RulemakingComments Resource

From: Travis Deti <tdeti@vcn.com>
Sent: Wednesday, August 26, 2015 12:30 PM
To: RulemakingComments Resource
Subject: [External_Sender] WMA Comments on Petition for Rulemaking - Linear No-Threshold Model and Standards for Protection Against Radiation
Attachments: 150825 WMA Comments on Petition for Rulemaking_Linear No Threashold Model and Standards for Protection Against Radiation1.pdf

To Whom it May Concern:

Attached please find comments of the Wyoming Mining Association on the NRC Petition for Rulemaking - Linear No-Threshold Model and Standards for Protection Against Radiation.

Thank you for your attention and consideration.

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August 25, 2015

Secretary
U.S. Nuclear Regulatory Commission
Washington, DC 20555–0001
ATTN: Rulemakings and Adjudications Staff

Subject: **Wyoming Mining Association (WMA) Comments *on Petition for Rulemaking - Linear No-Threshold Model and Standards for Protection Against Radiation* Federal Register Volume 80, Number 120 - Tuesday, June 23, 2015 pages 35870 to 35872**

Commissioners:

The Wyoming Mining Association (WMA) is an industry association representing mining companies, contractors, vendors, suppliers and consultants in the State of Wyoming. Among its mining industry members are uranium recovery licensees, including four (4) operating in-situ uranium recovery licensees, one conventional uranium recovery operator in standby, several companies planning new uranium recovery operations that are currently in the permitting or in the construction process and several companies conducting final reclamation/restoration operations.

Total uranium concentrate production in the United States in 2014 was 4,161,220 pounds U (World Nuclear Association (WNA)). 2014 Wyoming uranium production was 2,724,910 pounds U (World Nuclear Association (WNA)), accounting for 65.5% of United States production. Wyoming contributes the largest share of any state to the total production of uranium in the United States. As such the ***Petition for Rulemaking - Linear No-Threshold Model and Standards for Protection Against Radiation*** is of concern to the WMA and its uranium recovery industry members.

The WMA has the following comments regarding this petition for rulemaking:

Description of the Petition

The petition represents the consolidation of three (3) discrete petitions from Carol S. Marcus, Mark L. Miller, and Mohan Doss (the petitioners), dated February 9, 2015, February 13, 2015, and February 24, 2015, respectively addressing the same subjects those being:

- A request to "*...amend part 20 of title 10 of the Code of Federal Regulations (10 CFR), ''Standards for Protection Against Radiation,'' based on new science and evidence that contradicts the LNT hypothesis and request that the NRC greatly simplify and change 10 CFR part 20 to take into account the ''vast literature demonstrating no effects or protective effects at relatively low doses of radiation*.''
- A request that *"Worker doses should remain at present levels, with allowance of up to 100 mSv (10 rem) effective dose per year if the doses are chronic*."
- A request that "*ALARA should be removed entirely from the regulations*." Two of the initial petitioners argue that *''it makes no sense to decrease radiation doses that are not only harmless but may be hormetic.*''
- A request that "*Public doses should be raised to worker doses*." because the low doses may be hormetic.
- In addition, one petitioner suggests that the ''*LNT model is no longer justifiable*.''

General Position

The WMA believes that this Petition for Rulemaking has scientific merit based upon the technical literature referenced by the petitioners as well as the technical literature and other information discussed below and provided in the appendices to this letter. The WMA believes that this petition for rulemaking should serve as the starting point for a thorough and detailed examination and study by the Nuclear Regulatory Commission (NRC) of the applicability of the Linear No Threshold (LNT) model and the hormesis model for low dose radiation as well, with consideration being given following such examination of revising radiation protection standards in accordance with the results of the examination and study. This examination and study should be an open process that includes not only and examination of existing literature and studies, but testimony by recognized scientists and experts in the fields of radiation biology, health physics and epidemiology not only from this country but from other nations as well This effort while large would place this country in the forefront of radiation protection regulation and may ultimately result in this nation establishing reasonable and justifiable risk based standards for radiation protection that could ultimately be accepted worldwide.

In support of this petition for rulemaking the WMA offers the following additional information and supporting documentation:

2006 Paper by T.D. Luckey entitled *RADIATION HORMESIS: THE GOOD, THE BAD, AND THE UGLY*

This paper explains the fundamental issues regarding hormesis. It references the acceptance of radiation hormesis stating:

"*The good is acceptance of radiation hormesis by the French Academy of Sciences (Aurengo et al., 2005). That thorough and exemplary document makes it very clear that the Linear No Threshold (LNT) concept is not tenable*." In the conclusion this paper states, "*The bad is epitomized by the U. S. government with lost opportunities for industrial development due to unreasonable regulations which restrict radiation exposures for industrial workers to near ambient levels. The lack of popular acceptance of nuclear power is attributable to misleading information provided by the BEIR, NCRP, and ICRP committees which consistently and deliberately fail to consider confirmed scientific reports showing the biopositive effects of low dose irradiation. These restrictions contribute to potential devastation due to insufficient energy in the United States and the world*."

The greatest threats to public health are poverty and poor standards of living. Nations with the highest standards of living are generally those with the highest per capita electrical consumption rates. Iceland, Liechtenstein, Norway, Kuwait, Finland, United Arab Emirates, Canada, Sweden, Luxembourg and the United States in that order have the highest per capita electrical consumption rates in the world (as of January 1, 2014) and also possess the highest standards of living. Removal of unreasonable regulation of radiation based upon flawed models would encourage additional nuclear development, increasing the availability of electricity and living standards reducing real threats to public health.

Position of the French Academy of Sciences

France has the longest experience with radiation and radioactive materials of any nation on Earth. Henri Becquerel of Paris, France discovered radioactivity in 1896 for which he shared the 1903 Nobel Prize in Physics with Pierre and Marie Curie who discovered radium and polonium. The French Academy of Science does not support Linear No Threshold (LNT) and also discusses hormesis. In Appendix 2 are the following two (2) documents:

- Letter dated January 11, 2007 (ADAMS Accession Number: ML070160572) to the Honorable Dale E. Klein Chairman of the Nuclear Regulatory Commission (NRC) from the Advisory Committee on Nuclear Waste (ACNW) entitled *REPORT OF THE FRENCH ACADEMY OF SCIENCES, "THE DOSE-EFFECT RELATIONSHIP AND ESTIMATING THE CARCINOGENIC EFFECTS OF LOW DOSES OF IONIZING RADIATION"*

- This letter discusses the report stating,
  - "*The French Academy presenters stated that effects at low doses should not be extrapolated from effects at high doses because damage repair mechanisms at the cellular level can be quite different*."
- To a large extent, the Linear No Threshold (LNT) model developed in 1956 was based upon the extrapolation of effects from high doses of radiation from the detonations of nuclear devices at Hiroshima and Nagasaki, Japan down to much lower levels. This is the underlying assumption of the model, specifically that any dose of radiation no matter how small possess a proportional risk and that the proportional risks from low doses of radiation can be linearly extrapolated from the risks of very high doses of radiation. Clearly, the French Academy of Sciences does not agree with the very foundation of Linear No Threshold (LNT). The letter continues by stating,
  - "*The French Academy report, based on current data, raises doubts about the validity of using the LNT theory to estimate carcinogenic risks at doses less than 10 rem (< 100 mSv) and is even more skeptical of such estimates at doses less than 1 rem (< 10 mSv)*."
- This letter was prepared over eight (8) years ago by an advisory committee of the Nuclear Regulatory Commission (the Advisory Committee on Nuclear Waste) that has since been merged with the Advisory Committee on Reactor Safeguards (ACRS).

- Report of the French Academy of Sciences entitled *THE DOSE-EFFECT RELATIONSHIP AND ESTIMATING THE CARCINOGENIC EFFECTS OF LOW DOSES OF IONIZING RADIATION*
  - The report itself goes a lot further than merely discussing the Linear No Threshold (LNT) model. It clearly states that the Linear No Threshold (LNT) model is not justified in assessing stochastic risks at low does when it states;
    - "*These data show that it is not justified to use the linear no-threshold relationship to assess the carcinogenic risk of low doses observations made for doses from 0.2 to 5 Sv since for the same dose increment the biological effectiveness varies as a function of total dose and dose rate*."
  - However it goes further when it states,
    - "*It is likely that there are threshold doses or even hormetic effects, and many arguments have been put forward in the last decade suggesting that this is the case for chemical agents [125,148, 238]. In fact, the distribution of the results around a threshold is not random (if it were, there would be the same frequency of positive and negative effects), and the negative effects are more frequent, which is in favor of the hypothesis of hormesis [49]*.
  - The report argues for hormetic effects at low doses and dose rates. It continues by stating,
    - "*Among the experimental studies in which the incidence of cancer was sufficiently high in control animals, a reduction of this incidence was observed following low dose irradiation in 40% of them, an observation which is consistent with the concept of hormesis*."
  - The report extends hormetic effects to human being specifically survivors of the detonations of nuclear devices above Hiroshima and Nagasaki, Japan when it states:
    - "*In the analysis of the incidence of cancers in the survivors of the Hiroshima and Nagasaki bombs (HN), leukemias and solid cancers have been distinguished. With regard to radiation-induced leukemias, the dose-effect relationship is statistically incompatible with an LNT relationship and shows a threshold at approx. 150 mSv and a decrease in spontaneous risk (hormesis?) at doses lower than 100 mSv [155,156].* "

- The report attempts to explain hormetic effects stating:
  - "*Hormesis could also be explained in part by stimulation of immune mechanisms [157,286].*"
- The report concludes by stating,
  - "*We feel that the importance of hormesis should not be overlooked. Hormesis has been reported in 40% of the animal experiments [79], moreover, the biological bases of hormesis now seems to be understood [87], and its existence is beyond question [50].*"
- This report directly supports this rulemaking and the WMA requests that it be considered in evaluation of the petition.

The position of the French Academy of Sciences is supported by the following position of the Health Physics Society (HPS) specifically:

- Health Physics Society (HPS) Position Statement PS010-1, *Radiation Risks in Perspective* dated August 2004 which states:
  - *There is substantial and convincing scientific evidence for health risks following high-dose exposures. However, below 5–10 rem (which includes occupational and environmental exposures), risks of health effects are either too small to be observed or are nonexistent*

Paper Entitled *Evidence for beneficial low level radiation effects and radiation hormesis* (2005) by L.E. Feinendegen

- This paper included in Appendix 3 in the abstract states:
  - "*The LNT hypothesis should be abandoned and be replaced by a hypothesis that is scientifically justified. The appropriate model should include terms for both linear and non-linear response probabilities. Maintaining the LNT-hypothesis as basis for radiation protection causes unreasonable fear and expenses*." The paper concludes, "*The probability of radiation induced adaptive protection measurably outweighs that of damage from doses well below 200 mGy low-LET radiation. 4) The delayed and temporary adaptive protection at low doses involves damage prevention, damage repair, and immune responses. They appear to operate primarily against DNA damage from non-radiation sources.*"
- This statement gets to the core of radiation hormesis in that it concludes that protections afforded by low doses of radiation operate against DNA damage from causes other than radiation. This is a clear statement as to why radiation hormesis occurs.

Paper Entitled Integrated *Molecular Analysis Indicates Undetectable DNA Damage in Mice after Continuous Irradiation at ~400-fold Natural Background Radiation* (ENVIRONMENTAL HEALTH PERSPECTIVES - April 26, 2012)

- This paper discusses low dose rate radiation exposure in specialized laboratory mice, concluding:
  - "*Under low dose-rate conditions, we did not observe any changes in the levels of the DNA nucleobase damage products hypoxanthine, 8-oxo-7,8-dihydroguanine, 1,N6-ethenoadenine or 3,N4-ethenocytosine above background. The micronucleus assay revealed no evidence that low dose-rate radiation induced DNA fragmentation. Furthermore, there was no evidence of double strand break-induced homologous recombination. Finally, low dose-rate radiation did not induce Cdkn1a, Gadd45a, Mdm2, Atm, or Dbd2*"
- The paper concludes by stating:

- "*Using some of the most sensitive techniques available, low dose-rate radiation (approximately 400-fold natural background radiation) over five weeks, does not impact DNA base lesion levels, micronuclei formation, HR frequency or expression of DNA damage response genes. Importantly, an equal dose of radiation delivered acutely did induce DNA damage and DNA damage responses, thus demonstrating in an in vivo animal model that lowering the dose-rate suppresses the potentially deleterious impact of radiation. Current US policy dictates that a dose-rate of ~30X higher than background is too high to be permissible for human habitation (Federal Emergency Management Agency 2008). Given the enormous costs associated with making constraints on public policy too stringent (or too loose), these studies point to a significant need for additional knowledge regarding the impact of low dose-rate radiation*."

- This paper is a detailed document prepared by scientists working for the Massachusetts Institute of Technology (MIT) and the University of Pittsburgh. The work was funded by National Institute of Environmental Health Sciences within National Institutes of Health. It supports the conclusions of L.E. Feinendegen and T.D. Luckey.

Paper Entitled *Nuclear shipyard worker study (1980–1988): a large cohort exposed to low-dose-rate gamma radiation* (Ruth Sponsler and John R. Cameron - 2005)

- This paper examines a large cohort of nuclear shipyard workers (27,872 individuals) with exposure to external gamma radiation and compares that cohort to a group of shipyard workers (32,510 individuals) that worked on non-nuclear ships. By comparing two (2) cohorts of shipyard workers as opposed to a cohort of workers with members of the general public, errors to the "*healthy worker effect*" were eliminated. The large size of the cohorts provide a sound statistical basis. The paper concludes,
  - *"The standardised mortality ratio (SMR) for all causes of death of the cohort (SMR = 0.76) was 24% lower (p < 10–16) than that of the 32,510 controls (SMR = 1.00) (Table 3.1.B. on p.301 of Final Report). Among the cohort, 2,215 deaths occurred whereas 2,875.9 deaths would have been expected (Final Report, p.328). Among the non-nuclear controls, 3,749 deaths occurred whereas 3,685.4 deaths would have been expected (Final Report, p.332)."*
- This conclusion is interesting in that it supports radiation hormesis in that the mortality rates for all causes for the nuclear shipyard workers were less (24% less) than that for the non-nuclear shipyard workers and less than predicted for the cohort. A table containing this data from the paper is included below:

Table 2	Deaths from All Causes, Death Rates** and Standardised mortality ratios with 95% confidence intervals for the cohort (NW = 5.0 mGy)); low dose cohort (NW < 5.0 mGy); and controls (NNW)					
	NNW	NW < 5.0 mGy	NW ≥ 5.0 mGy	NW ≥ 5.0 mGy		
	Controls	Low Dose Cohort	Cohort	Cohort		
Subgrouping	All	All	All	0.5–	1.0–	5.0+
Number in Sample	32,510	10,348	27,872	5,431	13,357	9,084
Person-Years	4,25,070	1,39,746	3,56,091	69,489	1,72,531	1,14,071
Deaths	3,745	973	2,215	454	1,110	651
Death rate per 1000**	9	7.1	6.4	6.7	6.6	5.9
SMR	1	0.81	0.76	0.72	0.79	0.74
95% C.I.	(0.97-1.03)	(0.76–0.79)	0.73			
*Indicates that SMR is significantly lower than for NNW group at p < 0.05.						
**Adjusted for deaths excluded from analysis due to unknown date of death.						
Adapted from Tables 3.1.B and 3.1.C on pp.301, 302 of Final Report (Matanoski, 1991).						

- This paper presents statistical evidence of radiation hormesis. The WMA requests that it be considered when evaluating this petition for rulemaking.

Presentation Entitled *Future of Radiation Protection Regulations* by Dr. Jerry M. Cuttler that Was Given at the 60th Annual Meeting of Health Physics Society in Indianapolis, Indiana, on July 12-16, 2015

This presentation is included in its entirety in Appendix 6. He discusses the problems induced by the over regulation and fear of low dose radiation especially in relation to the Fukushima incident citing:

- *Major health problems due to fear of low level radiation and the emergency protective measures:*
  - *fearful rescue workers abandoned earthquake and flood victims*
  - *approx 1200 deaths due to evacuation and lack of care*
  - *more than 100,000 distressed residents for more than 4 years*
  - *major disruption of farming and food supplies*
- *50 reactors shut down; major electricity shortage*
- *Many hundreds of billions of dollars spent to import coal, oil and gas, to replace lost nuclear electricity generation*
- *Many other serious social and economic impacts*

The risks to protect individuals from low doses of radiation are greater than those of the radiation itself.

This presentation is included and used with the express permission of Dr. Jerry Cuttler.
The Atomic Man (Harold McCluskey) Incident

This incident while not a statistical study or an epidemiological one, provides anecdotal information regarding radiation exposure to a single individual. On August 30, 1976, an Hanford worker (Harold McCluskey) was exposed to a large amount of Americium-241 (an intake via inhalation and skin absorption in excess of 1mCi) due to a chemical explosion in a glove box. He received a very large dose as described in the table below:

Table 5. Summary of absorbed dose accumulated over 5.3* yr *post-exposure		
Organ	Assumed Weight of organ (g)	Absorbed dose (rads)
Lungs	1200	~130
Liver	1740	~160
Bone	7000	~*550*
Skin	20	~880,000

Source: ***1976 HANFORD AMERICIUM EXPOSURE INCIDENT: ORGAN BURDEN AND RADIATION DOSE ESTIMATES - Health Physics Volume 45, Number 4 -1983***

An entire issue of Health Physics (*Volume 45, Number 4 -1983)* was devoted to this case. Included in Appendix 7 is the paper entitled *1976 HANFORD AMERICIUM EXPOSURE INCIDENT: ORGAN BURDEN AND RADIATION DOSE ESTIMATES (*B. ROBINSON, K. R. HEID, T. L. ALDRIDGE and R. D. GLENN - 1983). Harold McCluskey "...*spoke in favor of developing nuclear power, saying he saw his injuries as the result of "purely an industrial accident."* (Wikipedia). He died on August 17, 1987 at age 75 of coronary artery disease.

This incident is being raised in this context because it is an extremely well-studied case of extreme radiation exposure to an individual in which the expected symptoms of such exposure specifically cancer did not occur.

Paper Entitled *TOWARD IMPROVED IONIZING RADIATION SAFETY STANDARDS* - Otto G. Raabe Center for Health and the Environment, University of California, Davis - 2011

This paper included in Appendix 8 entitled ***TOWARD IMPROVED IONIZING RADIATION SAFETY STANDARDS*** published by the Health Physics Society in 2011. Dr. Raabe assails the Linear No Threshold (LNT) model in the paper stating:

> *The LNT model does not predict the observed effects or lack thereof for protracted exposures to ionizing radiation exposure (Jaworowski 2010). Neither does the LNT model readily predict the results of a cumulative set of fractionated medical diagnostic x-ray exposures of the lung where there was no indication of increased lung cancer with the observed relative risk at a cumulative doses of 1 Sv being 1.00 [95% confidence interval 0.94 –1.07], contrasting with the high expected relative risk based on the atomic bomb survivors being 1.60 [95%confidence interval 1.27–1.99] (Howe 1995). Also, the large population exposures to long-term protracted ionizing radiation associated with the 1986 Chernobyl reactor accident in the Ukraine were predicted with LNT to result in a virtual epidemic of long term radiation-induced cancer (Anspaugh et al. 1988). Instead, there was no apparent major effect of this widespread protracted exposure to ionizing radiation except for thyroid disease associated with very high acute radiation doses from short-lived 131I in milk (WHO 2006; Jaworowski 2010).*

In this paper Dr. Raabe also states:

> *…. recent recommendations have calculated cancer risk as a function of cumulative dose using a linear no-threshold cancer risk model based on the acute high dose rate exposures received by the Japanese atomic bomb survivors. The underlying assumption in these current recommendations is that risk of radiation-induced cancer is proportional to cumulative dose without threshold. In conflict with this position are the studies of protracted exposures from internally-deposited radionuclides in people and laboratory animals that have demonstrated that cancer induction risk is a function of average dose rate for protracted exposures to ionizing radiation. At lower average dose rates, cancer latency can exceed natural lifespan leading to a virtual threshold.*

This is a significant point. As previously stated, the Linear No Threshold (LNT) model was developed in 1956 and based upon the extrapolation of effects from high doses of radiation from the detonation of two (2) nuclear devices. These doses were received over incredibly short periods of time, in other words at high dose rates. For example, the initial radiation dose from external exposure to radiation from the device following detonation is received within seconds. These types of extremely high dose rate exposures are not representative of dose rates received in normal settings in the nuclear industry and the risks related to them cannot be accurately extrapolated downward to the low doses at low dose rates received in industrial settings.

The WMA requests that this paper be considered in evaluating the petition for rulemaking.

Comments of Dr. Nancy Standler MD, Ph.D.

Included in Appendix 9 is a letter of comment on the *Petition for Rulemaking* prepared by Dr. Nancy Standler MD, Ph.D. The letter discusses the petition as well as some history related to the development of the Linear No Threshold (LNT) Model based upon Dr. Standler's discussions with Dr. Casarett, one of the developers of the model. The WMA concurs with and supports this letter.

Conclusions

The WMA has reviewed the petition for rulemaking and some literature associated with the validity (or lack thereof) of the Linear No Threshold (LNT) model as well as literature discussing radiation hormesis. Based upon its cursory review, it has reached the following conclusions:

- The consolidated petition for rulemaking has merits and there are substantial references in the existing literature in support of the fact that the Linear No Threshold (LNT) model fails to describe radiation risks at low doses, that there may well be a threshold below which radiation does no harm and in fact radiation hormesis exists and small/low doses of low dose rate radiation may in fact benefit animal and human health via various mechanisms including stimulation of the immune system.
- The petition raises valid points and the WMA believes that this petition for rulemaking should serve as the starting point for a thorough and detailed examination and study by the Nuclear Regulatory Commission (NRC) of the applicability of the Linear No Threshold (LNT) model and the hormesis model for low dose radiation as well, with consideration being given following such examination of revising radiation protection standards in accordance with the results of the examination and study.
- The lack of validity of the Linear No Threshold (LNT) model at low doses/low dose rates as well as the existence of radiation hormesis is supported by an organization no less prestigious than the French Academy of Sciences. This fact has been known to the Nuclear Regulatory Commission (NRC) since at least January 11, 2007. The WMA believes that the Nuclear Regulatory Commission (NRC) should vigorously pursue this information in the interests of effective risk based regulation.

- Regulation based upon overly conservative and invalid models poses risks in and of itself in that it can serve to deprive people of the standard of living enhancing benefits of reliable electric power derived from nuclear energy. Suppression of the standard of living is detrimental in its own right as poverty and a low standard of living possess health risks of their own.

The WMA appreciates the opportunity to comment on this Petition for Rulemaking. If you have any questions please do not hesitate to contact me.

Sincerely,

Jonathan Downing
Executive Director

cc: Katie Sweeney - National Mining Association
Dr. Nancy Standler - Valley View Medical Center

Appendix 1

Dose-Response 4(3):169–190, 2006
Formerly Nonlinearity in Biology, Toxicology, and Medicine

ISSN: 1559-3258
DOI: 10.2203/dose-response.06-102.Luckey

International Hormesis Society
www.HormesisSociety.org

RADIATION HORMESIS: THE GOOD, THE BAD, AND THE UGLY

T. D. Luckey □ Lawrence, KS

□ Three aspects of hormesis with low doses of ionizing radiation are presented: the good, the bad, and the ugly. The good is acceptance by France, Japan, and China of the thousands of studies showing stimulation and/or benefit, with no harm, from low dose irradiation. This includes thousands of people who live in good health with high background radiation. The bad is the nonacceptance of radiation hormesis by the U. S. and most other governments; their linear no threshold (LNT) concept promulgates fear of all radiation and produces laws which have no basis in mammalian physiology. The LNT concept leads to poor health, unreasonable medicine and oppressed industries. The ugly is decades of deception by medical and radiation committees which refuse to consider valid evidence of radiation hormesis in cancer, other diseases, and health. Specific examples are provided for the good, the bad, and the ugly in radiation hormesis.

Keywords: cancer, health, therapy, radon, BEIR VI, deception

INTRODUCTION

Hormesis is the stimulation of any system by low doses of any agent (Luckey, 1980a). Large and small doses of most agents elicit opposite responses. A dose that elicits a response which separates positive from negative effects is the threshold dose; it is the "zero equivalent point" (ZEP) for that specific parameter. Low dose is any dose below ZEP. Dose rate is also important. Taking one pill per day may be life-saving; taking 365 of most pills in one day would be lethal.

Radiation hormesis is the stimulation, often considered to be beneficial, from low doses of ionizing radiation. Large doses are harmful. The difference is quite clear in those dose-response curves which involve both biopositive and bionegative effects. At any given rate, the physiologic response to ionizing radiation is directly proportional to the logarithm of the dose (Luckey, 1991).

Following William Crookes' inventions of the radiometer in 1875 and the cathode ray tube in 1877, physicists began to understand the dualistic nature of radiation. Fundamental discoveries made in the last decade of the 19th century (Table 1) are the foundation for the use of ionizing radiation in physiology, immunology, medical diagnosis, and therapy (Brucer, 1990). Ionizing radiation includes electromagnetic rays and high linear energy particles. The rays are high energy photons: ultraviolet (UV) rays, X rays, and gamma rays. Ionizing particles include alpha rays (nuclei of

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TABLE 1. Nineteenth century tools for ionizing radiation (Brucer, 1990)

Year	Item	Person and Action
1890	Isotope	P. Schutzenburger suggested there are isotopes for many elements.
1891	Electron	G. Stoney defined the electron as one unit of electric charge.
1892	U Radiation	W. Crookes found that uranium fogged photographic film.
1893	Hydrogen	J. Mallet suggested hydrogen should be the unit atomic weight.
	(Proton	In 1920, E. Rutherford called the hydrogen atom a proton.)
1894	X Ray	A. Goodspeed threw away "freak" pictures found on some film.
1895	X Ray	W. Roentgen found (Nov. 8) Crookes tube rays pass through cardboard.
		J. Thomson found X rays ionize air.
	Helium	Ramsay & Rayleigh discovered helium in the gas from uranium ore.
	Ion Paths	C. Wilson built the first cloud chamber.
1896	X Ray	The X ray of Mrs. Roentgen's hand appeared in January news papers.
		Diagnostic X rays began in many countries.
		T. Edison invented the fluoroscope.
		W. Shrader found high doses of X rays kill bacteria.
		Many reported dermatitis from X rays.
		H. Becquerel discovered uranium produced this new radiation.
	Therapy	H. Gocht treated cancer; L. Freund treated inflammation.
	Hormesis	Schrader and Loret showed low doses of X rays stimulated immunity.
		New York Health Dept. found low doses stimulate TB bacilli.
	E.M. Rays	E. Rutherford detected electromagnetic waves.
1897	Electron	J. Thomson discovered electrons.
	Gamma Ray	J. Thomson discovered gamma rays.
	Sickness	D. Walsh described radiation sickness.
	Therapy	A. Ausset reported X rays helped a moribund patient with tuberculosis.
	RPC	Radiation Protection Committee formed in England.
1898	Actinium	A. Debierne discovered actinium produced rays.
	Radium	M. Curie discovered radioactive radium.
	Polonium	M. Curie discovered radioactive polonium.
	Radioactivity	M. Curie found thorium and potassium are radioactive.
1899	Radon	E. Rutherford noted thorium produces a gas (radon).
	Half-life	E. Rutherford used decay rates of radioactive elements for half-life values.
	Alpha Ray	E. Rutherford discovered alpha rays.
	Beta Ray	E. Rutherford discovered beta rays.
		S. Meyer noted that beta rays are electrons.
	Gamma Ray	E. Rutherford defined gamma rays.
	Dermatitis	M. Curie found X rays caused skin erythema.
	Neutron	S. Sutherland named neutrons.
	Actinium	A. Debierne discovered actinium and its radiation.
	Hormesis	J. Loeb found radiation stimulated parthenogenesis in sea urchins.

the element, helium), beta rays (electrons), protons (hydrogen with only one electron), and neutrons. Each ray and particle has a wide range of energies (often expressed as million electron volts (MeV)) which is defined by its source. The physiologic effects of other rays and particles (neutrinos, muons, positrons, and atoms) are poorly defined.

Although all elements decay, only tritium, carbon, potassium, and those heavier than bismuth are usually considered to be naturally radioactive. Radioactive atoms are used in diagnostic and therapeutic medicine, and in industry; some occur naturally and some are man made. Natural radiation

is in the air, water, earth, our bodies, and all the materials we use. In general, adults receive about 2 mGy/y, about 10,000 radiations per minute, from natural sources. Brucer estimated that 25% of all medical patients received some radiation, the average is about 0.54 mGy/y (Brucer, 1990).

Each minute some of the ten trillion cells in our body receive ionizing radiation from our natural background (Luckey, 1991). Depending upon its energy, one alpha ray might hit 2-50 cells (the 7 MeV alpha rays of radon progeny traverse 0.07 mm tissue), a beta ray could hit 10-500 cells (a 1 MeV beta ray penetrates 6.4 mm tissue), and each X and gamma ray might hit 1,000-100,000 cells.

The initial action of most ionizing radiation is on the water which constitutes about 98% of the total number of molecules in soft tissues. Ionizing radiation produces a variety of oxygen species from water (Table 2) (Gould, 1968, Luckey, 2005a). Each of these will avidly attack nearby material to make strange compounds and atomic fragments (free radicals) which can change the structure of DNA and RNA, drastically alter metabolic pathways, and kill bacteria and tissue cells. Low dose irradiation is insufficient to cause erythema or to kill healthy mammalian cells. If the rate of destruction is not too fast, damage in healthy tissues can be bypassed or repaired and the overall reaction is biopositive (Polycove and Feinendegen, 2003). A major effect is activation of the immune system. There is also a powerful direct action upon anaerobic bacteria which cause infection, gangrene for example. Each oxygen specie is devastating for anaerobic bacteria. Necrosis stops when the bacterial toxins are neutralized and our macrophages start the cleaning and healing processes.

A broad view of radiation hormesis includes the good, the bad, and the ugly. The good includes abundant evidence showing increased 1)

TABLE 2. Oxygen species in irradiated tissues (Gould, 1968)

Species	Name
H_3O^+	Hydronium ion
H_2O^+	Oxonium ion
HO^+	Hydroxonium ion
$HO\cdot$	Hydroxyl radical
$HO\cdot_2$	Perhydroxyl radical
$O\cdot$	Oxygen radical
$O\!:$	Atomic oxygen
O_2	Molecular oxygen
O_3	Ozone
O_2^-	Superoxide ion
O_2^{2-}	Peroxide ion
O_3^-	Ozonide ion
HO_2^-	Perhydroxide ion
H_2O_2	Hydrogen peroxide

physiologic performance, 2) immune competence, 3) health, and 4) mean lifespan. Some evidence indicates ionizing radiation is essential for life (Luckey, 2004). The bad is the false concepts that "all radiation is harmful" and partial dose-response curves that are "linear with no threshold" (LNT). This leads to fear of low doses of ionizing radiation. The bad also includes the cessation of beneficial uses of ionizing radiation without reason. The ugly is the consistent misrepresentation of biopositive effects by established scientists and our government advisory committees. With no direct evidence of harm, they ignore overwhelming evidence showing benefits from low dose irradiation. Examples of the good, the bad, and the ugly are provided.

THE GOOD

Over 3,000 scientific research papers show that low dose irradiation is stimulatory and/or beneficial in a wide variety of microbes, plants, invertebrates, and vertebrates (Luckey, 1980a, 1991, Muckerheide, 2001). Using the parameters of cancer mortality rates or mean lifespan in humans, no scientifically acceptable study was found which showed that less than 10 cGy was harmful. Radiation, Science, and Health, Inc. (Box 843, Needham, MA 02494) offers $1,000 for one report in English with scientifically acceptable evidence of harm (increased cancer death rate or decreased average lifespan) from low dose irradiation in normal (not immune deficient) humans or laboratory animals. This is opposed by several thousand studies which produced confirmed and definitive evidence of stimulation and/or benefit.

The good is acceptance of radiation hormesis by the French Academy of Sciences (Aurengo *et al.*, 2005). That thorough and exemplary document makes it very clear that the Linear No Threshold (LNT) concept is not tenable. "However, the use of LNT in the low dose or low dose range is not consistent with the current radiobiological knowledge." (p. 10) For doses <10 cSv, epidemiologic studies "have not been able to detect statistically significant risk even on large cohorts or populations." (p.8) "Indeed, a meta-analysis of experimental data shows that in 40% of animal experiments there is a decrease in the incidence of spontaneous cancers after low doses." (p.9) "These data show that the use of a linear no-threshold relationship is not justified for assessing by extrapolation the risk of low doses..." (p. 9) "In conclusion, this report doubts the validity of using LNT in the evaluation of the carcinogenic risk of low doses (<100 mSv) and even more for very low doses (<10 mSv)." (p.10) "For doses lower than 100 mSv, almost all studies do not evidence a significant effect." (p. 25) Regarding leukemia in atomic bomb victims: "the dose-effect relationship is statistically incompatible with an LNT relationship," (p. 25) "The LNT model cannot be used to estimate the effect of very low doses..." (p36)

The good includes the natural occurrence of increased ionizing radiation in certain parts of the world. Areas in Brazil, Egypt, Iran, and India have up to 20 times more radiation than the US average of 2 mGy/y (Cullan and Franca, 1977). Brazilians flock to beaches which have high radiation levels, 0.03 mGy/h, from black monazite sands. Many health spas throughout the world contain radioactivity comparable with the above sites; much of this is due to radium and radon in the water.

In a 600 page report, the French Academy of Sciences document other groups subjected to unusual levels of ionizing radiation with either no or beneficial effects (Aurengo *et al.,* 2005). 1) The incidence of solid cancers decreased in 21,500 exposed workers at Mayak, a Russian plutonium production complex. 2) The total cancer deaths in 8,600 cleanup workers at Chernobyl (who received an average of 5 cGy) was 12% lower than that of the general Russian population. 3) The leukemia death rate in 96,000 nuclear workers (in three countries) exposed to over 40 cSv was only half that predicted. 4) No increased cancer was found in 222,400 radiologists and radiation technicians who received more than 20 cGy in 20 years. 5) There was no increased cancer rate in 46,740 flight crews (mostly European) who received over 1.5 mGy/y. 6) Repeated diagnostic exposures of patients who have received less than 10 cGy radiation results in no perceptible leukemia, the most radiosensitive of all cancers. 7) There was no increased cancer in adjoining tissues which received less than 5 cGy radiation in160,000 women exposed to high doses of radiation to the cervix. 8) No excess thyroid cancer was found in two million children who were irradiated by the Chernobyl explosion. 9) Twin pregnancies receive twice the number of diagnostic radiobiologic examinations as do single pregnancies; some studies show considerably reduced cancer incidence in twins.

The best of the good is the work of Dr. Sadao Hattori (Fig. 1). He recognized the implications of radiation hormesis: “If radiation hormesis

FIGURE 1. Dr. Sadao Hattori, retired Senior Vice President and Director of Research, Central Research Institute of the Electric Power Industries (CRIEPI), Tokyo. (With permission of Dr. Hattori)

FIGURE 2. Dr. Kiyohiko Sakamoto, retired Professor, Medical School, Tohoku University, Sendai. (With permission of Dr. Sakamoto)

exists, our daily activities in radiation management have been extremely erroneous." (Hattori, 1994). Following a thorough literature review, the Central Research Institute of the Electric Power Industries (CRIEPI) inaugurated 15 research projects at 10 Japan universities. The resulting research papers, published in peer reviewed journals, confirmed the radiation hormesis thesis: low dose irradiation stimulates many physiologic parameters that are consistent with damage control and improved health. Today, parts of both government and industries of Japan accepted the concept of radiation hormesis. Some health care centers and hospitals in Japan use low dose radiation therapy (Sakamoto and Myojin, 1996).

CANCER

The best of the good includes the pioneering research of Dr. K. Sakamoto (Fig. 2) and associates who showed that low dose irradiation of the torso was the most effective treatment for malignant lymphoma (Sakamoto, 1996, 1997). Exposure of either the head and neck or the lower half of the body were without effect. They had previously established this selective area for low dose irradiation using decreased cancer death rates in mice. Sakamoto's concept was confirmed by a survey of 14,137 lymphoma patients treated with low dose, total body irradiation. "Data indicate that half of the patients in stage I (indolent lymphoma) are cured (with a 15 year follow-up) by radiotherapy alone. Addition of chemotherapy to radiotherapy does not indicate any improvement in overall outcome." (Gustavsson *et al.,* 2003).

The best of the good includes the epic study of Cohen which showed that lung cancer deaths decreased with increased radon concentration in homes (Fig. 3) (Cohen, 1995). The increased variability near 5 pCi/l suggests that 8 pCi/l is about the optimum level for radon in homes. Radon concentration was *the only one of 54 epidemiologic parameters* which showed

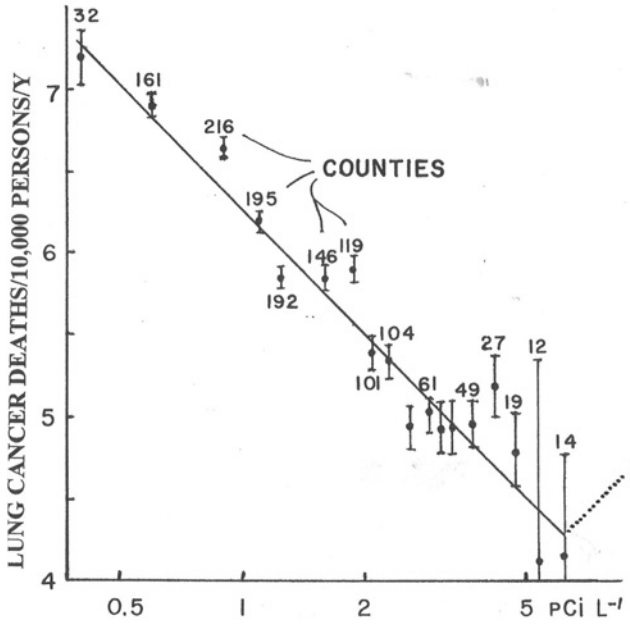

FIGURE 3. Home radon decreases lung cancer deaths. Data of B. Cohen (1995) from 200,000 radon samples from 1,600 counties in which live 90% of the United States population. One standard deviation is displayed. The dotted line suggests the optimum radon level is about 8 pCi/l.

good correlation between increased radon concentration and decreased lung cancer death rates. Other studies confirm this benefit from low doses of radon (Bogoljubov, 1988, Becker, 1995, 2005, Deetjen, 1998). One must conclude that increased home radon reduces lung cancer.

A serendipitous good appeared in Taiwan (Chen *et al.*, 2004). In 1983, about 10,000 Taipei residents moved into new apartments built with cobalt-60 contaminated steel bars. For two decades residents received an average of 1.5 cGy/y (the range was 0.1 to16 cGy/y), about 10 times more radiation than ambient levels in Taipei. In the first decade the cancer mortality rate of this exposed population dropped from 50 to 4 per 100,000 people while that of general population increased from 82 to 108 per 100,000. In the second decade the cancer death rate of the exposed residents remained at 3 per 100,000 people and that of the aging general population rose to 153 per 100,000. The Taiwan experience confirms reports from China.

A decades long epidemiologic study in China showed peasants living with three times the levels of natural radiation are more healthy in almost every characteristic than peasants living with lower levels of radiation (Luckey, 1991). The immunologic research of Liu and associated in Changchung provided understanding for some of the effects of low dose irradiation (Liu, 2003). China's current nuclear power program, with 10

nuclear power plants under construction and 100 more planned, indicates China rejects fear from low dose irradiation (Aurengo *et al.*, 2005).

REPRODUCTION

When compared with non-irradiated controls, cohorts exposed to low dose irradiation show statistically significant increased physiologic functions (Luckey, 1991). Lightly irradiated rodents were more fertile than controls through several generations (increased ovulation in dams, increased number, viability and growth rates of young, and faster physical development of young) with no evidence of mutations in the young exposed *in utero*. Irradiated colonies were maintained in good health through 21 generations.

Kaplan (Kaplan, 1949) successfully treated sterility in women with low dose irradiation (about 90 cGy of X rays to the ovary in three weeks). Three generations showed no adverse effects. There was no evidence of genetic damage from 351 pregnancies in 644 irradiated women, "... the incidence of genetic damage to the children and grandchildren of this group is less than that in the normal population."

IMMUNITY

Low dose irradiation activates the immune system in several ways: faster wound healing, and increased resistance to toxins, infections, and tumor cell injections (Luckey, 1991). Lightly irradiated animals survived doses of radiation which killed all unexposed controls. Lymphocyte production was increased by low dose irradiation. The search and destroy function of lymphocytes is facilitated by destruction of the radiation sensitive T repressor cells; this allows other T cells to be more efficient (Hellstrom and Hellstrom, 1979). When compared with strict controls, cancer mortality rates were significantly decreased (almost 50%) in accidentally irradiated nuclear workers (Luckey, 1991, 1997a).

The good certainly includes Dr. Liu and Dr. Ina and their associates who have revealed metabolic details of immune activation by low dose irradiation (Liu, 2003, Ina and Sakai, 2004, 2005). Changes in cell functions and enzyme characteristics support the radiation hormesis thesis. Cell concentrations of many important components of the immune system (enzymes and metabolites) are increased by low dose irradiation of the host.

For the first four decades of the last century, low dose irradiation ("mild radiation therapy") was the recommended treatment for many human disease states; it was particularly effective for infections from anaerobic bacteria (Kelly and Dowell, 1942, Berk and Hodes, 1991). Low dose irradiation was recommended for the non-invasive treatment of gas gangrene and severe ulcerative gingivitis (Luckey, 2005a, 2005b).

Low doses of radon are also effective. Good scientific data came from thousands of patients at two large radon hospitals in Russia (Bogoljubov, 1988). In this study, the placebo gas was additional nitrogen. More scientific data were provided by Deetjen with double blind studies comparing radon water and pure water baths in patients with a variety of illnesses (Deetjen, 1998). Every year, thousands of people visit radon rich mines to alleviate a wide variety of diseases and pains with and without the concurrence of the medical profession (Salak, 2003, Becker, 2004, Lewis, 2005). Anecdotes about improved health and relieved pain by these patients are substantially ignored. Increased immune competence contributes to increased mean lifespan in lightly irradiated laboratory animals and humans.

LIFESPAN

Low dose irradiation produced statistically significant increased average lifespan of laboratory animals and humans (Luckey, 1991, Ina and Sakai, 2004). Japanese bomb survivors exposed to low dose irradiation have statistically significantly longer average lifespan than those of control populations (Mine, 1991). When compared with the control population, the risk of non-cancer deaths in 22,777 Japanese atom bomb survivors increased only when the dose exceeded 155 cGy (Shimizu, *et al.* 1992, Pierce and Preston, 2001).

RADIATION IS AN ESSENTIAL AGENT

The ultimate good is: *ionizing radiation is essential for life.* All the criteria of an essential agent are met by low dose irradiation (Luckey, 1991, 2004).

When ionizing radiation is lowered below ambient levels, a wide variety of animals either do not survive, or become weak and perform poorly (Luckey, 1991, 1999a, Ruda and Kuzin, 1991). This is evidence that a radiation deficiency developed. Ionizing radiation uniquely prevents these syndromes. Low level irradiation increased the growth (replication) rate in protozoa (Luckey, 1991). Ionizing radiation promoted photosynthesis in both the presence and absence of light (Conter, *et al.* 1983, Luckey, 1980b). This suggests that radiation is a major source of energy for the abundant life at deep sea fissures and microbial metabolism underground in the deep hot biosphere (Gold, 1998). Supplementation with low dose irradiation lowered the cancer death rate, reduced infectious diseases, and provided a longer, healthy life in humans (Luckey, 1997b).

Premature cancer deaths are caused by insufficient radiation. Good evidence comes from 151,676 accidentally exposed workers in the nuclear industry (nuclear ships, bombs, and power plants) (Luckey, 1997a, 1999a, 1999b). There was no "healthy worker effect" because the exposed workers were matched with unexposed workers in equivalent jobs in the same factory with the same sex, age, economic, and sociolog-

ic conditions. When the average was weighted according to the number of participants in each study, the results showed that *irradiation decreased the total cancer death rate 48%*. These data indicate the United States has about 275,000 preventable, premature cancer deaths each year. The cause is attributed to insufficient radiation.

Each of the above examples indicates that we live in a state of partial radiation deficiency. The combined effects suggest we need radiation supplementation for more abundant health (Luckey, 1997b).

