-out and knock-in mice, mice with specific genes removed or added.

It is anticipated that three cycles of three-year grants will be funded as part of these studies. Research efforts will likely scale-up in the later years of the program as DNA sequence information and information on genetic polymorphisms becomes more broadly available from this and other program. Anticipated progress will be incremental, depending on results from previous experiments and research efforts. Thus, it is anticipated that research in this component of the program will continue for the duration of the program.

Funding area	Annual cost		
	Years 1-3	Years 4-6	Years 7-10
Genetic susceptibility to low dose radiation	$2.2 million	$5.6 million	$6.6 million

E. Communication of research results.

1) **Key Question: How can the information derived from the low-dose research program be best communicated to scientists, policy makers, stakeholders, and to the public?**

2) **Description**

The low-dose research program is expected to produce important new scientific data that may modify existing paradigms associated with radiation induced health risk. Since a new risk paradigm has the potential to impact existing standards and methods used in management of low-dose radiation exposures, communication between the scientific community, policy makers and the public about the potential risk associated with radiation induced disease is vital to the outcome of the low-dose program.

Communicating the results of this research program will be a difficult challenge, since simply presenting scientific findings in the scientific literature or at scientific meetings will not automatically impact risk policy or increase public

understanding and acceptance. Influencing policy decisions will require a major change in philosophy by stakeholders and policy makers. For this shift to occur it is essential to develop a scientific base on which most scientists agree. Next, stakeholders and policy makers must develop a good understanding of the underlying science and its implications. Finally, they must develop confidence that the public will accept any changes that the underlying science determines is reasonable and appropriate. It is well established that the public is extremely sensitive and averse to the issue of radiation exposure.[16] A high percentage of the public believes that any exposure to radiation is likely to lead to cancer. The linear-no-threshold hypothesis supports this public conception and fosters the view that no expense is too great to reduce the risks of radiation exposure or environmental contamination. Therefore, it is not surprising to find that radiation controls tend to be associated with extremely high costs per year of life saved.[15,17]

3) **Decision Making Value**

The information derived from the Low Dose Radiation Research Program must provide input for decision making but also for public acceptance of risk policy. For the decision making process, it is essential that there is adequate communication between the scientists involved in generation of the primary data and between scientists and those involved in risk policy and risk communication. Through this program the policy makers should have timely and understandable scientific information that enables them to make good decisions and communicate these decisions to the public. This communication must not be one way. Opportunities for public input to the decision making process are essential.

Effective communication of the results from this program should foster better public understanding of low dose radiation risk. Communication between the scientific community, the policy makers and the public about the potential risks associated with radiation induced disease is vital to the outcome of the Low Dose Radiation Research Program. Good communication will solve problems regarding low dose radiation, facilitate the best policy choices, and develop public understanding and support.

4) Recommendations and Costs

The Low Dose Radiation Research Program should have three main goals for communicating the Program's research results:

- develop a public communication program based on principles of risk communication
- develop a public education program based on principles of risk communication science
- develop a communication network between scientists, policy makers, and DOE administrators.

Communication with the public about low dose management, requires a well-developed plan based on strong basic social science research. The goal of communication research in this program should be to understand the likely public responses to scientific findings from the Low Dose Radiation Research Program and responses to the plans that might result to modify existing standards based on these scientific findings. The following topics should be included in determining public responses to issues regarding low dose radation exposures: (i) public perceptions of risk from exposure to radiation; (ii) the perceived importance of the activities and conditions that produce low dose radiation; (iii) trust and confidence in risk managers, regulators, and decision makers; (iv) the role of the media in characterizing different positions on risk controversies; (v) the role of advocacy groups; (vi) the manner by which risk is characterized and assessed; and (vii) procedures by which decisions are made.

To present developments from this program in a form that is useful and easily understood by the public, the education program could develop web pages, written resources for public schools, and coordinate multimedia coverage of research results and public meetings. Public meetings would provide opportunities for the public to meet with scientists and regulators involved in policy making, facilitating public input into the decision making process.

The Low Dose Radiation Research Program is highly dependent on effective interactions and collaborations among scientists with varied scientific and technical expertise. For this to be successful, a communication network must be developed that will ensure adequate communication. This network should encompass not

only the scientists directly involved in the conduct of studies as a part of this program but also those involved in the genome and structural biology programs. An expanded network including scientists, policy makers from a variety of agencies, and DOE administrators is required to keep the program focused on critical issues and facilitate the understanding and translation of result into public policy.

It is anticipated that three to four cycles of two- to three-year grants will be funded as part of these studies. It is anticipated that research in this component of the program will continue for the duration of the program.