RADIATION THERAPY

Historically, medical uses of ionizing radiation have received deserved enthusiasm. The January1896 publication of the X ray picture of Mrs. Roentgen's hand in the London Times made it "the most famous photo in history". This quickly led to the use of X rays for diagnosis and 1000 papers were published within one year (Brucer, 1990). Physicians and radiation physicists soon learned that an excess of X rays produced erythema, skin lesions, and cancer. Diagnostic radiation methods continued to be refined throughout the 20th century. Many patients walk out of hospitals carrying enough radioactivity from diagnostic compounds to cause them to be rejected if they tried to enter a nuclear reactor facility with portal monitors (Brucer, 1990).

Both large and small doses of X rays were used therapeutically (Brucer, 1990). In 1897, H. Gocht treated breast cancer, E. Ausset treated tuberculosis, and L. Freund treated inflammation with X rays. In 1901, G. Phaler reported remarkable success in treating skin cancer with X rays. In1902, therapy with low dose irradiation became a popular medical treatment for cancer and infections. Low doses were generally used: "...doses approaching the SED (skin erythema dose) are less successful than those treatments following the lower dose."(Borak, 1944). Responses were generally very positive, prompt, and often relieved pain with no side effects. Numerous reviews indicate the value of low dose radiation therapy for skin eruptions, eye infections, pneumonia, and gangrene (Cuttler, 2002, Heidenhain, 1926, Desjardins, 1931, 1942, Kelly and Dowell, 1942, Berk, 1991, Calabrese and Baldwin, 1999, Luckey, 2005a). Low dose irradiation became popular and effective therapy for some cancers. Brucer noted "Between 1910-1950 hundreds of thousands of patients (no one knows how many) received millicuries (no one knows how much) of radium." (Brucer, 1990). Radium and radon were successfully administered in tubes, needles, seeds, ointments and injection. "Mild radiation therapy", as distinguished from high dose irradiation, was fashionable in Europe and promoted in Marie Curie's 1921 lecture tour of America (Macklin, 1993). Radium containing harnesses were designed to activate the thyroid (necklace), adrenal glands, ovaries (waist), and

genitals (jockstrap). When he was dying with cancer, I helped Petr Beckman with a harness to fit a uranium rock close to his spleen.

The successes of radiation therapy for infection and inflammatory diseases abruptly ended in 1948. The financial advantage of antibiotics, the miracle drugs of World War II, made obsolete therapy with low dose irradiation. This was not good.

THE BAD

The bad is the promulgation of a false concept by many radiobiologists: *all radiation is harmful*. Brucer noted Health Physics had become a religious cult: "In 1979 the National Committee for Radiation Protection (NCRP) ... dropped all pretense at science and assumed there was a risk in every radiation exposure." (Brucer, 1990). In their attempt to obtain research money, geneticists predicted that genetic monsters (found in fruit flies subjected to large doses of radiation) would occur in people exposed to radiation from atom bombs. When geneticists chanted "all radiation is harmful" and "genetic monsters", financial support for research on the effects of low dose irradiation vanished. Suddenly, editors were not interested in papers showing stimulatory or beneficial effects from low doses of ionizing radiation. Although no genetic monsters can be attributed to low dose irradiation, including atomic bombs, laws are based upon the false dogma that all radiation is harmful. "This is the greatest hoax of the twentieth century." (Jaworowski, 1994).

The bad was the retreat to 19th century therapy, surgery, for patients with gangrene when bacteria became resistant to antibiotics about 30 years ago. Surgery is traumatic and the death rate from gangrene in diabetics remains high. "We have found only one really efficient means of prevention and treatment (of gas gangrene), and that is X-ray therapy without amputation, chemotherapy, or serum." (Kelly and Dowell, 1942). Kelly and Dowell summarized 97 case histories of patients with gas gangrene and other infections: "One cannot fail to observe .... favorable changes in the clinical signs if one treats a few patients with such diseases after they appear to be too seriously ill to be moved from bed for any purpose." Their conclusion was that neither chemotherapy nor serum was comparable with, nor compatible with, X ray treatment.

The bad is fear of low levels of radiation. The Nuclear Energy Agency (NEA) provided examples which include the hysteria in Europe from the radioactive cloud from Chernobyl (NEA, 1995). Thousands of needless abortions and suicides could have been prevented by education about low doses of radiation. Another example is the quandary people and governments of eastern Europe have about soils containing increased radiation from bombs containing spent uranium; they can not export their produce which has a small increase in radioactivity (Jovanovic, 2005). If

they knew the facts, they would welcome increased low levels of radiation. Fear of radiation would cause devastating disruption and evacuation of cities following a terrorist attack with a dirty bomb. Neither officials nor the media understand that education about low dose irradiation is a defense against this form of terror. Excepting those who feel the blast, or who receive physical harm from heat or flying debris, low dose irradiation is beneficial (Luckey, 2004).

The bad is the denial of health by laws which restrict radiation in homes and industry to near ambient levels. The bad is the billions of dollars wasted by United States industry following the Environmental Protection Agency (EPA) rulings which were recommended by the National Committee for Radiation Protection (NCRP) and the Biological Effects of Ionizing Radiation (BEIR) committees; these were based upon the dogma that all radiation is harmful (Muckerheide and Rockwell, 1997). "As soon as Health Physicists saw the money in radiation hysteria, the Maximum Permissible Dose came down to background." (Brucer, 1990).

A major bad is banning radioactive drugs by the U. S. Food and Drug Administration (FDA) without due process. This termination was triggered by the press coverage of a gruesome facial cancer and death of a celebrated millionaire, Eben Byers, who overdosed with 1500 vials of Radithor (each had 1 uCi Ra-228 and 1 uCi Ra-226 in 1/2 ounce of water) from 1928 to 1931 (Macklin, 1993). FDA ignored the benefits to thousands of people who took recommended doses.

The bad is: BEIR IV and BEIR VI committees downplayed the epic research of Cohen which proved ($p < 0.00001$) that home radon reduces lung cancer death rates (Cohen, 1995). They rejected radiation hormesis without providing any studies showing harm from ambient levels of radon. "...*in the absence of credible evidence to the contrary*, the committee adopted a linear-nonthreshold model for the relationship between radon exposure and lung cancer risk." (BEIR VI, 1999, p. 6, emphasis added). Cohen's data (Fig. 3) show the EPA recommendation to reduce home radon levels to less than 4 pCi/l is carcinogenic (Luckey, 1993).

The voluminous BEIR VII provides no solid dose-response data to prove or refute the committee statements (BEIR VII, 2005). The abandonment of scientific principles by national and international radiation protection committees is so bad, it is ugly. A few examples of many deceptions by radiobiologists are provided (Luckey, 2000).

THE UGLY

The ugly is the misguided conclusion about low dose radiation by authorities who advise the U. S. government. These include the BEIR and NCRP committees, and their international counterpart organizations, the ICRP and UNSCEAR. BEIR committee members are appointed by a permanent group within the National Research Council, previously the

Board of Radiation Effects Research (BRER), recently changed to the Nuclear and Radiation Studies Board (NRSB). The conclusions of these committees are not consistent with the results of the studies they report; nor do they consider confirmed results of thousands of studies that show hormesis and beneficial effects. The BEIR committees are drawn from, and supported by, the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine; "...the Academy has a mandate that requires it to advise the federal government on scientific and technical matters." (BEIR, 1999, p. vi). These committees have not substantively considered the voluminouss evidence showing low dose irradiation is stimulatory and/or beneficial. Luckey listed 55 reviews published between 1907 and 1977 showing low dose irradiation was stimulatory (Luckey, 1980b). There are now over 3,000 peer reviewed research papers showing biopositive effects of low dose irradiation (Luckey, 1980a, 1991, Muckerheide, 2001).

RADON AND LUNG CANCER DEATH IN MINERS

The BEIR committees have 1,100 pages devoted to the false dogma that radon and its progeny cause lung cancer in humans (BEIR, 1988,1999). They offer no creditable scientific evidence that radon increases lung cancer mortality in humans.

In order to evaluate the effect of radon in lung cancer deaths in homes, BEIR committees relied heavily on data from miners. "However, the results of dose models were used to extrapolate lung-cancer risks derived from the epidemiological studies of underground miners to the general population in indoor environments." (BEIR, 1988) "...the BEIR VI committee chose to use the lung cancer information from studies of miners, who are more heavily exposed to radon, to estimate the risks posed by radon exposures in homes." (BEIR, 1999). Their base was 11 major studies involving 68,000 miners and 2,700 lung cancer deaths. Their summary data (Fig. 4) showed conclusively that radon does not cause lung cancer deaths in miners (BEIR, 1999). Obviously, carcinogenic particulates and/or noxious gases, not radon and its progeny, must cause lung cancer in miners.

The BEIR VI committee continuously misrepresented their own data on lung cancer deaths in miners (BEIR, 1999). Compare their data (Fig. 4) with their statements:

> p. 2 "The committee agreed with several earlier groups of experts that the risk of developing lung cancer *increases linearly as the exposure increases*; for example, *doubling the exposure doubles the risk, and halving the exposure halves the risk*. Furthermore, the existing biologic evidence suggests that any exposure, even very low, to radon might pose some risk." (emphasis added)

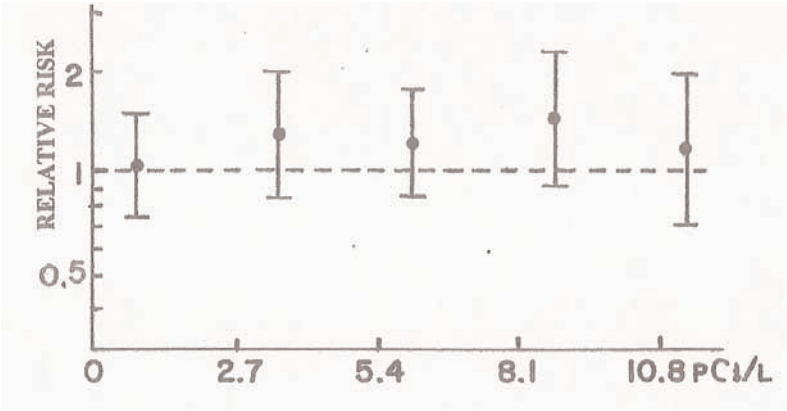

FIGURE 4. Lung cancer deaths from radon in miners. Pooled analysis of the relative risks of lung cancer deaths, with 95% confidence limits, from 11 underground miner studies (adapted from p. 89, BEIR VI, 1999).

> p. 4 " Radon, a naturally occurring gas formed from the decay of uranium in the earth, has been *conclusively shown in epidemiologic studies of underground miners to cause lung cancer.*" (emphasis added)
>
> p. 18 "The carcinogenicity of radon is convincingly documented through epidemiologic studies of underground miners, *all showing a markedly increased risk of lung cancer.*" (emphasis added)
>
> p. 114 "In each of these studies, miners have been shown to be at excess risk for lung cancer under past conditions of exposure."

These repeated statements by the BEIR VI committee are contradicted by their own data. The BEIR VI dose response curves (Figures 4 and 5) show that *radon and its progeny do not cause lung cancer deaths in homes or mines.*

RADON AND LUNG CANCER DEATH IN HOMES

The BEIR VI committee provides sparse data on lung cancer deaths in homes from case-control studies (BEIR, 1999). Eight studies with 4,263 lung cancer cases and 6,612 controls were examined using complex "meta analysis". Their summary data (Fig. 5) show that the relative risk of lung cancer deaths did not rise significantly with increased radon concentrations. The committee conclusions are not consistent with their own data (Fig. 5) as shown in the following statements:

> p. 9 "The committee selected a linear-nonthreshold relationship relating exposure to risk for the relatively low exposures at issue for indoor radon."

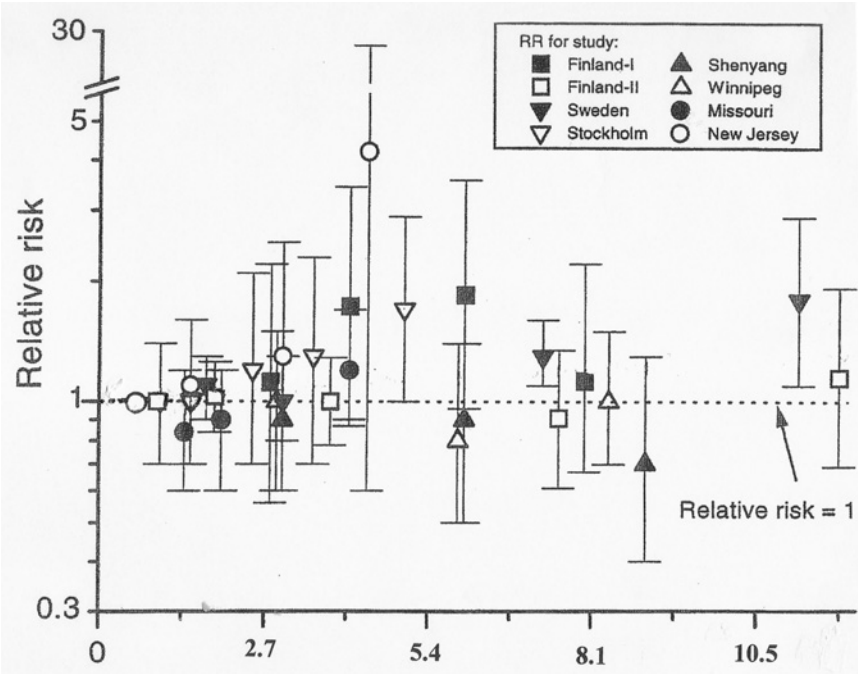

FIGURE 5. Lung cancer deaths from radon in homes. Eight case control studies of relative risks for lung cancer death rates of people in homes (adapted from p. 377, BEIR VI, 1999). Units for the abscissa are pCi/l. One standard deviation is indicated.

p. 19 "Nonetheless, this indicates a public-health problem and makes indoor radon the second leading cause of lung cancer after cigarette-smoking,..."

p. 19 "Perhaps one-third of the radon-attributed cases (about 4% of the total lung-cancer deaths) would be avoided if all homes had concentrations below the Environmental Protection Agency's action guideline of 150 Bqm^{-3} (4 $pCiL^{-1}$);"

p. 356 "... the data do support a small increase in lung cancer risk due to indoor radon..."

These misleading statements are then promulgated by the media, and used as advertising for a new industry, to take advantage of the misinformed public: lower the radon in your homes (BEIR,1988). The BEIR VI committee denigrates Cohen's definitive study (Fig. 3) which proves that higher residential *radon levels consistently decrease the lung cancer mortality.* These data show that lowering radon in homes, as recommended by the EPA, will cause many lung cancer deaths.

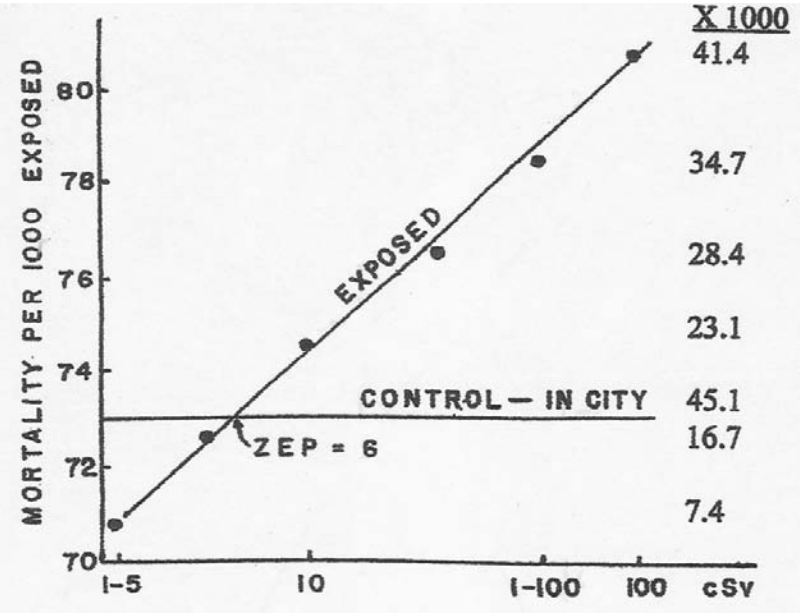

FIGURE 6. Cumulative cancer death rates in Japanese bomb victims. Numbers on the right list thousands of persons for each dose (Shimizu et al., 1989).

RADIATION VS CANCER DEATHS IN OTHER COUNTRIES

Ugly taints much of the good work done by the Radiation Effects Research Foundation (RERF), originally the Atomic Bomb Casualty Commission (ABCC), in Hiroshima which received millions of dollars each year for 50 years to study the effects of ionizing radiation on victims of atom bombs. The threshold appears to be 6 cSv. To their benefit, RERF authors did note that the cancer death rate of the control group (>3 km from the epicenter), which received low dose irradiation (0.2- 0.6 cSv), was lower than that for persons not in the city at the time of the bombing (the original control group) who received less ionizing radiation (Shimizu et al., 1992). This result shows hormesis.

Over 23,000 Japanese atom bomb victims received less than10 cGy; their cancer death rates were no greater than that of the 34,272 persons in the control population. A graph of cumulative total cancer death rates in Japanese atom bomb victims illustrates that small and large doses of ionizing radiation elicit diametrically opposite results (Fig. 6) (Shimizu,1992, Luckey, 1991). The RERF conclusion is misleading: "In general, the dose response ... failed to suggest the existence of hormesis." (Shimizu, 1992, p. 74). Since the chi square statistic showed the group with the least radiation had a significantly lower cancer death rate than the controls ($p < 0.01$), the authors' conclusion is misleading. Contrary to their stated conclusion, their data exhibit hormesis. The threshold was about 6 cSv.

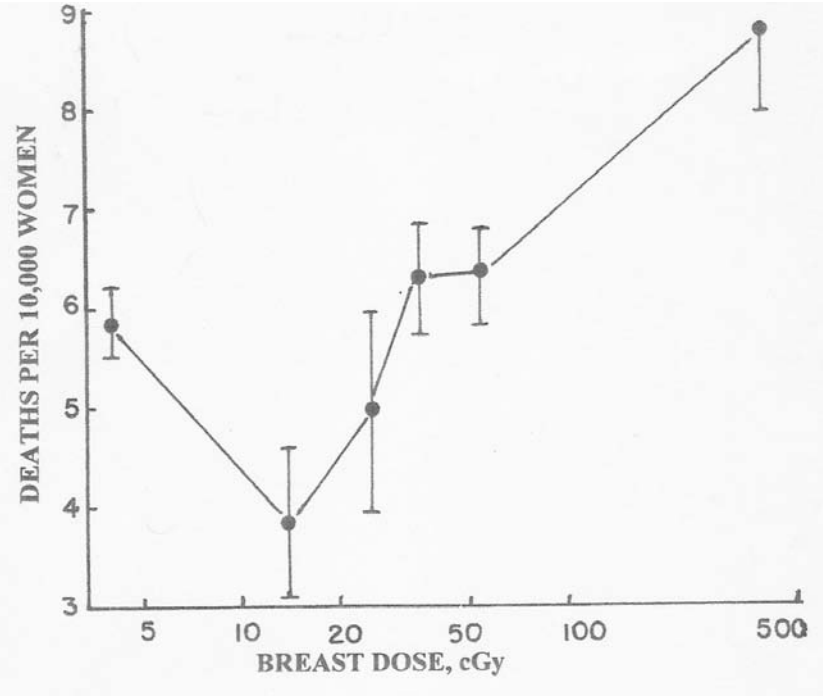

FIGURE 7. Breast cancer deaths in women treated for tuberculosis. Breast cancer death rates of Canadian women repeatedly X-rayed by fluoroscopy to monitor lung-collapse therapy for tuberculosis (Miller et al., 1989). One standard deviation is displayed.

More ugly comes from Canada. Although not mentioned in the abstract, introduction, discussion, or conclusion of their paper, the data of Miller and associates (Fig. 7) showed radiation hormesis in 31,700 women examined for tuberculosis with fluoroscopy (Miller *et al.*, 1989). Low dose irradiation significantly decreased ($p < 0.01$) the breast cancer death rate. The authors did not present a dose-response curve, and reported a conclusion that was inconsistent with their data: "The data were most consistent with a linear dose-response relation." and "The evidence ... indicates that the most appropriate form of the dose-response relation is a simple linear one." Both statements imply that all radiation was harmful; the authors gave no hint that low dose irradiation (<30 cGy) was beneficial.

DISCUSSION AND CONCLUSIONS

Radiation hormesis is a very general phenomenon; it extends from bacteria, through plants, insects, invertebrates, and mammals (Luckey, 1980). Low doses of physical, chemical, and biological agents evoke hormesis. Essential nutrients, antimetabolites, and other toxicants are hormetic (Luckey, 1959). Most drugs which have been tested in the low dose range exhibit hormesis (Townsend and Luckey, 1960). Hormesis

with heavy metals has been documented (Luckey *et al.*, 1975). Biological agents included hormones, wounds, stress, and adaptive cell responses (Luckey, 1999a, 1999b).

As perceived by Hippocrates more than two millennia ago, a given agent is neither toxic nor beneficial. The dose elicits a continuum response from not effective to biopositive, through optimum, and to excess (Luckey, 1977). Acknowledging harm from large doses, the focus here is on the biopositive effects of low dose irradiation. A wealth of data presents irrefutable evidence of the benefits that radiation provides for a great variety of organisms. This includes decreased infections, decreased cancer death rates, and increased fecundity and average lifespan in humans. Many of these benefits are associated with biological stimulation and suppression of genes, enzymes and other proteins that indicate an activated immune system. Some results, especially the debility caused by reducing radiation below average natural background levels in organisms, indicate that ionizing radiation is essential for life. That is good.

The French stand alone in Europe by accepting the benefits of low dose irradiation. France sells electricity from nuclear power plants to other European countries. The French Academy of Sciences and the French National Academy of Medicine unanimously approved a definitive statement which accepts radiation hormesis (Aurengo *et al.,* 2005).

Some Japanese radiobiologists realize that the abundant data on radiation hormesis support the use of low dose irradiation as an agent for health. Many of the Japanese medical profession rejects "all radiation is harmful" and accept low dose irradiation to "live in harmony with nature".

In China, an extensive epidemiologic study of two groups of peasants who received different amounts of ambient radiation indicated that low levels of irradiation may be beneficial (Wei, 1997). Intensive studies of the intricacies of a radiation activated immune system provide support for that conclusion (Liu,1998). China plans to build many new nuclear power plants in the near future (Muckerheide, 2005).

The bad is epitomized by the U. S. government with lost opportunities for industrial development due to unreasonable regulations which restrict radiation exposures for industrial workers to near ambient levels. The lack of popular acceptance of nuclear power is attributable to misleading information provided by the BEIR, NCRP, and ICRP committees which consistently and deliberately fail to consider confirmed scientific reports showing the biopositive effects of low dose irradiation. These restrictions contribute to potential devastation due to insufficient energy in the United States and the world.

The bad is misspent hundreds of billions of taxpayer and consumer dollars in industry and government, millions of needless cancer deaths, and a damaged nation (Muckerheide and Rockwell, 1997). This "science

cancer" extends to the National Research Council which consistently appoints biased people to the BEIR committee. The bad includes those foreign governments which capitulated to the deceptions promulgated by the BEIR, NCRP committees, and the United States government agencies (such as the EPA). Misinformation is the hallmark of radiation hormesis.

The health of many people is jeopardized by the refusal of our medical profession to recognize the benefits of low dose irradiation. For example, antibiotic resistance has turned previously accepted medical practice for diabetic patients, effective and painless treatment with low dose irradiation, into 19th century surgery to amputate limbs with the accompanying pain and poor survival rates (Luckey, 2005a).

Studies of cancer death rates in nuclear industries involved over 7 million person-years (Luckey, 1997a, 1999a). The results showed that low dose irradiation decreased cancer death rates by almost 50%. If families of cancer patients realized this, they would insist upon access to low dose irradiation. And they would want to prosecute BEIR and NCRP committee members for their decades of erroneous information causing needless suffering and deaths.

There is a hidden bad. Considerable information indicates that we live in a partial deficiency of ionizing radiation. Nuclear wastes could provide safe radiation spas throughout the world (Luckey, 1995a, 1995b, 2004). Low dose irradiation could be provided in hospitals as a public health measure. If we had 50 times more radiation than we now receive, we would reach a new plateau of health (Luckey, 1999a, 1999b).

The most ugly is the consistent failure by our BEIR and NCRP committees, and comparable international committees, to report on the voluminous data showing beneficial effects of low dose irradiation. Each year, millions of taxpayer dollars go to these committees, researchers, and consultants who use "meta analysis" and contrived units of measurement (working level months) to confuse the issues. The few examples provided above indicate how these committees, and many radiobiologists, mislead our government and the public. Some of their statements appear to be scientific falsifications and fabrications. Thousands of creditable results have been reviewed (Luckey, 1980, 1991, Muckerheide, 2001). Documentation of the ugly is good; it illustrates one half-century of producing incomplete and misleading statements by some radiobiologists and the lack of credibility of the BEIR and NCRP committees. Calabrese reviewed the history of the rejection of the concept of hormesis: "The effects of this century-long conflict have been as destructive as they have been overlooked, ..." (Calabrese, 2005).

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Appendix 2

UNITED STATES
NUCLEAR REGULATORY COMMISSION
ADVISORY COMMITTEE ON NUCLEAR WASTE
WASHINGTON, DC 20555 - 0001

ACNWR-0258

January 11, 2007

The Honorable Dale E. Klein
Chairman
U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001

SUBJECT: REPORT OF THE FRENCH ACADEMY OF SCIENCES, "THE DOSE-EFFECT RELATIONSHIP AND ESTIMATING THE CARCINOGENIC EFFECTS OF LOW DOSES OF IONIZING RADIATION"

Dear Chairman Klein:

In response to an SRM dated February 9, 2006, during its 174th meeting on November 13-16, 2006, the Advisory Committee on Nuclear Waste (the Committee) heard a presentation from representatives of the French Academy of Sciences. The report was titled "The Dose-Effect Relationship and Estimating the Carcinogenic Effects of Low Doses of Ionizing Radiation." This report provided the Committee with excellent and detailed insights regarding the French Academy's study of the current state of radiation biology related to low dose exposures; their views regarding the linear no-threshold (LNT) theory of radiation injury; and the appropriate context for uses of the LNT.

Observations

The Committee offers the following observations from the presentation and discussion of the Academy's report:

1. The French Academy of Sciences report focuses on the radiobiological science and does not try to interpret these results in a policy context. In contrast, the BEIR VII report attempts to interpret the current state of knowledge into a policy context. The French Academy of Sciences presenters pointed out that the LNT theory of radiation damage can be appropriately used as a risk management tool but not as a risk assessment tool.

2. The presenters reported that collective dose is useful as a management tool for work planning and assessing worker exposure (ALARA), but should not be used as a risk assessment tool. Cancer risks for individuals or groups cannot be estimated using collective dose, nor can potential future cancer risk be projected from estimates of dose. The presenters stated that extrapolation of cancer risk using the LNT theory assumes that a very low dose administered to many people has the same carcinogenic effect as high doses administered to a small number of people. They further noted that this assumption does not have a scientific foundation, as UNSCEAR and ICRP have pointed out. The Committee has concurred with this view and reiterates it here.

3. The French Academy report, based on current data, raises doubts about the validity of using the LNT theory to estimate carcinogenic risks at doses less than 10 rem (< 100 mSv) and is even more skeptical of such estimates at doses less than 1 rem (< 10 mSv). However, an actual threshold in the probability of cancer as a function of dose cannot be demonstrated with data available today.

4. In contrast to the French Academy report, the BEIR VII report states:

   "The [National Academy of Sciences] Committee concludes that the current scientific evidence is consistent with the hypothesis that there is a linear, no-threshold dose-response relationship between exposure to ionizing radiation and the development of cancer in humans."

   The BEIR VII report does not conclude that the LNT theory is correct but the data appear to be consistent with the LNT theory. The report does not rule out the possibility of a threshold.

5. A recent paper by several authors of the French Academy study compares their report with the BEIR VII report and the recent ICRP Report on cancer risk from low doses of radiation. One forward looking conclusion from this paper observes:

   > "The controversy related to the carcinogenic effect of low doses of genotoxic agents started over a decade ago (Abelson 1994, Ames and Gold 1997). However, the recent biological data have brought about new arguments which, when confirmed, would be convincing. The epidemiological studies have not yet been able to demonstrate a detrimental effect of low dose irradiation. They should be pursued and a meta-analysis of the available data should be carried out. The controversy between the reports should not be ignored. Discussion could clarify the problem and pave the way for new investigations and hopefully a consensus on many points. A few years ago the general impression was that it was important to obtain quantitative data regarding the effect of low doses but that it would always be impossible to reach a reliable conclusion. The perspectives have dramatically changed over the past few years. It clearly appears that in a decade or so we shall have conclusive data. In the meantime it would be proper to reconsider the ways the detrimental effects of low doses are assessed since an overestimation of the risks currently has a negative effect on the physical and mental health of the population."

6. Radiobiology studies at the cellular, tissue, organ, and organism level are useful because, through these studies, understanding of the fundamental mechanisms of radiation injury and the response to such injury is being developed. Many factors influence biological responses to radiation at the cellular, tissue, organ

and organism levels. These include dose, dose rate, duration of exposure, and radiation quality. This information contributes to developing understanding of radiation carcinogenesis. As the Committee noted in its letter (dated November 8, 2006) to the Commission on the current efforts on low-dose research:

> "This body of DOE research is unearthing interesting radiobiology on the mechanisms for radiation injury, repair, and responses to radiation mainly at the molecular and cellular level. However, much of the work is evaluating effects at doses several times to orders of magnitude above levels at which exposures to the public and to most workers are regulated. Extrapolation to lower doses and reconciliation with epidemiology studies have so far not been performed at a level of detail that would be directly useful in policy making or in revising current or developing new radiation protection standards at this time."

7. The French Academy presenters stated that effects at low doses should not be extrapolated from effects at high doses because damage repair mechanisms at the cellular level can be quite different. Further, extrapolating observations at the cellular level to the tissue, organ, or organism level is also uncertain.

8. The French Academy report considered data from the Department of Energy (DOE) low-dose study, while in a letter dated July 15, 2005 from Raymond Orbach (Director, Office of Science, U.S. Department of Energy) to the National Academies it was pointed out that some epidemiological studies and new biological research were left out of the final deliberations of the BEIR VII Committee. It is not apparent to the ACNW that these differences in the data reviewed by either group would explicitly impact the ACNW's recommendations.

9. Exposure to a particular source cannot be evaluated in isolation. There are many sources of ionizing radiation (see public health statement for ionizing radiation at http://www.atsdr.cdc.gov/toxprofiles/phs149.html). Radiation exposure for any individual includes contributions from:

   a. Terrestrial background
   b. Cosmic radiation
   c. Radon
   d. Radioactive materials incorporated into the body
   e. Medical exposures from diagnosis and therapy
   f. Other man-made sources and human activities including air travel, consumer products, and nuclear power

The Committee has learned that the National Council on Radiation Protection and Measurements (NCRP) is undertaking a detailed study that will produce an update of NRCP Report No. 93, *Ionizing Radiation Exposure of the Population of the United States*, which was published in 1987. The scope of work includes all sources of radiation exposure: background radiation, industrial sources, medical patient, occupational, consumer products, and miscellaneous sources.

Conclusions and Recommendations:

1. Based on the Committee's review of the French Academy report and the BEIR VII report, the Committee finds the current state of knowledge does not warrant any change to current NRC radiation protection standards or limits.

2. The Committee affirms its earlier recommendations that the Committee and NRC staff should remain informed of continuing developments in this area. In support of this recommendation, the Committee plans a half-day Working Group session. The focus of the Working Group would be to give summaries of the state of knowledge of radiation biology with emphasis on implications for radiation risk models and radiation protection practice.

3. The Committee also reaffirms its previous recommendations that collective dose is only appropriate as a measure to be used in comparing alternatives and not as a method of estimating absolute cancer risk.

Sincerely,

/RA/

Michael T. Ryan
Chairman

References:

1. Dose-effect relationships and estimation of the carcinogenic effects of low doses of ionizing radiation, Académie des Sciences [Academy of Sciences] - Académie nationale de Médecine [National Academy of Medicine], André Aurengo[1] (Rapporteur), Dietrich Averbeck, André Bonnin[1] (†), Bernard Le Guen, Roland Masse[2], Roger Monier[3], Maurice Tubiana[1,3] (Chairman), Alain-Jacques Valleron[3], Florent de Vathaire.[1] Member of the Académie nationale de Médecine. [2] Correspondent Member of the Académie nationale de Médecine. [3] Member of the Académie des Sciences

2. Health Risks From Exposure To Low Levels Of Ionizing Radiation: BEIR VII PHASE 2, Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation Board on Radiation Effects Research, Division on Earth and Life Studies, NATIONAL RESEARCH COUNCIL *OF THE NATIONAL ACADEMIES,* THE NATIONAL ACADEMIES PRESS, Washington, D.C. **www.nap.edu**

3. September 30, 2005 Letter to The Honorable Nils J. Diaz Chairman U.S. Nuclear Regulatory Commission, Washington, D.C. 20555-0001 "COMMENTS ON USNRC STAFF RECOMMENDATION OF THE USE OF COLLECTIVE DOSE"

4. OPINION The debate on the use of linear no threshold for assessing the effects of low doses M Tubiana, A Aurengo, D Averbeck and R Masse J. Radiol. Prot. 26 (2006) 317–324

5. ICRP 2004 ICRP Draft report of Committee I/Task Group. Low dose extrapolation of radiation related cancer risk

6. November 8, 2006 Letter to The Honorable Dale E. Klein, Chairman, U.S. Nuclear Regulatory Commission, Washington, DC 20555-0001 titled "DOE LOW DOSE RADIATION RESEARCH WORKSHOP (VI)"

7. July 15, 2005 letter to Dr. Ralph Cicerone, President National Academy of Sciences, 500 Fifth Street, NW, Washington, DC 20001

8. National Council on Radiation Protection and Measurements, Program Area Committee on Radiation Measurements and Dosimetry PAC 6, Subcommittee on Radiation Expo-sure of the U.S. Population SC 6-2 (available at http://www.ncrponline.org/Current_Prog/SC_6-2.html)

Académie des Sciences [Academy of Sciences] - Académie nationale de Médecine [National Academy of Medicine]

Dose-effect relationships and estimation of the carcinogenic effects of low doses of ionizing radiation

March 30, 2005

André Aurengo[1] (Rapporteur), Dietrich Averbeck, André Bonnin[1] (†) , Bernard Le Guen, Roland Masse[2], Roger Monier[3], Maurice Tubiana[1,3] (Chairman), Alain-Jacques Valleron[3], Florent de Vathaire.

Executive Summary

The assessment of carcinogenic risks associated with doses of ionizing radiation from 0.2 Sv to 5 Sv is based on numerous epidemiological data. However, the doses which are delivered during medical X-ray examinations are much lower (from 0.1 mSv to 20 mSv). Doses close to or slightly higher than, these can be received by workers or by populations in regions of high natural background irradiation.

Epidemiological studies have been carried out to determine the possible carcinogenic risk of doses lower than 100 mSv, and they have not been able to detect statistically significant risks even on large cohorts or populations. Therefore, these risks are at worse low since the highest limit of the confidence interval is relatively low. It is highly unlikely that putative carcinogenic risks could be estimated or even established for such doses through case-control studies or the follow-up of cohorts. Even for several hundred thousands of subjects, the power of such epidemiological studies would not be sufficient to demonstrate the existence of a very small excess in cancer incidence or mortality adding to the natural cancer incidence which, in non-irradiated populations, is already very high and fluctuates according to lifestyle. Only comparisons between geographical regions with high and low natural irradiation and with similar living conditions could provide valuable information for this range of doses and dose rates. The results from the ongoing studies in Kerala (India) and China need to be carefully analyzed.

Because of these epidemiological limitations, the only method for estimating the possible risks of low doses (< 100 mSv) is extrapolation from carcinogenic effects observed between 0.2 and 3 Sv. A linear no-threshold relationship (LNT) describes well the relation between the dose and the carcinogenic effect in this dose range where it could be tested. However, the use of this relationship to assess by extrapolation the risk of low and very low doses deserves great caution. Recent radiobiological data undermine the validity of estimations based on LNT in the range of doses lower than a few dozen mSv which leads to the questioning of the hypotheses on which LNT is implicitly based: 1) constancy of the probability of mutation (per unit dose) whatever the dose or dose rate, 2) independence of the carcinogenic process which after the initiation of a cell evolves similarly whatever the number of lesions present in neighboring cells and the tissue.

Indeed, 1) progress in radiobiology has shown that a cell is not passively affected by the accumulation of lesions induced by ionizing radiation. It reacts through at least three mechanisms: a) by fighting against reactive oxygen species (ROS) generated by ionizing radiation and by any oxidative stress, b) by eliminating injured cells (mutated or unstable),

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through two mechanisms: i) apoptosis which can be initiated by doses as low as a few mSv, thus eliminating cells the genome of which has been damaged or misrepaired, ii) death of cells during mitosis when lesions have not been repaired. (Recent works suggest that there is a threshold of damage under which low doses and dose rates do not activate intracellular signalling and repair systems, a situation leading to cell death.) c) by stimulating or activating DNA repair systems following slightly higher doses of about ten mSv. Furthermore, intercellular communication systems inform a cell about the presence of an insult in neighboring cells. Modern transcriptional analysis of cellular genes using microarray technology reveals that many genes are activated following doses much lower than those for which mutagenesis is observed. These methods have been a source of considerable progress by showing that depending on the dose and the dose rate not the same genes are transcribed.

At doses of a few mSv (< 10 mSv), lesions are eliminated by disappearance of the cells; at slightly higher doses damaging a large number of cells (therefore capable of causing tissue lesions), repair systems are activated. They permit cell survival but may generate misrepairs and irreversible lesions. For low doses (< 100 mSv), the extent of mutagenic misrepairs is small but its relative importance, per unit dose, increases with the dose and dose rate. The duration of repair varies with the complexity of the damage and its amount. Several enzymatic systems are involved and a high local density of DNA damage may lower their efficacy. At low dose rates the probability of misrepair is smaller. The modulation of the cell defense mechanisms according to the dose, dose rate, the type and number of lesions, the physiological condition of the cell, and the number of affected cells explains the large variations in radiosensitivity (variations in cell mortality or the probability of mutations per unit dose) depending on the dose and the dose rate that have been observed. The variations in cell defense mechanisms are also demonstrated by several phenomena: initial cell hypersensitivity during irradiation, rapid variations in radiosensitivity after short and intense irradiation at a very high dose rate, adaptive responses which cause a decrease in radiosensitivity of the cells during hours or days following a first low pre-conditionning dose of radiation, etc.

2) Moreover, it was thought that radiocarcinogenesis was initiated by a lesion of the genome affecting at random a few specific targets (proto-oncogenes, suppressor genes, etc.). This relatively simple model, which provided a theoretical framework for the use of LNT, has been replaced by a more complex one including genetic and epigenetic lesions, and in which the relationship between the initiated cells and their microenvironment plays an essential role. This carcinogenic process is counteracted by effective defense mechanisms in the cell, tissue and the organism. With regard to tissue, the mechanisms which govern embryogenesis and direct tissue repair after injury appear to play also an important role in the control of cell proliferation. This is particularly important when a transformed cell is surrounded by normal cells. These mechanisms could explain the lower efficacy of heterogeneous irradiation, i.e. local irradiations through a grid, as well as the absence of a carcinogenic effect in humans or experimental animals contaminated by small quantities of α-emitter radionuclides. The latter data suggest the existence of a threshold. This interaction between cells could also help to explain the difference in the probability of carcinogenesis according to the tissues and the dose, since the death of a large number of cells disorganizes the tissue and favors the escape of initiated cells from tissue controls.

3) Immunosurveillance systems are able to eliminate clones of transformed cells, as is shown by tumor cell transplants. The effectiveness of immunosurveillance is also shown by the large increase in the incidence of several types of cancers among immunodepressed subjects (a link seems to exist between a defect in DNA repair (NHEJ) and immunodeficiency).

All these data suggest that the lower effectiveness of low doses, or the existence of a practical threshold which could be related to either the failure of a very low doses to sufficiently activate cellular signalling and thereafter DNA repair mechanisms or to an association between apoptosis error-free repair and immunosurveillance.. However on the basis of our present knowledge, it is not possible to define the threshold level (between 5 and 50 mSv?) or to provide the evidence for it. The stimulation of cell defense mechanisms, in particular to cope with reactive oxygen species. Indeed, a meta-analysis of experimental animal data shows that in 40% of these studies there is a decrease in the incidence of spontaneous cancers in animals after low doses. This observation has been overlooked so far because the phenomenon was difficult to explain.

These data show that it is not justified to use the linear no-threshold relationship to assess the carcinogenic risk of low doses observations made for doses from 0.2 to 5 Sv since for the same dose increment the biological effectiveness varies as a function of total dose and dose rate. The conclusion of this report is in fact in contradiction with those of other authors [43,118], which justify the use of LNT by the following arguments.

1. for doses lower than 10 mGy, there is no interaction between the different physical events initiated along the electron tracks through the DNA or the cell;
2. the nature of lesions caused and the probability of error prone or error free repair and the elimination of damaged cells by cell death is neither influenced by the dose nor the dose rate;
3. cancer is the direct and random consequence of a DNA lesion in a cell apt to divide and the probability of the initiated cell to give rise to cancer is not influenced by the damage in the neighbor cells and tissues;
4. the LNT model correctly fits the dose-effect relationship for the induction of solid tumors in the Hiroshima and Nagasaki cohort;
5. the carcinogenic effect of doses of the order of 10 mGy is proven for humans by results from *in utero* irradiation studies .

The first argument concerns the initial physico-chemical events which are proportional to dose; however, the nature and efficiency of cellular defense reactions that are activated vary with dose and dose rate. The second argument is contradicted by recent radiobiological studies considered in the present report. The third argument does not take into account recent findings on the complexity of the carcinogenic process and the particular role of intercellular relationships and the stroma.. Regarding the fourth argument, it can be noted that besides LNT, other types of dose-effect relationships are also compatible with data concerning solid tumors in atom bomb survivors, and can also satisfactorily fit epidemiological data that are incompatible with the LNT concept, notably the incidence of leukemia in these same A-bomb survivors. Furthermore, taking into account the latest available data, the dose-effect relationship for solid tumors in Hiroshima-Nagasaki survivors is not linear but curvilinear between 0 and 2 Sv. Moreover, even if the dose-effect relationship were demonstrated to be linear for solid tumors between, for example, between 50 mSv and 3 Sv, a generalization would not be possible because of experimental and clinical data show that the dose effect relationship considerably varies according to type of tumor and age of individuals at the time of irradiation. The global annd empirical relationship observed for solid tumors corresponds to the sum of relationships which can be quite different according to the type of cancer, for example, some being linear or quadratic, with or without threshold.

Finally, with regard to *in utero* irradiation, whatever the value of the Oxford study, some inconsistencies between the availbable data sets call for great caution before concluding the existence of a causal relationship from data showing simply an association. Furthermore, it is highly questionable to extrapolate from the fetus to the child and adult, particularly, since

the developmental state, cellular interactions and immunological control systems are very different.

In conclusion, this report raises doubts on the validity of using LNT for evaluating the carcinogenic risk of low doses (< 100 mSv) and even more for very low doses (< 10 mSv). The LNT concept can be a useful pragmatic tool for assessing rules in radioprotection for doses above 10 mSv; however since it is not based on biological concepts of our current knowledge, it should not be used without precaution for assessing by extrapolation the risks associated with low and even more so, with very low doses (< 10 mSv), especially for benefit-risk assessments imposed on radiologists by the European directive 97-43. The biological mechanisms are different for doses lower than a few dozen mSv and for higher doses. The eventual risks in the dose range of radiological examinations (0.1 to 5 mSv, up to 20mSv for some examinations) must be estimated taking into account radiobiological and experimental data. An empirical relationship which has been just validated for doses higher than 200 mSv may lead to an overestimation of risks (associated with doses one hundred fold lower), and this overestimation could discourage patients from undergoing useful examinations and introduce a bias in radioprotection measures against very low doses (< 10 mSv).

Decision makers confronted with problems of radioactive waste or risk of contamination, should re-examine the methodology used for the evaluation of risks associated with very low doses and with doses delivered at a very low dose rate. This report confirms the inappropriateness of the collective dose concept to evaluate population irradiation risks.

Glossary

Apoptosis Programmed cell death. Apoptosis plays an important part in embryogenesis, in tissue regeneration following an insult, and can eliminate cells whose DNA has been damaged and not repaired with a high fidelity.

Carcinogenesis Process that leads to the formation of a cancer. It involves several stages (resulting from successive alterations of the genome). The first stage is that of initiation (this may, for instance, be due to the mutation of a proto-oncogene into an oncogene). For a normal cell to be "transformed" i.e. for it to become preneoplasic, its genome has to undergo several modifications (appearance of an oncogene, inactivation of both copies of a suppressor gene, immortalization i.e. acquisition of an unlimited capacity to proliferate, changes affecting the apoptosis system, etc.). A transformed cell can give rise to an invasive cancer at the end of the second stage, known as "promotion", which is associated with the proliferation of the descendants of the initiated cell, and the escape of one of them from the control of the normal surrounding cells and of the body.

Cytokines Chemical agents that are secreted by certain cells and act on other cells (such as the lymphocytes). Several hundreds have been identified. They bind to specific receptors in the type of cell to which they are destined. Alongside hormones, antibodies etc., they play an important role in intercellular communication. Two of them are mentioned in the report: Transforming growth factor β (TGF β), and tumor necrosis factor α (TNF α).

Dose The concept of dose is used to measure the effect of ionizing radiations, it involves three different quantities:

- **the absorbed dose**: the energy absorbed per unit mass. The unit used for the dose absorbed is the **gray** (Gy).
- **The equivalent dose**: the absorbed dose multiplied by a "*biological weighting factor*" which expresses the relative harmfulness of the various types of radiation. The biological effect of radiations depends on the nature of the particles involved; for an equal dose (in Gy) it is greater for radiations that have a high ionization density along the track of the particles (i.e. a high linear energy transfer, or LET).

  The biological weighting factor is, for example, equal to 1 for photons and electrons, but equal to 20 for α particles. The unit used for the equivalent dose is the **Sievert** (Sv). The equivalent dose is used, for the purposes of radioprotection, for adding doses delivered by various types of radiations (X-rays and neutrons, for instance).
- **The effective dose**: the equivalent dose multiplied, for each tissue, by a "*tissue weighting factor*", which expresses the relative risk of carcinogenesis. The tissue weighting factor for the thyroid is, for example, equal to 0.05. The unit used for the effective dose is the Sievert (Sv). The effective dose was introduced for the purposes of radioprotection, because it makes it possible to add the doses received on different areas of the body (on a limb and the thyroid for instance).

The units used for the equivalent dose and the effective dose, although these are in distinct quantities, are called by the same name (the Sv), which can give rise to confusion if it is not clearly stated which is being referred to. If the whole body has been exposed uniformly, then the equivalent dose is equal to

the effective dose. In the case of exposure to X- or gamma rays, the doses in Gy and in Sv are equal.
To make this report easier to follow, we have generally used Sv. Unless otherwise specified, it is used as a unit of equivalent dose.

Magnitude of doses

- **Natural irradiation**: is that to which all living beings are exposed: cosmic rays, radioactive substances present in the earth's crust, potassium 40 present in the body, etc. In France, this natural dose averages 2.5 mSv/year with geographical variations ranging between 1 and 6 mSv/year. Worldwide, it ranges from 1 to 80 mSv/year.
- **X-ray examinations**: depending on the type of examination, they deliver an equivalent dose of 0.1 to 20 mSv. On average, in France, they deliver 1 mSv/year per person, but this exposure varies widely, concentrated in a small number of individuals.
- **Radiotherapy**: the doses used for a treatment range from 60 to 80 Gy to the tumor and the target volume (and from a few Gy to a few mGy to the rest of the body).
- **Nuclear energy**: this leads to the exposure of workers directly assigned to work under radiation to 2 mSv/year on average, and to exposure of the general public to less than 0.015 mSv/year (effective dose).

Dose rate: Dose per unit time (Gy/min or Sv/min, for example)

Low doses There is no consensus about the doses described as being "low" or "very low" doses. Depending on the author, low doses may be less than 200 or less than 100 mSv, and very low doses those that are below 20 or 10 mSv. In the context of this report we take low doses to be less than 100 mSv, and very low doses to be less than 10 mSv.

Suppressor genes: genes that oppose the continuous proliferation of cells. They are also known as "tumor suppressor genes".

Genome the full set of DNA molecules present in the cell nucleus.

Gray (Gy) unit used for the absorbed dose. A tissue is said to have received a dose of 1 gray (Gy) when the energy transferred by the radiation to the tissue is 1 joule/kg.

Hormesis Some physical or chemical agents have one effect at high doses and the reverse effect at low doses. This phenomenon is known as hormesis. It probably results from the activation of defense mechanisms. Hormesis is observed with several drug molecules that are toxic at high doses, but which can have a beneficial protective effect at low doses.

ICRP International Commission on Radiological Protection

Proto-oncogene gene generally active in the embyo and fetus, and during proliferation processes. A mutation can result in the permanent activation of a proto-oncogene, which then becomes an oncogene.

Dose-effect relationship

Linear no-threshold relationship $E = \alpha\ d$ (where d is the dose and E the effect)

Linear-quadratic relationship $E = \alpha\ d + \beta\ d^2$

Quadratic relationship $E = \beta\ d^2$

Curvilinear relationship: non-linear function, such as linear-quadratic or quadratic.

DNA repair

Error-free repair: the molecule is reconstituted with a high fidelity, i.e. without loss of information.

Misrepair or error prone repair: reconstitution with a loss of information (for instance, deletion due to the loss of a fragment of the molecule, or mutation or translocation).

Sievert (Sv) unit used for the equivalent dose and the effective dose. It is equal to the dose in Grays multiplied by a weighting factor.

Oxidative stress. Formation of reactive oxygen species (ROS) in and outside cells, such as those resulting from the lysis of water molecules induced by ionizing radiation. This stress can not only damage cellular constituants and generate inflammatory processes but also activate several enzyme systems and modify the transcription of genes. These reactions are known collectively as oxidative stress**.**

TGFβ TGFß (Transforming Growth Factor beta) is a cytokine which regulates many of the biological processes essential for embryo development and tissue homeostasis, and therefore plays a role in the healing of a tissue and carcinogenesis. The effects of TGFß may differ depending on the tissue concerned. For instance, TGFß inhibits the proliferation of epithelial cells, but stimulates that of fibroblasts.

TNFα TNFα (Tumor Necrosis Factor alpha) is classified as a cytokine. It is a mediator of natural immunity, because it can be secreted without the involvement of any antigen.

UNSCEAR United Nations Scientific Commission on Effects of Atomic Radiation

1 Introduction

1.1 The risk of low doses of ionizing radiations cannot be assessed directly. The only way to evaluate them is therefore by extrapolating from the effects of high doses. Depending on the dose-effect relationship used for this extrapolation, the risk attributed to low doses may range from zero (or even a negative value in hormesis) to a value proportional to the dose (or even supralinear). The evaluation of the cancer risk of low doses is of great importance in medicine, as illustrated by three examples:

- Approximately 70 million radiological examinations are performed in France every year, delivering an average of 1 mSv per year to every French person. Depending on the dose-effect relationship used, it can be deduced from this, either that these exams. could be leading to about three thousand cases of cancer a year, or that they do not represent a significant hazard.
- Nuclear energy delivers about 0.001 mSv/year to each person in France; in the vicinity of power stations, the dose can reach 0.015 mSv/year. People working in the nuclear industry receive on average 2 mSv/year. The impact on health varies widely, depending on how it is estimated, between zero impact and several dozen lethal cancers cases per year for the entire French population, and between zero and a few lethal cancers per year for workers.
- An erroneous estimation of the risk associated with exposure to radon at home could lead either to overlooking a serious public health problem's, given the number of people exposed, or conversely, to incurring considerable pointless expense in order to limit such exposure.

1.2. In 1995, the Académie des Sciences published a report discussing the effects of low doses [4], and subsequently organized a symposium on this topic [5]. The Académie de Médecine has issued several statements on this subject [2,3].

These documents pointed out that following exposure to low doses, epidemiological studies have not evidenced any significant effect: because either there is no effect, or the effect is too small to be detected by such studies. These results, which are sometimes described as "negative results", are useful, because they help to assess the upper limit of the potential risk, and can be included in the meta-analyses. Over the past decade, new epidemiological data have been published. Some important new facts have emerged, such as the feasibility and value of studies comparing the morbidity and mortality in regions with high and low levels of natural irradiation but similar lifestyles, the questioning of the linear relationship between dose and the incidence of solid tumors among survivors of atom bombs [224,291], the fact that risk factors calculated from the survivors of atom bombs cannot be applied to medical irradiations (notably to fractionated irradiation or low dose rates). Nevertheless, despite their interest, they have not yielded to any conclusive data. With regard to the dose-effect relationship, the main contribution to progress has come from biological research: the new data have revealed the complexity and efficacy of defense mechanisms against genotoxic (physical and chemical) agents at the level of the cell (DNA repair and apoptosis), of the tissue (role of neighboring cells) and of the whole body (immunosurveillance). It has now been established that the cell reacts to low doses of irradiation, by stimulating defense mechanisms and possibly by inducing apoptosis of cells whose DNA has been damaged. The rapidity and effectiveness with which the cell reacts to irradiation had been previously considerably under-estimated, and these reactions depend on the dose and dose rate. Consequently the impact of a given dose of radiation can vary markedly depending on the

conditions of irradiation.

1.3 The effect of low doses is usually estimated by extrapolation using a linear, no-threshold dose-effect relationship (LNT). This method of assessing the carcinogenic risks of low doses was introduced in the 1960s by the International Commission on Radiological Protection (ICRP [117] for simplifying the collect and interpretation of the data. The LNT relation indeed makes it possible to add the various doses received by a worker during his/her working life, irrespective of dose rate, of exposure or type of radiation. Understandably, this led to the use of LNT for pragmatic purposes to estimate the effect of low doses by extrapolation in order to help decision making [133]. This use was subsequently justified by postulating that doses always accumulate, and that no matter how low they are, they all have the same radiocarcinogenic potential per unit dose, since each directly or indirectly ionizing particle crossing a cell or its nucleus acts independently and has the same efficacy. This postulate was supported when, during the 1970s, the link between DNA damage and carcinogenesis was established, and it was accepted that carcinogenesis is caused by stochastic mechanisms. This made it logical to assume that all irradiation, however low the dose, could cause irreversible DNA damage likely to develop into cancer, and therefore that the LNT model was valid, even for the lowest measurable doses. LNT therefore acquired the status of a scientific model, without any detailed discussion of its validity for estimating the risks of very low doses [133].

This validity has now been challenged [1,84,272,273], particularly in the light of recent demonstrations of the existence of mechanisms for safeguarding the genome (essentially involving DNA repair [10,15,56,192,251,298,302] and the elimination of cells whose DNA has been damaged via death. In themselves, these defense mechanisms would not have been sufficient to challenge the validity of LNT if their efficacy per unit dose had been constant irrespective of dose and dose rate. However, it is now clear that it is erroneous to assume such constancy. We knew that the repair effectiveness was greater at a low dose rate, but recent studies [60,73,241], by demonstrating the extent of these differences, have removed any scientific justification for extrapolations from high doses to low doses. The purpose of this report is, therefore, to update the multidisciplinary data (biological, biophysical, epidemiological) which make it possible to identify more clearly the quantitative and qualitative differences between low and high doses and their carcinogenic effects.

1.4 In order to take into account the variation in the probability of genotoxic effect per dose unit according to the dose rate in mammalian cells adjustments were introduced by ICRP, which implicitly recognize that LNT overlooks clinical and biological data. A dose, dose rate, effectiveness factor (DDREF) has therefore been introduced to describe the effects arising from exposure to a low dose of photons at a low dose rate. There is no consensus about the validity of this concept, either at UNSCEAR, or within ICRP Committee 1, which is responsible for evaluating risks. UNSCEAR had suggested a DDREF range of 2 to 10 to take the experimental data into consideration [281,282]. Somewhat arbitrarily, and conservatively, the ICRP [117] has adopted a DDREF of 2: the validity of this choice has been challenged [118].

1.5 Improved understanding of the defense mechanisms of cells and tissues against low doses of IR suggests that their effect per unit dose must be much lower than in the case of high doses, but does not allow us to assess the respective carcinogenic risk. This is why the choice of the dose-effect relationship (linear, linear-quadratic -- i.e. both linear and quadratic -- or quadratic; with or without a threshold), in particular for the assessment of the risks of low doses, has to be based on knowledge of the genotoxic effects, the carcinogenic mechanisms, experimental and clinical data.

The quantitative discrepancy between the results of the various epidemiological and animal

experimental studies supports the view that there are several dose-effect relationships rather than only one, and that their parameters depend upon the type of cancer, the type of ionizing particles, radiation dose, dose rate, fractionation of irradiation, species, breeding line within the same species, target tissue, volume irradiated, age, individual sensitivity factors and, possibly, co-factors interacting with radiation, such as exposure to other carcinogens.

There is still controversy about whether a threshold exists [36,86,108,111,118,134,226]. A threshold could be due to the elimination of lesions from the genome by mechanisms including the absence of intracellular signalling, and therefore the lack of activation of DNA repair systems at very low doses or dose rates, and the combination of error-free DNA repair with the death of the cells of which the DNA has not been repaired [60,92,134,144,241].

1.6 We shall examine subsequently the mechanisms of radiocarcinogenesis, the physical and biological phenomena caused by the exposure of cells, tissues and organisms to ionizing radiation, the experimental data on radiocarcinogenesis, and the epidemiological data. These topics are covered in more detail in the appendices. Finally, in the light of this data, we shall discuss the validity of the LNT relationship, and envisage the practical implications of these discussions.

2. The mechanisms of carcinogenesis

2.1 The process leading to the transformation of a normal cell into a tumor cell is interpreted as a Darwinian selection process determined by a series of genetic or epigenetic events, each of which gives the initiated cell a selective advantage in terms of survival or proliferation within the tissue to which it belongs.

The main steps in this transition are analyzed in Appendix 1. First of all, the cell must be able to divide autonomously, i.e. it must autonomously produce growth factors or be able to proliferate without them, and it must have become insensitive to suppressor genes. Other events, such as impairment of the mechanisms of apoptosis and immortalization, are also necessary [100,101].

The conventional model acknowledges that, by a series of stages, modifications of the genome confer a selective advantage on the cell, during carcinogenesis [9]. We now know that these phenomena cannot be described by a linear process, during which successive genome damages accumulate at random. Carcinogenicity is a phenomenon that cannot be reduced to a series of mutations due to independent stochastic lesions occurring in the same cell. Indeed it affects all aspects of genome function [100,101]. The association of genetic and epigenetic mechanisms is now well-established [20,81,127,139,212,262].

2.2 The cell, the tissue and the body all have defenses against carcinogenic processes, and these must be successively overcome for carcinogenesis to occur.

2.2.1 There are intracellular systems of proliferation control (suppressor genes), mechanisms involving the death of initiated cells that tend to eliminate or prevent the proliferation of cells in which a proto-oncogene has mutated into an oncogene, with damaged DNA, which do not obey systems regulating proliferation, or which are no longer receiving the growth factors required for their growth.

Cell death therefore appears to be a main safeguard mechanism, in particular programmed death or apoptosis. The loss of a cell's ability to kill itself may result from changes in the genes involved in this process [106] Ionizing radiation is likely to induce, at different levels depending on the tissues, apoptotic responses, which are the consequence of intra- and

intercellular signalling. However, IR can also induce mutations, which interfere with apoptosis and which therefore permit the survival of damaged cells, which in turn constitutes one of the steps in carcinogenesis [105].

2.2.2 At the tissue level, we must emphasize the control exerted by neighboring cells (contact inhibition of proliferation, exchange of signalling and regulation molecules via intercellular junctions, bystander effect, secretion of regulation factors by neighboring cells and stroma). There are multiple interactions between a cell, in which a potentially oncogenic genetic event has occurred, neighboring cells of the same type, the extra-cellular matrix and the stroma. These interactions between cells play a crucial role in embryogenesis, in growth, in cell turnover of certain tissues in adults and in the regeneration of injured tissues. They are involved in the carcinogenic process, either inhibiting or promoting it. The exchange of information between the cell undergoing malignant changes and its microenvironment, the cytokines, (notably TGF-β, which plays a crucial role in regulating cell proliferation) can, depending on the context, either slow or accelerate the carcinogenic process [19,26,29,151,299]. The microenvironment can either stop or stimulate the proliferation of clones of cells undergoing neoplastic transformation and affects the genetic instability [71,94,231]. Pathology studies had in fact already shown that tissue disorganization almost always preceeds the appearance of invasive cancer [57].

At low doses and low dose rates of ionizing radiation, the pro-apoptotic effect dominates and the damaged cells, of which there are only a few, can be eliminated or controlled. But at doses in excess of 0.5 Gy with a high dose rate, the greater number of mutant cells and the accumulation of mutations, the tissue disruption and above all the proliferation of the surviving cells to compensate for the death of a high proportion of the cells allow some cells to escape from these controls, which are intended to maintain tissue integrity and to regulate proliferation. These escape processes vary considerably depending on the tissues, the type of initiated cells (stem cells or progenitor cells) and the type of tumor as, for example, has been shown in the analysis of the carcinogenesis of multiple myelomas [71] and colo-rectal cancer [137].

In animals that have received chemical carcinogens, irradiation has little influence on the emergence of cancer [124], whereas, following X-ray irradiation, UV irradiation promotes the appearance of cancers.

2.2.3 At the whole body level, escape from the immune surveillance responsible for eliminating tumor cells is based on selection of cells that are capable of escaping from it [210], for instance by the loss of expression of the components of the major histocompatibility complex. Carcinogenesis may be facilitated by a reduction in immune defenses when a large segment of the body has been irradiated.

3 Physical and biological phenomena caused by ionizing radiation

3.1. Reactive oxygen species, formed by water radiolysis induced by irradiation, damage some cell constituents and produce oxidative stress. This oxidative stress stimulates enzyme systems that detoxify active species of oxygen formed and induces the synthesis of enzymes that destroy them. In parallel, oxidative stress also activates numerous signalling pathways [53,54,85,305].

3.2 In the case of low Linear Energy Transfer (LET) radiations, such as photons or electrons, when the whole body is exposed to 1 mGy, each cell is on average crossed by one electron. Each electron induces on average 2 DNA lesions, including one single-strand break (SSB)

and 4 x 10^{-2} double-strand breaks (DSB) of the DNA molecule, and 10^{-4} chromosome aberrations. This initial effect is proportional to the dose as, in general, a DSB is not the result of two SSBs located opposite each other on the 2 strands and caused by different particles, but is the direct or indirect consequence of a high transfer of energy within or alongside a DNA molecule, mainly by means of radiation-induced reactive oxygen species [44,97,199,201].

The first physico-chemical events trigger a series of signals and reactions that can profoundly alter the fate of the DNA lesions. It is not the initial physico-chemical events that change, but their outcome. The defense mechanisms induced in a cell depend on the number and nature of cellular damages.

The number of DSBs caused by a 1 Gy dose has been estimated to be 40 [44] and 30 by Vilenchik [290]. In contrast, the number of DSBs of endogenous origin, produced in each cell by the oxygen metabolism, remains controversial; it has been estimated to be 8 per day [44] and 50 per cell cycle by Vilenchik [290], who estimates that about 1% of SSBs turn into DSBs (there are about 3000 SSBs per day).

In the light of theoretical considerations and *in-vitro* experimental studies, it has been proposed that ionizing radiations could induce multiple localized lesions, consisting of SSBs, oxidative damage to bases and clusters of DSBs, located within a distance of less than 20 base pairs within the DNA [96,115,200,201]. These very complex lesions are considered to be responsible to a large extent for the genotoxic effects of radiation. However, the number of such lesions induced in a cell and their impact have not yet been clearly established.

With regard to the oxidative damage of bases and DSBs from endogenous sources, the variability of the published values suggests that all experimental variables are not entirely under control, in particular the degree of oxidative stress during the extraction of the DNA [46,232]. Furthermore, their number varies considerably depending on the rate of proliferation, as almost all of these endogenous DSBs are produced during the S phase. Moreover, the comparison between the number of DSBs due to cell metabolism and to irradiation is of limited significance, because the proportion of error-free repairs seems to be greater for endogenous DSBs than for those caused by irradiation.

The dose rate at which the number of DSBs caused by irradiation is equal to the number produced during the same period of time by cellular metabolism in proliferating cells (endogenous DSBs) is 5 mGy /min; in both cases 0.14 DSBs occur per minute [290]. Note that at a dose rate of 1.5 mGy/min, the signalling systems are not activated, whereas they are at a dose rate of 5 mGy/min or more [60], a dose rate that approximately doubles the number of DSBs, from one DSB per cell every 7 minutes (basic rate) to 1 every 3.5 minutes. If it takes approx. 5 minutes to repair most DNA lesions, as some data suggest, lesions could then accumulate. It therefore appears plausible that the additional DNA lesions caused by low dose rate irradiation do not significantly modify the basic function of the constitutive repair systems (and the RBE), whereas irradiation delivered at higher dose rates activates other repair systems [60,289]. The rate of error free repair of DSBs caused by irradiation, and the time taken for repair vary considerably according to dose and dose rate [240,289], for example from 5 mGy/min. to 1 Gy/min. This leads to considerable variations in the yield of mutations. For very low doses (a few mSv), the numbers of DNA lesions (and therefore the biological response) may vary considerably from one cell to the other because of statistical fluctuations; nevertheless the absorbed dose absorbed remains the only parameter to which one can refer to.

The DSBs caused by natural irradiation of 2 to 25 mSv/year only corresponds to a very small fraction of the total number of DSBs (less than 1 ‰) [44,86,289].

Mitotic cell death or chromosomal aberrations seem to result from error prone rejoining when two chromosome breaks were generated close to each other in space (< 0.1 μm [225,227]) and in time on the same chromosome or on two neighboring chromosomes [62]. Thus, it is understandable that the probability of simple or complex chromosome exchanges is influenced by the dose rate [63,160] and that in addition to the linear component, the dose-effect relationship has a quadratic component [80] which disappears at very low dose rates [63].

3.3 *The irradiation of a cell causes several types of responses* which modify the effects of irradiation, and therefore the radiosensitivity:

3.3.1 Oxidative stress (see §3.1) induces the transcription of many genes implicated in the signalling that activates cell defenses [70,85,142,305]. The efficacy of the defenses against reactive oxygen species decreases at high dose rates.

3.3.2 Different signalling systems are activated in yeast [168] and mammalian cells [15,16,70,302], after passage of an electron: cytosol (MAP kinases), mitochondria, nucleus (protein kinases). In addition, in the nucleus, different levels of damages lead to the activation of different families of genes [7,27].

3.3.3 DNA damages or modifications of the chromatin are detected by signalling proteins. Their activity is modulated by the number of lesions (and therefore by the dose, the dose rate and LET) and by messages from neighboring cells. These proteins activate phosphokinase transmitters, in particular the protein encoded by the ATM gene (which is mutated in ataxia-telangiectasia) [138,215,251,302]. In turn, these transmitters modulate the action of proteins involved in cell cycle control (the interruption of which promotes repair), DNA repair [82,298], or in triggering apoptosis [172].

Studies carried out with the DNA micro-array technique in yeast show that continuous irradiation, at a dose rate of 20 mGy/h, i.e. lower than the level of irradiation that causes a detectable (lethal, mutational) biological effect, is enough to change intracellular signalling without modifying the genome [168] and to activate or inhibit numerous genes involved in the general metabolism and in defenses against ionizing radiation [7,37,53,177]. Such mechanisms bring into play defenses at doses of the same order as those due to natural irradiation, which makes it possible to reduce or prevent its potentially harmful effects.

3.3.4 For exposures greater than 1 mGy to photons or electrons, each cell is traversed by several tracks separated by time intervals inversely proportional to the dose rate. Some SSBs are quickly repaired with a half-time of approx. 5 minutes. DSBs are repaired more slowly and sometimes imperfectly [73,145]. As regards DSBs, we should distinguish between two situations: on the one hand, when the dose [241] or the dose rate [60] is very low, intracellular signalling and detection systems are not triggered below a certain threshold, therefore repair systems are not activated, and the damaged cells die. The elimination of these cells protects the organism against cells potentially undergoing malignant transformation [205]. On the other hand, at doses exceeding this threshold, repair systems are activated, which expose cells to a risk of misrepair, which is small at low doses but increases with dose and dose rate [73,147,240,289,290].

3.3.5 The dose rate determines the average time interval between physical hits; it has a major effect on the cellular response. In general, the biological effects of irradiation (lethality, mutagenesis, chromosomal aberration etc.) decrease as the dose rate decreases [10,283]. The biological effect of the irradiation depends on two distinct factors: the greater efficacy of the DNA repair at low dose rates, and the probability of damaged cells to be eliminated by death. A very low dose rate can damage the DNA without activating the repair system and the

damaged cells die [60]. There is indeed a dose and dose rate threshold below which the intracellular signalling systems and therefore some DNA repair systems are not activated [60,241].

When the dose rate is low, the number of lesions simultaneously present in the cell is limited. Conversely, a high dose rate leads to the simultaneous presence of a large number of lesions. This high local density of lesions interferes with the coordinated action of repair systems, and also increases the probability of error prone endjoining [63] due to the presence of several DSBs in a restricted volume.

3.3.6 These conclusions regarding differences in the efficacy of the protection system are supported by various experimental or clinical data, which highlight the impact of repair on the biological consequences of irradiation:

- the lack of any reduction in the mutagenic and lethal effect as the dose rate decreases in the cell lines in which the signalling or the DNA repair systems are impaired [207] or blocked, for example, in hereditary diseases with defects in repair systems (reparatoses). This lack of repair is also observed when yeasts or mammalian cells are exposed to gamma rays at 0°C (a temperature that inhibits the repair enzymes), the number of DNA double strand breaks is then identical at high and low dose rates, whereas at room temperature, it is much smaller at lower dose rates.
- A dose of 80 Gy delivered over 14 days (at a dose rate of approx. 4 mGy/min.) does not cause the same rearrangement of the genome as that caused by DSB misrepair. However, when mutant cells deficient in non-homologous endjoining (NHEJ) are irradiated under the same conditions, rearrangement of the genome can be observed in approx. 10% of the cells [240]. Note that the technique used in this study (pulsed field gel electrophoresis) does not allow to detect small deletions or point mutations.

3.4 *Variation of mutagenesis and lethality* depending on the dose and timing of the irradiation.

At equal doses, the mutagenic effect varies markedly with the dose rate [160,241,289,290]. When the dose rate increases , the mutation frequency after having passed through a minimum (hormesis?) increases strongly [289]. If the number of lesions which are present simultaneously is small, repair is generally more effective; thus it is more effective at a low dose rate than at a high dose rate. A limited number of lesions induces a reversible arrest of the cell cycle which enhances repair. A high amount of lesions prolongs the cell cycle arrest which can lead to apoptosis [82,205]. The time taken by repair depends on the complexity of the lesions and the repair system operating. A high local density of lesions reduces the repair efficacy [303].

3.4.1 The lower lethality following *fractionated* irradiation cannot only be explained by the repair of DNA lesions between sessions. Recent data also show that the effectiveness and rapidity of repair depend on the time, the type of tissue and its proliferative status.

3.4.2. *Initial hypersensitivity.* For some cell types, mortality is very high (per dose unit) at the onset of irradiation (during the first two hundred mGy), then falls to a very low level before subsequently increasing again. This low dose hypersensitivity [53,54,60,126,165,176,241,253] is observed in many cell types (leading to a high mortality rate per unit dose) for doses of less than a few hundred mGy of low LET irradiation. An induced radioresistance is observed at doses of over 0.5 Gy; and the mortality rate per unit dose then becomes very low before increasing again [126]. These variations in the mortality rate (per unit dose) indicate that the cellular defense mechanisms against lethality, which initially show little efficacy, becomes more effective during irradiation. These rapid changes

in the mortality rate (per unit dose) are not correlated with either the cell's capacity to undergo apoptosis or the defect in cell cycle arrest caused by irradiation. Conversely, stimulation of the activity of certain enzyme systems (PARP) by hydrogen peroxide, abolishes it [164], and inversely, a toxic substance, aminobenzamide, a PARP inhibitor, increases it [53], which demonstrates the role played by the induction of the enzyme systems in these variations of radiosensitivity. This initial hypersensitivity eliminates damaged cells with mutagenic potential after low doses of radiation[126].

3.4.3. After high dose rate irradiation of short duration, sudden changes in radiosensitivity can be observed (increased mortality rate), which seem to depend on the activity of the PARP-1 enzyme [88,218].

3.4.4 The existence of an *adaptive* response is now well established [173,297]: a first low dose of radiation leads to a reduction in the mortality of organisms *in vivo* [267], the number of mutations and the rate of neosplastic transformations [25,47,83,178,233,235,236,246] caused by a second irradiation carried out during subsequent hours or days. This inducible and transient protective effect seems to occur also in humans [93,265], and appears to result from a stimulation of cell defense and DNA repair systems. At the cellular level, an increase in lethality may be observed as a result of apoptosis and delayed mortality due to a bystander effect.

Genotoxic physical agents (solar ultraviolet and ionizing radiation) were present when life appeared on earth, and very likely, at that time irradiation was generally more intense than today. Recent work has revealed the efficacy and multiplicity of defense mechanisms which developed during evolution. Many of these systems are targeted against reactive oxygen species produced by irradiation.

3.4.5 Some DNA repair systems are activated by low doses of ionizing radiation. DNA repair systems differ in terms of velocity and efficacy; in particular, the repair kinetics for DSBs and the probability of repair vary with dose and dose rate [240]. They are associated with apoptosis, that also varies with dose and dose rate [37,98,172,206]. Thus, although the number of lesions, in particular, that of DSB, is proportional to dose even at very low doses, at doses of a few dozen mGy, no damaged cells are found during the following days. The disappearance of damaged cells seems to result from the lack of activation of repair systems, which leads to an absence of repair and to cell death [60,241] or from high fidelity repair by constitutive systems [240]. When only a few cells are damaged, this elimination strategy seems to be optimal, because repair systems are sometimes error prone and can potentially lead to the emergence of pre-cancerous and subsequently cancerous cells.

When a large number of cells in the same tissue are killed or damaged, repair and proliferation mechanisms are triggered, which are intended to protect the integrity and functions of the tissue. By means of intercellular communication systems the reaction of a cell to irradiation therefore seems to be influenced by the number of cells affected.

Hence, the cell reacts to irradiation by a global and integrated response that involves several enzyme systems [22] which govern the efficacy of DNA repair and the probability of cell death eliminating damaged cells. Albeit DNA damage is constant (per unit dose), the probability of mutation is modulated within a framework of what could be called a strategy of least cost.

3.4.6 Schematically, one can distinguish between four dose ranges.

- At doses of a few mGy or low dose rates, no effect can be detected because the damaged cells die [60,241]. At these doses, the signalling systems are not triggered. Only constitutive repair systems, which are constantly active, operate (such as BER).

The doses or dose rates above which apoptosis is stimulated are lower than those that activate the repair systems.

- For doses of less than about 100 mGy or those deliveredat low dose rates, damaged cells are eliminated or whenever possible, repaired by high fidelity mechanisms. When this elimination/repair mechanism has been induced by irradiation, it also acts upon the cells damaged by oxidative metabolism. In combination with the detoxification mechanisms induced by oxidative stress, these defenses can also explain the hormesis effect which is observed in experimental animals [11,25,50,79,84,87,174,233,244]. However, radiation-induced cell damage induced by low LET radiation differs from the damage induced by cell metabolism i) by a higher proportion of double strand breaks, ii) by the presence of clustered lesions (caused by the attack by hydroxyl radicals) and iii) by the more heterogeneous (non-compartmentalized) distribution of impacts at the cellular level.

  Another mechanism that could be responsible for a hormesis effect has been evidenced by *in-vitro* experiments: the selective death of cells that have been pre-disposed to neoplastic transformation. This seems to be dose related [235,236].

- At higher doses, over approx. 200 mGy, the number of damaged cells increases and the DNA repair systems supposed to avoid cell death and tissue injuries are associated with a risk of misrepair, which is greater when the number of lesions inside the cells is high [73,240]. In the absence of apoptosis, these errors lead to mutations. When apoptosis predominates, the risk of cancer is very low, but the tissue looses cells, and the rate of ageing is accelerated). When repair predominates, the risk of cancer increases. This is a phenomenon that is also observed during ultraviolet irradiation of the skin [78,273]. Because of these variations in effectiveness of DNA repair and in the probability of apoptosis (in relation to dose or dose rate), the carcinogenicity of irradiation increases more rapidly than the dose in the range from a few dozen to several hundred mGy.

- Above 500 mGy, also an accelerated proliferation, in order to compensate for cell deaths, is observed. Cell divisions interfere with repair and increase the likelihood of errors[59,136].

The cell response therefore seems to depend on the dose, the dose rate and the cell type, and, without doubt, on the number of damaged cells. It varies over time. This strategy of defense that the organism raises against cellular lesions induced by ionizing radiation is distinct from, but somewhat similar to the strategy observed after ultraviolet irradiation. Once again, the accumulation of lesions hinders and delays repair, and therefore increases harmful effects per unit dose of exposure.

3.4.7 One can also draw a parallel between dose effect relationships for ionizing radiation and the numerous experimental data that reveal major differences between the toxicities of chemicals depending on dose, and that have shown very small (if any) carcinogenic effects of low concentrations [6]. However, these variations are also partly linked to changes in metabolism, which may contribute to non-linearity [50,238].

3.5 *Role of neighboring cells, bystander (or "abscopal") effect and genetic instability.*

3.5.1 In multi-cellular organisms, in particular vertebrates, the fate of an irradiated cell depends upon signals emitted by neighboring cells (gap junction, bystander effect, contact inhibition, proliferation control mechanisms by means of cytokines). Normal cells appear to

be capable of inhibiting the development of potentially malignant clones [19,29,71,231]. Many experimental data support this concept in the context of radiocarcinogenesis, for example, the influence of the volume irradiated on the likelihood of a carcinogenic effect [263], and the lower efficacy of heterogenous irradiation [167], in particular of irradiation through a grid [45]. Conversely, non irradiated cells can become cancerous in the vicinity of highly irradiated cells [19,41,42].

Besides an inhibitory effect (such as contact inhibition), or a stimulation of cell division, intercellular relationships can also elicit damage in neighboring cells, which have not been irradiated; this is known as the bystander effect. The influence of intercellular interactions on low dose hyperradiosensitivity suggests that there is a link between this phenomenon and the bystander effect [54]

The bystander effect originates from potentially genotoxic signals sent to neighboring cells. There are at least two different mechanisms. The first is based on the production by cells exposed to low LET radiation, of "clastogenic" plasmatic factors, which can cause chromosome aberrations in neighboring or remote cells. This mechanism is independent from p53. Clastogenic factors can persist for years after irradiation, as has been shown in earlier studies on plasma of patients who have received radiotherapy [249], or of survivors of Hiroshima Nagasaki [209].

More recently, another mechanism has been demonstrated after high LET irradiation [193], which involves inter-cellular gap junctions [12,17,28] through which free radicals, likely to play a role in the bystander effect, can pass [28]. It is dependent upon p53 [122]. This mechanism causes a bystander effect in the immediate environment of the irradiated cells, which decreases as the dose increases [41,247]. This effect is considerably reduced when alpha irradiation is preceded by a low dose (20 mGy) of low LET radiation [178]. It therefore appears to be modulated by adaptive responses. Similar effects have been observed after localized irradiation of the cytoplasm, and the bystander effect has been compared to an inflammatory-type reaction. Various mechanisms are therefore involved in the so-called bystander effects (intercellular signalling, clastogenic factors, passage of active oxygen species and other molecules through gap junctions, stimulation of the production of reactive oxygen species).

This "bystander signal" has many consequences for the unirradiated cells (apoptosis, induction of genetic instability, delayed cell death, mutations that are in 90% of cases point mutations and seldom deletions, which sugests that they are induced by reactive oxygen species). These effects depend upon many factors, which are still poorly identified. Mothersill [188,189] suggested that the bystander effect could induce in the neighboring cells an adaptive response similar to that induced by pre-irradiation (see §3.4.4.). These effects on the neighboring non-irradiated cells could therefore, depending on the context, have either protective or harmful effects; they are not proportional to the dose, but on the contrary appear to diminish with increasing doses [58,191].

The bystander effect is mainly expressed at low doses of alpha radiation and its significance for X or gamma irradiation has still to be established [17,42]. After exposure to low-dose X-rays, it leads to the death of cells in which the repair of DNA damage is defective [190].

3.5.2 It has been shown both *in vitro* and *in vivo* that approx. 10% of the descendants of irradiated cells display an abnormally high frequency of genome modifications, sometimes persisting after several tens of generations. This effect, which is known as "*genetic instability*", was first observed in bacteria and yeasts [61], then in cultures of human cells and in mouse embryos after high LET irradiation (alpha particles) and after high doses of low LET irradiation (over 2 Gy) [129]. Instability can be induced in a cell when it is traversed by a

single alpha particle (micro-beam)) [128]. Radiation-induced genetic instability varies according to cell line, but does not seem to be caused by specific genetic lesions [129]. The bystander effect also induces an increase in genetic instability [153]. Since mutations also exist in non-irradiated cells, it is difficult to find out whether there is a threshold. Nevertheless, some experiments do demonstrate the existence of a threshold in some cell lines [166], but it is difficult to say whether there is a threshold in all cases [255]; what is clear is that the maximum effect is reached at relatively low doses (150 to 500 mGy) and that between 2 and 12 Gy, the incidence of genetic instability is constant [152].

Various genetic abnormalities are observed in the descendants of irradiated cells: rearrangements and chromosome aberrations, gene amplification, aneuploidy, formation of micronuclei, microsatellite instability, mutations [152,153,237,255].

Several mechanisms can cause this instability, which can be interpreted as genomic changes that only become apparent in the descendants, as is suggested by the following:

- the importance of the induction of genetic instability when there are changes in p53 gene [149].
- the reduction of genetic instability by the elimination of free radicals or when the cells are confluent (contact inhibition), which permits the repair of potentially-lethal lesions [150];

In most cases, this genetic instability appears to be the prelude to cell death, and there are proteins, such as clusterin which induce the death of such unstable cells by attaching themselves to the ends of the chromosome breaks [301]. This research area is developing rapidly [140,220]. The aim of this research is to find out whether this instability could play a part in the onset of late arising radio-induced cancers [154,227]. Some experiments suggest that this is the case, such as for instance the fact that the instability in mouse bone-marrow stem cells leads to non-specific mutations seen in radiation-induced leukemia [162]. However, other experiments do not support this hypothesis, and in the mouse, genetic instability does not seem to be involved in the initiation of leukemia [39]. Some strains of mice show high predisposition for the induction of genomic instability, whereas others show a high predisposition for radiation-induced leukemias and lymphomas: however, these strains are unrelated [40], which implies different mechanisms. In contrast, in other strains of mice, in which the predisposition for the induction of genetic instability is due to a DNA repair defect, one observes also a predisposition for the induction of breast cancers [207,219,278,279,304]: it thus would appear that in that case the susceptibilities to the induction of a breast tumor and to the induction of genetic instability are genetically co-determined, and a deficiency in the repair of DSBs (linked to a defect of DNA PKcs) may lead to permanent instability of the genome. There could also be a link between a deficiency in DNA repair, the instability of the genome and the integrity of the telomeres, however, it is not known which of these phenomena is the cause of the other [13,38]. These findings should be considered in relation to the studies that have revealed links between telomere dysfunction, impaired DNA repair and tumorigenesis [158,171]

In this context, two human studies provide some interesting data. In the leukemias that occurred in elderly survivors of the atomic bomb explosions, an excesss of complex chromosome aberrations with translocations have been reported [195]. This supports the hypothesis according to which irradiation would trigger an early onset of genetic instability associated with telomere shortening [158]. In studies of a group of patients suffering from Hodgkin's disease, M'Kacher *et al.* [179] have made interesting observations:

i) *before treatment* a notable increase (compared both to normal individuals and to patients suffering from solid tumors before treatment) in the frequency of simple and complex (with translocation and deletions) chromosome aberrations in circulating lymphocytes. The telomeres are shorter than in normal subjects or in patients suffering from other cancers. There is a correlation between telomere shortening and the rate of simple and complex chromosome aberrations.

ii) *After treatment* (radiotherapy ± chemotherapy): there is a marked increase in the incidence of simple and complex aberrations, but this increase is not influenced by the dose and extent of the treatment (radiotherapy or chemotherapy). Hypermutability is present, which suggests a DNA repair defect, and which seems to be correlated with the high frequency of aberrations before treatment and the shortening of the telomeres.

iii) There is a considerable increase in complications, in particular in second cancers in subjects who, before treatment, had a high incidence of chromosomal aberrations and after treatment displayed a marked increase in this incidence, whereas, on the contrary, second cancers seem to be rare in subjects with a small number of aberrations. The increase in this incidence and hyper-radiomutability are therefore risk factors that can be used to identify subjects who are likely to be susceptible to radiocarcinogenicity, although at present it is still not possible to identify the mechanism by which these factors contribute to radiocarcinogenesis. This may involve a genetic defect in DNA repair, since it is observed in both tumor tissues and in circulating lymphocytes, but viral infection is also a possibility. Active proliferation of EBV and papilloma virus is observed in these patients. The effects of irradiation and viral infection may therefore be associated.

This study demonstrates both the possible role of genetic instability in radio-carcinogenicity when it is combined with other disorders, and the extreme complexity of the phenomena involved.

As shown by these studies, cancer cells may involve [Fouladi 2000] genetic instability. Theoretically, instability might be transmitted via the parental germ cells to children. which would have lead to an increase in the cancer incidence in the children of parents who have been irradiated; however, this has not been observed in humans and can thus be ruled out [123].

Overall therefore, at the experimental level, the existence of direct link between carcinogenic effects and genetic instability remains hypothetical, in particular after low doses of low LET radiation [129]. However, genetic instability could be an indicator, cause, or consequence of cellular defects, such as impaired DNA repair. The most convincing evidence against the bystander effect and genetic instability playing arole in inducing human cancers is provided by studies on subjects contaminated by radium or thorium and followed-up until their death [52,91,229] over more than fifty years after contamination, and in whom no cancer was detected when the dose was below about 10 Gy, whereas there were many cancers at higher doses (see §5.5). If present in these individuals, the bystander effects or genetic instability would have shown up as a long term effect in the form of an increased cancer incidence.

3.5.3 Current studies highlight similarities between the adaptive response, the bystander effect and genetic instability [36,140,159]. These phenomena underline the importance of intra- and intercellular signaling in the biological effects induced by low dose radiation. It could be speculated that these phenomena could either increase or decrease carcinogenic risks. The bystander effect could induce an adaptive response in unirradiated cells leading subsequently to radioresistance [188]. Activation of enzyme systems are involved in the phenomenon of low dose hypersensitivity followed by an induced radioresistance (see

§3.4.2.), and in the W variations in radiosensitivity (§3.4.3). The mechanisms induced by irradiation, even at very low doses, therefore appear to be very complex, and arejust starting to be analysed. What is already clear, is that cells and tissues defend themselves by multiple and effective mechanisms against radiation-induced stress [69,74,84,111,216,300] The cell response is based on a complex network of intra-and inter-cellular signaling, and may be expressed in several ways, including the repair of damage, apoptosis, delayed death or prolonged quiescence of initiated cells. Very importantly, the modalities of the response are adapted to the context and vary according to the dose, fractionation, dose rate, LET, cellular redox-state, cell status before irradiation (in particular, whether or not integrity is conserved of the genes involved), and presence of signals emitted from neighboring cells and, possibly, of other toxic agents.

3.6 The subject of this report is ionizing radiation. However, it is apparent that most of its conclusions can also be applied to other physical (U.V. radiation) and chemical (genotoxic) carcinogenic agents, for which often, for administrative reasons there is also a tendency, to apply a linear no-threshold relationship. It seems that time has come to challenge this trend, whose scientific bases are questionable [1,6] and which can provoke unjustified fears and expenses. The problem is more complex for chemicals than for physical agents, because two aspects of the products studied have to be considered: their genotoxicity and their metabolism, which may include detoxification. Any toxic effect is the result of numerous biochemical reactions. Like X-rays, some agents are genotoxic by inducing directly or indirectly DNA lesions as a result of the production of highly-reactive chemical species (free radicals, potent electrophils, reactive species of oxygen), whereas others induce defense reactions. For each toxic effect, there are specific defense mechanisms. For instance, glutathione captures free radicals and electrophils, in the same way that metallothioneines trap heavy metals, whereas superoxide dismutases degrade the superoxide anion. The outcome depends on the balance between these two types of reaction. If the dose is low and defenses are sufficient, there will be no toxic effect. If the dose is high, and defense reactions are overwhelmed, like buffers when exceeding the pH , a toxic effect emerges and becomes proportional to the dose.