Funding area	Annual cost		
	Years 1-3	Years 4-6	Years 7-10
Communication of research results	$0.5 million	$0.9 million	$1.0 million

VI. PROGRAMMATIC STRUCTURE, MONITORING PROGRESS, DIRECTION AND FOCUS

The Low Dose Radiation Research Program is a basic research program focused on the specific goals outlined in this Program Plan. While individual research projects will be investigator initiated, these projects will be proposed based on guidance provided in requests for proposals that are published in the Federal Register and on the DOE Office of Science grants web site (http://www.er.doe.gov/production/grants/grants.html). Requests for applications will be based on this Program Plan and on overall progress in the Low Dose Radiation Research Program.

A critical component of this research program will be its ability to continue addressing both the original and changing goals over time. As with any basic research program, especially one that is focused on a specific challenge, program needs will change as results are accumulated from this and other research programs. In addition, as interactions between scientists in this program and at regulatory agencies develop and mature (see next section), program goals will be further clarified and new goals will be identified.

Scientific progress, at the individual project level, will be monitored and evaluated through the use of *ad hoc* peer review panels and occasional *ad hoc* mail reviews, under the guidance of program managers from the Office of Biological and Environmental

Research (BER). The results of these peer reviews will be evaluated and used by BER management to make decisions on the funding of individual projects across the program. BER program managers will also evaluate progress among groups of related projects and across the entire program.

A standing Low Dose Radiation Research Subcommittee of the Biological and Environmental Research Advisory Committee (BERAC) will interact with BER program managers to evaluate overall program progress, direction, and focus. This subcommittee should be comprised of scientists with expertise representing the entire range of program goals. In addition, the subcommittee should include individuals with expertise in or responsibility for developing human exposure regulatory policy. This committee should meet with BER program managers to assess the portfolio of grants within this program, and to recommend changes in emphasis and balance. In addition, the committee should identify areas that require increased and/or decreased emphasis based on results of this program, advances in other fields relevant to this program, and new issues related to risk management. Recommendations may be reflected in the issue of new requests for applications if sufficient research funds are available. The subcommittee will also participate in Low Dose Radiation Research Program contractor workshops (see next section) to be held approximately every 18 months. A major review of the program, involving this subcommittee, should be scheduled at the end of five years.

Subcommittee findings will be reported, in writing, to BERAC for further discussion, comment, and approval. Final reports will be distributed to scientists in the Low Dose Radiation Research Program, BER management, the Director of the Office of Science, program staff at other agencies, and interested congressional staff. The reports will be publicly available in hard copy and on the BERAC web site at http://www.er.doe.gov/production/ober/herac.html. The reports will serve as the basis for future program solicitations, the development of special research workshops or symposia to help clarify or debate specific program topics, or to inform scientists and the public on program progress and future directions.

VII. PROGRAM CONTRACTOR WORKSHOPS – INVOLVING CUSTOMERS AND STAKEHOLDERS

The ultimate success of this program will depend on the quality of the science produced and the usefulness of that science to the people and organizations charged with using research results to develop public health protection policy. To facilitate the kinds of interactions that will improve both the science and, hopefully, the usefulness of the results for developing public health protection policy, program contractor workshops will be held approximately every 18 months.

All principal investigators funded in the Low Dose Radiation Research Program research program will be expected to participate in these workshops. BER program staff, program staff at other agencies, BERAC low dose radiation research subcommittee members, and scientists from other DOE-funded programs whose research has useful links to the Low Dose Radiation Research Program will also be invited to participate. Finally, staff from regulatory agencies, e.g., the Environmental Protection Agency, the Nuclear Regulatory Commission, etc., will be invited to actively participate in these workshops. It is recommended that members of the BERAC low dose radiation research subcommittee act, in conjunction with BER program managers, as the Scientific Program Committee for this meeting. The subcommittee's principle charge in the context of this meeting would be to organize a highly focused symposium on a single theme or issue, in which the current state of the art is reviewed and potential future directions are discussed and assessed.

The goal of these workshops will be several-fold. They will serve as forums for exchanging research results, for communicating and discussion ongoing or changing program directions, and as opportunities to evaluate the overall balance of Low Dose Radiation Research Program portfolio. They will serve as opportunities for scientists in the program to broaden their scientific perspectives and their understanding of how their research project fits into and contributes to the Low Dose Radiation Research Program. Finally, and perhaps most importantly, it will provide opportunities for people involved in developing public health protection policy to discuss, with research scientists, the types of new or clarifying information that they need or can use from research.

These workshops will change the way that research scientists think about and conduct their research. They will open new lines of communication among program scientists and between those scientists and the users of the research results being developed in the program. Research results will still be published in peer-reviewed scientific journals; however, the dialogues, the exchanges of information, and the new understandings of the relationship between basic research the development of health protection policy that occur at these program workshop may be among the most significant outcomes of this research program.

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