It is likely that there are threshold doses or even hormetic effects, and many arguments have been put forward in the last decade suggesting that this is the case for chemical agents [125,148, 238]. In fact, the distribution of the results around a threshold is not random (if it were, there would be the same frequency of positive and negative effects), and the negative effects are more frequent, which is in favor of the hypothesis of hormesis [49]. This has been observed in approx. 40% of toxicological studies [50], i.e. a proportion similar to that observed in Duport's meta-analysis [79] concerning experimental radiocarcinogenesis.

3.7 *Overall*, the genotoxicity of ionizing irradiation varies considerably, depending on the dose rate, the dose already received, and the time interval following the last exposure. These facts show that the cell's reactions and its defense capacities are to a large extent determined by these factors.

The cell is not passive, its response to an irradiation depends on intra- and intercellular signaling mechanisms, the characteristics of radiation and the state of the tissue. Elimination of damaged cells by death is effective when there are only a few damaged cells around; but it challenges survival of the organism when there is a high number of such cells. In this case, it is necessary to repair the DNA damage even if it may include error-prone repair and the induction of mutations. Mutations rise proportionally more rapidly than the dose and with the dose rate [240,289,290]. The efficacy of cellular defense mechanisms is very high in the dose range corresponding to natural irradiation (1 to 20 mSv/year), but it declines at higher doses. The question is above which dose it declines. Furthermore (see §2), the likelihood that an initiated cell escapes from cell and tissue control increases with the number of cells killed and

the tissular disorganization.

More data are given in Appendices 1 and 2.

4 Experimental animal data

Animal experimentation has made a major contribution to our understanding of the carcinogenic effects of ionizing radiation, and has confirmed the efficacy of DNA repair mechanisms from the simplest to the most complex organisms. In multicellular organisms, there are also additional mechanisms that can eliminate mutant and potentially carcinogenic cells or control their proliferation. Nevertheless, when the dose is high enough carcinogenic effects have been reported in all species [116]. However, the proportions of radiocancers vary, depending on the species, age, sex and tissues concerned and the dose-effect relationships are very variable. It has been possible to carry out numerous experiments regarding settings for which there was no epidemiological data available, and to assess the role of the following:

- the type of radiation: X, gamma, beta, alpha, neutrons, protons, fission fragments [198],
- the dose rate,dose fractionation and less uniform dose distributions as they may occur after internal contamination [281],
- concomitant exposures to other genotoxic agents [283] and the size of irradiated volume [263].

Few studies have evidenced an effect of low doses. Animal experiments benefit from specific, potentially favorable conditions such as the control of exposure conditions and thegenetic homogeneity of laboratory animals, the short life span of rodents, making it possible to replicate studies, routine histopathological examinations, the relatively large number of animals included in the studies (a few tens of thousands of rats and mice and a few thousand Beagle dogs). Despite these favorable conditions, it has neither been possible to establish a statistically significant carcinogenic risk for doses less than 100 mSv, nor to exclude its existence, which is obviously much more difficult. With only few exceptions, no excess tumors is observed below 500 mGy for low LET radiations [283].

Animal experiments, notably in the mouse, allow to study dose-effect relationships for cancer induction over a large range of external exposure levels [95,275,276,277,284]. A large number of data is compatible with a linear-quadratic model [116,282]. However, some data are not satisfactorily fitted with this model.

In properly conducted studies in the mouse, some data are better fitted by a quadratic relationship without a linear component [183,245] or by relationships with a threshold [64,74,163,300] than by a model with a linear, no-threshold component. In rats, a considerable reduction in the carcinogenic effects has been observed with low LET, low dose and low dose rate radiation. This attenuation is particularly obvious after contamination of the lungs by beta and gamma emitters [14] and after exposure to radon [21,184]. Attenuation is observed for all the tumors induced by external low LET irradiation [186]. This observation explains why the RBE (Relative Biological Effectiveness) of neutrons increases constantly as an inverse function of the square root of the neutron dose without ever levelling off [135,296]. This suggests that photons exhibit dose-effect relationships that either have a threshold, or are purely quadratic. Threshold relationships have also been established for pulmonary tumors induced by alpha radiation in rats [246,247], and for bone tumors in dogs [230]. However, in

the case of thyroid tumors after exposure to iodine^{131} the diminution due to dose rate remains open to question [197].

In general, heterogeneous irradiation, in particular following internal contamination by radionuclides, shows major reduction of the low dose rate effects, with a quasi-threshold, in most cases [196,217]. This lower efficacy compared to the same dose of uniform irradiation seems to be associated with the control exerted by neighboring cells [19]. This same phenomenon is also observed in human beings (see §5.5).

Among the experimental studies in which the incidence of cancer was sufficiently high in control animals, a reduction of this incidence was observed following low dose irradiation in 40% of them, an observation which is consistent with the concept of hormesis. This finding does not justify generalization of this concept [286], however, it does confirm its existence [79,174,244].

Appendix 3 provides more detailed information.

5 Epidemiological data

For doses above approx. 200 mSv, epidemiological data permit to establish with fair accuracy the relationship between dose and carcinogenic effect. However, for low doses (below 200 mSv) and *a fortiori* below 20 mSv generally encountered within the context of radioprotection, epidemiology can neither confirm nor refute the existence of an increased incidence of cancer. In order to estimate the effects of these low doses, three conditions need to be satisfied:

- hundreds of thousands of subjects must be included and monitored for a sufficiently long time; this is stressed in the article by Brenner [43] that is discussed below.
- the absence of any correlation between the dose received and all the other potential risk factors (such as tobacco) should be established. If such factors are present, they must be taken into account by appropriate statistical methods. This point is particularly important with regard to the study of low doses, because the specific effect of the confounding factors can be much greater than the effect of radiation. It is not enough to postulate that such a correlation has no logical reason to exist; it is necessary to establish that it did not appear by chance in the sample studied. For example, in a study investigating the risk of lung cancer due to radon in homes, not taking smoking into account would make the results impossible to interpret [66].
- accurate information must be available about all exposures to ionizing radiation, including those unrelated to the source of irradiation being investigated. This is difficult, given the frequent and possibly repeated exposures to small doses of radiation: natural irradiation (differences of natural irradiation can reach 20 mSv/year), X-ray examinations, air travel. Often these exposures are not controlled or integrated into the calculation of the dose studies. They may introduce biases even when they are smaller than the irradiation investigated.

5.1 Many epidemiological studies on cohorts that are often very large have been performed in order to quantify the carcinogenic risk associated with exposure to ionizing radiation. These studies, listed in Appendix 4, cover a wide range of conditions: age and gender of subjects, pathological conditions (patients treated by radiotherapy or apparently normal individuals), type and duration of exposure, dose and dose rate.

These studies encounter so many methodological and logistic difficulties that it is justified to

perform a rigorous analysis of the conditions under which each of them has been conducted. The main problems are as follows:

- Solid tumors and leukemia have a spontaneous incidence which is high and which varies according to lifestyle. Moreover, the possible increase in this incidence following irradiation is relatively low, so the studies must have sufficient statistical power, which requires large cohorts.
- The difficulty of obtaining accurate dosimetry is encountered in many studies. Collective dosimetric determinations are imprecise and individual determinations are sometimes difficult to obtain. Usually, it is only in medical studies (diagnostic or therapeutic irradiation) that doses can be estimated with accuracy on the basis of medical records. Dosimetry is also reliable in workers wearing dosimeters.
- The variability of the conditions of exposure of the population studied and in dosimetric accuracy make meta-analyses difficult to perform although not impossible. However, hopefully, they can be more powerful from a statistical point of view than single studies.
- For doses lower than 100 mSv, almost all studies do not evidence a significant effect. Nevertheless, they could provide an upper boundary to the possible carcinogenic effect, though they cannot rule out the existence of a small risk. Since the time of Aristoteles, we learned that it is impossible to prove the absence of a risk.

5.2 In the field of low doses, the available data can be classified into three groups: A-bomb survivors who received a low level of irradiation during the explosions (high dose rate); data obtained in residential or working environments (low dose rate irradiations); data obtained after diagnostic or therapeutic procedures (high dose rates and fractionated irradiation).

5.2.1 In the analysis of the incidence of cancers in the survivors of the Hiroshima and Nagasaki bombs (HN), leukemias and solid cancers have been distinguished. With regard to radiation-induced leukemias, the dose-effect relationship is statistically incompatible with an LNT relationship and shows a threshold at approx. 150 mSv and a decrease in spontaneous risk (hormesis?) at doses lower than 100 mSv [155,156]. There has been considerable controversy about the dose-effect relationship for solid tumors; the latest analysis reveals that the dose effect relationship is not linear but curvilinear, possibly linear quadratic with a fairly similar value for the parameters [224]. This new data benefited from a longer follow-up and from the revision of the dosimetry in 2002 [132]. At low doses, the excess risk of death due to solid cancers per Sv (ERR/Sv) is now estimated to be 0.19 (95%CI: 0.03-0.37) [224], i.e. less than half of the previous estimation [223]. Preston *et al.* limit the scope of this relationship for evaluating the risks, by invoking anomalies in the distribution of the excess relative risk for the lowest doses; it is difficult to accept this reasoning, particularly, because the RBE of the neutrons can, at very low doses, have values very much greater than 10, about 30 or more [291]. Such high RBE value would lead to a revision of some of the high excess relative risk (ERR) in the range of very low doses which presently cause these doubts. The linearity of the first part of the curve (linear component of the linear quadratic relationship) should be reconsidered, and the contribution of low LET irradiation to solid tumor excess in the range of low doses should be reassessed.

Incidence data have not yet been revised; the ERR seems to be similar in the ranges 5-50, 50-150, 50-500 mSv and 50-4000 mSv, and the dose-effect relationship is compatible with an LNT model but also with a model with a threshold that could be up to 60 mSv or with a quadratic relationship [213]. The correction of the RBE for neutrons should reinforce the hypothesis of a threshold for the photon contribution. A possible influence on the risk of

cancer of injuries sustained during the bombings has also been reported [260].

5.2.2 Several other studies have shown that low doses, delivered at low or high rates, either have no statistically significant effect on the increase in mortality or the incidence of cancers, or have significantly lower effects than those predicted on the basis of the risk coefficients calculated on the basis of the HN data.

For example, the data obtained for the 21,500 workers at the Mayak complex show an excess relative risk of death of 0.15 for solid cancers (90%IC: 0.09-0.20), lower than that observed in the HN cohort; however, the dosimetry (external and internal) for plutonium remains quite imprecise [250].

Similarly, a recent study on 8600 people involved in cleaning up after the Chernobyl accident, who had received a mean dose of 50 mSv, shows an incidence of all cancers which is 12% lower than that of the general Russian population. There is no dose-effect relationships [121]. Similarly, the analysis of the incidence of leukemias in these workers did not reveal any significant dose effect relationship [146].

The IARC's meta-analysis relating to 96,000 workers in the nuclear industry [51] had shown a risk of death by leukemia with doses higher than 400 mSv (the risk is, however, half of that of the HN estimations) and no significant increase in deaths from solid tumors. An extension of this meta-analysis to 600,000 workers is under way. It includes 9 other studies conducted on workers in the nuclear industry (Japan involving 171,000 workers, USA 125,000, United Kingdom 106,000 and 13,000, France 58,000 and 22,400, Finland 16,000, Russia 11,000, Slovakia 2,700).

Amongst radiologists and radiology technicians who started work in the 1960s (or 1970s in China) and who received annual doses in the region of 10 to 50 mSv, and therefore cumulative doses of several hundred mSv, studies of large cohorts have shown that the cancer risk is not significantly increased (USA 87,000 [180,181,254] and 117,000 [76], China 17,000 [292], England 1,400 [23]. In all these studies, no excess risk was observed for particularly sensitive organs such as the breast, thyroid and hematopoietic tissue.

Airline flight crews receiving exposures of 1.5 to 6 mSv per year have been studied. No increase in the total number of cancers or of cancers in the most radiosensitive organs has been detected in 44,000 members of flight crews [31,306] or in 2,740 Canadian pilots [18]. An excess of melanomas was observed in these populations, and this can be explained by their more frequent exposure to the sun.

5.2.3 As the epidemiological studies including hundreds of thousands of people who have been occupationally exposed to tens of mSv are not powerful enough to detect or exclude a statistically significant risk for doses below 100 mSv, it appears that only comparisons of populations exposed to different natural levels of irradiation could provide quantitative information about the effect of low doses (< 20 mSv/year) administered at very low dose rates, but they have to be carried out on sufficiently large populations. Currently, the studies carried out in regions where the natural natural irradiation is markedly higher than in France do not evidence any correlation between the level of natural irradiation and cancer mortality, although chromosomal aberrations in the circulating lymphocytes confirm the high level of irradiation [268]: the Indian State of Kerala (up to 70 mSv per year [194]); the Chinese region of Yangijang, (comparative monitoring for ten years of 100,000 inhabitants of zones at 6, 4 mSv and 2 mSv per year [262,264,293,294]); Japan (irradiation due to radon [169,202,256]). In all cases, the dose rates are very low. Studies are in progress to confirm these initial findings, their updating should bring interesting information.

Within the framework of medical diagnostic irradiation (high dose rate), none of the studies

including a reconstitution of the exposure based on medical records or on another reliable dosimetry has shown an increase in the risk of leukemia after radiological examinations, even if repeated, for doses lower than 100 mSv [32,35,67,258]. The only study showing an excess risk was based on non-verifiable case studies and witness interviews, bias could therefore been introduced [228]. With regard to thyroid cancer,there is no data showing that they can be caused by frequent radiological examinations in children or adults [90.120]. Three cohort studies have shown an increase in the risk of breast cancer after repeated radiodiagnostic examinations, with a linear dose-effect relationship from 100 mSv upward; relative risk decreases markedly with age at the time of exposure [32,77,109,114,170,222]. None of these studies has shown any increase in risk below 100 mSv. A meta-analysis of doses of less than 100 mSv, in particular between 50 and 100 mSv would be very useful, Appendix 4 shows that this could be done. In this context, it is important to point out that, although fractionated doses of the order of 10 mGy lead to an increase in the risk of breast cancer, for a cumulative dose of the order of one Gy [113] (the breast is the only organ for which this has been demonstrated), it does not seem justified to conclude that a single dose of 10 mGy is carcinogenic as the recent draft report by the ICRP does [118]. In fact, the study of women followed up for pneumothorax is informative only for doses above 500 mGy: below this dose, the excess risk is virtually nil, 9%, and not significant. It would also be interesting to check whether these women, who were suffering from tuberculosis, had the same other breast cancer risk factors as the general Canadian population, in particular, with regard to age at the first pregnancy and the number of children.

In radiotherapy, the doses are much higher and are administered at a high dose rate. Tissues not located in the target volume receive doses ranging from several mGy to several Gy. This risk has been assessed in several studies including several thousand to one hundred thousand patients, and it varies considerably with the dose and age of the irradiated subjects. For example, an increased risk of cancer has been found in 160,000 women cured of cervical cancer and treated by radiotherapy, but without any carcinogenic effect on organs that had received less than 50 mGy [34]. In children for a same given dose, the excess of cancers induced is greater, and the types of cancers induced are different.

A signficant excess in the relative risk of breast cancer (2.25 with IC: 0.59-5.62) was found in women treated during childhood with radiotherapy for hemangioma, with mean doses of 1.5 Gy on the breast [161].

A purely quadratic dose-effect relationship, without a linear component, has been observed in a cohort of 7700 women treated by radiotherapy at the Institut Gustave Roussy for breast cancer [243]. The risk in this case is much lower that that observed in the HN cohort and is negligible for doses lower than several Gy. The relative risk is 0.003 for a dose of 1 Gy. Is this because the irradiation is delivered during 5 sessions per week and the dose per session can vary from 2 Gy per session in tissues located in the target volume to very much lower doses per session in tissues located outside the target volume? This hypothesis has led to analyze the influence of the dose per session; the data show that no carcinogenic effect is observed for doses per session of less than 160 mGy (even though the total dose can reach 5 Gy), whereas a significant carcinogenic effect is observed for high doses per session. This effect of fractionation has been confirmed by the study of the number of sessions. The data suggest that doses administered by fractions of 150 mGy or less, delivered at intervals of 24 hours, do not cumulate their carcinogenic effect, which could be due to the elimination of damaged cells or the repair of lesions (see §3)). These results would be worth confirming.

It has been possible to make comparisons between patients treated by external radiotherapy at high dose rate (1 Gy/minute) or by implantation of radioactive sources (1 Gy/hour). The reduction in carcinogenic effect in the latter case is in accordance with what is observed in

animals.

Metabolic radiotherapy with iodine^{131} results in much lower dose rates than with external radiotherapy. The administration of iodine-131 does not increase the risk of thyroid cancer in adults (10,000 patients treated for hyperthyroidism [110] and 36,800 subjects who have had scintigraphies [72]. No effects were observed in children, the numbers of children studied were limited (1900 under 20 and 800 under 18 years of age [99]), and their average age was higher than that of the children of the former USSR who developed thyroid cancer following Chernobyl. Amongst the 2000 thyroid cancers observed after Chernobyl, 80% of patients were under 5 years old at the time of the accident. These children, who were generally deficient in iodine, were exposed to iodine-131 but also to iodines with shorter half-lives (in particular ^{132}I), responsible for high dose rates. Note that amongst the 2 million children whose thyroids were irradiated as a result of Chernobyl, some received doses higher than 1 Gy. No excess thyroid cancer has been observed outside the former USSR, even in Poland. A study is being carried out by the IARC, on the evaluation of doses received by children suffering from thyroid cancer in Russia and Belarus.

5.3 Medical irradiation *in utero* has been the subject of a large-scale cohort study known as the "Oxford Study" [75]. This study concluded that cancer risk was increased at doses of about 10 mSv. Although conducted rigorously, this study is not without weaknesses, and is not consistent with some other data.

5.3.1 In the 807 children exposed *in utero* in Hiroshima and Nagasaki and monitored until 1992, the upper boundary of the excess relative risk was 0.6% for 1 mGy [68], a value only one tenth of that obtained [30] in the Oxford study (5.1%, with a confidence interval of 2.8 to 7.6). Furthermore, the Oxford studies on the one hand, and the studies by Monson and McMahon [185] on the other, did not find any increased risk for children who died before the age of 10 years, whereas the Hiroshima Nagasaki study covers a longer follow-up. No increase in the incidence of the various types of leukemia following irradiation in utero was detected in a Swedish study (198 bis)The very limited number of cases in these studies makes it difficult to put a value on the risk, and some authors [33,208,269] feel that the positive findings of the Oxford study might be linked with a memory bias, or to underlying maternal disorders which required X-rays during pregnancy, rather than the irradiation itself.

5.3.2 The excess risk found in the Oxford study is similar for almost all cancer sites (leukemias, lymphomas, neuroblastomas…), whereas in all the other populations studied, the dose-effect relationships are very different depending on the tissues and organs: in the survivors of the HN cohort, who were exposed when very young, one observes, for example, an excess relative risk of about 17 per Gy for leukemias, but of only 2 per Gy for other cancers.

5.3.3 For doses of over 100 mSv, animal experiments have shown that there is indeed a carcinogenic risk in dogs, rats and mice, after irradiation *in utero* during the late stages of development [116]; however, they do not demonstrate that the embryonic tissues have a greater susceptibility to carcinogenesis or radiosensitivity than tissues of young animals, except in a few tissues, such as the nerve tissue in the rat [187] and the ovary in the mouse [280].

5.3.4 Twin pregnancies are monitored more closely than other pregnancies. For this reason, in the past, they were submitted to approx. twice as many diagnostic radiological examinations [282]. Comparisons between the incidence of cancers in populations of twins with the incidence observed in the general population has therefore provided an opportunity to evaluate the effects of irradiation on the subsequent cancer risk. Studies of twins avoid the potential bias of other studies, because the reason for having more X-ray examinations is not

associated with problems occurring during the pregnancies (which could be linked to a pathology that itself, and irrespective of any irradiation, involves a subsequent risk of cancer for the unborn infant).
Apart from a single case-control study (with regard to which a case history bias cannot be ruled out, as cases tend to remember the details of exposure better than controls) [102], these studies do not show excess cancers in twins [239], with some showing a considerable reduction in the incidence of cancers [119.182].

It therefore appears that the data on the carcinogenic effect of *in utero* irradiation has not sufficient robustness to be the basis for evaluating the risk of low doses in children and adults.

5.4 Overall, with the possible exception of the results of *in-utero* irradiation, no correctly conducted epidemiological cohort or case-control study has been able to detect any carcinogenic effect for doses of ionizing radiation of less than approx. 100 mSv in adults. Some of these surveys have studied populations of large size, their total being much larger than the population of survivors of Hiroshima and Nagasaki. Although some sources of information suffer from shortcomings, such as the absence of individual dosimetric estimations for radiologists (which decreases the power of the studies), others do not. In several of these studies, the dosimetry is of high quality and is based on fewer non-verifiable hypotheses than that for the Hiroshima and Nagasaki survivors.

The epidemiological data do not therefore provide any convincing argument in favor of a LNT relationship at doses lower than 200 mSv, but they do not rule out the possibility that there could be a carcinogenic effect within this dose range. The search for the relationship most closely matching the available data should be continued. However, it should be emphasized that the dose-effect relationship probably varies markedly with the tissue, the age at irradiation and above all, with the dose rate. There is no scientific justification for assuming that only one type of relationship exists.

Given the specificity of the body's defense mechanisms at low doses, the epidemiological studies can only provide information about the carcinogenic effect by specifically studying populations that have received doses likely to cause similar biological effects (for example, between 30 and 80 mSv as a single dose), rather than including much higher or lower doses. This procedure should avoid incorrect conclusions. However, given the smallness of the effects (if they exist) the confidence intervals are likely to be large, which make it hard to reach any conclusions. This explains the interest of studying natural irradiation, which can involve very large numbers of subjects.

5.5 Carcinogenesis by long half-life α-emitting radionuclides

When an α-particle crosses a nucleus, the dose received by the cell is approx. 370 mGy and from 1 to 20 events can occur in the DNA molecules, causing important damage. Most cells are killed, but not all because cancers do occur. However, relatively few cells are affected, and they are surrounded by normal cells;

Painters of luminous dials contaminated with radium-226 and 228 have been subjected to several investigations covering over fifty years of monitoring [52,91,242,257,266]. Other investigations have studied patients who had received thorotrast, a thorium-based contrast product used in the past in vascular radiology [8,203,270,271,287]. They have also been monitored for more than 50 years.

Painters of luminous dials have presented a high frequency of osteosarcomas, but no excess cancers have been observed for absorbed doses of less than 10 Gy [52], contrasting with a

marked increase for doses of more than 20 Gy. Patients who have received thorotrast have presented hepatomas. In this case also, a threshold is observed: at about 2 Gy for hepatomas. Several non mutually-exclusive hypotheses have been put forward to explain the lack of effect with lower doses, which contrasts with the very high incidence with larger doses [273]:

1. It might be necessary for several alpha-particles to cross the cell to trigger carcinogenesis.
2. The process triggered in a cell can lead to cancer only if the adjacent cells are non-functional (which, in the case of α-particles would necessitate high doses) and so no longer exercise normal tissue control on the proliferation of the initiated cell.
3. If there are few cells damaged, these are eliminated by apoptosis, this elimination would not take place when there are large numbers of damaged cells.
4. Cells that cause cancers may not be induced directly but by a bystander effect. This mechanism is effective only at high doses.

On the basis of present knowledge, it is difficult to choose between these hypotheses but these data show that, with this type of irradiation, the bystander effect and radiation-induced genomic instability do not cause cancer when the number of damaged cells is small. Moreover, none of these hypotheses is compatible with the postulates on which the LNT relationship is based.

6 Validity of the linear no-threshold (LNT) relationship

The LNT model used in 1956 by Russell to evaluate the radio-induced mutations in the germ cell line in the mouse, was introduced between 1960 and 1980 for the purposes of regulation in radioprotection with regard to all mutagenic and carcinogenic effects in Man. At that time, this was a convenient pragmatic relationship but not a model based on data [133].

A predictive value was subsequently attributed to this linearity at a time when people were unaware of the complexity of carcinogenesis, and the diversity and effectiveness of the responses of a cell to irradiation.

The rapidly growing knowledge in the last decade should lead us to reconsider the validity of the hypotheses on which the use of LNT has been based for assessing the carcinogenic effect of low doses (< 100 mSv) and *a fortiori* of very low doses (< 10 mSv) on the basis of that observed in the range of doses of 0.2 to 3 Sv.

6.1 The LNT model postulates that the cell reacts in the same way regardless of dose rate and dose, which implies that the probabilities of death and mutation (per unit dose) and the contribution to carcinogenesis of each physical event remains constant irrespective of the number of lesions in the cell and in the neighboring cells. This constancy implicitly admits several hypotheses:

1. In the range of the doses and dose rates under consideration, there is no physical, chemical or biological interaction between the effects caused by the various tracks of ionizing particles in a cell.
2. Any absorbed dose of energy in a cell nucleus leads to a proportional probability of mutation. The probabilities of successful repair or misrepair (per unit dose) are always the same. Similarly, the probability of apoptosis does not vary with dose.

3. Any DNA lesion has the same probability of giving rise to a cancer, irrespective of the number of other lesions in the same cell and the neighboring cells.

6.2 These hypotheses are not consistent with current *radiobiological knowledge* that could be tentatively summarized as follows (see §3):

6.2.1 The oxidative stress induced by the irradiation induces defense mechanisms against the reactive oxygen species; the effectiveness of these defenses varies with dose.

6.2.2 The dose rate influences the effectiveness of DNA repair and of mutagenesis (see §3). The signaling systems are not activated for dose rates of less than about 5 mGy/min, apoptosis is triggered by doses of over 5 mGy and the repair system (and therefore the possibility of misrepair) is triggered from about 10 mSv.

These figures are only indicative and far from being definit. Moreover, within this range of very low doses, they can vary considerably from one cell to another, depending on the damage produced in DNA [86]. They also vary depending on the cell line and tissues. Despite these fluctuations, the data show that the safeguard mechanisms and their effects (elimination by death of damaged cells, and the probability of error free and error-prone repair) vary with dose and dose rate (see §3.4.6).

6.2.3 The radiation-induced cell mortality (per unit dose) varies during the cell cycle, although the probability of DNA damage is the same; the change in the mortality is therefore mainly attributable to differences in the probability of error-free repair depending on the cell cycle phase.

6.2.4 The probability of DNA misrepair increases with the dose rate and dose. Similarly, the lethal or mutagenic effects (per unit dose) vary considerably with dose and dose rate. In particular, from about 0.5 Gy, the initial hyperadiosensitivity (see §3.4.2.) decreases and then disappears, as a result of the activation of repair systems.

6.2.5 Most of the cells with unrepaired DNA lesions are eliminated either by death, when these lesions are not repaired, or by triggering *apoptosis. In vitro*, the damaged cells disappear at very low dosesbut this is not the case at doses above about 10 mSv (see §3.3.4 & 3.4.6). The efficacy of the elimination of potentially mutant cells varies with the dose, the cell line, and the tissue [206, see §3.4.5.]. In the work of Hendry [104,105], concerning the apoptosis of intestinal crypt cells after gamma irradiation, apoptosis reaches a plateau at doses of 200 to 400 mGy. The experiments of Rothkamm [241] have shown that after a low dose, 24 h after the irradiation no cell with a DSB can be detected; this disappearance can be due either to cell death caused by the absence of repair, or to a combination of error-free repair and apoptosis. The lower the dose or the dose rate [60], the more effectively lesions are eliminated (see §3.4.5).

At doses above a few tens of mSv, the larger dose rate or dose by fraction diminish the efficacy of the safeguard mechanisms probably linked to the increased number of intracellular lesions (see §3.3.3., 3.3.1, 3.3.5, 3.3.6, and 3.4)

6.2.6 The adaptive response (see §3.4.4.) results in a temporary induction of the defense mechanisms, which proves that their mobilization reduces the mutational effect.

6.2.7 No excess of chromosome aberrations has been reported for doses of less than 20 mSv for low LET radiations, despite the attempts made to evidence them [283]. Thus, there may be a threshold for this effect. The generally accepted form of the dose-effect relationships for chromosome aberrations is linear-quadratic. This makes it possible to reliably determine the dose for chronic irradiation, and for the dose reconstitutions after accidents. However, although the linear-quadratic relationship forecasts a small level of aberrations, at low dose

and dose rates no effect is detectable below 20 mSv, either because the initial slope of the linear component is less steep than that calculated from doses over 100 mSv, or because there is a practical threshold (see §3.2), and perhaps even a hormetic effect. This is an important problem because chromosome translocations and deletions play a fundamental role in carcinogenesis.

The lack of validity of the LNT relationship for chromosome aberrations at low doses with low LET radiation is not surprising [62] since the occurrence of a chromosome aberration is observed when there are two or more DNA double-strand breaks in the same chromosome or neighboring chromosomes, and that the rejoining of the fragments either does not restore the molecule to its initial condition (inversion or translocation within the same chromosome), or even rejoins fragments that do not belong to the same chromosome. The probability of such error-prone endjoining therefore depends on the number of breaks simultaneously present in a limited volume, and therefore decreases markedly with dose rate and is not proportional to dose but to the square of the dose. LNT cannot be used to predict chromosome aberrations for very low doses (see §6.5.3).

6.2.8 The dose-effect relationship for cell lethality is not linear but linear-quadratic. The phenomenon of initial hyperadiosensitivity shows that it is necessary to introduce a correction into the linear-quadratic relationship for doses of less than 200 mGy.

All data clearly show that the efficacy of defense mechanisms against the lethal effect and the mutagenic effect of ionizing radiations, varies with the cell line. This efficacy appears to be in all cell lines very high at low doses and dose rates such as those delivered by the natural irradiationbut it declines at higher doses. These variations in the efficacy with dose is not surprising since these mechanisms have emerged during evolution to protect procaryote cells against the lethal effect of the natural ionizing (or U.V) radiation. After the appearance 600 million years ago of multicellular organisms the aim of defense mechanisms was also to protect multicellular organisms against the appearance of mutant cells.

6.3 The process of carcinogenesis (see §2)

As discussed earlier, mechanisms exist to protect multicellular organisms against the cells that have escaped the systems that controls cell proliferation within the tissues. The effectiveness of these mechanisms can be overcome or impaired by high doses (mutation of the genes responsible such as p53).

6.3.1 In animals, depending on the species (and strain in mice), the tissue and type of cancer, the dose-effect relationship for carcinogenesis is extremely variable and is seldom linear. In animal, not only does a threshold seem to exist, but also in 40% of experiments, there is even a hormesis [79]. Dose rate has a major influence.

Furthermore, heterogeneous irradiation is less effective than homogenous irradiation, and the size of the irradiated volume is important, which would not be the case if only damage to the DNA in the initiated cell were involved.

6.3.2 *In vitro*, in studies of the neoplastic transformation of hybrid cells (hela-fibrostart) the incidence of transformation is not increased at doses between 0.5 mGy and 220 mGy, and there is even a reduction in the incidence of spontaneous transformations at doses between 0.5 mGy and 11 mGy [141]. According to UNSCEAR [283], no cellular neoplastic transformation is observed at doses of less than 100 mSv. Other data show that low-dose irradiation can reduce the number of transformations [233,234,235,236].

6.3.3 Carcinogenesis does not seem to be attributable to a simple, random accumulation of independent DNA lesions. Some cancers are caused by a specific translocation, whose frequency is too high to be explained by stochastic phenomena [272] and which cannot be

attributed to lesions induced directly by the radiation [273]. The epigenetic mechanisms (which seem likely to have a threshold) play a notable role.

6.3.4 In Man, carcinogenesis is a complex process that varies depending on the tissues and types of cancer involved, and in which genetic and epigenetic mechanisms are associated (see §2). The extreme susceptibility to radiocarcinogenesis in some human diseases with DNA repair disorders shows the essential role played by repair systems in this process. The efficacy of these systems is modulated by various factors, in particular, by the dose and dose rate (see §3).

6.3.5 During carcinogenesis, the micro-environment and the interactions between the initiated cells and the normal cells, as well as the mechanisms regulating proliferation linked to the tissue organization play a capital role (see §2.2.2 and 4). The proliferation of the initiated cell is controlled by the neighboring cells within the tissue (see §2.2.2). Tissue disorganization often heralds the emergence of a cancer [57]. Possibilities of escape certainly do exist but these are increased after a dose that has killed a high proportion of cells (> 0.5 Gy), and has therefore disorganized the tissues. The acceleration of the proliferation induced by a high dose (> 0.5 Gy) could interfer with the repair of lesions, and allow cells to escape from control mechanisms.

6.3.6 At the level of the whole organism, *immunosurveillance* has an important role (see §2.2.3). The impairment of immunosurveillance mechanisms after irradiation of a large segment of the organism could account for the increase in the carcinogenic effect in this case [263]. The high incidence of cancers in immunodepressed patients (AIDS, patients treated with immunodepressive drugs after an organ transplant) confirms their efficacy.

It is difficult to imagine that phenomena that are as complex and as variable from tissue to tissue, and which depend on the nature of the initiated cell (stem cell or progenitor cell [48]) and the volume irradiated [263], depend solely on the lesions produced in the initiated cell. The hypothesis that the incidence of radiocancers can be predicted by simple proportionality with the dose received by the cells also conflicts with the absence of radiocarcinogenicity of α-emitting radionuclides at low doses (see §5.5). The concept that radiocarcinogenesis is a stochastic phenomenon must be revisited [272].

6.3.7 That a cancer could be induced by very low doses is a possibility which cannot be excluded, but all the available biological data indicate that at very low doses the combination of the failure to repair the DNA damage [60,241] leading to cell death (apoptosis) and error-free DNA repair should make this risk minimal or non-existent [143]. These phenomena, and the effort to counteract reactive oxygen species may account for a *hormesis* effect [49,50,79,86,87,125,130]. Hormesis could also be explained in part by stimulation of immune mechanisms [157,286]. Some preliminary data suggest that a hormesis effect can be observed in humans [55,131,155,285].

6.3.8 The hypothesis has been made that the bystander effect (see §3.5.1) and the induction of genomic instability could cause a significant number of cancers at low doses, and that they could even lead to a supralinear dose-effect relationship at low doses. However, this hypothesis does not seem plausible (see § 3.5). In humans (see § 5.5) and in animals (see §4), the existence of a threshold after contamination by αalpha-emitting radionuclides makes it possible to exclude a significant contribution of a bystander effect when only a few cells are affected in an undamaged tissue. The animal data (see §4) demonstrate a hormesis effect, highlighting the implausibility of this hypothesis.

6.3.9 *Epidemiology* (see §5) cannot exclude one of the two following hypotheses: i) the absence of a detectable carcinogenic effect at doses of less than 100 mSv is due to the

insufficient statistical power of the surveys or ii) it is attributable to the lack of any carcinogenic effect due to the existence of a threshold. The data relating to contamination by α-emitting radionuclides (radium, thorium) in animals and humans does definitely demonstrate the existence of a threshold in some situations.

Scientific rigor demands that when looking for a universal model we should first analyze all the epidemiological data for doses between 50 and 100 mSv, and then look for a model compatible with all radiobiological and epidemiological available data. Assuming linearity is a precautionary not a scientific attitude. It is not consistent with the recent data regarding solid tumors in survivors of Hiroshima-Nagasaki [224, 291]. Using LNT to estimate the carcinogenic effect at doses of less than 20 mSv is not justified in the light of current radiobiologic knowledge.

6.4 *Article by Brenner et al. 2003*. In 2003, several well-knownradiobiologists and epidemiologists published an article that puts forward arguments in favor of a linear no-threshold relationship (LNT). Their conclusions differ from those in this report.

6.4.1 – Biological arguments This article considers that a carcinogenic effect occurs in humans after acute irradiation with a dose of 10 mSv. At this dose, approx. 10 electrons cross the nucleus, and the authors rightly state that there is no interaction between the physical events caused by each electron. They deduce from this that a single electron (1 mSv) causes a carcinogenic effect equal to a tenth of the effect caused by 10 electrons. This reasoning ignores the defense reactions triggered in the cell, it only considers physical events and overlooks defense reactions caused by initial cell damage. The physical events caused by each electron are identical, but the cell defenses induced by doses of a few mSv (when the nucleus is crossed by several electrons) activates detoxification by enzymatic systems of reactive oxygen species and signaling mechanisms (see §3).

6.4.2 The induction of carcinogenesis after irradiation of the fetus at a dose of about 10 mSv is still open to question (see §5.3). Furthermore, extrapolating from the fetus to the child or adult is debatable. For many tumor sites in the range of doses between 50 and 500 mSv the carcinogenic effect varies markedly with age. There are grounds for thinking that the differences might be even greater between a fetus and a child, even a young child.

6.4.3 Studies carried out on survivors of atom bombs

6.4.3.1. All authors agree that there is no significant increase in the incidence of cancers (for all ages and both sexes) below 100 mSv. However, as at lower doses, there is a non-significant increase, but with a similar excess relative risk (ERR), Brenner *et al.* [43] deduce from this that one can consider all subjects who have received between 5 and 125 mSv together as they constitute a homogenous group and that there is a significant increase for this whole population. This conclusion is questionable from a methodological point of view. The significant excess observed for this whole group could indeed be due to a simple increase in power due to the greater number of subjects in the 5-125 group than in the 5-100 group, as the authors postulate. However, it is also compatible with the existence of a threshold at a few tens of mSv or a non-linear relationship. Therefore, this excess cannot be used as an argument in favor of LNT.

6.4.3.2 In fact, studies have shown that the HN data are compatible with a threshold of about 60 mSv [155,156,213]. Brenner *et al.* [43] have over-interpreted the findings suggesting a linear relationship with a consistent slope between 0 and 125 mSv. They overlooked the unreliability of that apparent constancy of the slope and did not take into acount the large confidence intervals of each point. Indeed, the new data published by Preston [224] now correspond to a curvilinear relationship. The nonlinearity of the new data would be even

greater if a higher value of the RBE had been used for the neutrons at low doses [291], in accordance with the experimental data.

There is therefore no convincing evidence that casts doubt on the traditional conclusion (an increase above 100 mSv, no significant increase for doses due to low LET radiation below 100 mGy) (see § 5.2.1). This conclusion has the advantage of concurring with other epidemiological data and with the leukemia data from Hiroshima and Nagasaki.

6.4.4. The other studies used in this publication to support the carcinogenic effect of doses lower than 100 mSv seem to have been selected arbitrarily. The study of thyroid cancers after irradiation of the scalp for treatment of childhood ringworm suffers from a dosimetric methodological bias, and it is the only study to draw the conclusion of an increased risk at doses this low, whereas several similar studies on the same topic did not find the same result. Two other investigations quoted on leukemia in children in areas contaminated by the fall-out from Russian and American nuclear tests [65.259] are based on geographical correlations, which suffer from the limitations of this type of study. Their results are in disagreement with those of other studies of the same type conducted on the consequences of the Chernobyl accident [211] and with the results of all the cohort or case-control studies carried out on leukemias after irradiation in childhood, including studies on survivors of Hiroshima and Nagasaki.

6.4.5 Altogether, therefore, the article by Brenner *et al.* [43] does not prove the validity of a linear no-threshold relationship, or even the existence of a significant excess of cancers at doses of less than 100 mSv. This conclusion is not surprising, because the authors themselves state that a much larger number than in the HN cohorts would be necessary in order to show the possible effect of low doses. This discussion underlines the importance in this area of a multidisciplinary approach, combining epidemiology and biology.

6.5 A draft report of an *ICRP task group* was posted on the Web in December 2004 [118]. It discusses the problems raised by the choice of the relevant dose-effect relationships. This document, of high scientific quality, analyses recent radiobiology data. However, and sometimes surprisingly, the conclusions of the various sections and the general conclusion although recognizing that one cannot rule out the hypothesis of a threshold, which is described as being very plausible, do advocate the use of the LNT, at least on a provisional basis. The main arguments advanced in favor of this position are as follows:

6.5.1 At the *epidemiological* level, the authors feel that it is very likely that there is a carcinogenic effect in Man of a dose of 10 mSv, given the effect on the fetus *in utero* and the breast cancers observed after repeated fluoroscopies to monitor pneumothorax. They also consider that the findings of other surveys, despite being statistically without significance, do suggest that there is a carcinogenic effect between 10 and 100 mSv.

In reply, we can say that:

1. the data from the Oxford study of *in-utero* irradiation are too unreliable to provide scientific validation for LNT (see §5.3 and §6.4.2), and that furthermore, they concern the fetus. Extrapolation to a child or adult calls for caution. Finally, even if this effect were to be confirmed, it would not justify extrapolation to doses of less than 10 mSv since we know that a dose of about 10 mGy activates repair systems that could cause misrepair, whereas these systems are not activated by lower doses [60,241].
2. the carcinogenic effect of repeated X-ray examinations is only observed when the cumulative dose exceeds 0.5 Gy. Indeed, very few women in the cohort investigated in the publication cited by the ICRP task group [113] had received doses of less than 500 mSv. This publication does not provide any information about the effect of these

doses. This study therefore demonstrates that doses of the order of ten or a few tens of mSv can have an additive effect, if the cumulative dose reaches 500 mSv or more, but not that ten mSv are carcinogenic [113].

3. A study showing a non-significant increase cannot be used to deduce that a risk exists. At the very least, what needs to be done is to review all the studies carried out after such doses and to compare the frequencies of positive, negative and nul effects. Until this preliminary work has been done, no indication can be drawn from data that are not statistically significant.

6.5.2 At the *radiobiologcal level*, the authors indicate that a high proportion of the lesions induced by ionizing radiation are complex and difficult to repair, and so cannot be compared to lesions of endogenous origin. In addition, they also stress that apoptosis is an effective mechanism but there is nothing to indicate that its is totally effective, and so, it is conceivable that some damaged cells could survive, avoid the control and give rise to a clone of initiated cells.

These comments are pertinent, but in reply, we could point out:

1. that it is unlikely that the cells with complex lesions that are difficult to repair would avoid being eliminated by death (mitotic death or apoptosis),
2. in fact the problem with regard to LNT does not lie here, it is finding out whether the probability of misrepair is the same if the number of genomic lesions is low or high. The LNT model is based on the assumption that the probability of each DNA damage to transform a normal cell into a neoplastic cell and for this neoplastic cell to give rise to an invasive cancer is constant whether this damage is isolated or is associated with other damages in the same cell and in neighboring cells. Rather surprisingly, this crucial question has not been dealt with in that report. However, all the data available show that this probability in fact varies with dose (see §3). Similarly, the efficacy of apoptosis is not constant, but varies with dose. No apoptosis occurs if the genes implicated, such as p53, have been damaged.
3. the probability that an initiated cell will escape depends on tissue organization. If its tissue structure has not been perturbed, the initiated cell may remain quiescent in the tissue for many decades and possibly until death (see §5). The very rapid fall in the incidence of lung cancers in smokers after smoking cessation (even if they had previously smoked for twenty years of more) demonstrates the prominent role of promotion mechanisms, i.e. the influence of cell proliferation and tissue disorganization in the escape of the initiated cell. This observation also shows that initiated cells can remain quiescent until the death of the subject. Indeed, microcancers are found during autopsy in 10 to 30% of people over 60 years of age.

An escape from control regulations is always possiblebut it is unlikely if the tissue has retained its organization undamaged (see §5.5). Furthermore the absence of any carcinogenic effect at doses of several hundreds of mSv in some tissues, such as the small intestine, bone, skin, and even the breast and thyroid of adult subjects, highlights the importance of the tissue structure and the safeguard mechanisms since the genome is the same in all cells. For the thyroid and the breast, the difference between the radiocarcinogenicity seen in small children illustrates the role of tissue organization and intercellular relationships. The latter strongly influence carcinogenesis (see §2).

6.5.3 The authors affirm that the frequency of chromosome aberrations is a linear function of the dose.

Reply: UNSCEAR report 2000 [283],pointed out that despite the attempts to find them, no aberrations have been detected at doses of less than 20 mSv. Above this dose, the relationship is linear-quadratic for low LET radiations (see §3.2). At very low dose rates (about 1 mGy /min) the relationship is linear for doses of 20 to 100 mGy but the efficacy, estimated in terms of the number of aberrations per unit dose, is much lower (about 20 times lower) than that of doses delivered at a high dose rate [63].

6.5.4 The authors think that it will be possible to rule out the possibility of a carcinogenic effect due to the genetic instability and to the bystander effect induced by low doses only when the mechanisms of these effects have been elucidated.

Reply: It can be noted that much of the data suggests that there is a threshold or a dose-effect relationship for these two phenomen. Moreover, despite the efforts made, no evidence has been found of any carcinogenic effect at low doses (see §3.5.2). The absence of any carcinogenic effect after contamination with α-emitting radionuclides (see §5.5) makes it unlikely that these mechanisms contribute significantly to carcinogenesis in humans.

6.5.5 The authors feel that the animal data support a LNT model.

Our conclusions disagree on this point (see §4). We feel that the importance of hormesis should not be overlooked. Hormesis has been reported in 40% of the animal experiments [79], moreover, the biological bases of hormesis now seems to be understood [87], and its existence is beyond question [50]. In addition, Tanooka's meta-analysis [262] shows that there is a practical threshold for virtually all experimental tumors. The viewpoint that simply introducing a DDREF factor will allow these facts to be taken into account does not appear justified. The influence of the dose rate and of fractionation on carcinogenesis in animals shows that the phenomena are too complex to be accounted for by a LNT model.

6.5.7 *Conclusion*: This very high quality report shows that we cannot rule out the possibility of a carcinogenic effect at doses of the order of 10 mGy. However, when the arguments presented are analyzed, it appears that this effect, if it exists, must be very low for such doses. The authors have not analysed differences in the efficacy of safeguard mechanisms related to dose and dose rate. Their report assumes that the efficacy of the defense reactions is constant which is inconsistent with current data. It does not establish the validity of the LNT model between 10 and 100 mSv. The hypothesis of a carcinogenic effect for doses of less than 5 mGy is implausible, even if it cannot be completely ruled out. Further research is needed. However, in the meantime, it would be detrimental to put too much weight on the very hypothetical risk when balancing cost and benefit of X-ray examinations [274]. Most X-ray examinations deliver doses of less than 5 mGy, the estimation of their risk must be based on plausible scientific data; overestimating this risk would have a harmful impact on the health of populations. The LNT model cannot be used to estimate the effect of very low doses, particularly, because it considers all solid tumors together. In this pooled study, the relationship may seem to be linear only because for each of the cancers concerned the dose-effect relationship is different.

At the beginning of the preliminary ICRP report [118], it is stated that the concept of a collective dose, which is a direct consequence of the LNT model, assumes that a very low dose administered to a large number of subjects has the same carcinogenic effect as a higher dose administered to a small number of subjects, and that the available data suppport this assumption. The present report comes to an opposite conclusion; it considers that for a given

collective dose, the risk is much greater when doses of more than 0.2 Gy are delivered than when the doses are below 20 mGy.

7 Implications of the dose-effect relationship

The hypothesis of a linear no-threshold relationship should be considered as a tool which is useful for regulatory purposes because it simplifies the administrative task. However, it is at the price of a probably marked over-estimation of the risk of doses lower than a few dozen mSv. It is not a model validated by scientific data [84,133,272,273].

A dose-effect relationship is used in different contexts:

7.1 For the protection of people occupationally exposed to ionizing radiation. If the irradiations received are considered to be additive and independent, and the dose rate is not taken into consideration, then the reference to a linear, no-threshold relationship is implicit.

The limit doses which are recommended seem to have considered industrial possibilities rather than aiming at a scientific assessment of the health risk. With present industrial techniques, they are easy to comply with, except in a few specific cases. On the other hand, in some medical professions (interventional radiology), the annual limits constitute a constraint, the appropriateness of which has not really been assessed, and the consequences of which with regard to some medical professions, and therefore for some patients, might be detrimental.

7.2 The ALARA principle is based implicitly on the concept of a LNT relationship because it postulates that the lowest dose may be harmful when it is given to a large number of individuals. For decades, doses received occupationally were relatively high, and it was justified to aim at reducing them. At present, one may wonder whether the ALARA principle is justified in all circumstances because the values reached are sometimes so low that to reduce them any further would have no meaning in terms of improving public health, since the number of cancers avoided by means of complex and expensive practices would probably be extremely small or zero. The money spent in this sector should be subjected to a rigorous cost-benefit analysis and compared to expenses in other areas of public health.

7.3 The choice of the dose-effect relationship influences the priorities of public health in terms of radiation protection. If the LNT model is selected, a desire for effectiveness would tend to lead to reducing the low doses received by the greater number. On the other hand, if low doses are thought to present very little or no danger, this costly reduction is unnecessary, and efforts should instead be made to reduce the higher doses. This example shows that any prevention strategy is implicitly based on quantitative assessment of the risks [295].

7.4 In medical practice, one could similarly be led to concentrate efforts on the most common examinations (chest X-rays) rather than focusing on those that deliver the highest doses to the most vulnerable subjects (CT scans in children). We fear that the former strategy would be counter-productive. In medicine, diagnostic or therapeutic procedures using ionizing radiation must, like any medical procedure, be subject to the principle of justification. The legislation explicitly requires the risk of irradiation involved in a procedure to be weighed against the expected benefit to the patient[4], thus it is necessary to compare two potential

[4] Article R.43.51 of the Code of Health amended by modified by Administrative Order 2003-270 of March 24 2003 concerning the protection of individuals exposed to ionizing radiation for medical and medico-legal purposes and which transposes European Directive 97/43 specifies:

health risks. A risk assessment based on linear no-threshold dose-effect relationships [24], would lead to an over-estimation of the risks of of X-ray examinations, and would therefore distort comparisons of the benefits and risks of these examinations [274].

- Thus the LNT relationship could lead to the refusal of useful examinations because of a hypothetical risk. Conversely, if we consider that the risk (per unit dose) increases with the dose, then efforts should be focussed on situations in which examinations (for example CT scans for children) or their frequent repetition results in doses of more than a few tens of mSv. This strategy seems to be more pertinent than attempting to reduce the doses for all examinations, which would be more costly and probably be less effective.
- In the case of therapeutic irradiation, on the other hand, the doses are much higher, and the risks clearly identified. It is therefore necessary, as with any therapeutic procedure, to evaluate for each patient the benefits of treatment versus its adverse effects, and to look for irradiation techniques, which make it possible to reduce the volume of normal tissue exposed to doses greater than approx. 150 mGy per session(§see 5.2.4).

7.5 Finally, this LNT relationship is often applied incorrectly to large numbers of people, multiplying the effects of trivial doses by large populations on the basis of a LNT model. One example of this erroneous use is to "calculate" the number of deaths induced if millions of people were exposed to a few micro-sieverts. These calculations based on collective doses do not have any meaning, as UNSCEAR and ICRP have pointed out. Nevertheless, some people are still applying them, which leads to inappropriate conclusions (for instance evacuation of a large population after the Chernobyl accident). Without any scientific justification, these calculations propagate the idea that even a very small dose of radiation is dangerous. The debate around radioactive waste and the calculations of risk based on the LNT model show that the form of this relationship and the calculations that are based on it do not contribute to an understanding of the biological and medical problem, and can, on the contrary, make them more obscure.

8 Proposals

8.1 Thanks to new techniques of molecular biology, considerable progress has been made in the past decade in understanding the mechanisms of action of radiation at the sub-cellular and cellular level and the defense reactions of the cell, tissues and the whole organism against the carcinogenic effects of ionizing radiation This ability of living organisms to defend themselves against aggression is not surprising, and was established in the 19th century (Claude Bernard). Without it, living species would not have survived. Advances in biology have enabled a better understanding of these mechanisms; nevertheless more detailed investigation is possible and should be performed.

The efficacy of defense mechanisms, the diversity of the strategies used by the cells, the tissues and the whole organism to reduce or eliminate carcinogenic risk are now better understood. They strongly suggest that a threshold or a practical threshold does exist and even, for some cancer sites, as in animals, so does a hormesis effect. It seems that during

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For the application of the principle mentioned in §1 of article L. 1333-1 (this concerns the principle of justification. Editor's note.), *any exposure of any individual to ionizing radiation for purposes of a diagnosis, therapy, occupational medicine or screening, must be subjected to a preliminary analysis to ensure that this exposure provides a sufficient direct medical advantage relative to the risk that it may involve and that no other technique is available, which is of comparable effectiveness and involves less risk or does not carry any such risk.*

three billion years of evolution in a sea of ionizing and ultraviolet radiation living beings have developed systems of defense and repair capable of preventing harmful effects due to doses of the same order of magnitude as those received due to natural radiation (1 to 20 mSv/year). These defenses seem to be overwhelmed at higher doses and the effect of intermediate dose zones should be determined, especially for doses between 20 and 100 mSv at high dose rates and moderate irradiations (< 500 mSv) at low dose rates. In these areas, efforts should be made in epidemiology (meta-analyses, analysis of the frequency of the different types of cancers and the age of the subjects affected) and in cell biology.

Determining these risks quatitatively is a main goal [204,295] but one that is difficult to achieve by epidemiology alone, even by comparing geographical regions that receive different doses of natural irradiation. This means that surveys must be associated with biological research.

Dose-effect relationships have to be used for estimating the risks, in particular, the carcinogenic effects. Experimental and clinical data show that the shape of the dose-effect relationship varies considerably, notably with regard to its initial part, depending on the type of cancer, the age of the subject and the characteristics of the irradiation. A relationship obtained for all the solid tumors of individuals of various ages may appear to be linear, even if for each of the cancers under consideration it has a very different shape. Such a relationship may be of pragmatic interest with regard to radiation protection within certain dose limits but has no scientific validity for predicting the effect of much smaller doses, given the complexity of radiobiology and carcinogenesis.

8.2 Many attempts are currently being made to improve the modeling of the stages of radiocarcinogenesis by introducing recent cell biology data [48,103,108,214]. Efforts should be made in this field in order to estimate the upper limit of the risks.

8-3 Research is mandatory in several other areas. Here is a non-exhaustive list.

1. *Epidemiological studies make it possible to investigate the effect of very low doses* (< 20 mSv) notably those comparing the frequencies of cancers and congenital malformations in regions where the natural irradiation is high (> 10 mSv/year). Few studies have been carried out in this field in Iran [93] and Brazil, even though in these countries there are regions with particularly high natural irradiation. However, it is also necessary to develop other epidemiological studies likely to provide information in the 50 to100 mSv dose range and to analyze the histological type of the excess cancers. In epidemiological studies, for instance, we need to find out which types of cancer are in excess and the age of the subjects affected in order to find out whether, between 50 and 150 mSv, these characteristics are different from those of the general population. There are major discrepancies between the data published; we need to find out how to interpret them and envisage meta-analyses.
2. *Experimental studies of the reductionof the cancer rate after irradiation or exposure to a genotoxic agent (hormesis)*. The interest of the dose-effect relationship and possible hormesis effect extends beyond ionizing radiation because of their possible implications for the evaluation of the toxicity of chemical genotoxic agents. It would be proper to coordinate the research carried out in these areas.
3. Research in radiobiology should help us to understand and *quantify the effect of low doses* (< 100 mSv), and of very low doses (< 10 mSv). The bystander effect, genetic instability and adaptive response deserve more research. In radiocarcinogenesis, the role of the tissue and stroma factors and the control exerted by normal cells need further investigation. Huge progress has been made in recent years in these areas, and

they have paved the way for further research.

Differences in the dose-effect relationships depending on age and tissue should be investigated. We are beginning to understand why tissues such as the small intestine and the skin are so resistant to radiocarcinogenesis but the influence of age on the predisposition to radiocarcinogenesis of the thyroid or mammary gland deserves further research.

We should explore the contribution of *genetic factors* to radiocancers [248].

4. On the practical level (radiodiagnosis), major efforts should be made to reduce the doses received during examinations delivering more than 5 mSv, especially, in the case of children.
5. Investigations of the biological mechanisms triggered by exposure to combinations of genotoxic agents (smoking and radon or UV-Xrays, for instance [252]), should be continued. So far, this research has tended to conclude that there is an additive effect rather than a synergistic one, except in the case of radon and smoking, where inframultiplicative synergism is observed [112].
6. In the field of public health, it should be useful to discuss when a carcinogenic effect becomes significant for a society and at which level it is pertinent to take it into account. It would be also of interest to define to which extent the representation of a risk may influence the means which are devoted to fight against it. It is impossible to banish all the risks from a society but it is difficult to establish a hierarchy amongst them and to determine the cost and the benefits of every procedure, notably radiological procedure.
7. It is also necessary to carry out research in the field of sociology in order to investigate the perception of the risk of radiocarcinogenesis, the concept of acceptable risk, and more generally the reactions of the society with regard to the medical and industrial use of ionizing radiation [261]. Radiophobia, which did not exist until 1950, i.e. several years after the first atomic explosions, actually became preeminent in the mid-1950s. It would be interesting to investigate its sources and consequences, and more generally to study when the fear of risk becomes an obstacle to scientific and technical progress in our society.

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Appendix 3

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3.3 Evidence for beneficial low level radiation effects and radiation hormesis

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Abstract

Low doses in the mGy range cause a dual effect on cellular DNA. One effect concerns a relatively low probability of DNA damage per energy deposition event and it increases proportional with dose, with possible bystander effects operating. This damage at background radiation exposure is orders of magnitudes lower than that from endogenous sources, such as ROS. The other effect at comparable doses brings an easily observable adaptive protection against DNA damage from any, mainly endogenous sources, depending on cell type, species, and metabolism. Protective responses express adaptive responses to metabolic perturbations and also mimic oxygen stress responses. Adaptive protection operates in terms of DNA damage prevention and repair, and of immune stimulation. It develops with a delay of hours, may last for days to months, and increasingly disappears at doses beyond about 100 to 200 mGy. Radiation-induced apoptosis and terminal cell differentiation occurs also at higher doses and adds to protection by reducing genomic instability and the number of mutated cells in tissues. At low doses, damage reduction by adaptive protection against damage from endogenous sources predictably outweighs radiogenic damage induction. The analysis of the consequences of the particular low-dose scenario shows that the linear-no-threshold (LNT) hypothesis for cancer risk is scientifically unfounded and appears to be invalid in favor of a threshold or hormesis. This is consistent with data both from animal studies and human epidemiological observations on low-dose induced cancer. The LNT hypothesis should be abandoned and be replaced by a hypothesis that is scientifically justified. The appropriate model should include terms for both linear and non-linear response probabilities. Maintaining the LNT-hypothesis as basis for radiation protection causes unreasonable fear and expenses.

Ionizing radiation and endogenous toxins at low doses

All agree that cellular responses to low values of absorbed doses of ionizing radiation are not readily predictable by extrapolation of responses observed at high doses. One reason for this unpredictability is in the physics of energy distribution in low-dose exposed tissues. In case of penetrating radiation, particle tracks arise stochastically throughout the exposed tissue with the relatively low density at low doses **[1]**. These tracks generate on the one hand unevenly distributed ionizations and excitations of constituent molecules along the track path, as well as bursts of reactive oxygen species (ROS) **[2]**. In case of exposure to internal emitters, the distribution of particle tracks is determined by the distribution of the emitter in tissue **[3]**.

The lower the radiation fluence or number of particle emitters in a given tissue mass, the less crowded are the particles in the exposed mass and with them the more heterogeneous is the distribution of ionized molecules and of ROS bursts.
The other reason is the presence of compounds that may aggravate or reduce radiation effects; there is especially the abundant and constant metabolic generation of ROS and of other endogenous toxins, on top of which low-dose radiation acts **[2, 4]**. The quotient between the rates of endogenous and radiogenic ROS production at background radiation exposure strongly favors the former. In fact, the average production rate of endogenous DNA double strand breaks (DSB) per cell per day in the body is about 10^3 times higher than that of radiogenic DSB from background irradiation assumed overwhelmingly to be low-LET type. However, at low-LET irradiation the probability of radiation induced DSB per primary DNA alteration of any type is about 10^5 times higher than that caused endogenously **[5]**. This data set attests not only that endogenous DNA damage far outweighs radiation induced DNA damage at background level exposure, but also that irradiation is far more effective in causing DSB than are endogenous ROS.

Ratio of DNA damage and cancer probabilities

Radiation induced DNA damage increases with absorbed dose **[6]**. Such cellular effects come through direct energy deposition events from traversing particle tracks by which DNA damage rises proportional with dose. Dependent of the amount of energy deposited per cell, bystander effects in non-irradiated neighboring cells may add to this damage in tissue at low doses **[7, 8]**. By measuring damage in multicellular systems, values of damage per exposed cell or defined micromass are calculated averages. This implies that any bystander phenomenon that may have occurred is coregistered and expressed in the oberved values from which these calculations were made **[9]**. A dose of 1 mGy of low-LET radiation, such as 100 kVp x-rays, causes on average the following effects per potentially oncogenic stem cell with an average mass of 1 nanogram: 1 particle track; about 150 ROS; 2 DNA alterations of any kind; 10^{-2} DSB; 10^{-4} chromosomal aberrations; and the probability of an oncogenic transformation of the hit cell with lethal outcome is about 10^{-13} to 10^{-14} **[10, 11, 12]**. In other words, the ratio of the probabilities for radation induced lethal cancer and the corresponding DSB is about 10^{-11} to 10^{-12} . This means that the statement of even one DSB to pose a risk of causing a lethal cancer to develop from the affected cell is unreal and, in fact, scientifically unfounded.

Adaptive Responses, Protection

A sudden suprabasal yet non-lethal rise of toxin concentration in a biological target tends to elicit stress responses and to stimulate adaptation usually in terms of protective mechanisms in the sense of hormesis **[13].** Increasing evidence in the literature over the past 25 years indicates that adaptive protection responses occur in mammalian cells *in vivo* and *in vitro* after single as well as protracted exposures to X- or γ-radiation at low doses. Not only the occurrence of adaptive protection but also the nature of some biochemical mechanisms involved have been reported **[4, 11, 12, 14, 15, 16, 17].** There appear to be two principal types of adaptive protection, one is to prevent and repair DNA damage and in doing so to keep cells alive and functioning properly. The other is to remove damaged cells from tissue by inducing apoptosis, terminal differentiation, and immune responses and thus to reduce genomic instability in the tissue system and eliminate mutated cells.

Contrary to the immediate begin of repair after DNA damage has occurred, adaptive protection develops as adaptive response relatively slowly within a few hours, may last for several weeks to months, and resemble physiological stress responses that protect against accumulation of DNA damage in tissue. This damage may be from any source such as from metabolically generated or environmental toxins or renewed irradiation **[18].** Such protective responses occur in various ways. They appear to depend on mammalian species, individual genomes, cell types, cell cycle, and cell metabolism. Adaptive protection categories after single low-dose, low-LET irradiation, are as follows:

Damage prevention

Stimulation of the radical detoxification system that appears to reach a maximum at about 4 hours after irradiation and lasts for several hours to even weeks, depending on tissue and cell type. In mouse bone marrow *in vivo*, there was a delayed and temporary reduction of the incorporation of DNA precursors and of thymidine kinase activity to some 70 % of control with a concomitant rise of free glutathione; the effect slowly declined over a period of about 6 hours. **[10, 19, 20, 21].** In other low-dose irradiated rodent tissues, increased levels of superoxide dismutase (SOD) occurred in parallel with decreased lipid peroxidation lasting for weeks **[22, 23]** and an elevated level of glutathione up by a factor of close to five in spleen cells was involved in an increase in natural killer cell activity **[24].** ROS detoxification was also linked to gene activation. Thus, mRNAs for glutathione synthesis-related proteins in the

mouse liver became elevated after low-dose gamma irradiation **[25]**. The increase in intracellular glutathione caused by low-dose in RAW 264.7 cells had its maximum between 3 and 6 hours after exposure; this effect was mediated by transcriptional regulation of the gamma-glutamylcysteine synthetase gene, predominantly through the AP-1 binding site in its promoter **[26]**.

Damage repair

Protection against high-dose induced chromosomal aberrations in human lymphocytes increased to a maximum about 4 hours after a conditioning low-dose low-LET irradiation; the protection also operated against other DNA damaging agents **[27, 28]**. This protection covered up to about 30 % of the damage seen in non-conditioned controls and varied between individuals and cells types; it was absent in some individuals and is probably determined genetically **[29, 30]**. Where it operates, it appears to last up to about 3 days, as reported for various human cells *in vivo* as well as in culture **[15]**. This adaptive response probably involves a several-fold enhancement of the DNA repair rate **[31, 32]** with the slow component of DSB repair being much faster at 0.5 Gy x-rays than that seen at 2 Gy **[33]**. Another adaptive response of this type appeared regarding micronuclei formation in human fibroblasts **[34]**. In these cells, conditioning doses from 1 to 500 mGy were equally effective; this also indicated that at the lowest dose, when approximately 40 % of the cells did not experience an energy deposition event, a bystander effect was involved in causing the adaptive protection **[35]**. A similar set of data in fibroblasts showed constancy of the adaptive protection over a dose from 1 to 100 mGy gamma-rays using the micronucleus assay **[36]**. The degree of inhibition of DNA synthesis and cell growth in rat glial cells in culture by a high dose of x-rays was reduced by about one fourth to one third at several hours following a conditioning low-dose exposure, when the cells were obtained from young rats. The adaptive response decreased with age of the donor rats. This adaptive response involved protein-kinase C (PCK), DNA-dependent protein-kinase (DNA-PK), and phosphatidylinositol 3-kinase (PI3K), as well as the activity of the ataxia-telangiectasia gene (ATM) **[37]**.

*Damage removal by apoptosis*Damaged cells may be induced into apoptosis by intra- and intercellular cellular signaling. Apoptosis also may occur within hours after high-dose irradiation. Low-dose induced apoptosis of pre-damaged cells with replacement by healthy cells may be a major route of *in vivo* removal of oncogenically transformed cells **[38, 39, 40, 41, 42, 43, 44]**. Low-dose induced apoptosis is assumed to operate also through intercellular

signaling from normal cells, which may also be activated by transformed cells in culture **[45, 46]**. Non-growing human fibroblasts in culture with DSBs from low-dose low-LET irradiation readily lost this damage to the level of DSBs in non-irradiated control cells after induction of proliferation; this damage removal was mainly due to apoptosis **[47]**. Low-dose induced enhancement of DNA repair may be responsible for the observation in rat thymocytes, where the incidence of radiation-induced apoptosis first declined at low doses and only rose with higher doses **[48]**. The induction of apoptosis apparently requires a certain level of DNA damage.

Stimulation of immune response

Removal of damaged cells occurred *in vivo* by way of a low-dose induced immune competence **[49, 50]**. This was, in another study, associated with a reduction in the incidence of cancer metastases to less than one third of control concomitantly with an increased number of circulating cytotoxic lymphocytes **[51]**. Such response had its maximum *in vivo* at about 0.2 Gy **[52]**. Low-dose induced immune competence may last for several weeks **[53]**.

Protection and cell cycle

Damaged cells also may exit the system by premature differentiation and maturation to senescence **[54]**. This was observed to occur also via bystander effect in microbeam experiments directed to single cells in complex tissue **[55]**. The various mechanisms of protection may be directly or indirectly linked to transient changes in the activity of the G_1 cell cycle checkpoint **[56]**. Another mechanism in this category of damage removal is known to occur in a number of tissue culture cell types by way of hypersensitivity to low-dose radiation that disappears at higher doses **[57, 58]**. This hypersensitivity in some cells was linked to the cell cycle **[59, 60]** and it disappeared in a number of culture cells within about 4 hours, but not immediately, after a single low-dose, low-LET irradiation **[61]**. Radiation-induced predisposition to genetic instability in culture cells also declined following low-dose irradiation **[62]**. These data indicate prevention of damage removal by way of low-dose induced DNA repair.

Reduction of carcinogenesis

The coordinated action of these protective responses, in one form or another may be responsible for the observation of a reduction of spontaneously occurring cancers. In fact, single low doses of low-LET radiation in tissue culture cells initiated with a delay of 1 day,

but not immediately, a significant reduction of spontaneous clonogenic transformation to about one third of control **[63, 64, 65]**. There is indication that this low-dose suppression of oncogenic transformation is not in response to cellular glutathione **[66]**. It can involve bystander phenomena likely through extra-cellular signaling exchange **[67]**. In mice heterozygous for the Trp-53 gene, a single low dose of low-LET radiation given at the age of about 2 months significantly delayed the appearance of "spontaneous" lymphoma and spinal osteosarcoma later in life **[68]**. A review on tumor development following low-dose, low-LET irradiation in rodents showed the existence of a threshold dose **[69]**. This is supported by a recently published study of induction of lymphomas, solid tumors, and ovarian tumors in BC3F1 female mice that at the age of 1 month or 3 months received single whole body doses up to 32 cGy of low-LET radiation; the threshold dose was 4 cGy **[70]**. Several human epidemiological studies also indicate either a threshold or a reduced cancer incidence below control following a single low-dose irradiation **[5, 15, 16, 40]**.

Low-dose induced changes in gene expression

The above listed categories of adaptive protection involve changes in gene expression **[4, 25, 26, 37, 71]**. An example for DNA repair gene activation refers to the telangiectasia gene **[37]**. Human fibroblasts in culture showed DNA repair in the course of adaptive protection against micronucleus formation following acute high-dose irradiation; the repair was more effective in the gene poor chromosome than in the gene rich chromosome of the cells **[72]**. Another data set showed that exposure of human skin fibroblasts in culture to a single dose of 20 mGy γ-radiation caused more than 100 genes to change their expression within 2 hours. This gene group included stress response genes and was different from the group of genes in parallel cultures that concomitantly responded to 500 mGy **[73]**. A similar pattern of expression amongst a total of 1574 genes developed in the γ-irradiated mouse brain more at 30 min. than at 4 hours, with 30 % of the genes exclusively affected by 0.1 Gy **[74]**.

A common pattern

Despite the disparity of the examined systems and responses, there appears to be a common pattern in the data. In fact, adaptive protection following low doses of low-LET radiation appears to be the consequence of changed cellular signaling and to be ubiquitous. Adaptive protection is a physiological expression of cellular capabilities to maintain integrity of tissue structure and function in the face of various exposures to potentially toxic agents including ROS, be they from endogenous sources or from ionizing radiation **[5, 75, 76]**. One

might speculate that DNA damage accumulation from any source eventually conditions a cell to become susceptible to apoptosis induced by low doses including that from background radiation exposure **[2]**. In this sense, background radiation exposure comes into focus as a possible trigger for maintaining tissue homeostasis.

Regarding their dependence on absorbed dose, the above listed categories of adaptive protection are schematically summarized in Figure 1. Except for apoptosis and terminal cell differentiation, all the above protective responses to single exposures tend to be expressed maximally after less than 0.1 and not after more than 0.5 Gy X- or γ- radiation **[10, 77, 78]** and to increasingly fail with higher doses depending on type of adaptive protection in a given cell system, as summarized previously **[5, 10, 11, 12]**; in most mammalian cells so far examined, the expression of adaptive protection had a maximum above 5 mGy and below about 200 mGy.

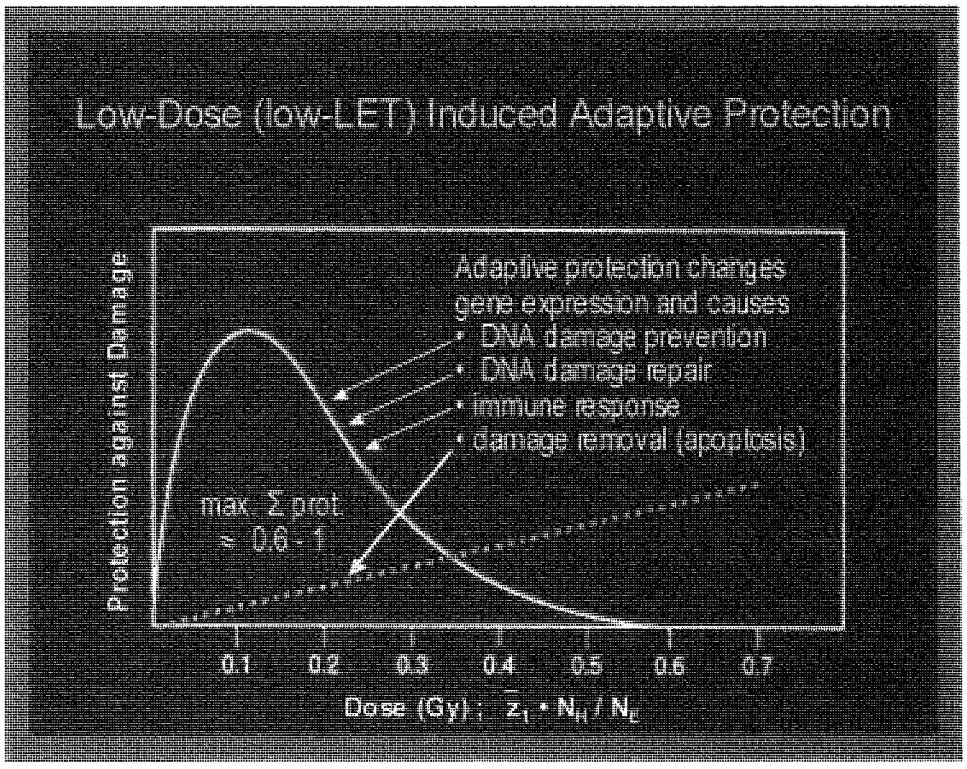

Fig. 1:
Single low-dose induced adaptive responses have a protecting function through various mechanisms. Note that mechanisms of DNA damage prevention and repair and the immune stimulation decrease after a maximum at doses between 0.1 – 0.2 Gy, in contrast to apoptosis incidence that increases with dose. Absorbed dose is in Gy and also in terms of microdosimetry, in that the mean energy deposition per particle traversal per defined micomass (specific energy $\bar{z}_1$) (ICRU 1983) is multiplied by the number of such events (N_H) in the number of exposed micomasses (N_E).

Regarding the duration of their effectiveness, Figure 2 gives a schematic summary of available published data. The time scales of duration of adaptive protection of various kinds are crucially important for the assessment of dose rate effects [79]. Depending on radiation type and dose rate, energy deposition events per defined miocromass such as a cell happen at certain average time intervals. The time interval between repetitive energy deposition events in a defined biological target at a given dose rate may determine to what degree damage or adaptive protection prevails.

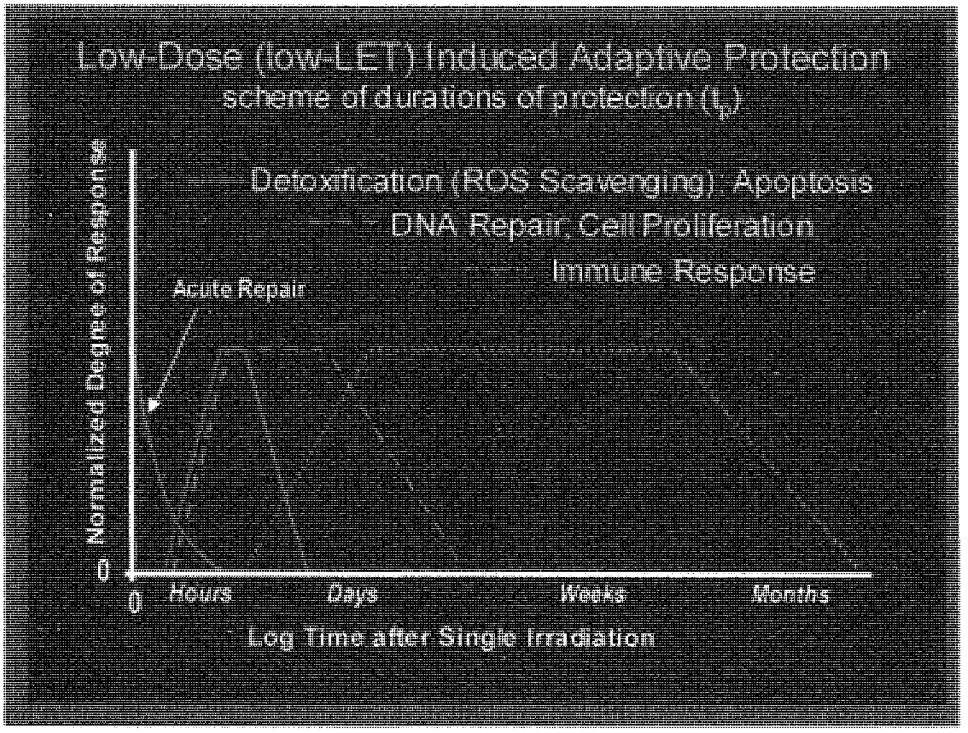

Fig. 2:
Single low-dose induced adaptive responses have different times of duration depending on protective mechanisms, that begin with a delay of several hours and may last for up to months regarding immune response. Note that repair in response to radiation damage begins immediately after damage has occurred.

Since DNA damage and cancer in mammals arise mainly from non-radiogenic sources, it is justified to relate the low-dose induced various adaptive protection mechanism mainly to non-radiogenic, i.e., "spontaneous" DNA damage and cancer in addition to their potential effect against radiogeneic damage and cancer, as presented in more detail in a model elsewhere [5, 11, 12, 17]. A summarizing graphical display applying the model of risk evaluation after single low-dose irradiation is shown in Figure 3. It illustrates in principle that low-doses induce adaptive protection against DNA damage and its accumulation in tissue, mainly from endogenous, i.e., "spontaneous" sources and thus counterbalances effects from radiation

exposure. The net risk of cancer, then, becomes lower than predicted by the LNT-hypothesis, or even negative with more benefit than damage to the low-dose exposed system.

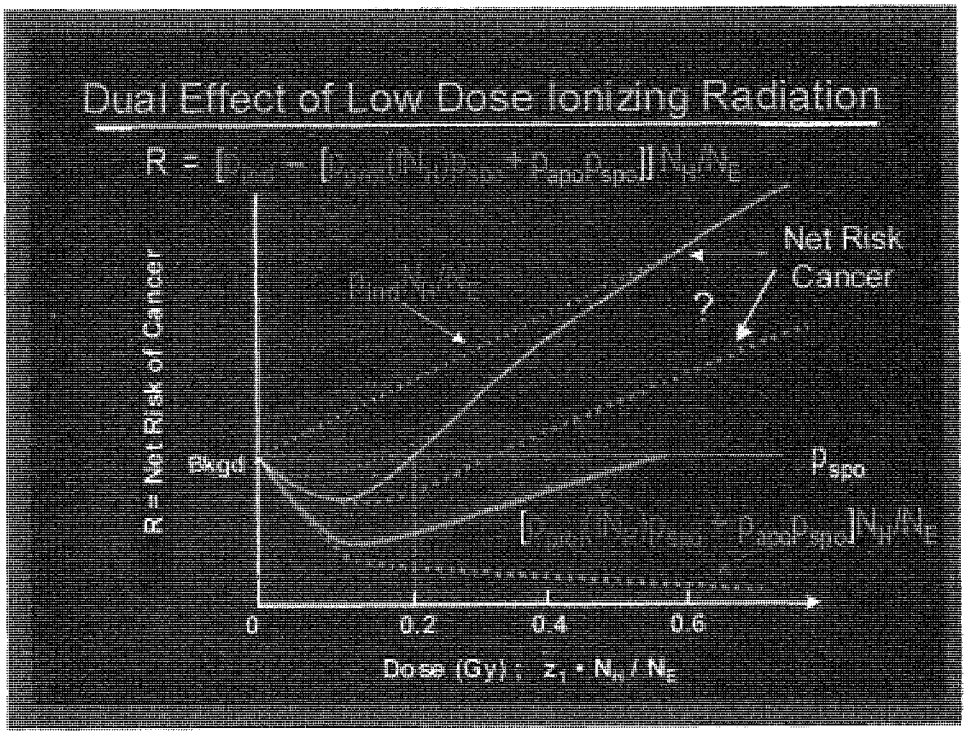

Fig. 3:
The dual effect of single low-dose irradiation is schematically analyzed according to a simplified model (see also text). This encompasses as a function of dose D, i.e. of N_H/N_E for a given radiation quality, the following probabilities: a) of DNA damage induction per energy deposition event $\bar{z}_t$ (see Fig. 1), p_{ind}, with a potential contribution from bystander effect, in red; this function appears linear with dose beyond the contribution from bystander effect; b) of the net protection provided by dose dependent mechanisms, $p_{prot}(fN_H)$, plus of apoptosis $p_{apo,}$ - both against spontaneous cancer with the probability p_{spo} per affected cell, in green. The net cancer risk derives from the difference between cancer induction and prevention at the various dose levels; the solid curve of net cancer risk is without protection from apoptosis, and the dotted curve of net cancer risk is with protection from apoptosis.

Summary

1) Ionizing radiation causes DNA damage in mammalian cells proportional with dose with additional possible bystander effects. 2) At background radiation exposure levels, DNA damage comes overwhelmingly from non-radiation sources. 3) The probability of radiation induced adaptive protection measurably outweighs that of damage from doses well below 200 mGy low-LET radiation. 4) The delayed and temporary adaptive protection at low doses involves damage prevention, damage repair, and immune responses. They appear to operate

primarily against DNA damage from non-radiation sources. Moreover, apoptosis and terminal cell differentiation also occur at higher doses and tend to remove susceptible damaged cells as does the low-dose induced stimulation of the immune system. Cell removal reduces genomic instability and mutated cells from tissue. 5) At higher absorbed doses in tissue, cell and DNA damage appear increasingly to overrule, negate, or annihilate the more subtle signaling effects seen after low doses that lead to adaptive protection, whereas apoptosis and terminal cell differentiation continue to function. 6) The linear-dose-risk function appears invalid and should be replaced by a function that includes both linear and non-linear terms. Basic research data and human epidemiological data conform to threshold or hormesis in the low-dose range.

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Appendix 4

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Integrated Molecular Analysis Indicates Undetectable DNA Damage in Mice after Continuous Irradiation at ~400-fold Natural Background Radiation

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Integrated Molecular Analysis Indicates Undetectable DNA Damage in Mice after Continuous Irradiation at ~400-fold Natural Background Radiation

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Running title: Low dose-rate radiation and DNA damage *in vivo*

Keywords: DNA damage, gene expression, in vivo, ionizing radiation, low dose-rate, micronucleus assay, mouse

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The authors declare they have no actual or potential competing financial interests.

Abbreviations and definitions:

Fluorescent yellow direct repeat (FYDR)

White blood cell (WBC)

Homologous recombination (HR)

Abstract

BACKGROUND: In the event of a nuclear accident, people are exposed to elevated levels of continuous low dose-rate radiation. Nevertheless, most of the literature describes the biological effects of acute radiation. Our major aim is to reveal potential genotoxic effects of low dose-rate radiation.

OBJECTIVES: DNA damage and mutations are well established for their carcinogenic effects. Here, we assessed several key markers of DNA damage and DNA damage responses in mice exposed to low dose-rate radiation.

METHODS: We studied low dose-rate radiation using a variable low dose-rate irradiator consisting of flood phantoms filled with ^{125}Iodine-containing buffer. Mice were exposed to 0.0002 cGy/min (~400X background radiation) continuously over the course of 5 weeks. We assessed base lesions, micronuclei, homologous recombination (using fluorescent yellow direct repeat [FYDR] mice), and transcript levels for several radiation-sensitive genes.

RESULTS: Under low dose-rate conditions, we did not observe any changes in the levels of the DNA nucleobase damage products hypoxanthine, 8-oxo-7,8-dihydroguanine, 1,N^6-ethenoadenine or 3,N^4-ethenocytosine above background. The micronucleus assay revealed no evidence that low dose-rate radiation induced DNA fragmentation. Furthermore, there was no evidence of double strand break-induced homologous recombination. Finally, low dose-rate radiation did not induce Cdkn1a, Gadd45a, Mdm2, Atm, or Dbd2. Importantly, the same total dose, when delivered acutely, induced micronuclei and transcriptional responses.

CONCLUSIONS: Together, these results demonstrate in an *in vivo* animal model that lowering the dose-rate suppresses the potentially deleterious impact of radiation, and calls attention to the need for a deeper understanding of the biological impact of low dose-rate radiation.

Introduction

Life has evolved in the midst of a continuous background radiation dose-rate, which varies depending on local geological formation, and can be further impacted by nuclear reactor accidents and nuclear weapons detonations (Hall et al. 2009). Since our environment is naturally radioactive, the question becomes: how much additional radiation is too much?

Epidemiological research on low dose-rate radiation has been made difficult by the fact that the biological consequences are subtle and are sometimes obfuscated by inter-individual variation (Mobbs et al. 2011). To overcome this problem, inbred animals housed in controlled conditions have been used to study low dose-rate radiation. Key animal studies show that low dose-rate radiation leads to an increase in the number of anti-inflammatory CD4+ and CD8+ T-cells and to an increase in the antioxidant gene superoxide dismutase (Ina and Sakai 2005; Tsuruga et al. 2007). Moreover, fractionated low dose radiation over several weeks increased the number of T-regulatory cells (Tago et al. 2008; Tsukimoto et al. 2008). Radiation induced up-regulation of anti-inflammatory immune cells has been associated with a lower frequency of lymphomas (Courtade et al. 2002; Ina et al. 2005; Lacoste-Collin et al. 2007; Mitchel 2007; Nakatsukasa et al. 2008; Tago et al. 2008; Tsukimoto et al. 2008; Tsuruga et al. 2007). In contrast, however, a higher frequency of hematological malignancies and chromosome aberrations has been reported in mice and dogs after continuous low dose-rate irradiation (Seed et al. 2002; Tanaka et al. 2007; Tanaka et al. 2008; Tanaka et al. 2009). Thus, it remains unclear to what extent (and at what dose-rate) low dose-rate radiation impacts cancer risk.

Of particular interest is radiation-induced DNA damage. Carcinogenic radiation exposures are known to induce DNA strand breaks and chromosomal rearrangements (Bekker-Jensen and Mailand 2010; Chadwick and Leenhouts 2011; Holland et al. 2011). Importantly, a single acute dose of radiation can give rise to cancer over a decade later, which is consistent with DNA damage being predictive of downstream cancer risk (Ron 1998). Therefore, in this study, we have focused on measurements of DNA damage and DNA damage responses.

Here, we show that, despite continuous exposure to radiation at a dose that is ~200-fold higher than the permissible exposure limit by the International Commission on Radiological Protection (ICRP 2007), there was no significant change in the levels of DNA base lesions, homologous recombination, micronucleus frequency, or transcriptional stress responses. These studies suggest that exposure to continuous radiation at a dose-rate that is orders of magnitude higher than background does not significantly impact several key measures of DNA damage and DNA damage responses.

Materials and Methods

Radiation exposure of mice. Three and seven week old C57Bl6 mice were purchased from Taconic and acclimatized for 1-2 weeks prior to experiments. Fluorescent yellow direct repeat (FYDR) mice and positive control FYDR-Rec mice in the C57Bl6 background, were bred in house. All animals were housed in pathogen free barrier facilities and treated humanely with regard for alleviation of suffering. Experimental cohorts included a 1:1 male to female ratio and litters were split into treatment and control groups. Group sizes for base lesion analysis, gene expression analysis, and micronucleus assay were 6, 16 and 6, respectively. Group sizes for the

homologous recombination assay were 60 and 24 animals for the continuous radiation and acute exposure experiments, respectively. Two treatment conditions were used throughout the experiments: continuous low dose-rate radiation and acute radiation exposure. For low-dose rate exposures, four week old animals were exposed for five weeks using an ^{125}Iodine (^{125}I) based variable low dose-rate irradiator (Olipitz et al. 2010). Briefly, to create a large, uniform exposure area, commercially available plexan boxes (flood phantoms) were filled with ^{125}I in NaOH buffer. Flood phantoms were placed below the animal cages resulting in a dose-rate of 0.00017 cGy/min ± 0.00002 (see Supplemental Material, Figure S1). For acute exposures, nine week old mice were irradiated for 1.4 min at a dose-rate of 7.1 cGy per minute using a Philips RT250 X-ray machine (Philips Medical Systems, Bothell, WA) at 75kV and a 0.2 mm Cu filter in place. All exposed mice received a total dose of 10.5 cGy.

DNA base lesion analysis. All animals were sacrificed by CO_2 euthanasia immediately after cessation of radiation exposure. Spleens were removed and DNA isolated from spleens using a commercially available kit (Roche Diagnostic Corporation, Indiana, IL). All buffers were supplemented with the deaminase inhibitors coformycin (5 μg/ml) (National Cancer Institute, Bethesda, MD) and tetrahydrouridine (50 μg/ml) (Calbiochem, San Diego, CA), and the antioxidant desferrioxamine (0.1 mM) (Sigma, St. Louis, MO)(Pang et al.). 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG), 2'-deoxyinosine (dI), 1,N^6-etheno-2'-deoxyadenosine (εdA) and 3,N^4-etheno-2'-deoxycytidine (εdC) were analyzed using liquid chromatography-coupled tandem mass spectrometry (LC-MS/MS) as previously described (Pang et al. 2007). Briefly, DNA was enzymatically hydrolyzed to 2'-deoxynucleosides that were resolved by reversed-phase HPLC, with fractions containing the 2'-deoxynucleosides collected at empirically-determined elution

times. Individual 2'-deoxynucleosides in the HPLC fractions were then analyzed by isotope-dilution tandem quadrupole mass spectrometry using internal standards and calibration curves based on defined molecular transitions.

Gene expression analysis. Blood samples were drawn from individual four week old mice prior to continuous low-dose rate radiation exposure by retroorbital bleeding and immediately after cessation of radiation exposure by terminal heart puncture. For acute exposure experiments retroorbital bleeding was performed on eight week old animals, which were then exposed at nine weeks of age and sacrificed immediately after radiation exposure. White blood cells (WBCs) were isolated as previously described (Olipitz et al. 2002), except that whole mouse blood was lysed twice in lysis buffer (Simga, St. Louis, MO) for 6 min on ice. WBCs were washed in PBS, resuspended in 100µl RNAlater (Qiagen, Hilden, Germany) and stored at -80°C. RNA was isolated using a commercially available kit (RNeasy, Qiagen, Hilden, Germany). cDNA was generated using an archive kit (Applied Biosystems, Foster City, CA). Using GAPDH as internal control, relative gene expression was assessed using the Taqman system on an AB7100 thermal cycler (Applied Biosystems, Foster City, CA). For low dose-rate studies, there were 16 animals per group. For acute irradiations, two experiments were performed, each with 6 animals per group.

Bone marrow micronucleus assay **in vivo.** Mice were humanely euthanized by CO_2 asphyxiation immediately after cessation of continuous low-dose rate radiation and 24 hours after acute radiation exposure and the bone marrow was removed from the femurs and tibiae. A single cell suspension was generated by mechanical dissociation, passed through a cellulose

column, spread onto a slide, fixed in 25 ^{o}C methanol for 10 min, and stained with acridine orange (Fisher Scientific, Hanover Park, IL) at a concentration of 20 μg/mL in 19 mM NaH2PO4 and 81 mM Na2HPO4 for 10 min at 4^{o}C. Slides were washed for 10 min in 4^{o}C staining buffer, air dried, stored at 4^{o}C, and examined using a Labophot microscope (Nikon, Garden City, NY). Representative micrographs were acquired using a Sony DSC-P93A Cyber-Shot digital camera. Acridine orange stained cells were scored using a 40X oil-immersion objective and fluorescence (100W Hg lamp excitation). The cytologist was blinded to the identity of slides and differential cell counting was used to enumerate relevant cell types and thus quantify the percentage of micronucleated polychromatic erythrocytes (MN-PCEs) among total polychromatic erythrocytes (PCEs). PCEs, which are also known as reticulocytes, still contain RNA and thus fluoresce red after acridine orange stain, allowing them to be distinguished from mature red blood cells (faint green) and nucleated cells (bright yellow). MN-PCE contain small amounts of nuclear DNA that is left behind when an erythroid progenitor undergoes DNA damage while differentiating into a PCE. More than 2000 PCEs were scored per slide and experiments were performed in duplicate, each with six animals per group.

Analysis of homologous recombination frequency in pancreatic tissue. Fluorescent yellow direct repeat (FYDR mice) carry a direct repeat recombination substrate that contains two differently mutated copies of the coding sequence for Eyfp (Hendricks et al. 2003). An homologous recombination (HR) event can restore full length *Eyfp* coding sequence, thus yielding a fluorescent cell. The positive control FYDR-Rec mice arose spontaneously through a recombination event in a gamete and all cells within the positive control mice carry the full length *Eyfp* cDNA. The frequency of fluorescent yellow recombinant cells can be assessed using

flow cytometry analysis of disaggregated pancreatic tissue, or by *in situ* imaging (DM Wiktor-Brown et al. 2006a). Briefly, pancreata were harvested immediately after cessation of continuous low-dose rate exposure and 3.5 weeks after acute radiation exposure. The period of 3.5 weeks was designed for potential radiation induced HR events to occur and to adjust for previously determined age related increase in HR events (both, continuously exposed animals and acutely exposed animals were of the same age at analysis). Pancreata were compressed to a uniform thickness of 0.5 mm and images were taken under a 1x objective on a Nikon 600 eclipse fluorescent microscope. Using Adobe Photoshop 5.0 (Adobe Systems, San Jose, CA) images were then adjusted for brightness and contrast and compiled to represent the entire area of a pancreas. Fluorescent spots were then counted in a blinded fashion. For flow cytometry analysis, pancreata were dissociated into a single cell suspension and analyzed on a Becton Dickinson FACScan flow cytometer (BD, Franklin Lakes, NJ) as previously described (DM Wiktor-Brown et al. 2006a). Statistical analysis was performed using the Mann-Whitney test.

Results

Variable low-dose irradiator. A recently developed ^{125}I based low dose-rate irradiator provides an effective method to continuously expose mice to low dose-rate radiation (Olipitz et al. 2010). While ^{125}I is not a radionuclide found in nature, it's photon emissions are a reasonable surrogate for both background radiation (the majority of background radiation tracks through our bodies are photon tracks) and environmental contamination (the radionuclide of most concern for long-term contamination following nuclear reactor accidents or nuclear weapons explosions is ^{137}Cs, a photon emitter).

We previously showed that the average dose-rate delivered to the animals across the phantom is 0.00017 cGy/min ± 0.00002 (Olipitz et al. 2010). This dose-rate is ~400X higher than background radiation and ~ 200 times higher than the ICRP's one-year limit for radiation workers (ICRP 2007). However, it is still considered to be a low dose-rate as it is only about five times the level of natural radiation found in certain places, such as in Iran (Ghiassi-Nejad et al. 2002), and it is also lower than the dose-rate known to impact cancer and longevity in animals studies (NCRP 64, 1980). An exposure period of five weeks was chosen to reach a cumulative dose of 10.5 cGy, because ~10 cGy of ionizing radiation delivered acutely has been shown to affect DNA damage endpoints (Abramsson-Zetterberg et al. 1996; Bhilwade et al. 2004; Uma Devi and Sharma 1990; Amundson et al. 2000; Gruel et al. 2008).

DNA base lesion levels in splenic tissue. Radiation-induced reactive oxygen species (ROS), such as hydroxyl radical ($OH^{\bullet}$), superoxide radical ($O_2^{\bullet}$-) and hydrogen peroxide (H_2O_2), can create mutagenic and cytotoxic DNA base lesions (Halliwell and Aruoma 1991). In addition, the cellular damage caused by ionizing radiation can potentially cause inflammation, with local generation of high levels of reactive nitrogen species (RNS), including nitric oxide (NO), nitrous anhydride (N_2O_3) and peroxynitrite ($ONOO^-$) (Dedon and Tannenbaum 2004). While ONOO- causes DNA oxidation, N_2O_3 can cause nitrosative deamination of DNA nucleobases (Dedon and Tannenbaum 2004). We therefore set out to determine the extent to which continuous low dose-rate radiation impacts DNA damage levels, either by direct mechanisms or by indirect mechanisms that potentially modulate the formation or clearance of DNA damage.

LC-MS/MS is highly sensitive and can be used to measure the steady-state levels of DNA lesions (Dedon et al. 2007). Here, we quantified mutagenic and cytotoxic base lesions, including 8-oxodG (a DNA oxidation product), dI (a nucleobase deamination product), and •dA and •dC, (two lesions derived from reactions of DNA with lipid peroxidation products). The spleen was chosen for analysis given its radiosensitivity. After exposure to ~400X background radiation for five weeks, we did not detect any significant changes in the levels of base lesions in spleen tissue from irradiated mice (Figure 1A-1D).

One possible reason that base damage might not accumulate is that radiation-induced DNA damage may be rapidly repaired. We therefore asked if the same total dose of radiation induces base damage when delivered acutely, at a dose-rate that was ~four orders-of-magnitude higher (7.1 cGy/min). Even under acute conditions, we did not detect any significant difference in the levels of base lesions (Figure 1). Together these results show that exposure to 10.5 cGy does not significantly impact the levels of several key DNA base lesions that are known to be formed in response to radiation and inflammation, regardless of the dose-rate (ranging from 0.0002 to 7.1 cGy/min).

Micronuclei analysis in red blood cells. Although far less frequent than radiation-induced base lesions, radiation-induced double strand breaks are severely cytotoxic and mutagenic (Helleday et al. 2007). The micronucleus assay is an exquisitely sensitive approach for detecting DSBs (Hayashi et al. 2000). Using the *in vivo* red blood cell micronucleus assay, small chromosomal fragments can be detected in enucleated red blood cells (Figure 2A) (Kirsch-Volders et al. 2000). To explore the impact of dose-rate on susceptibility to DSBs, we compared the extent to which

10.5 cGy radiation induces micronuclei when delivered either acutely versus delivered over a long period of time. Consistent with previous studies, exposure to 10.5 cGy delivered acutely (7.1 cGy/min) resulted in a significant increase in micronuclei in mice *in vivo* ($p < 0.005$) (Figure 2C) (Abramsson-Zetterberg et al. 1996; Bhilwade et al. 2004; Uma Devi and Sharma 1990). In contrast, no significant increase in micronuclei was observed in continuously irradiated mice (Figure 2B). These data reveal that dose-rate can significantly impact radiation-induced DNA damage levels.

Frequency of homologous recombination events in the pancreas. An alternative approach for studying DSBs is to assess DSB repair activity. We have recently developed FYDR mice that allow investigation of mitotic homologous recombination, one of the major DSB repair pathways in mammals (DM Wiktor-Brown et al. 2006a; DM Wiktor-Brown et al. 2006b). FYDR mice carry a direct repeat recombination substrate for which an HR event can restore full length *Eyfp* coding sequence (Figure 3A) (Hendricks et al. 2003). The frequency of fluorescent yellow recombinant cells can be assessed using *in situ* imaging or flow cytometry (Figure 3A-3C). Recombinant cells can continue to fluoresce for their lifespan, making it possible to monitor the accumulation of recombinant cells over time (Wiktor-Brown et al. 2006b). Thus, while induction of recombination can potentially be detected by an increase in the frequency of recombinant cell foci (compare Figure 3B and 3C), no difference was observed in the frequency of HR among irradiated and non-irradiated animals (Figure 3D and 3F).

While these data suggest that low dose-rate radiation did not affect the frequency of HR, it remained formally possible that radiation caused silencing of the *Eyfp* gene (Suzuki et al. 2011),

which could lead to a false negative result. We therefore exploited FYDR-Rec positive control mice to test for radiosuppression of *Eyfp* expression, however no suppression was detected (Figure 3H). Therefore, we conclude that low dose-rate radiation does not significantly impact HR.

To explore the possibility that acute exposure might induce HR, animals were exposed to 10.5 cGy at a dose-rate 7.1 cGy/min. Although there appears to be a slight increase in HR frequency by *in situ* imaging, the difference is not statistically significant (Figure 3E, 3G). Taken together, our analysis of DSB repair indicates that long-term low dose-rate irradiation at ~400-fold background for five weeks does not lead to a detectable increase in the frequency of either micronuclei or homologous recombination.

Gene expression analysis of DNA damage response genes. Gene expression changes have been observed in response to acute irradiation delivered at doses as low as 1 cGy (Alvarez et al. 2006; Amundson et al. 2000; Amundson et al. 2001; Fujimori et al. 2005). Several genes found to be consistently affected by radiation are part of the p53 DNA damage response: Cdkn1a, Gadd45a, Mdm2, Atm, and Ddb2 (Gruel et al. 2008). As WBCs are particularly responsive to radiation exposure (Amundson et al. 2000; Amundson et al. 2003), we assessed gene expression levels for Cdkn1a, Gadd45a, Mdm2, Atm, and Ddb2 in primary WBCs after exposure to low dose-rate radiation (0.0002 cGy/min). We found that there was no significant difference in gene expression between irradiated and non-irradiated animals for any of the five genes (Figure 4A). To explore the impact of dose-rate, we exposed mice to 10.5 cGy irradiation delivered acutely (7.1 cGy/min). At this higher dose-rate, Cdkn1a was significantly up-regulated (Figure 4C),

indicating that DNA damage responses are dose-rate dependent, which is consistent with previous studies (Amundson et al. 2003).

A significant challenge for all animal studies is variability due to inter-individual differences. We therefore developed an approach for a paired analysis, wherein blood samples were collected from the same animals both prior to and after radiation exposure. Regardless of whether the data was paired or pooled, Cdkn1a was significantly induced by acute irradiation, though we detected a greater induction using the paired experimental design (Figure 4C and 4D). Furthermore, using paired analysis conditions, we also detected a significant increase in expression of Mdm2 (Figure 4D). These studies suggest that longitudinal assessment increases the sensitivity of the assay to subtle changes in gene expression. Nevertheless, under the conditions of low dose-rate exposure (0.0002 cGy/min), there were no significant changes in gene expression, even with a paired analysis (Figure 4B).

Taken together, studies of animals that live under conditions of prolonged continuous exposure to radiation at ~400X background do not show any evidence of increased levels of base damage (for 8-oxodG, dI, εdA, εdC) nor double strand breaks (micronuclei and homologous recombination), nor induction of a DNA damage response (at the level of p53-inducible gene expression). Importantly, when delivered acutely, the same total dose induced micronuclei and induced key genes involved in the DNA damage response.

Discussion

In the event of radioactive contamination, the majority of the population will be exposed to low dose radiation over extended periods of time (UNSCEAR 2000). Despite appreciation of the importance of preparedness, the biological effects of continuous low dose radiation are poorly understood (for excellent reviews on the biological impact of low dose radiation, see Mobbs et al. 2011; Muirhead et al. 2009; Virjhead et al. 2007; Wall et al. 2006). Here we have explored the impact of continuous low dose-rate radiation through studies of DNA damage and responses in an animal model.

Based on published studies, we estimate that the steady state level of base lesions is ~10,000/cell, whereas exposure to 10.5 cGy is only expected to induce ~400 base lesions/cell (Pouget et al. 1999; Pouget et al. 2002). HPLC MS/MS is an exquisitely sensitive method to detect DNA base lesions and has been successfully used to detect base lesion levels after exposure to ionizing radiation and other ROS/RNS generating conditions, such as chronic inflammation (Frelon et al. 2000; Pang et al. 2007; Pouget et al. 2002). While directly induced lesions may be too low to be detectable above background, it remained possible that radiation could indirectly alter the steady state levels of damage by changing the physiological state of the tissue or by modulating DNA repair. However, steady state base lesion levels in splenic DNA were not changed as compared to non-irradiated controls. Additionally, the same total dose given at a high dose-rate (7.1 cGy/min) did not affect base lesion levels. Taken together, this is the first time that base lesions have been measured *in vivo* following low dose-rate radiation, and there was no significant impact on the steady state levels of several key DNA base lesions.

DSBs are highly cytotoxic and mutagenic and potentially result in deletions, chromosomal translocations or loss of heterozygosity that can promote cancer (Friedberg et al. 2006; Goodhead 1994; Helleday et al. 2007; Ward 1988). The micronucleus assay is a sensitive assay that detects chromosome breaks (Hayashi et al. 2000). Consistent with published studies (Abramsson-Zetterberg et al. 1996; Bhilwade et al. 2004; Uma Devi and Sharma 1990), we observed radiation-induced micronuclei in acutely exposed animals (10.5 cGy at 7.1 cGy/min). However, when the same total dose was delivered continuously at a very low dose-rate of 0.0002 cGy/min, no significant differences in micronuclei frequency were observed between the irradiated and control cohort. Micronuclei persist for 24 hours after exposure, after which time the mature red blood cells enter the blood stream, cycling for ~120 days. Thus, under chronic exposure conditions one would not only detect micronuclei induced by the most recent radiation exposure, but also those micronuclei in RBCs that re-enter the highly perfused bone marrow. Thus, even though the micronucleus assay is highly radiation sensitive and has the potential to detect accumulated DNA damage, low dose-rate radiation did not induce micronuclei.

As an alternative approach for analysis of DSBs, we assayed for induction of homologous recombination by low dose-rate radiation. We found that 10.5 cGy delivered either at a low dose-rate or acutely did not induce HR in the pancreas. Assuming a linear relationship between the number of double strand breaks and the total dose, a radiation dose of 10 cGy will induce about 2 DSBs per cell (Hall 2000), which is likely below the limits of detection. Nevertheless, the FYDR mouse studies can also be used to detect changes in steady state levels of HR, which could be impacted by exposure (*e.g.*, by induction of an adaptive response). Thus, low dose-rate radiation neither directly nor indirectly induced HR.

Acutely delivered low dose radiation has been shown to induce transcriptional changes at doses as low as 1 cGy (Amundson et al. 2000; Gruel et al. 2008, Fujimori 2005). The most sensitive and most consistently radiation affected genes belong to the DNA damage response network (Alvarez et al. 2006; Amundson et al. 2000; Amundson et al. 2003; Gruel et al. 2008). In an attempt to address the consequences of a protracted radiation exposure to low doses, Belspug and coworkers exposed mice to a daily acute dose of 5 cGy to simulate chronic exposure. Importantly, after 10 days of irradiation the strongest transcriptional response was found in genes of the p53 signaling network, similar to acute exposure effects (Besplug et al. 2005). We therefore used a group of genes known to be induced by low dose radiation (Cdkn1a, Gadd45a, Mdm2, Ddb2 and Atm), to query gene expression changes in WBCs. Interestingly, we did not detect a significant difference in gene expression between irradiated and control groups. This result indicates that exposure to ~400 fold background radiation is not sufficient to affect radiation-sensitive genes in DNA damage response pathways, a finding consistent with the absence of a stress response.

To increase the sensitivity of our approach for detecting radiation-induced changes in gene expression, we used a paired analysis approach that suppresses inter-individual differences. While two genes were found to be induced under acute conditions, there was no change in gene expression under low dose-rate conditions. Such a dose-rate threshold has been described previously in studies of the hematopoietic system of dogs. Below a threshold dose-rate of 0.0002 cGy/min (approximately the same as the dose-rate used in the present study) dogs did not display any changes in bone marrow morphology, while dogs exposed to dose-rates above this threshold

displayed severe hematopoietic dysfunction, such as aplastic anemia, myeloproliferative disease and leukemia (Seed et al.1981; Seed et al. 2002a; Seed et al. 2002b). Taken together, continuous low dose-rate radiation not only shows a dose-rate threshold for cell morphology (Seed et al. 2002a; Seed et al. 2002b) but also for DNA damage responses.

Despite the use of highly sensitive assays for DNA damage responses, it remains possible that genetic changes are induced by low dose-rate radiation, but that such changes are below the limits of detection for the assays used. Chromosome aberrations offer an alternative approach for detecting chromosome breaks, and using this approach, others have shown that low dose-rate radiation indeed induces aberrations *in vitro* (although the dose-rate was ~10X higher than that used here) (Tanaka et al. 2009a). In addition, it is also important to consider the possibility that the biological impact of DNA damage varies according to the type of radiation. While most DSBs are rapidly repaired, a minor proportion of breaks are associated with additional DNA lesions. Such complex breaks have been shown to be resistant to DNA repair (Asaithamby et al. 2011; Sutherland et al. 2000) and thus may persist at undetectable levels. High LET radiation induces more complex breaks compared to low LET radiation (such as that used in this study) (Hall 2000), although elevated radiation levels from a contaminated environment result primarily in additional exposure to low-LET radiation (particularly from ^{131}I and ^{137}Cs). Nevertheless, the current study has important limitations in terms of the types of assays selected and the focus upon specifically low LET radiation. These limitations must be taken into consideration with regard to the potential impact of radiation exposure on human health.

Exposure to radiation is inevitable. Here, we have assessed the impact of long-term low dose-rate radiation on genomic stability using several highly sensitive end points for DNA damage and DNA damage responses. Using some of the most sensitive techniques available, low dose-rate radiation (approximately 400-fold natural background radiation) over five weeks, does not impact DNA base lesion levels, micronuclei formation, HR frequency or expression of DNA damage response genes. Importantly, an equal dose of radiation delivered acutely did induce DNA damage and DNA damage responses, thus demonstrating in an *in vivo* animal model that lowering the dose-rate suppresses the potentially deleterious impact of radiation. Current US policy dictates that a dose-rate of ~30X higher than background is too high to be permissible for human habitation (Federal Emergency Management Agency 2008). Given the enormous costs associated with making constraints on public policy too stringent (or too loose), these studies point to a significant need for additional knowledge regarding the impact of low dose-rate radiation.

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Figure Legends

Figure 1. Exposure to 10.5 Gy acute (7.1 cGy/min) and chronic irradiation (0.0002 cGy/min) does not change steady state base lesion levels. Effects of continuous and acute low dose radiation exposure on DNA base lesion levels of (A) 8-oxodG, (B) dI, (C) εdA, and (D) εdC were measured by LC-MS/MS in splenic DNA. Data represent mean ± SEM for n=6 and were analyzed by Student's t-test.

Figure 2. Acute irradiation (C) induces micronuclei in polychromatic erythrocytes (PCEs), while low dose-rate IR (B) does not (dose and dose rates as described in Figure 1). Representative image of a PCE containing micronuclei (MN-PCE; arrowhead) and of a normal red blood cell (arrow) isolated from bone marrow. Bar, 20 μm (A). Data are representative of two independent experiments; % MN-PCE calculated from > 2000 scored PCE per sample; error bars indicate SEM. Statistical analysis was performed using unpaired, two-tailed Student's T-test (*$p<0.05$) (%MN-PCE, % micronucleated polychromatic - mononuclear erythrocytes).

Figure 3. Continuous (D,F) and acute (E,G) irradiation do not affect HR frequency in the pancreas. FYDR mice carry a recombination substrate (A) that results in expression of *Eyfp* upon recombination repair. The Eyfp signal can be detected by *in situ* imaging and the frequency of Eyfp positive cells increases with age (B, four week old (young) mouse; C, 24 week old (old) mouse). Continuous irradiation does not affect Eyfp expression (H). Doses and dose rates as described in Figure 1. Bars indicate the medians. Statistical analysis was performed using two-tailed Mann-Whitney test.

Figure 4. Effects of continuous (A, B) and acute (C, D) ionizing radiation on gene expression in WBCs. Gene expression changes were compared between control and treated groups after irradiation (A, C) and in irradiated animals before and after irradiation (B, D). Dose and dose rates as described in Figure 1. Data are representative of two independent experiments (mean ± SEM is shown). Statistical analysis was performed using unpaired, two-tailed Student's T-test (A, C) and paired, two-tailed Student's T-test (B, D) (*$p < 0.05$).

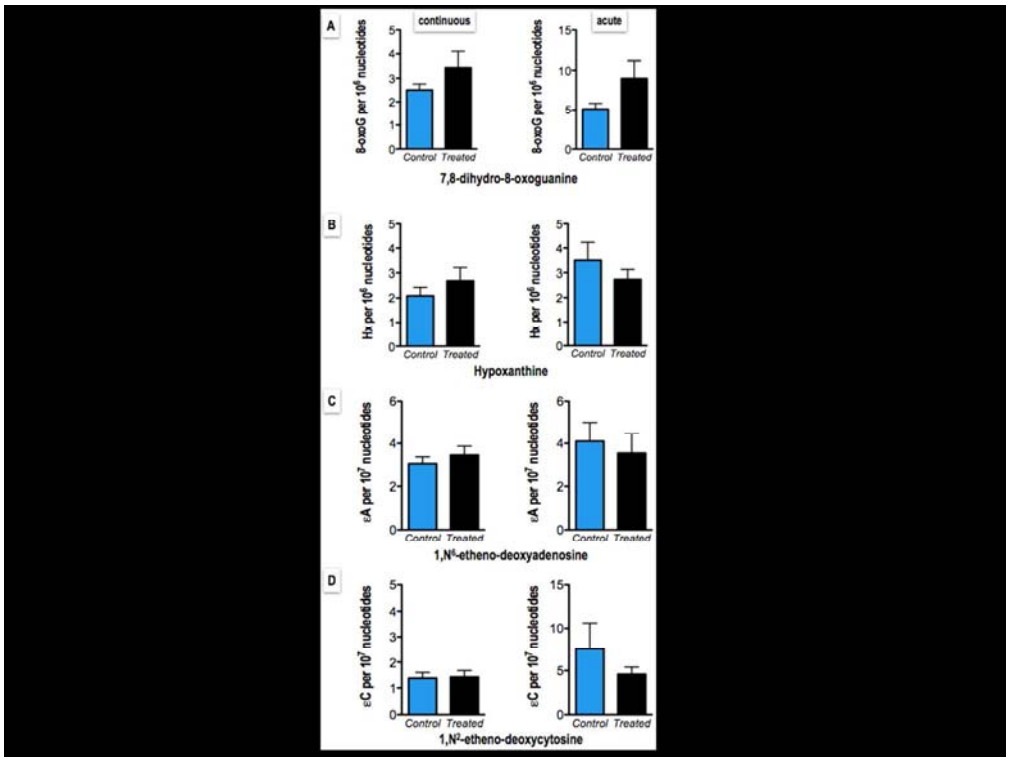

Figure 1. Exposure to 10.5 Gy acute (7.1 cGy/min) and chronic irradiation (0.0002 cGy/min) does not change steady state base lesion levels. Effects of continuous and acute low dose radiation exposure on DNA base lesion levels of (A) 8-oxodG, (B) dI, (C) εdA, and (D) εdC were measured by LC-MS/MS in splenic DNA. Data represent mean ± SEM for n=6 and were analyzed by Student's t-test.
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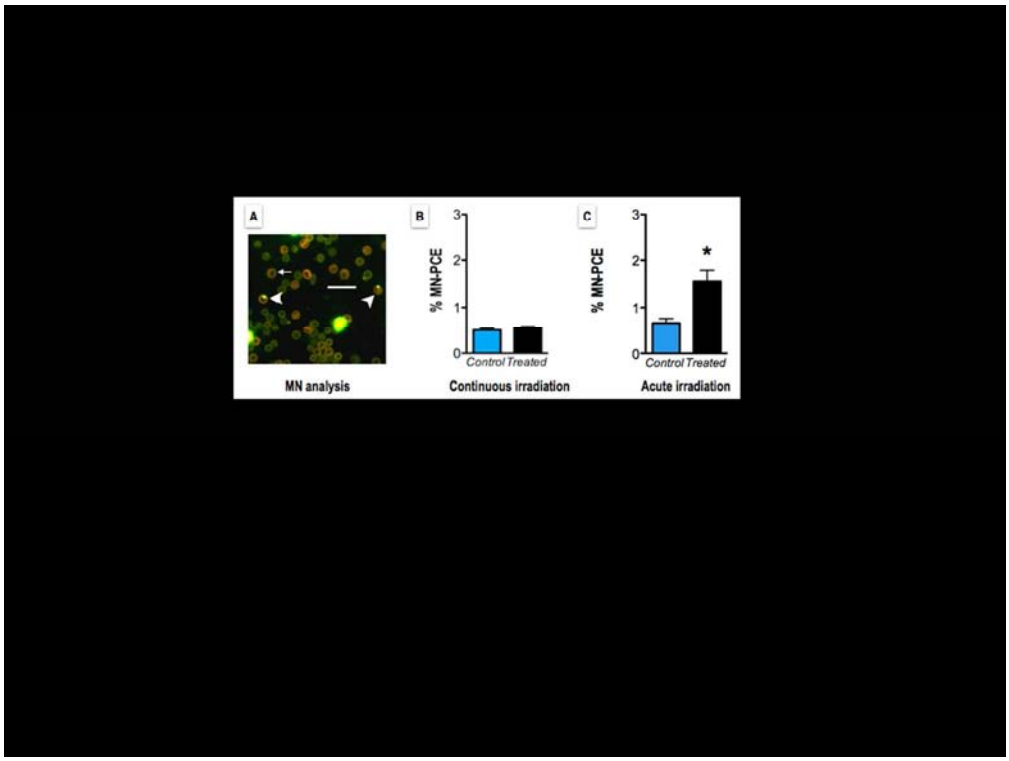

Figure 2. Acute irradiation (C) induces micronuclei in polychromatic erythrocytes (PCEs), while low dose-rate IR (B) does not (dose and dose rates as described in Figure 1). Representative image of a PCE containing micronuclei (MN-PCE; arrowhead) and of a normal red blood cell (arrow) isolated from bone marrow. Bar, 20 μm (A). Data are representative of two independent experiments; % MN-PCE calculated from > 2000 scored PCE per sample; error bars indicate SEM. Statistical analysis was performed using unpaired, two-tailed Student's T-test (*p<0.05) (%MN-PCE, % micronucleated polychromatic - mononuclear erythrocytes).

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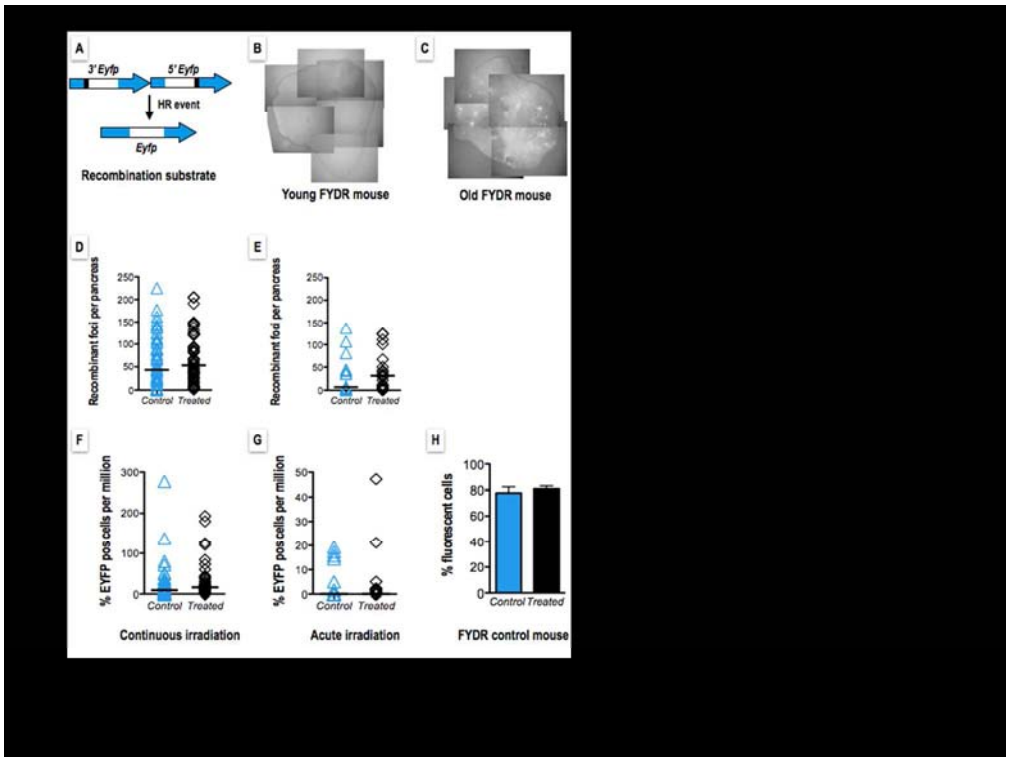

Figure 3. Continuous (D,F) and acute (E,G) irradiation do not affect HR frequency in the pancreas. FYDR mice carry a recombination substrate (A) that results in expression of Eyfp upon recombination repair. The Eyfp signal can be detected by in situ imaging and the frequency of Eyfp positive cells increases with age (B, four week old (young) mouse; C, 24 week old (old) mouse). Continuous irradiation does not affect Eyfp expression (H). Doses and dose rates as described in Figure 1. Bars indicate the medians. Statistical analysis was performed using two-tailed Mann-Whitney test.
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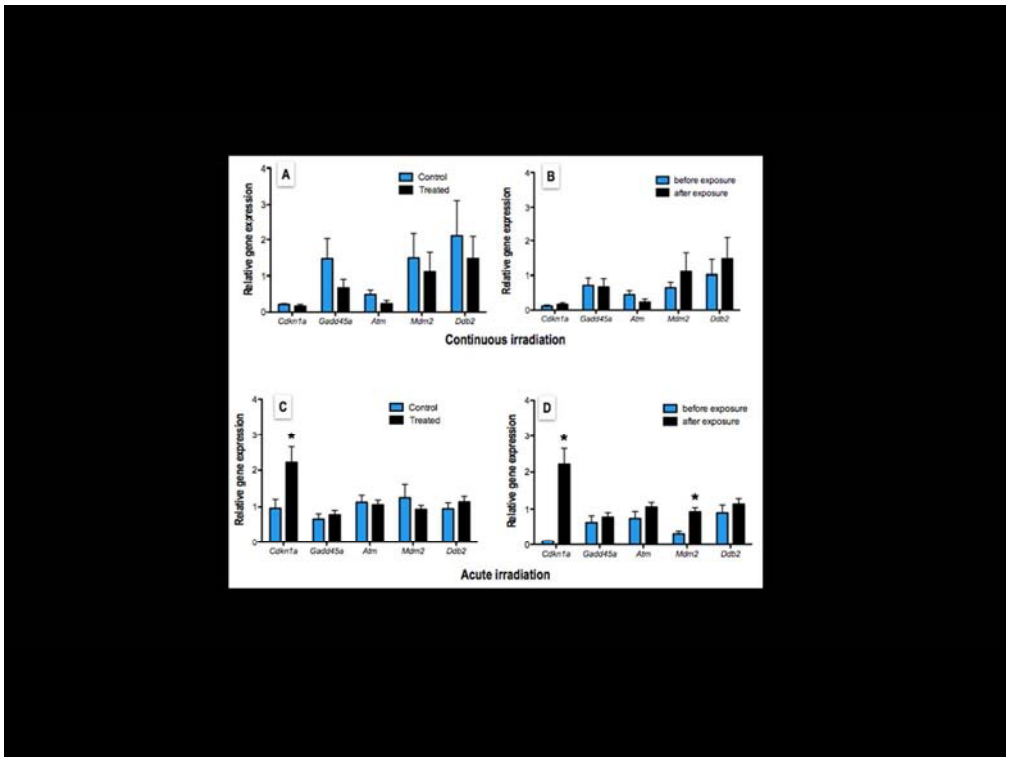

Figure 4. Effects of continuous (A, B) and acute (C, D) ionizing radiation on gene expression in WBCs. Gene expression changes were compared between control and treated groups after irradiation (A, C) and in irradiated animals before and after irradiation (B, D). Dose and dose rates as described in Figure 1. Data are representative of two independent experiments (mean ± SEM is shown). Statistical analysis was performed using unpaired, two-tailed Student's T-test (A, C) and paired, two-tailed Student's T-test (B, D) (*$p < 0.05$).
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Appendix 5

Nuclear shipyard worker study (1980–1988): a large cohort exposed to low-dose-rate gamma radiation

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Abstract: This paper is a summary of the 1991 Final Report of the Nuclear Shipyard Worker Study (NSWS), a very comprehensive study of occupational radiation exposure in the US. The NSWS compared three cohorts: a high-dose cohort of 27,872 nuclear workers, a low dose cohort of 10,348 workers, and a control cohort of 32,510 unexposed shipyard workers. The cohorts were matched by ages and job categories. Although the NSWS was designed to search for adverse effects of occupational low dose-rate gamma radiation, few risks were found. The high-dose workers demonstrated significantly lower circulatory, respiratory, and all-cause mortality than did unexposed workers. Mortality from all cancers combined was also lower in the exposed cohort. The NSWS results are compared to a study of British radiologists. We recommend extension of NSWS data from 1981 to 2001 to get a more complete picture of the health effects of ^{60}Co radiation to the high-dose cohort compared to the controls.

Keywords: low-dose-rate gamma radiation; nuclear shipyard workers; cohort; cardiovascular disease; cancer; mortality.

Reference to this paper should be made as follows: Sponsler, R. and Cameron, J.R. (2005) 'Nuclear shipyard worker study (1980–1988): a large cohort exposed to low-dose-rate gamma radiation', *Int. J. Low Radiation*, Vol. 1, No. 4, pp.463–478.

Biographical notes: Professor John R. Cameron was trained in nuclear physics but spent most of his career applying physics to medicine. In the 1960s, he and his graduate students developed thermoluminescent dosimetry (TLD) and invented bone densitometry for detection of osteoporosis. In 1981, he was the founding chair of the Medical Physics Department at the University of Wisconsin. From 1980–1988, he was a member of the external panel that advised scientists doing the US nuclear shipyard worker study. He was disappointed that the scientists who did the research chose not to publish the details of this excellent study.

Ruth Sponsler has an MS in Entomology from Auburn University and is interested in biostatistics. She also has active hobby interests in geology.

1 Introduction

This paper provides information from the unpublished final report of the nuclear shipyard worker study (NSWS) (Matanoski, 1991), herein referred to as 'Final Report'. The NSWS is the world's largest and most thorough study of health effects of low-dose- rate ionising radiation to nuclear workers. The detailed results of the NSWS have not yet been published in any journal even 14 years after the study was finished. The NSWS was a rigorously performed search for health risks of radiation to civilian employees of eight shipyards that overhauled and repaired nuclear-propelled US Navy ships and submarines under the leadership of Adm. Hyman G. Rickover. Neither author of this paper was directly involved with the research. The second author was a member of the Technical Advisory Panel (TAP) of the NSWS that reviewed the study twice per year from 1980 to 1988.

The NSWS was performed by the School of Public Health of Johns Hopkins University under a contract with DOE at a cost of about $10 million. The principal investigator for the contract was Professor Genevieve Matanoski, an epidemiologist and Head of the Department of Epidemiology. The study was initiated in response to a small study at the Portsmouth N.H. shipyard, where excess leukaemia mortality had been reported (Najarian and Colton, 1978). Rinsky et al. (1981) subsequently refuted these results.

The present paper is the first publication of a comprehensive report of the NSWS results that details radiation doses and causes of death. Brief summaries of main points of the NSWS results were previously published (Cameron, 1992, 2001; Matanoski, 1993; Pollycove, 1998; Boice, 2001).

The US Department of Energy (DOE) received the contractor's report in 1991, more than three years after the completion of the study. The report is in the public domain. The NSWS was peer reviewed twice a year from 1980 to 1988 by a Technical Advisory Panel (TAP) as called for in the DOE contract. The TAP also reviewed the final report of the study. The TAP consisted of eight external scientists with relevant expertise: Arthur Upton, (chair); Gilbert Beebe, John Cameron (co-author of this paper), Carter Dennison (resigned in 1983), Merrill Eisenbud, Philip Enterline, Philip Sartwell and Roy Shore. The TAP members reviewed and approved the final NSWS report early in 1988. The final report shows no criticism of the study by any of the TAP members.

The NSWS is the only radiation study where nuclear workers were compared to age-matched and job-matched unexposed workers as controls. This was designed to avoid the 'healthy worker effect', a bias introduced when workers are compared with the general population (Monson, 1986; Choi, 1992). The Final Report states (p.357): "Therefore this is an ideal population in which to examine the risks of ionising radiation in which confounding variables could be controlled".

The NSWS used a large cohort of 27,872 nuclear workers drawn from a pool of over 100,000 nuclear shipyard workers. The 32,510 controls were job and age matched to the cohort. They were chosen from nearly 600,000 non-nuclear shipyard workers. The large size of the cohort and control groups enabled a strong statistical power in the study that is uncommon in many epidemiological studies. Uniform standards for dose assessment were established in the shipyards. Nuclear shipyard workers were primarily exposed to external ^{60}Co gamma rays resulting from neutron activation of cobalt in the reactor that was deposited in pipes and valves associated with the reactor cooling systems. Dose

assessment was unusually accurate because the Nuclear Navy programme had substantial discipline in assigning radiation-monitoring badges and in accurate recording of results. There was little missing personnel dosimetry data and little possibility of internal contamination or high LET exposure since few workers were involved with radiochemical environments or with any radionuclide other than external exposure to ^{60}Co. The elimination of confounding from high LET radiation or internal doses permits comparison with other large groups of radiation workers exposed to low LET radiation, such as radiologists and radiology technologists (Smith and Doll, 1981; Doody et al., 1998; Berrington et al., 2001).

Doses to the shipyard workers were relatively low compared to pre-1955 exposures to radiologists (Matanoski et al., 1975; Berrington et al., 2001). Common shipyard doses were 0.5–22.5 mGy y^{-1}, and are comparable to doses currently experienced by employees in nuclear and medical facilities, as well as to people exposed to high natural background radiation in locations such as Ramsar, Iran (10–260 mGy y^{-1}) (Ghiassi-nejad et al., 2002) and Kerala, India (approx. 7.5–70 mGy y^{-1}) (Nambi and Soman, 1987; Nair et al., 1999).

Workers in eight shipyards were studied: Charleston Naval Shipyard, Charleston SC; General Dynamics Corp. Electric Boat Division, Groton, CT; Mare Island Naval Shipyard, Vallejo CA; Newport News Shipbuilding and Drydock Co., Newport News, VA; Norfolk Naval Shipyard, Norfolk, VA; Pearl Harbor Naval Shipyard, Pearl Harbor, HI; Portsmouth Naval Shipyard, Portsmouth NH; and Puget Sound Naval Shipyard, Bremerton, WA.

NSWS data collection began with workers exposed during the first overhaul of a nuclear submarine in 1957 in the Groton, Connecticut, shipyard. Radiation doses and worker mortality were assessed through 31st December 1981.

2 Materials and methods of the NSWS

2.1 Selection of study groups

A total pool of 692,812 shipyard workers was available for the NSWS, of whom 107,976 were badged nuclear workers (p.18, Final Report). The primary cohort consisted of 27,872 nuclear workers who had received cumulative doses of 5 mGy or more by January 1, 1982 (NW = 0.5). The other two groups involved randomly selected shipyard workers who were stratified by age, number of years on the job, job classification and job hazard index to make the composition of the groups equivalent to that of the cohort (Final Report, p.44–60). The controls were 32,510 shipyard workers who did not enter radiation areas of the ships. The other study group was the low-dose cohort consisting of 10,348 nuclear workers with less than 5 mGy cumulative dose (Table 3.1.B. on p.301 of Final Report). Exposures to job hazards such as chemicals and asbestos were similar between nuclear and non-nuclear workers (Final Report, pp.237–258).

2.2 Dosimetry

The NSWS had better dosimetry records for analysis than any other radiation worker study. NSWS dosimetry and records were carefully maintained under central Naval management of the shipyards. All dosimetry data in the Final Report were given as rem or mrem. As gamma radiation has a quality factor of 1.0, we have converted those figures to mGy. Badging and recordkeeping were consistent across the shipyards and were more rigorously enforced than for radiation workers in other nuclear facility worker studies (Final Report, p.125, 133, 167). As almost all exposure was from ^{60}Co gamma rays, dosimetry lacked the problems often associated with dosimetry for mixed exposures. Doses were measured with film badges through 1976 and thermoluminescent dosimetry (TLD) after 1976. There was a transition period to TLD from 1973 to 1976 (Final Report, p.8). Most doses received by the cohort were received in annual increments of 1 mGy or greater, which probably were received in relatively short intervals rather than very gradually over the entire year (Final Report, p.154).

The Final Report (p.371) states, "In summary all data of radiation exposures to shipyard workers in the Navy nuclear propulsion program have indicated that doses are accurately recorded, carefully monitored, and are a true reflection of the dose received by the marrow which makes this population ideal for studies of effects of low-dose radiation."

The average annual dose to the cohort was 7.59 mGy y^{-1} (Table 1), while the median dose was 2.80 mGy y^{-1} and the 90th percentile dose was 22.6 mGy y^{-1}. Allowable doses ranged up to 120 mGy y^{-1} prior to 1967, although very few workers exceeded 50 mGy y^{-1}. Average annual doses declined over the span of the study, as the shipyards reduced man-rem exposure.

2.3 Mortality data

Vital status of shipyard workers was ascertained using a large number of sources including Social Security records and records of the various States (Final Report, pp.77–104). Data were recorded for 21 sites and types of cancers, including those likely to be radiogenic such as leukaemia and lymphatic and haematopoietic cancers. Data were also recorded for lung cancer and mesothelioma. Mesothelioma is strongly linked with asbestos exposure. Data were also recorded for all major causes of mortality, including diseases of the circulatory system, respiratory system, digestive system and the nervous system, also infectious diseases, mental illnesses and external causes. SMRs (standardised mortality ratios) for total mortality and various causes of death were computed by comparing mortality of cohort, low-dose cohort and controls with mortality of US white males (Final Report, p.289). This provided numbers of expected deaths for comparison of the shipyard cohorts with the US white male population. Internal comparisons between the three shipyard study groups were made for all causes of mortality (Final Report, pp.290–303) as well as for leukaemia, lymphatic and haematopoietic cancers, mesothelioma and lung cancer (Final Report, pp.304–324). The internal comparisons of mortality between groups of shipyard workers represent a major strength of the NSWS compared to other studies of nuclear workers. Sampling was stratified by age, birth year, year of hire and job hazard Final Report, pp.44–60).

Table 1 Summary statistics for annual dose equivalents received by the cohort

Time period	*Shipyard Location*	*Mean* Annual dose, $mGyy^{-1}$	*Median* Annual dose, $mGyy^{-1}$	*sd* %ile	*25* %ile	*75* %ile	*90* %ile	*99* %ile
1957–1981	All Shipyards	7.59	2.8	12.32	0.54	9.7	22.6	46.3
1957–1973	All	9.31	3.53	14.38	0.7	13.01	27.83	50
1973–1981	All	7.2	3.61	9.37	0.7	10.51	20.35	35.23
1974–1981	All	4.35	1.76	6.85	0.28	5.52	12.11	28.41

Shipyard dosimetry adapted from Tables 2.7.N. on p.189 and 2.7.S on p.194 of Final Report.

Original figures have been converted to mGy.

Excludes privately owned shipyards Groton and Newport News.

Percentage columns represent percentiles of the dose range.

Beginning year for each shipyard is the first year that the shipyard conducted nuclear overhaul (see Table 2.1.A., p.18 of Final Report).

2.4 Selection bias considerations

The NSWS used numerous techniques to reduce 'selection bias', also known as the 'healthy worker effect' (Choi, 1992; Chen and Seaton, 1996). These techniques are listed below:

- Workers were compared with other shipyard workers, rather than with the general population or with workers not exposed to shipyard conditions. This ensured that the nuclear worker groups and the non-nuclear group would come in contact with similar work conditions other than radiation exposure to the nuclear workers.
- Non-nuclear workers who did not work during the period that the nuclear ships were undergoing overhauls were excluded. (Final Report, p.5). Seventy percent of the excluded non-nuclear workers did not work in their shipyard during nuclear overhaul periods or had worked in the particular shipyard for less than a year. This helped to ensure the temporal consistency of the non-nuclear worker sample with the nuclear worker sample. (Final Report, p.7).
- Excluded from both the cohort and the controls were workers who had worked less than a year, non-shipyard workers, military personnel, visitors, females, persons with missing personnel records, etc. (Final Report, pp.25–40; Table, pp.42, 43).
- Each nuclear worker with a cumulative dose = 5.0 mGy was included in the cohort as long as complete data were available. (Final Report, p.44). Stratified sampling (shipyard, birth year, date of starting employment, job hazard index and number of years in shipyard prior to starting nuclear work) was used for the <5.0 mGy sample. (Final Report, pp.45–48).

- The sampling technique provided for racial consistency between the <5.0 mGy group and the = 5.0 mGy group. Racial records were not available for all shipyards. Data for certain yards indicated similar racial composition of the cohort and controls (Final Report, p.25).
- Controls were sampled randomly from blocks with similar work duration compared to nuclear workers, i.e., exposure to other aspects of working environment. Blocks were grouped to control for age and job hazard index. (Final Report, p.52).
- The controls were made equivalent to the cohort in age, job hazards and time since hire. (Final Report–Table, p.54, 55; graph, pp.56–60).
- Vital records were searched thoroughly. 'Status unknown' was equal between the cohort and controls. The low-dose cohort had a slightly higher 'status unknown' rate. (Final Report, p.101).

Virtually all of the workers involved in the NSWS were 'blue collar' workers and thus results were less susceptible to favourable socio-economic biases that may affect studies of 'white collar' occupational groups. Among occupations included in the nuclear shipyard worker study were machinists, toolmakers, pipefitters, shipfitters, electricians, engineers, carpenters, boatbuilders, welders, labourers, riggers, sheetmetal mechanics and warehouse men. Distribution of occupations amongst the cohort and controls was roughly similar in the shipyards (Final Report, p.237).

The lack of incentive pay for radiation work helped to avoid the possibility of positive selection bias that would favour more-skilled or higher-income shipyard workers. There was no prohibition on the hire of smokers for radiation work. The physical examination given to shipyard workers for radiation work was a possible source of confounding. Authorities differ on the role of the annual check-up in reducing mortality. Franks et al. (1996) found no reduction in mortality for men who received annual physicals compared to men who did not, while a 16-year study (Friedman et al., 1986) found a 30% reduction in mortality from 'potentially postponable' causes, largely colorectal cancer and hypertension. This reduction was most pronounced in the early years of the study. However, the two groups did not differ to a statistically significant degree in mortality from all other causes (84% of total mortality) or in total mortality. Nuclear workers were given radiation medical examinations prior to assignment and follow-ups every three years if they were exposed to 5.0 mGy or more in any year (Final Report, pp.124, 125).

3 Results of the NSWS

Table 2 presents all-cause mortality results from the three groups of shipyard workers. The cohort is split into three groups ranked by cumulative dose. The standardised mortality ratio (SMR) for all causes of death of the cohort (SMR = 0.76) was 24% lower ($p < 10–16$) than that of the 32,510 controls (SMR = 1.00) (Table 3.1.B. on p.301 of Final Report). Among the cohort, 2,215 deaths occurred whereas 2,875.9 deaths would have been expected (Final Report, p.328). Among the non-nuclear controls, 3,749 deaths occurred whereas 3,685.4 deaths would have been expected (Final Report, p.332).

Table 2 Deaths from All Causes, Death Rates** and Standardised mortality ratios with 95% confidence intervals for the cohort (NW = 5.0 mGy)); low dose cohort (NW < 5.0 mGy); and controls (NNW)

	NNW	*NW < 5.0 mGy*	*NW ≥ 5.0 mGy*	*NW ≥ 5.0 mGy*		
	Controls	*Low Dose Cohort*	*Cohort*	*Cohort*		
Subgrouping	All	All	All	0.5–	1.0–	5.0+
Number in Sample	32,510	10,348	27,872	5,431	13,357	9,084
Person-Years	4,25,070	1,39,746	3,56,091	69,489	1,72,531	1,14,071
Deaths	3,745	973	2,215	454	1,110	651
Death rate per 1000**	9	7.1	6.4	6.7	6.6	5.9
SMR	1	0.81	0.76	0.72	0.79	0.74
95% C.I.	(0.97-1.03)	(0.76–0.79)	0.73			

*Indicates that SMR is significantly lower than for NNW group at $p < 0.05$.

**Adjusted for deaths excluded from analysis due to unknown date of death.

Adapted from Tables 3.1.B and 3.1.C on pp.301, 302 of Final Report (Matanoski, 1991).

Table 3 presents a breakdown of deaths from various causes, which shows that SMRs from diseases of the circulatory system are significantly decreased in the cohort. No significant differences or trends were present between the groups from external causes including accidents and crimes.

The Final Report (p.334) states:

> "The SMRs from the categorical analysis in which the individual remains in the same group throughout follow-up (Table 4.1.A) indicate that the risks of death in the NNW group of shipyard workers are similar to that of the general population but the risks of total mortality in both groups of nuclear workers are lower than the US rate. The all cause mortality is highest for the NNW group and lowest for the NW = 0.5 [the cohort], which certainly does not suggest that radiation causes a general risk of death. In fact, in the NW = 0.5 group [the cohort], the mortality is only 76% of that of the general population and is significantly lower than would be expected."

The magnitude of the difference in mortality between cohort and the controls is so large that a physical examination for entry into the nuclear programme cannot account for the entire difference that is significant at $p < 1 \times 10^{-16}$. There was no prohibition against the hire of smokers for the nuclear programme and no incentive pay.

The dose range covered by the NSWS is relatively small but matches or is slightly higher than contemporary dose ranges [1970 and after] for nuclear workers and radiology workers. There is a pattern within the cohort of a decrease in overall mortality from the low-dose to the higher-dose groups, contrary to what all non-threshold models of radiation risk would predict. The low-dose cohort had a SMR of 0.81 (95% CI: 0.76, 0.86) compared to 0.76 (0.73, 0.79) for the cohort. The lowest SMR (0.74) was registered for the subgroup of the cohort who received 5.0 mGy or more.

Surprisingly, the text of the NSWS final report did not compare the cancer mortality of the cohort to that of the controls. Table 4 (a summary of Table 3.6 of the Final Report) indicates that SMR from all malignant neoplasms for the cohort was 0.95 (0.88, 1.03), significantly lower at $p < 0.01$ than that for the controls (1.12 (1.06, 1.20)).

The significantly lower cancer death rate of the cohort compared to the controls suggests that increased low LET radiation may have stimulated their immune systems, as reported in other irradiated populations (Calabrese and Baldwin, 2000).

Table 3 Deaths from various causes, Death Rates** and Standardised mortality ratios with 95% confidence intervals for the cohort (NW = 5.0 mGy cumulative dose); cohort (NW < 5.0 mGy); and controls (NNW). O/E = observed/expected

Category	*NNW (control)*		*NW<5.0* mGy *(low dose cohort)*		*NW ≥ 5.0* mGy *(cohort)*	
Cause of death	*O/E*	*SMR*	*O/E*	*SMR*	*O/E*	*SMR*
Total morality ***	3749/3685.41	1.02 (0.98–1.05)	973/1173.50	0.83 (0.78–0.88)*	2215/2875.91	0.77 (0.74–0.80)*
All diseases of circulatory system	1626/1751.85	0.93 (0.88–0.97)	418/549.86	0.76 (0.69–0.83)*	970/1325.99	0.73 (0.69–0.78)*
Arteriosclerotic heart disease	1166/1263.23	0.92 (0.87–0.98)	316/400.79	0.79 (0.70–0.88)	719/975.47	0.74 (0.68–0.79)*
Vascular lesions of CNS	183/199–38	0.92 (0.79–1.06)	37/58.60	0.63 (0.44–0.87)	96/132.81	0.72 (0.59–0.88)
Allergic, Endocrine, Metabolic	53/63.08	0.84 (0.63–1.10)	13/20.01	0.65 (0.35–1.11)	25/46.83	0.51 (0.33–0.76)
Nervous and sensory organs	29/34.50	0.84 (0.56–1.21)	4/11.16	0.38 (0.10–0.92)	12/27.78	0.43 (0.22–0.75)
All disease of digestive system	189/193.24	0.98 (0.84–1.13)	45/63.98	0.70 (0.51–0.94)	115/163.48	0.70 (0.56–0.84)
Diabetes mellitus	39/51.58	0.76 (0.54–1.03)	9/16.30	0.55 (0.29–1.06)	24/39.56	0.61 (0.39–0.90)
Cirrhosis of liver	104/114.72	0.91 (0.74–1.10)	19/38.6	0.49 (0.29–0.76)	67/102.36	0.65 (0.51–0.83)
All respiratory disease	201/208.89	0.96 (0.83–1.10)	42/64.41	0.65 (0.47–0.88)	82/151.58	0.54 (0.43–0.67)*
Pneumonia	66/66.93	0.99 (0.76–1.25)	13/20.24	0.64 (0.34–1.10)	33/47.15	0.70 (0.48–0.96)
Emphysema	42/51.08	0.88 (0.64–1.10)	11/15.52	0.71 (0.35–1.27)	14/35.74	0.39 (0.21–0.66)
Asthma	9/5.08	1.77 (0.81–3.36)	0/1.59	0.00 (0.00–230	4/3.75	1.07 (0.29–2.73)
All genito-urinary	44/37.36	1.18 (0.66–1.58	9/11.31	0.80 (0.32–1.64)	11/26.06	0.42 (0.21–0.76)
Mental and personality	27/26.37	1.02 (0.67–1.49)	7/8.78	0.80 (0.32–1.64)	10/22.83	0.44 (0.21–0.81)
All infectious and parasitic	18/28.58	0.63 (0.37–1.00)	2/9.12	0.22 (0.02–0.79)	19/22.05	0.86 (0.52–1.35)
All external causes	413/474.26	0.87 (0.79–0.86)	133/153.99	0.86 (0.72–1.02)	253/388.20	0.65 (0.57–0.74)*
All accidents	245/305.10	0.80 (0.71–0.91)	91/98.89	0.92 (0.74–1.13)	168/245.70	0.68 (0.58–0.80)
Motor vehicle accidents	120/155.62	0.77 (0.64–0.92)	50/50.04	1.00 (0.74–1.33)	95/123.52	0.77 (0.62–0.94)
Suicide	1.6/109.82	0.97 (0.79–1.17)	27/36.10	0.75 (0.49–1.09)	60/92.51	0.65 (0.49–0.83)

*Indicates that SMR is significantly lower than for NNW group at $p < 0.05$.

**Adjusted for deaths excluded from analysis due to unknown date of death.

***Using age-calendar time specific rates for US white males.

Adapted from pp.326–333 of Final Report (Matanoski, 1991).

Table 4 Cancer mortality classified by site. Also includes figures for mortality from all cancers and groupings of sites. Standardised mortality ratios with 95% confidence intervals for cohort (NW = 5.0 mGy cumulative dose)); low-dose cohort (NW < 5.0 mGy); and controls (NNW). O/E = observed/expected

Category	*NNW (control)*		*NW<5.0 mGy (Low dose cohort)*		*NW≥5.0 mGy (cohort)*	
Cause of death	*O/E*	*SMR*	*O/E*	*SMR*	*O/E*	*SMR*
All malignant neoplasms	878/784.60	1.12 (1.06-1.20)	243/254.23	0.96 (0.84–1.08)	603/632.30	0.95 (0.88–1.03)*
Cancers of digestive organs	224/199.40	1.12 (0.96–1.28)	65/63.72	1.02 (0.79–1.30)	146/156.08	0.94 (0.79–1.10)
Buccal cavity and pharynx	23/24.63	0.93 (0.59–1.40)	6/8.18	0.73 (0.27–1.60)	15/20.82	0.72 (0.40–1.19)
Esophagus	27/18.47	1.46 (0.96–2.13)	7/6.08	1.15 (0.46–2.37)	16/15.37	1.04 (0.59–1.69)
Stomach	48/32.25	1.49 (1.10–1.97)	13/10.15	1.28 (0.68–2.19)	23/24.52	0.94 (0.59–1.41)
Large intestine	59/67.55	0.87 (0.66–1.13)	21/21.48	0.98 (0.60–1.49)	41/52.42	0.78 (0.56)–1.06)
Rectum	20/20.44	0.98 (0.60–1.51)	7/6.46	1.08 (0.43–2.23)	6/5.59	1.03 (0.59–1.67)
Liver	15/13.68	1.10 (0.61–1.81)	3/4 34	0.69 (0.14–2.02)	17/10.53	1.61 (0.94–2.58)
Pancreas	48/41.57	1.15 (0.85–1.53)	11/13.43	0.82 (0.41–1.47)	26/33.25	0.78 (0.51–1.15)
All respiratory system cancers	323/288.93	1.12 (1.00–1.25)	110/95.54	1.15 (0.95–1.39)	259/242.27	1.07 (0.94–1.21)
Lung cancer	306/274.61	1.11 (0.99–1.25)	98/90.83	1.08 (0.88–1.31)	237/230.41	1.03 (0.90–1.17)
Mesothelioma†		2.41 (1.15–4.43)		5.75 (2.48–11.33)		5.11 (3.03–8.08)
Skim	18/17.80	1.06 (0.63–1.67)	7/5.62	1.25 (0.50–2.57)	7/14.47	0.48 (0.91–1.00)
Kidney	26/20.26	1.28 (0.84–1.69)	4/6.68	0.60 (0.16–1.53)	15/16.95	0.89 (0.50–1.46)
Bladder	17/19.68	0.86 (0.50–1.38)	6/5.99	1.00 (0.37–2.18)	18/13.86	1.30 (0.77–2.05)
Testis	6/5.38	1.12 (0.41–2.44)	1/1.73	0.58 (0.01–3.21)	1/4.28	0.33 (0.00–1.30)
Cancer of prostate	55/41.51	1.32 (1.09–1.72)	13/11.93	1.09 (0.56–1.86)	27/25.99	1.04 (0.58–1.51)
Cancer of brain and CNS	29/26.43	1.09 (0.73–1.58)	4/8.98	0.45 (0.12–1.14)	22/23.24	0.95 (0.59–1.43)
Bone	4/3.43	1.17 (0.31–2.89)	0/1.10	0.00 (0.00–1.35)	0/2.68	0.00 (0.00–1.37)
Leukemia	29/30.96	0.94 (0.63–1.39)	4/9.67	0.42 (0.11–1.04)	21/24.20	0.87 (0.54–1.33)
All lymphopoietic cancer	84/79.07	1.06 (0.85–1.32)	13/25.59	0.51 (0.27–0.87)	50/63.59	0.79 (0.58–1.04)
Hodgkins disease	12/9.78	1.23 (0.63–2.14)	1/3.21	0.31 (0.00–1.73)	5/8.00	0.62 (0.20–1.46)
Lymphosarcoma Reticulosarcoma	18/16.10	1.12 (0.84–1.77)	4/5.26	0.76 (0.20–1.95)	5/13.11	0.38 (0.12–0.89)
Other lymphatic tissue	24/21.33	1.13 (0.72–1.67)	4/6.96	0.57 (0.15–1.47)	17/17.56	0.97 (0.56–1.55)

*Indicates that SMR is significantly lower than for NNW group at $p < 0.05$.

†Related to asbestos exposure. Mesothelioma data adapted from Table 3.4.A., p.317 of Final Report.

Source: Adapted from Table 3.6.B (pp.328–329), Table 3.6.C (pp.330–331), and Table 3.6.D (pp.332–333) of Final Report (Matanoski, 1991). Adjusted for deaths excluded because of unknown date of death. See Tables 3.1.A (p. 296) and 3.1.B (p. 301) of Final Report (Matanoski, 1991)

In addition, the cohort had lower rates for the most radiation-sensitive cancers, leukaemia and haematopoietic cancers than the controls: the unadjusted SMRs were 1.06 (0.85, 1.32) for the controls; 0.79 (0.58, 1.04) for the cohort; and 0.51 (0.27, 0.87) for the low-dose cohort. The Final Report (p.334) states:

> "The SMRs for leukaemia and all lymphatic and haematopoietic cancers indicate risks of these diseases among nuclear workers which are below those of the general population."

The cohort had a higher rate of mesothelioma than did the controls, who also had excess mesothelioma. This is likely related to asbestos exposure in the cramped conditions of submarine work.

4 Discussion

The Summary of the Final Report did not mention the 24% lower SMR from all causes of the cohort ($p < 10^{-16}$) compared to the controls. A 24% lower SMR implies a 2.8-year increase in average lifespan.

The NSWS results are in general agreement with reductions in overall mortality from other studies of workers in nuclear facilities and radiology practice in the USA, UK, Canada and Australia (Smith and Doll, 1981; Smith and Douglas, 1986; Fraser et al., 1993; Gilbert et al., 1993; Luckey, 1994, 1997; Boice et al., 1995; Rodriguez et al., 1997; Doody et al., 1998; Berrington et al., 2001; Sont et al., 2001; Habib, 2002). Most of these studies also demonstrated reductions in all-cancer mortality of the radiation workers.

Workers in many professions experience reduced mortality compared to the general population due to the 'healthy worker effect'. This is because employee populations do not include individuals who are too sick to work or to commute. There are also fewer individuals with serious alcohol and drug abuse problems among employee populations. For this reason, a study that compares radiation workers with a group of unexposed similar workers is preferable to a study that compares radiation workers with members of the general population.

The 100-year study of British radiologists (Berrington et al., 2001) shows health benefits from radiation, which agree qualitatively with those of the NSWS. The radiologists' exposures were low LET and the all-male physicians group was matched for occupation. The SMR for deaths from all causes for British radiologists who joined a radiological society from 1955–1979 was 32% lower ($p < 0.001$) than that of all male physicians in England and Wales.

A comparison of doses between the British radiologists and US shipyard workers along with their respective relative risks (SMRs of exposed group compared to control group) is of interest. Both studies involved chronic radiation exposure for multiple years at low-dose rates 3–5 times natural background dose rate.

It is estimated that the 1955–1979 British radiologists were exposed to 5 mGy each year, reaching a cumulative lifetime (20 years) dose of 100 mGy (Berrington et al., 2001). The main cohort of shipyard workers was exposed to a median dose of 2.80 mGy each year (Table 1). The average number of working years of the main shipyard cohort was 12.8 years (obtained by dividing the value of 356091 person-years

by the sample number of 27872 in Table 2). Therefore, the median cumulative dose for the main cohort of shipyard workers is 35.8 mGy (2.8 mGy × 12.8 years).

The SMRs for British radiologists registered from 1955–1979 are 0.68 for deaths from all causes and 0.71 for deaths from cancer, while those for the cohort of shipyard workers are 0.76 for deaths from all causes and 0.85 (0.95/1.12) for deaths from all cancer. The reduction in all-cause death in the NSWS was greater than that for cancer deaths in both the cohort and the low-dose cohort. Low-dose-rate radiation has been shown to have anti-inflammatory properties (Rodel et al., 2002). Cardiovascular disease and stroke have been linked with inflammatory processes (Ridker et al., 1997; Leinonen and Saikku, 2000; Kaplan and Frischman, 2001; Koenig, 2001). It is conceivable that low-dose-rate radiation, through a mechanism involving immune response, protects against inflammatory processes involved in the development of cardiovascular disease and stroke.

If the degree of the beneficial effect of radiation on human health depends on the dose rate (up to an optimum dose rate), the British radiologists would be expected to display a stronger beneficial effect, (smaller SMR) for both all-cause death and cancer death than the shipyard cohort, if both groups received doses that are below the optimum dose rate (maximum benefit). This is seen in the results from the two groups, since the shipyard cohort, exposed to a median of 2.8 mGy y^{-1}, experienced a 24% reduction in SMR for all causes, compared to a 32% reduction in SMR for the 1955–1979 radiologists with an estimated 5 mGy y^{-1}. The optimum dose rate may be higher than the annual dose rate received by 1955–1979 British radiologists.

The health benefits of radiation shown in the NSWS and the British radiologist study suggest radiation stimulation of the immune system (Congdon, 1987; Caratero et al., 1998; Calabrese and Baldwin, 2000, 2002; Cameron, 2001, 2002). The results are consistent with the lower cancer mortality of individuals exposed to high natural background levels in mountain regions of the USA (Frigerio et al., 1973; Jagger, 1998).

The DOE contract for the NSWS was to examine ‘risks’ rather than ‘health benefits’. The Conclusion of the Final Report (p.357) states correctly, ‘The [exposed] population does not show any risk which can be clearly associated with radiation exposure in the current analysis’. Even though the NSWS was looking for risks, it would have been appropriate for the authors to mention the significant health benefits found among the nuclear workers. If the goal of the study had been to look for health benefits of low-dose-rate radiation, it would have been a success.

Since the NSWS was rigorously designed to eliminate confounding factors as much as possible and had the overview of outside experts, health benefits from radiation are almost certainly present. The Final Report discusses the possibility that selection favours the cohort compared to the controls. There may be a slight selection factor related to medical examinations for acceptance into the nuclear programme, despite the lack of financial incentive. This weak ‘healthy worker effect’ should diminish with time after beginning of employment. Thus, it would be expected to be stronger for workers recently selected to be nuclear workers (i.e., the low-dose cohort) than for those working long enough to qualify to be in the cohort. However, this is contradicted by the reduced mortality for the cohort, compared to the low-dose cohort. The Final Report states (p.336): “… all cause mortality, (Tables 3.1.A-3.1.B) cardiovascular mortality (Tables 3.6.B-3.6.D) and lung cancer mortality (Tables 3.5.A-3.5.B) actually show higher mortality rates in the NW < 0.5 rem [low-dose cohort] than in the NW = 0.5 rem

[cohort]." While historical high acute and chronic exposures have been demonstrated to increase cancer mortality (Matanoski et al., 1975; Koshurnikova et al., 1994; Kossenko and Degteva, 1994; Berrington et al., 2001; Nyberg et al., 2002), doses below 200 mGy (acute) have not been demonstrated to be hazardous (Heidenreich et al., 1997). Residents of mountain states have lower cancer rates than residents of Coastal Plain states (Frigerio et al., 1973; Jagger, 1998). Additionally, life expectancies in mountain states are approximately one year greater than in Coastal Plain states (Murray et al., 1998). Natural background (excluding dose from radon progeny) in mountain regions is approximately twice that of Coastal Regions (NCRP, 1988). The average shipyard dose rate of ~7.6 mGy y^{-1} is somewhat higher than most natural background levels in the USA, but is within the range of high natural background areas worldwide (Ghiassi-nejad et al., 2002).

The shipyard and radiologist data provide assurance that it would be ethical to do a double blind randomised controlled trial of giving increased background radiation to senior citizens in the US Gulf States equal to the dose rate found in the mountain states (Cameron, 2001).

Boice (2001) states that the relatively small doses and small range of doses in the NSWS 'limits interpretation'. This is not a limitation since the range is the typical dose range for modern radiation workers.

Decreased mortality at relatively young ages in a group such as the shipyard workers or radiologists results in increased average longevity, similar to an observation of US radiologists (Matanoski et al., 1987).

The key comparisons in the NSWS were between non-nuclear and nuclear workers with the same jobs and ages and among dose-ranked groups of nuclear workers. Since cohorts and controls were compared to each other, there should be little 'healthy worker effect', especially of the magnitude of a 24% difference in SMR. The second author (JRC), who was also a member of the Technical Advisory Panel (TAP), recalls no discussion of 'selection bias' during the many meetings of the TAP. All TAP members approved the NSWS Final Report and evidence of selection bias could have been brought up at that time.

Omission of publication of 'null-harm' or 'benefit' studies such as the NSWS may contribute to a publication bias (Stern and Simes, 1997) in favour of studies that yield harmful effects. Lea et al. (2000) and Pollycove and Feinendegen (1999) noted errors in methodology and small sample sizes in smaller published studies that have been cited as evidence of harm from low-dose-rate radiation where harm did not exist.

5 Conclusion and recommendations

The NSWS is the world's largest and most rigorously controlled study of radiation workers. Significantly lower total mortality was observed in both groups of nuclear workers. Significantly lower mortality from all causes was observed among the cohort of nuclear workers who were exposed to an average dose rate of 7.59 mGy y^{-1} and median dose rate of 2.80 mGy y^{-1} than among unexposed controls. In addition, the cohort had significantly reduced mortality for all cardiovascular disease, arteriosclerotic heart disease, respiratory diseases and cancer. This significantly lower mortality contradicts the linear non-threshold (LNT) model of radiation risk.

It is possible that healthy workers would be able to spend more time at work to accumulate the higher doses than unhealthy employees, who might have accumulated lower doses because they spent fewer years on the job. This may be partly responsible for the lower cardiovascular and all-cause mortality among the higher-dose group. We recommend an extension of the NSWS data collection and analysis from 1981 to 2001 to help resolve these questions.

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Appendix 6

Health Risks from Low Ionizing Radiation
60th Annual Meeting of Health Physics Society
Indianapolis, Indiana, July 12-16, 2015

Future of Radiation Protection Regulations

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Main Points

- We have 120 years medical radiation experience and data
- The 1934 ICRP regulations protected radiologists very well
- The 1950s NAS-NCRP recommendations to use LNT were *not* scientific; regulators accepted them *without* any review
- International consensus exists to use LNT model to predict cancer risks and to follow ALARA policy
- Regulatory *error of omission*: evidence low-dose benefits
- Need public education program; science-based regulations to stop radiation fear and keep valuable benefits of low-dose treatments, medical imaging and nuclear energy

Learn the important lessons of Chernobyl, Fukushima regarding the many victims of “emergency measures”

Past radiation protection policy

- Safe “tolerance dose” limit 0.2 R/day for 1920s radiologists
- 1% of 600 R erythema dose, spread over a month (30 days)
- Dose rate was based on experience from 1896 until ~1920
- 0.2 R/day x 250 days/year = 50 R/y x 9.3 = 470 mGy/year
- The 1934 ICRP standard recommended 0.2 R/day
- Later studies on British radiologists found *lower* mortality and *lower* cancer mortality compared to unexposed groups
- This method was adequate for radiation protection.

Present radiation protection policy

- LNT model to assess risk of radiation-induced cancer
- Radiation protection policy is based on ALARA
- Deception by geneticists Herman Muller and Curt Stern
- Scientists wanted to stop a-bombs; create fear of fallout
- In 1956 US NAS (with Rockefeller Foundation) misled the world by recommending LNT to assess genetic risk
- In 1958 NCRP recommended LNT to assess radiation-induced cancer risk for somatic cells (no evidence)
- World regulatory agencies accepted LNT without review
- Worldwide fear of radiation-induced genetic damage and cancer limits LDR treatment, CT imaging, nuclear energy

Calabrese 2013, How US NAS misled world community on cancer risk assessment

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REVIEW ARTICLE

How the US National Academy of Sciences misled the world community on cancer risk assessment: new findings challenge historical foundations of the linear dose response

Edward J. Calabrese

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Abstract This paper extends several recent publications indicating that Hermann J. Muller: (1) Made deceptive statements during his Noble Prize Lecture on December 12, 1946, that were intended to promote the acceptance of the linear dose-response model for risk assessment for ionizing radiation and (2) that such actions of Muller were masked by a series of decisions by Muller's long-time colleague and esteemed radiation geneticist Curt Stern, affecting key publications in

Introduction

It was recently discovered that the 1946 Nobel Prize Lecture for Biology and Medicine by Laureate Hermann J. Muller misled the audience on the nature of the dose response in the low-dose zone concerning the effects of ionizing radiation on germ-cell mutagenicity to advance an ideologically motivated risk assessment policy (Calabrese 2011a, b, 2012). Evidence to support this conclu-

Calabrese 2015, NAS scientific misconduct in recommending LNT for risk assessment

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LETTER TO THE EDITOR, NEWS AND VIEWS

Cancer risk assessment foundation unraveling: New historical evidence reveals that the US National Academy of Sciences (US NAS), Biological Effects of Atomic Radiation (BEAR) Committee Genetics Panel falsified the research record to promote acceptance of the LNT

Edward J. Calabrese

Received: 15 December 2014 / Accepted: 6 January 2015

Abstract The NAS Genetics Panel (1956) recommended a switch from a threshold to a linear dose response for radiation risk assessment. To support this recommendation, geneticists on the panel provided individual estimates of the number of children in subsequent generations (one to ten) that would be adversely affected due to transgenerational reproductive cell mutations. It was hoped that there would be close agreement among the individual risk estimates. However, extremely large ranges of variability and uncertainty characterized the wildly divergent expert

Keywords Mutation · Cancer · Risk assessment · Linear no-threshold (LNT) · Threshold dose response

In 1956, the US National Academy of Sciences (NAS) published their long-awaited reports addressing national concerns about how ionizing radiation may affect such entities as oceans/fisheries, agriculture/food supply, meteorology/atmosphere, medicine/pathology, genetics and disposal of radioactive wastes. As it turns out, the report that domi-

Failure of regulators to assess LNT model recommended by NAS prior to their acceptance

Arch Toxicol
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LETTER TO THE EDITOR, NEWS AND VIEWS

An abuse of risk assessment: how regulatory agencies improperly adopted LNT for cancer risk assessment

Edward J. Calabrese

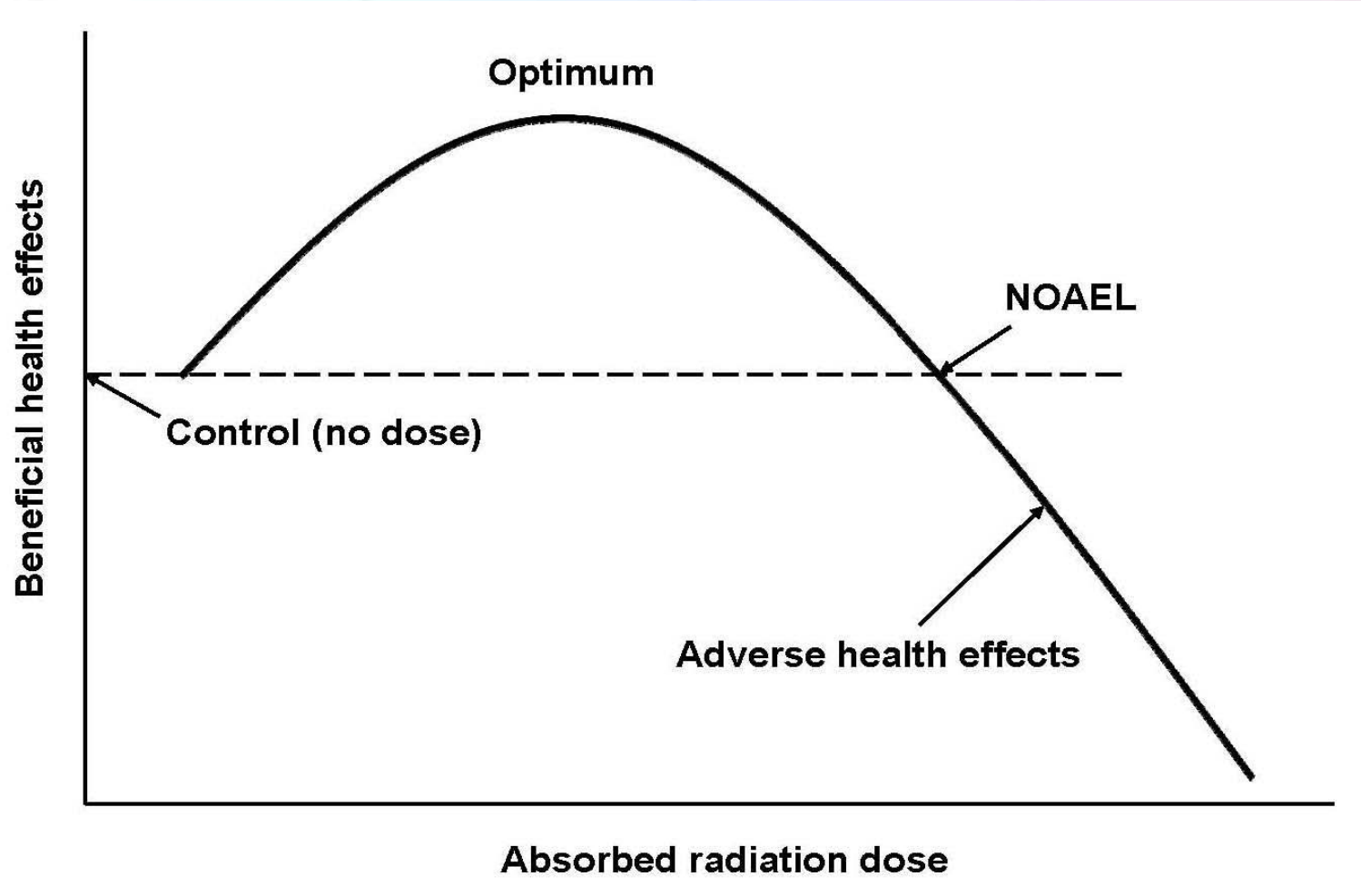
Received: 15 December 2014 / Accepted: 6 January 2015

Abstract The Genetics Panel of the National Academy of Sciences' Committee on Biological Effects of Atomic Radiation (BEAR) recommended the adoption of the linear dose–response model in 1956, abandoning the threshold dose–response for genetic risk assessments. This recommendation was quickly generalized to include somatic cells for cancer risk assessment and later was instrumental in the adoption of linearity for carcinogen risk assessment by the Environmental Protection Agency. The Genetics Panel failed to provide any scientific assessment to support its recommendation. The most significant event in the history of environmental risk assessment was the recommendation by the United States National Academy of Sciences (NAS), Biological Effects of Atomic Radiation (BEAR) Committee, Genetics Panel in 1956 to switch from a threshold to a linear dose–response model for the assessment of genomic mutation risk (Anonymous 1956; NAS/NRC 1956). Within a brief period of time, this recommendation became generalized to somatic cells by other governmental advisory committees and was eventually applied to cancer risk assess-

Future radiation protection policy

- Radiation protection should be science-based; biology!
- Have 120 years medical irradiation experience and data
- Have biological model based on radiation hormesis
- Two types of risk: risk of harm and risk of losing a benefit
- Regulators focus on risk of harm and ignore the benefits
- Regulatory *error of omission*: risk the loss of the benefits
- Future regulatory exposure limits should be as high as reasonably safe (AHARS) based on measured NOAELs in radiation hormesis model, for: acute or chronic or fractionated exposures

Radiation hormesis dose-response model



Beneficial Effects of Low Radiation

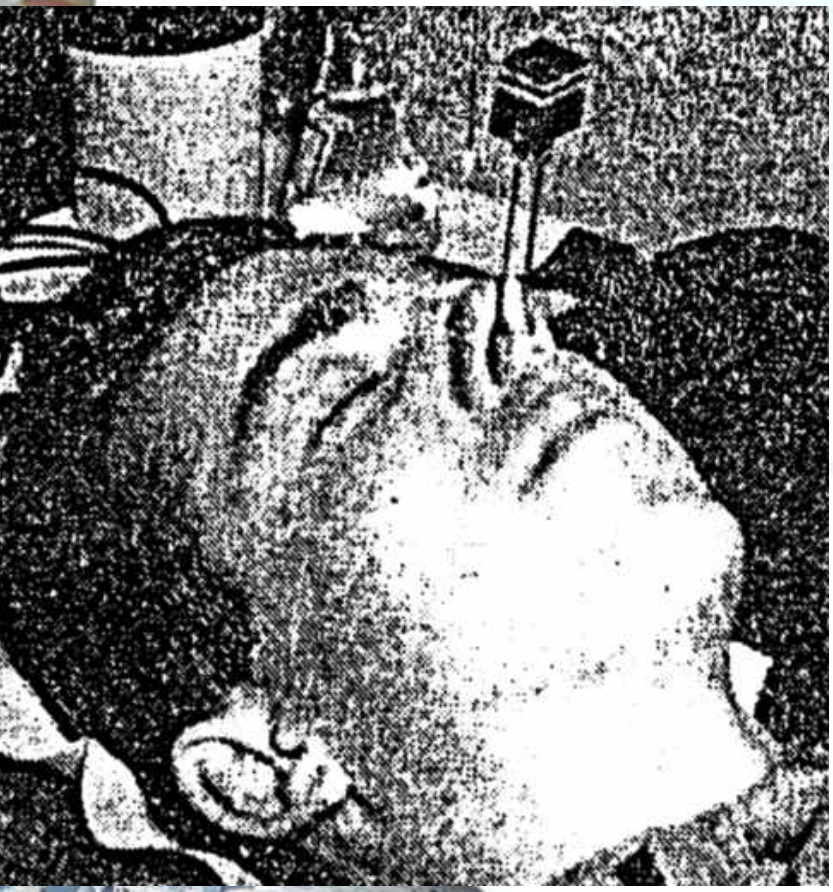
Medical practitioners used radiation ~1900 to ~1960, to:

- Eliminate metastases or slow cancer growth
- Accelerate healing of wounds
- Stop infections: gas gangrene, carbuncles and boils, sinus, inner ear, etc.
- Treat arthritis and other inflammatory conditions
- Treat swollen lymph glands
- Cure pneumonia
- Cure asthma

with no apparent increase of cancer incidence

Nasal Radium Irradiation

US CDC estimate: up to 2,600,000 children received NRI from 1945-1961 as a standard medical practice to shrink adenoids. Typical Navy protocol: four 10 minute irradiations 2-4 weeks apart. **Contact** gamma dose = 2000 rad (20 Gy); **1 cm depth** dose = 206 rad (2 Gy) Beta dose 68 rad (0.7 Gy) from each applicator. Excess lymphoid tissue at Eustachian tube openings tended to prevent pressure equalization, aggravation middle ear problems.



Position of the child patient during treatment

Anesthesia with cocaine precedes introduction of the applicator which is then left in place for twelve minutes on each side
(From Proctor, D.F., *"The Tonsils and Adenoids in Childhood"*, p. 17, Charles C. Thomas, Publisher, 1960)

http://www.cancer.gov/cancertopics/factsheet/Risk/nasopharyngeal-radium

National Cancer Institute
at the National Institutes of Health

Reviewed: January 10, 2003

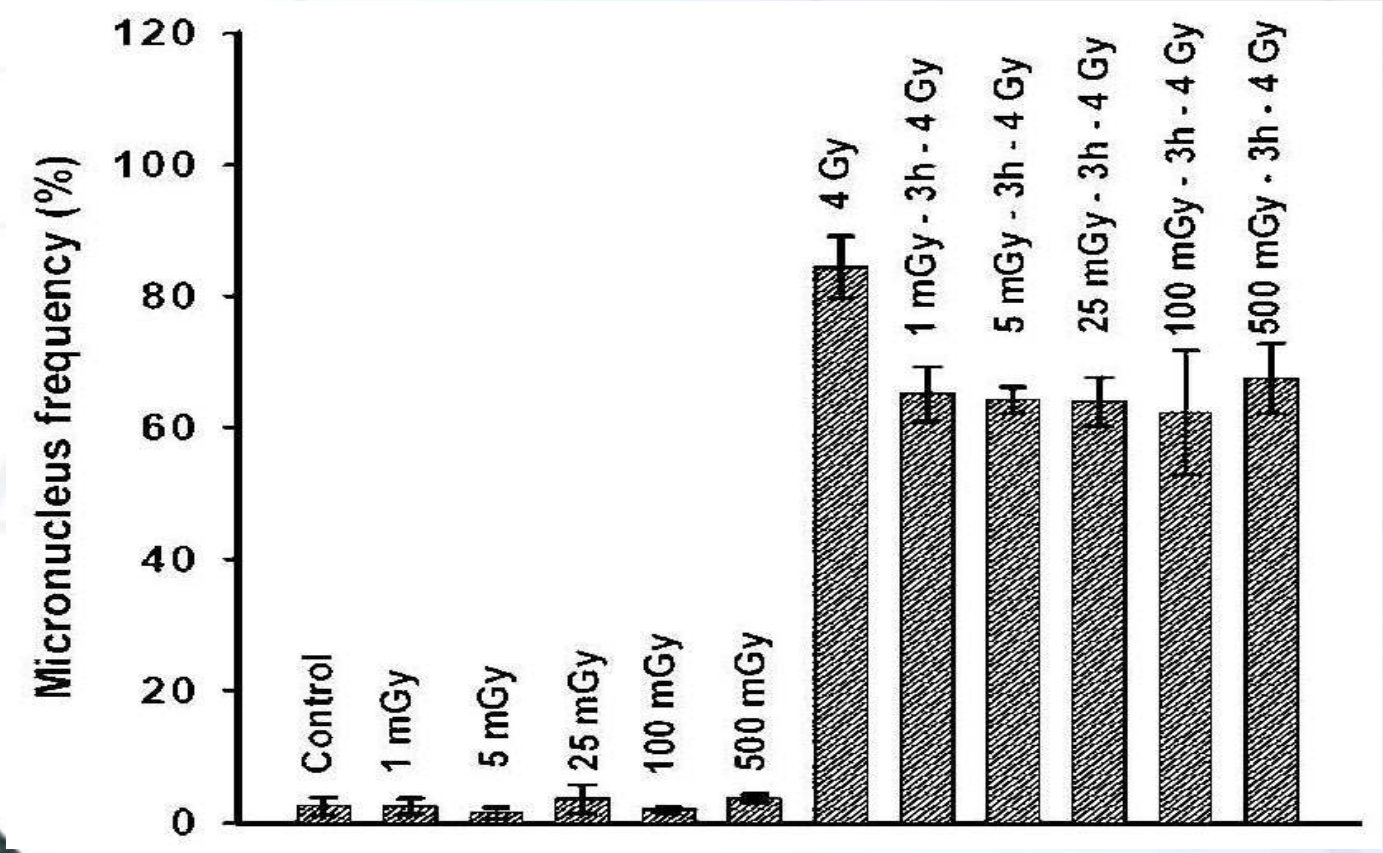
Nasopharyngeal Radium Irradiation (NRI) and Cancer: Fact Sheet

Key Points

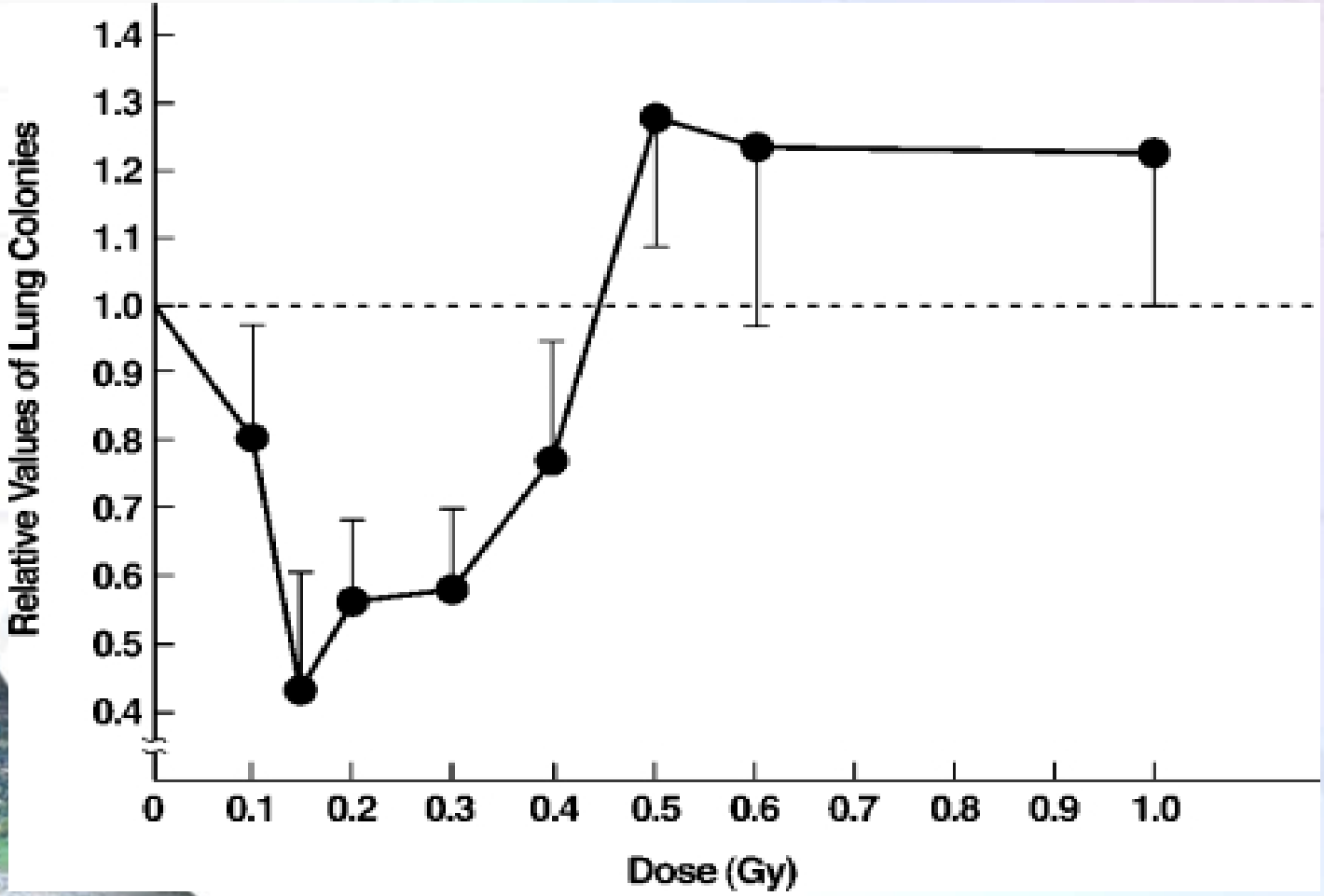
- Nasopharyngeal radium irradiation, (NRI) was widely used from 1940 through 1970 to treat ear dysfunctions in children and military personnel. Use of NRI was stopped when concern arose about possible adverse effects, including cancer.
- The purpose of NRI was to shrink swollen tissue in the nasopharyngeal cavity—the opening behind the nose and mouth. The treatment involved inserting a radioactive compound through the nostril into the nasopharyngeal opening for short periods of time. Some radiation exposure to the salivary, thyroid, and pituitary glands, and to brain tissue also occurred during this process.
- NRI was used in several European countries, Canada, and the United States. In the United States, it is estimated that between 0.5 million and 2.5 million children and at least 8,000 military personnel were treated with NRI.
- Children are considered to be the most vulnerable to radiation-related cancers.
- At this time, worldwide studies have not confirmed a definite link between NRI exposure and any disease.

Adaptive Response

A low radiation dose up-regulates human cell repair capability
1 to 500 mGy decreases risk of 4 Gy challenging dose

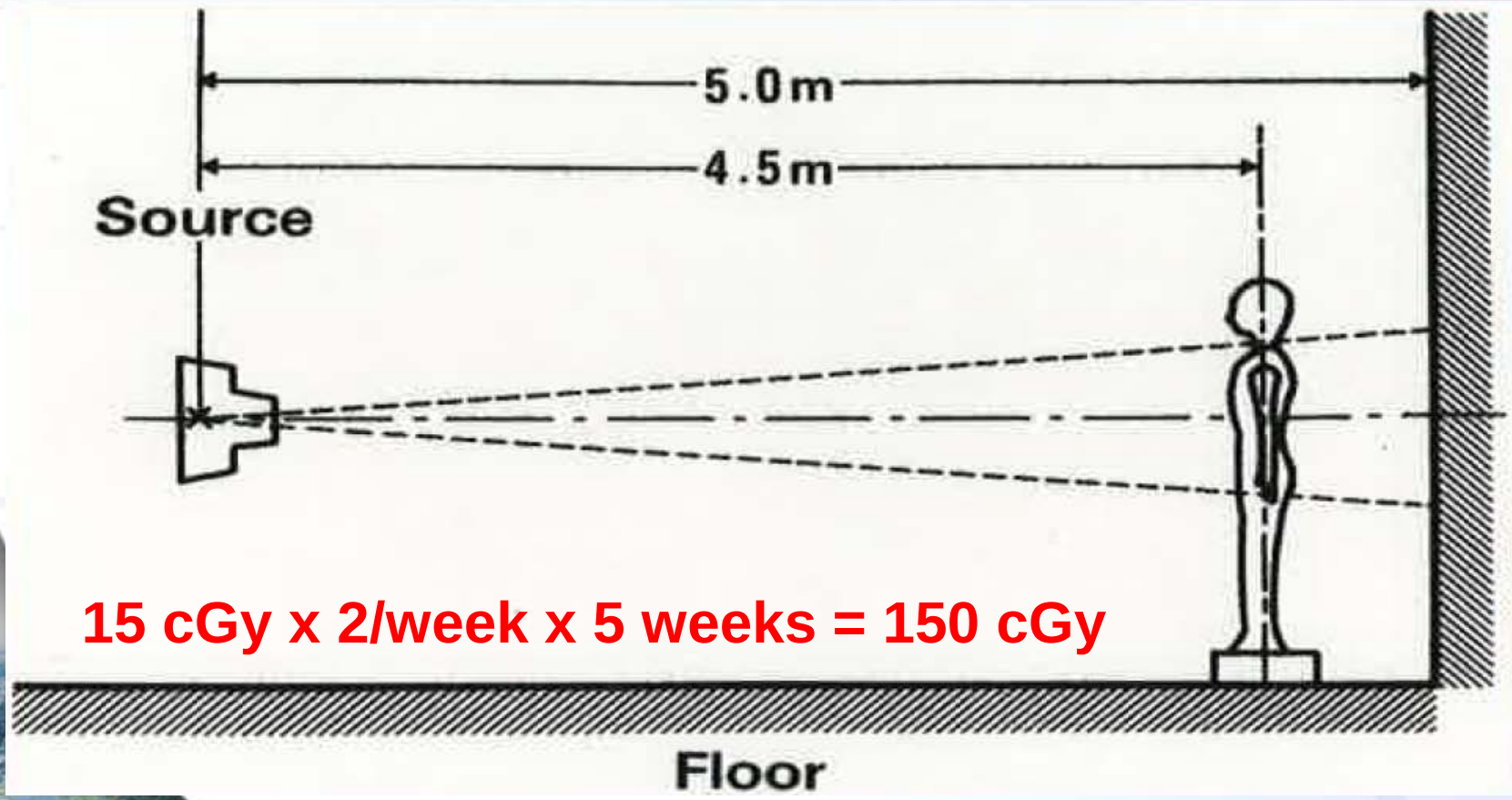


Results of one of Sakamoto's studies:
Spontaneous Lung Metastasis vs. Total Body Dose



Source – Patient Schema for Half Body LDR

"Observed the total removal of tumors in all regions of the body of a patient with advanced ovarian cancer."



HB-LDI Therapy 1500 mGy; prophylaxis against cancer

RADIATION RESEARCH 171, 1–8 (2009)
0033-7587/09 $15.00

Reduction in Mutation Frequency by Very Low-Dose Gamma Irradiation of *Drosophila melanogaster* Germ Cells

Keiji Ogura,[a,b,1] Junji Magae,[a,b] Yasushi Kawakami[b] and Takao Koana[a,2]

[a] *Radiation Safety Research Center, Central Research Institute of Electric Power Industry, Iwado-Kita 2-11-1, Komae, Tokyo 201-8511, Japan; and*
[b] *Biotechnology Department, Institute of Research and Innovation, Takada 1201, Kashiwa, Chiba 277-0861, Japan*

Ogura, K., Magae, J., Kawakami, Y. and Koana, T. Reduction in Mutation Frequency by Very Low-Dose Gamma Irradiation of *Drosophila melanogaster* Germ Cells. *Radiat. Res.* 171, 1–8 (2009).

To determine whether the linear no-threshold (LNT) model for stochastic effects of ionizing radiation is applicable to very low-dose radiation at a low dose rate, we irradiated immature male germ cells of the fruit fly, *Drosophila melanogaster*, with several doses of ^{60}Co γ rays at a dose rate of 22.4 mGy/h. Thereafter, we performed the sex-linked recessive lethal mutation assay by mating the irradiated males with nonirradiated females. The mutation frequency in the group irradiated with 500 μGy was found to be significantly lower than that in the control group ($P < 0.01$), whereas in the group subjected to 10 Gy irradiation, the mutation frequency was significantly higher than that in the control group ($P < 0.03$). A J-shaped dose–response relationship was evident. Molecular experiments using DNA microarray and quantitative reverse transcription PCR indicated that several genes known to be expressed in response to heat or chemical stress and *grim*, a positive regulator of apoptosis, were up-regulated immediately after irradiation with 500 μGy. The involvement of an apoptosis function in the non-linear dose–response relationship was suggested. © 2009 by Radiation Research Society

for the estimation of cancer risks, because cancer risk was considered to be proportional to mutation rate, and the mutation rate was found to be proportional to radiation dose in high dose ranges. Therefore, cancer risk was considered to be proportional to radiation dose at high doses.

Much later, the mutation frequency in murine spermatogonia was found to be dependent not only on the total radiation dose but also on the dose rate (*3*). It was inferred that the repair function of irradiated cells was sufficient with chronic irradiation and that the cells are able to repair radiation-induced DNA damage without errors. However, doses exceeding the repair capacity would cause incomplete repair and/or misrepair, which would occasionally result in mutations. Although Russell *et al.* (*3*) indicated that a low dose rate resulted in a low inclination of the dose–response curve, a threshold dose was not found at any dose rate.

In contrast, we reported previously that in the somatic mutation assay using *Drosophila*, there was a threshold dose at approximately 1 Gy and that a mutation in the DNA repair function decreased the threshold value (*4*). The existence of a threshold, as determined in the sex-linked recessive lethal assay, using repair-proficient immature germ cells (spermatogonia and spermatocytes), was also indicated, and it was inferred that the excision repair function was

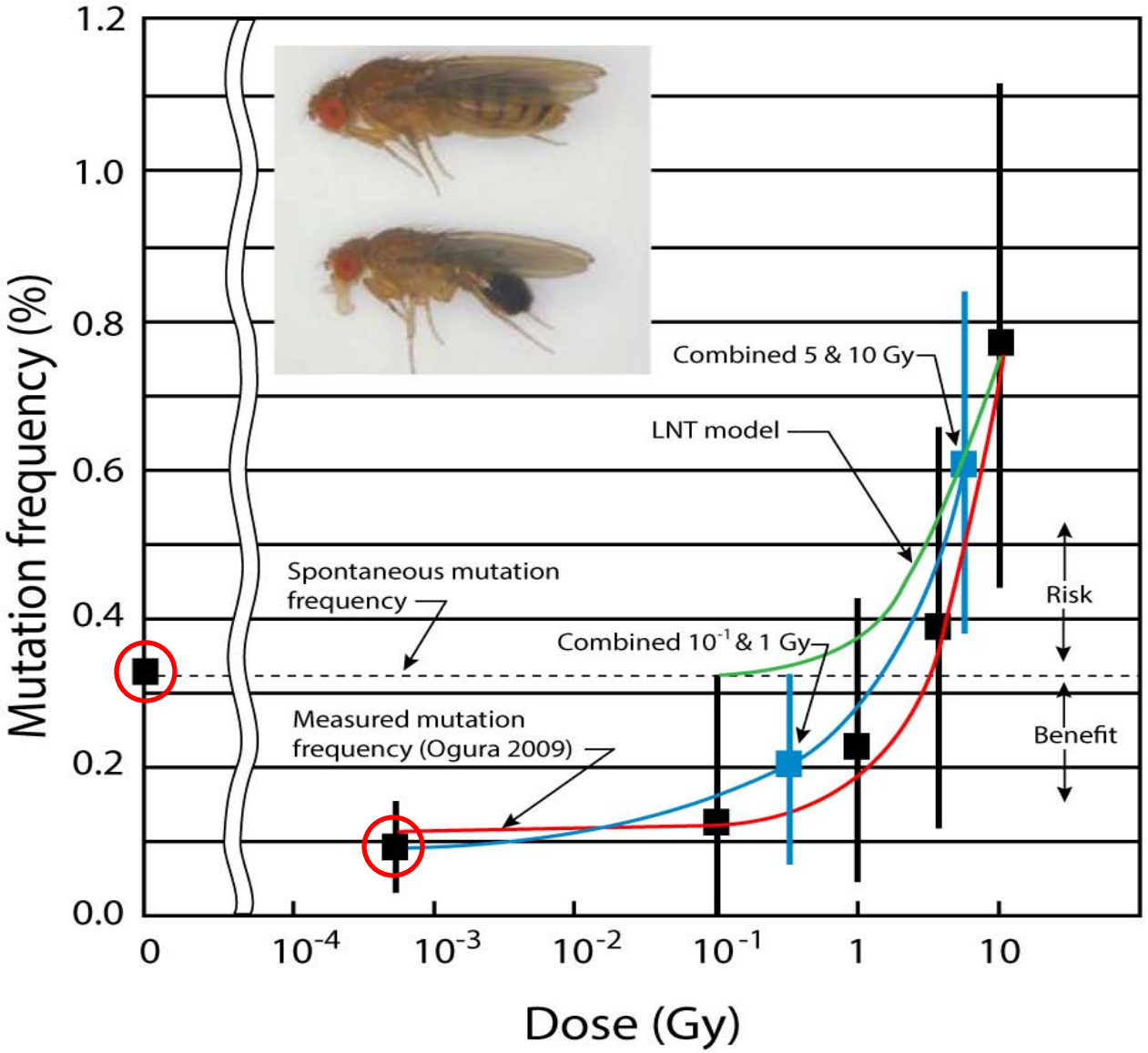
Binomial statistics applied to fruit fly mutation data measured by Ogura et al. 2009

Dose Gy	Number Lethals y	Chromo somes n	Mutat'n Freq. p = y/n	q = 1–p	Var σ^2 n•p•q	Std. dev. σ	2σ/n %	p + 2σ/n %	p – 2σ/n %
0.0005	9	10,500	0.0009	0.9991	9.441	3.07	0.06	0.15	0.03
0.1	2	1507	0.0013	0.9987	1.957	1.399	0.186	0.32	-0.06
1	6	2662	0.0023	0.9977	6.109	2.472	0.186	0.42	0.04
5	8	2055	0.0039	0.9961	7.983	2.825	0.27	0.66	0.12
10	21	2730	0.0077	0.9923	20.86	4.567	0.33	1.10	0.44
0.3	8	4169	0.0019	0.9981	7.906	2.81	0.13	0.32	0.06
7	29	4785	0.0061	0.9939	29.01	5.386	0.225	0.84	0.38

Mutation frequency for controls = 0.0032

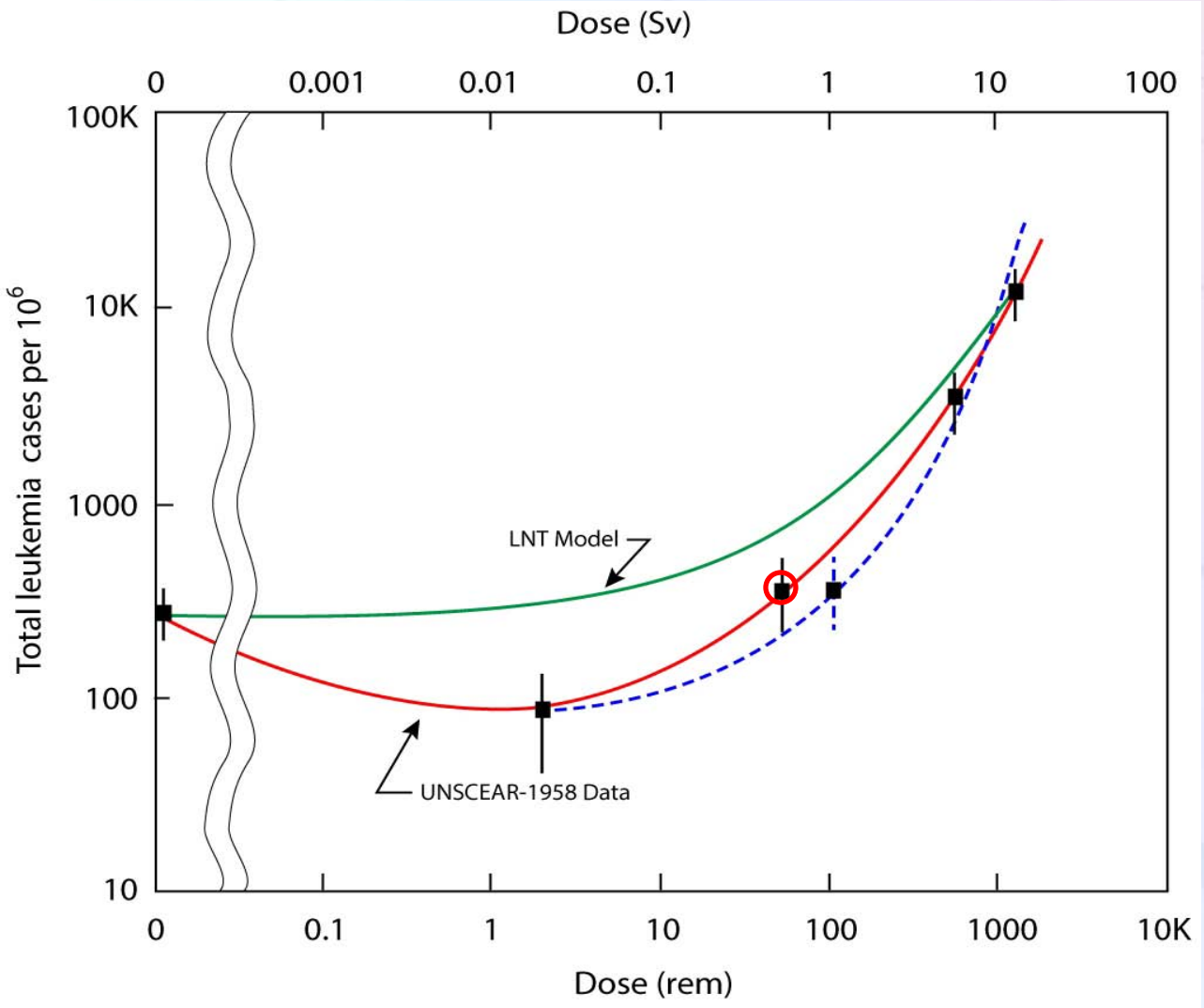
Muller's LNT from 4000 R @ 8,000 R/h (74,400 mGy/h);
In 1946, Caspari 0.5 Gy threshold @ 0.1 R/h or 1 mGy/h

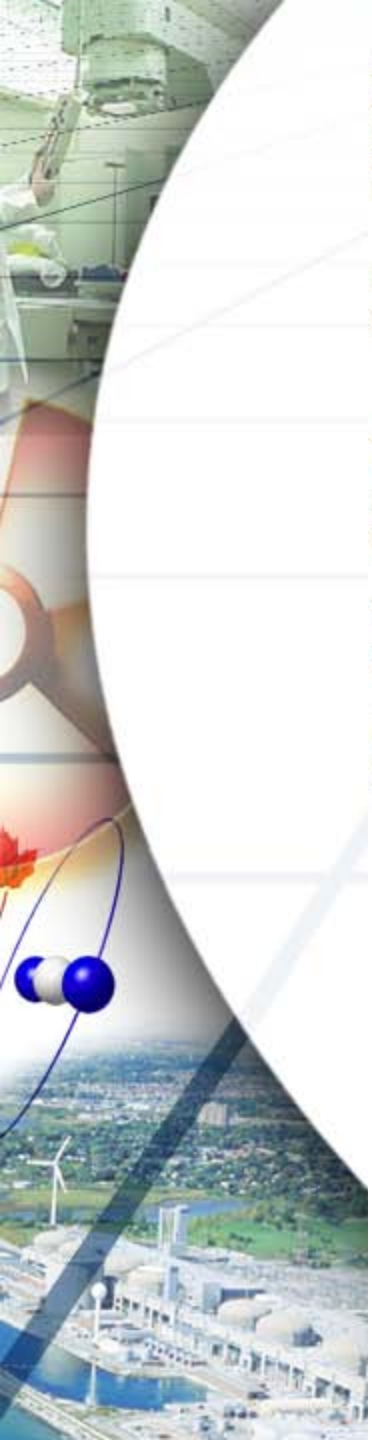
Germ cell mutation frequency - fruit flies, 22.4 mGy/h



Hiroshima Atomic Bomb Survivor Leukemia

NOAEL (threshold) at ~ 50 rem or 500 mSv





Dose-Response, 10:644-663, 2012
Formerly Nonlinearity in Biology, Toxicology, and Medicine

ISSN: 1559-3258
DOI: 10.2203/dose-response.12-014.Feinendegen

International Dose-Response Society

HEMOPOIETIC RESPONSE TO LOW DOSE-RATES OF IONIZING RADIATION SHOWS STEM CELL TOLERANCE AND ADAPTATION

Theodor M. Fliedner, Dieter H. Graessle □ Radiation Medicine Research Group and WHO Liaison Institute for Radiation Accident Management, Ulm University, Germany

Viktor Meineke □ Bundeswehr Institute of Radiobiology Affiliated to the University of Ulm, Germany;

Ludwig E. Feinendegen □ Heinrich-Heine-Universtät Düsseldorf, Germany, and Brookhaven National Laboratory, Upton, NY, USA

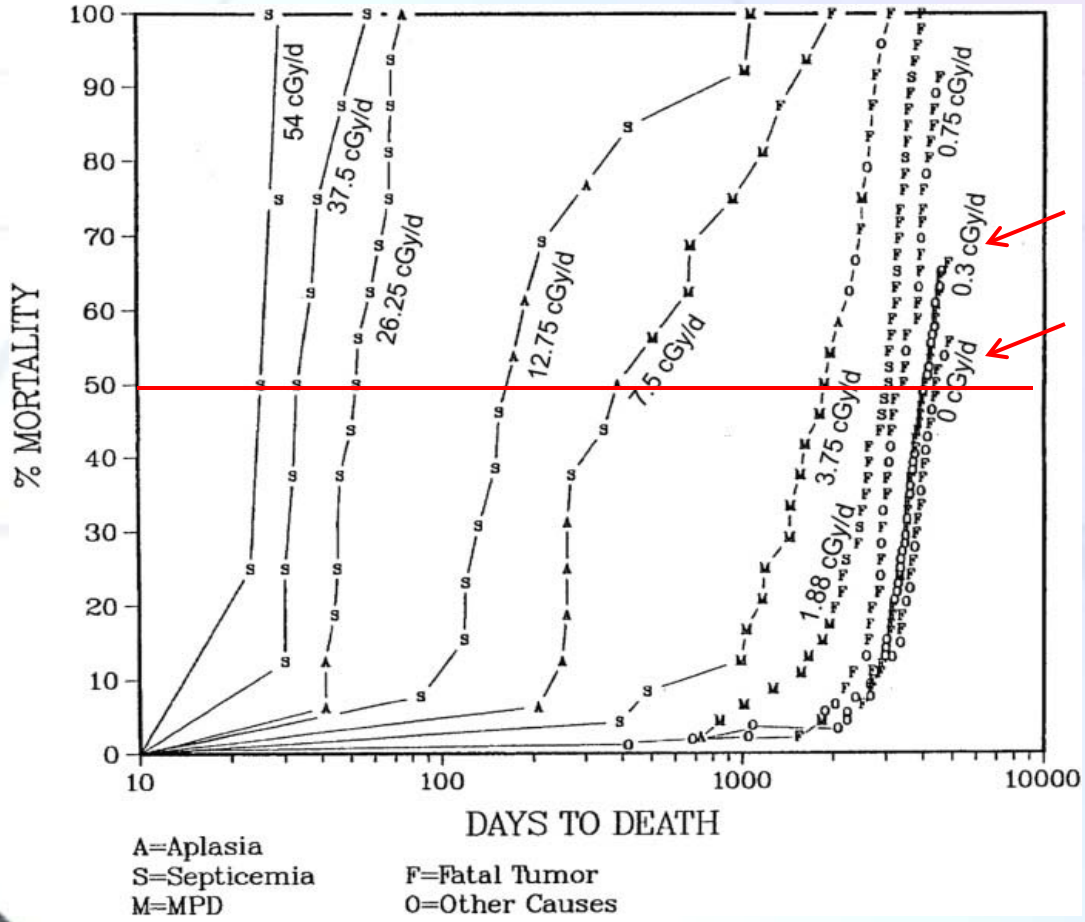
□ Chronic exposure of mammals to low dose-rates of ionizing radiation affects proliferating cell systems as a function of both dose-rate and the total dose accumulated. The lower the dose-rate the higher needs to be the total dose for a deterministic effect, i.e., tissue reaction to appear. Stem cells provide for proliferating, maturing and functional cells. Stem cells usually are particularly radiosensitive and damage to them may propagate to cause failure of functional cells. The paper revisits 1) medical histories with emphasis on the hemopoietic system of the victims of ten accidental chronic radiation exposures, 2) published hematological findings of long-term chronically gamma-irradiated rodents, and 3) such findings in dogs chronically exposed in large life-span studies. The data are consistent with the hypothesis that hemopoietic stem and early progenitor cells have the capacity to tolerate and adapt to being repetitively hit by energy deposition events. The data are compatible with the "injured stem cell hypothesis", stating that radiation–injured stem cells, depending on dose-rate, may continue to deliver clones of functional cells that maintain homeostasis of hemopoiesis throughout life. Further studies perhaps on separated hemopoietic stem cells may unravel the molecular-biology mechanisms causing radiation tolerance and adaptation.

Continuous Co-60 irradiation of dogs

0.3 cGy/d = 1100 mSv/year = 110 rad/year

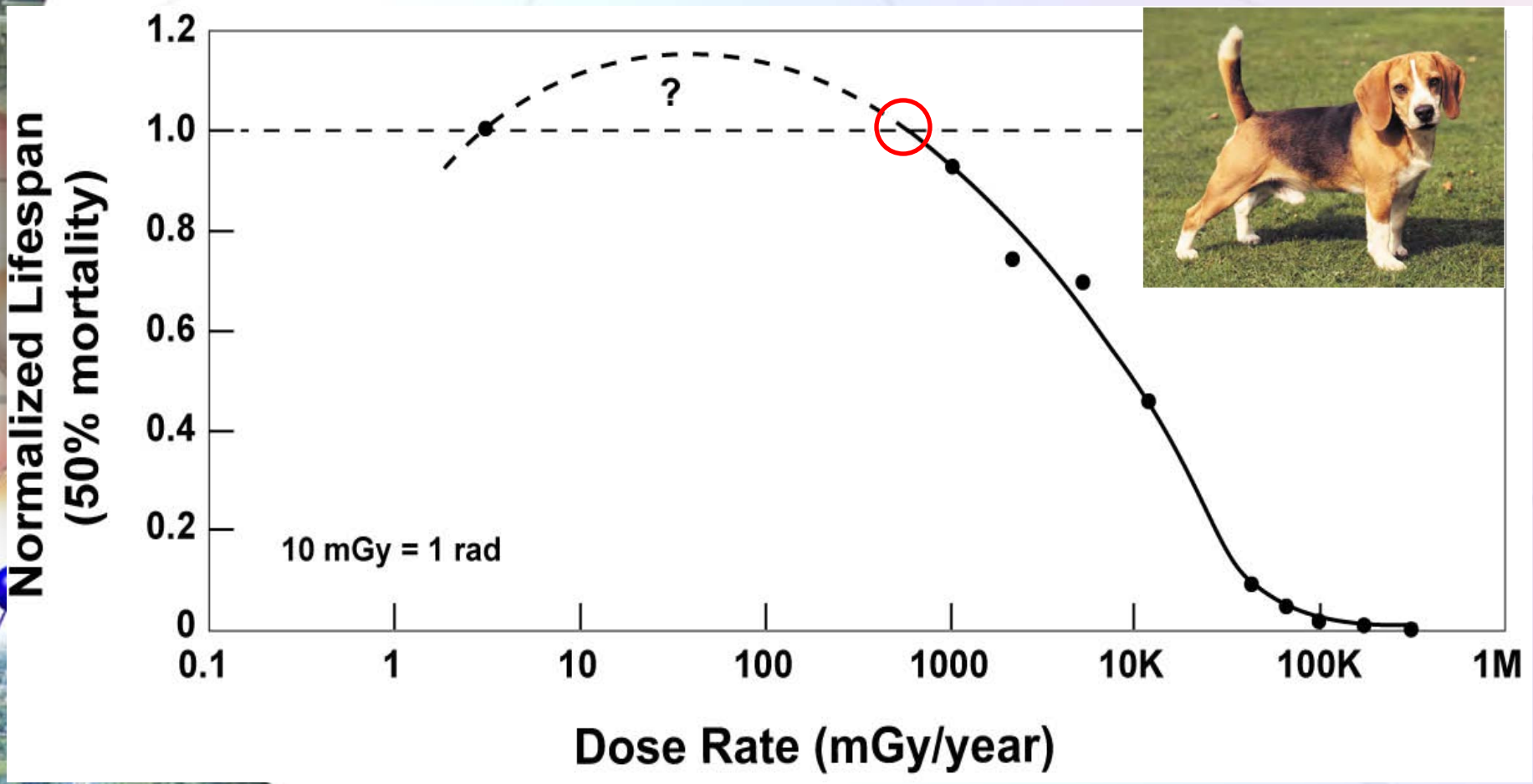
Blood counts of 0.3 cGy/d <u>same</u> as 0 cGy/d

Fatal tumors of 0.3 cGy/d <u>same</u> as 0 cGy/d



Lifespan versus Co-60 radiation level

NOAEL (threshold) for shorter lifespan ~ 700 mGy/year



CARCINOGENESIS FROM INHALED $^{239}PuO_2$ IN BEAGLES: EVIDENCE FOR RADIATION HOMEOSTASIS AT LOW DOSES?

Darrell R. Fisher and Richard E. Weller*

Abstract—From the early 1970's to the late 1980's, Pacific Northwest National Laboratory conducted life-span studies in beagle dogs on the biological effects of inhaled plutonium ($^{238}PuO_2$, $^{239}PuO_2$, and $^{239}Pu[NO_3]_4$) to help predict risks associated with accidental intakes in workers. Years later, the purpose of the present follow-up study was to *reassess* the dose-response relationship for lung cancer in the $^{239}PuO_2$ dogs compared to controls—with particular focus on the dose-response at relatively low lung doses. A $^{239}PuO_2$ aerosol (2.3 μm activity-median aerodynamic diameter, 1.9 μm geometric standard deviation) was administered to six groups of 20 young (18-mo-old) beagle dogs (10 males and 10 females) by inhalation at six different activity levels, as previously described in Laboratory reports. Control dogs were sham-exposed. In dose level 1, initial pulmonary lung depositions were 130 ± 48 Bq (3.5 ± 1.3 nCi), corresponding to 1 Bq g^{-1} lung tissue (0.029 ± 0.001 nCi g^{-1}). Groups 2 through 6 received initial lung depositions (mean values) of 760, 2,724, 10,345, 37,900, and 200,000 Bq (22, 79, 300, 1,100, and 5,800 nCi) $^{239}PuO_2$, respectively. For each dog, the absorbed dose to lungs was calculated from the initial lung burden and the final each. However, the incidence of lung tumors at zero dose was significantly greater than the incidence at low dose (at the $p \leq 0.053$ confidence level), suggesting a protective effect (radiation homeostasis) of alpha-particle radiation from $^{239}PuO_2$. If a threshold for lung cancer incidence exists, it will be observed in the range 15 to 40 cGy.

Health Phys. 99(3):357–362; 2010

Key words: alpha particles; analysis, risk; dogs; ^{239}Pu

INTRODUCTION

Inhaled plutonium dioxide (insoluble) deposits with high efficiency and is retained for long times (years) in the lungs (ICRP 1994). Desire to understand the health effects of internally deposited, alpha-particle-emitting plutonium isotopes stimulated a vast amount of research involving several research institutes and universities (Stannard 1988). Life-span studies in beagle dogs have provided

Inhaled plutonium-dioxide in beagle dogs

Lung tumor incidence (%)

100
80
60
40
20
0

Fisher and Weller (2010) data

LNT model

Controls, natural incidence of lung tumors

NOAEL ~ 60 cGy

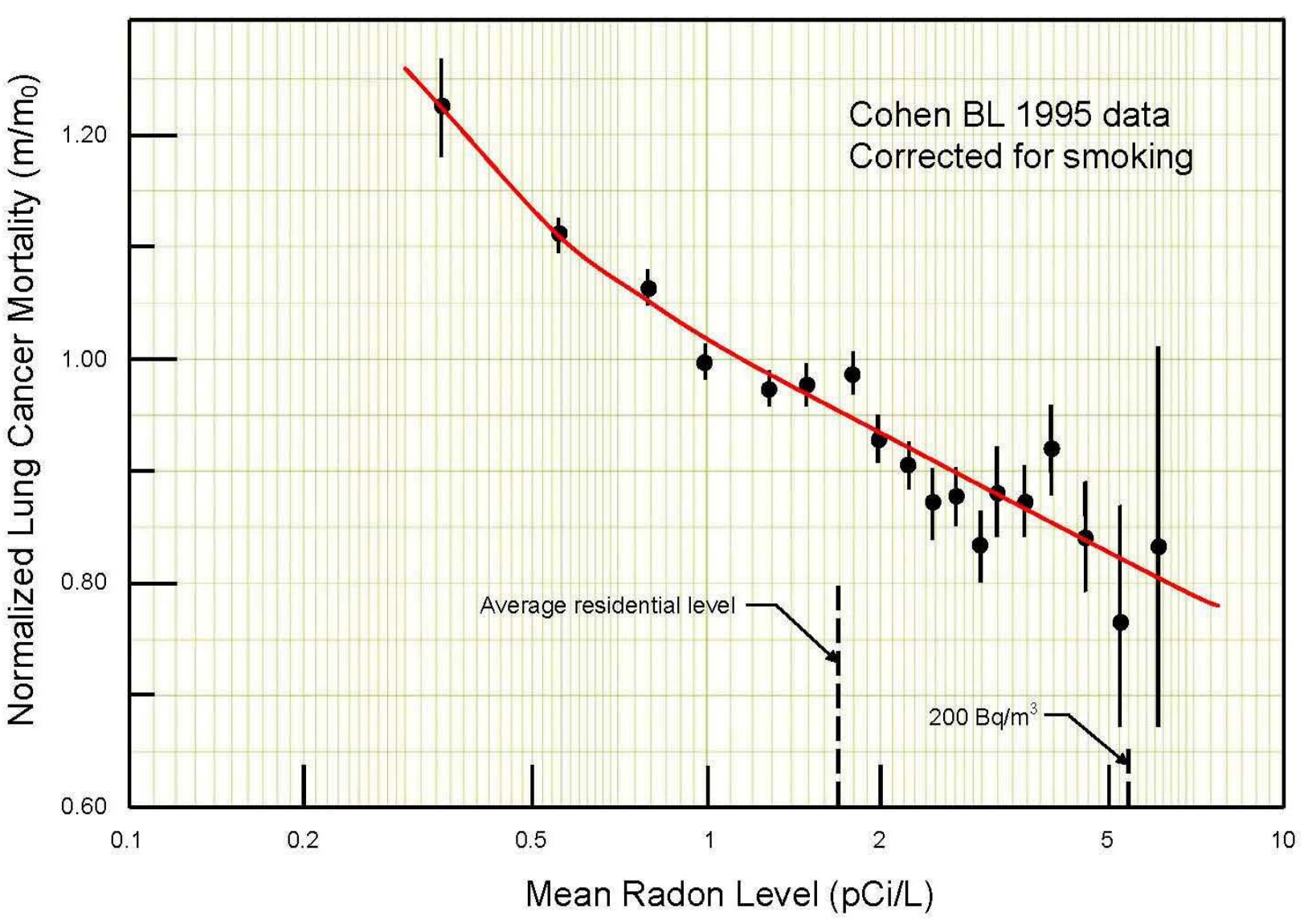
0
1
10
100
1000
10K

Cumulative absorbed dose to lungs (cGy)

Threshold-NOAEL for radon-induced cancer

- Raabe (2011): The average dose rate determines the cancer risk
- Dose rate of inhaled $^{239}PuO_2$ NOAEL = 60 cGy ÷ 15 year = **4 cGy/year**
- ICRP-115 (2010) gives 17 mSv/year as effective dose for 300 Bq/m^3 with 0.4 equilibrium factor and 80% occupancy factor
- Absorbed dose $D_{T,R} = E/(w_R \times w_T)$; 17 mSv/y ÷ (20 x 0.12) = 7.1 mGy/y
- Radon level of 300 x 4 ÷ 0.71 = **1700 Bq/m^3** is the radon NOAEL that corresponds to 4 cGy/year NOAEL of inhaled $^{239}PuO_2$
- EPA action level is 150 Bq/m^3, which is 11 times below 1700 Bq/m^3
- Recommend radon limit of 1000 Bq/m^3, which gives optimum benefit

Inhaled radon in homes



RADIATION RESEARCH 170, 736–757 (2008)
0033-7587/08 $15.00

Radiotoxicity of Inhaled $^{239}PuO_2$ in Dogs

Bruce A. Muggenburg,[a] Raymond A. Guilmette,[a] Fletcher F. Hahn,[a] Joseph H. Diel,[a] Joe L. Mauderly,[a] Steven K. Seilkop[b] and Bruce B. Boecker[a,1]

[a] *Lovelace Respiratory Research Institute, Albuquerque, New Mexico 87108; and*[b] *SKS Consulting Services, Siler City, North Carolina 27344*

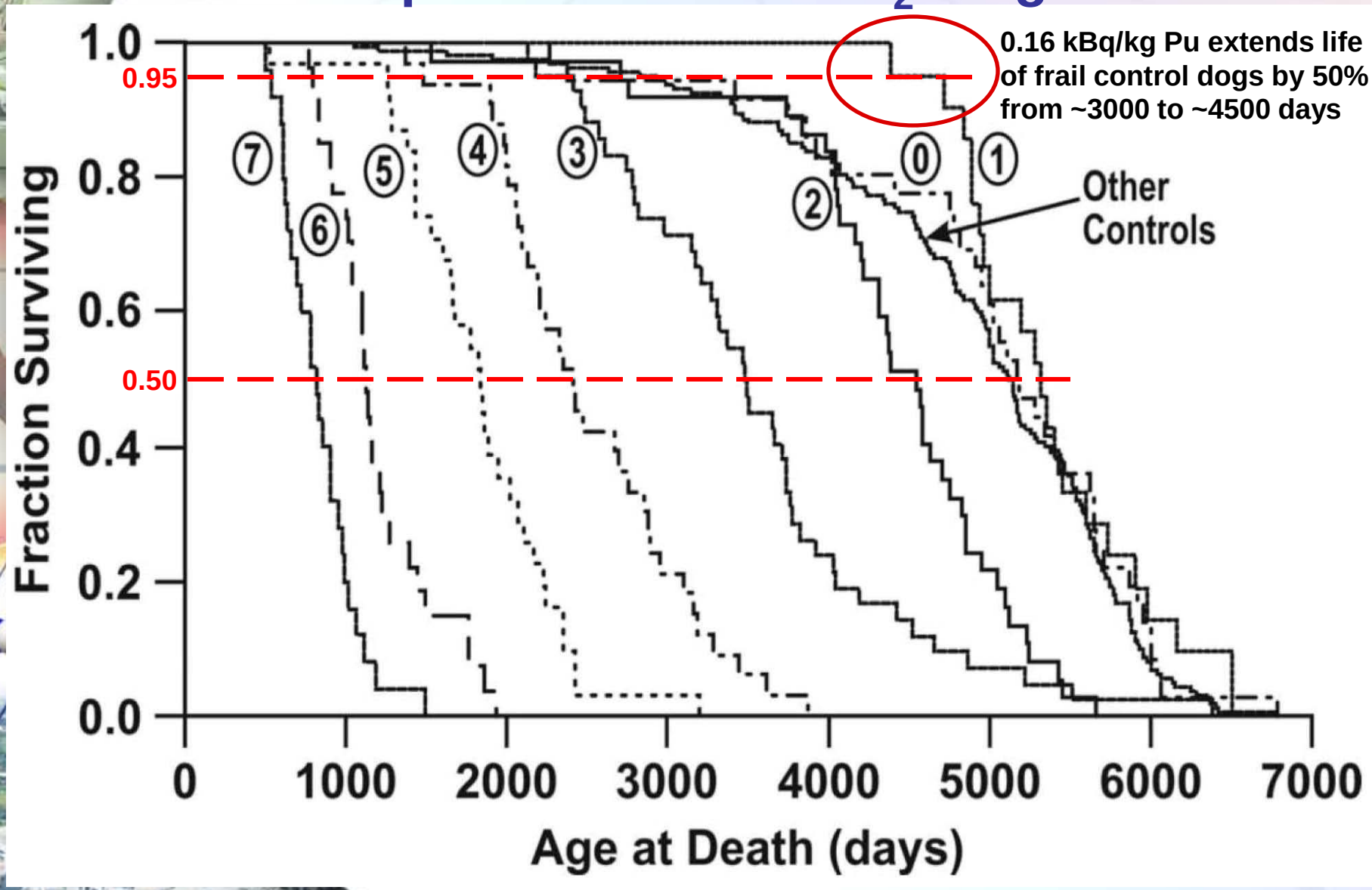
Muggenburg, B. A., Guilmette, R. A., Hahn, F. F., Diel, J. H., Mauderly, J. L., Seilkop, S. K. and Boecker, B. B. Radiotoxicity of Inhaled $^{239}PuO_2$ in Dogs. *Radiat. Res.* 170, 736–757 (2008).

Beagle dogs inhaled graded exposure levels of insoluble plutonium dioxide ($^{239}PuO_2$) aerosols in one of three monodisperse particle sizes at the Lovelace Respiratory Research Institute (LRRI) to study the life-span health effects of different degrees of α-particle dose non-uniformity in the lung. The primary noncarcinogenic effects seen were lymphopenia, atrophy and fibrosis of the thoracic lymph nodes, and radiation pneumonitis and pulmonary fibrosis. Radiation pneumonitis/pulmonary fibrosis occurred from 105 days to more than 11 years after exposure, with the lowest associated α-particle dose being 5.9 Gy. The primary carcinogenic effects also occurred almost exclusively in the lung because of the short range of the α-particle emissions. The earliest lung cancer was

erations, the possibility of plutonium environmental exposure exists through a severe reactor accident such as that at Chernobyl, various nuclear weapons testing activities, and waste disposal practices at various nuclear sites. Of increasing concern is the possible use by terrorists of ^{239}Pu in an improvised nuclear device (IND) or in a radiological dispersal device (RDD). The inventories of ^{239}Pu that exist around the world are mainly in the metallic or dioxide form. ^{239}Pu has a radioactive half-life of about 24,000 years and decays primarily by α-particle emissions. Due to its abundance and long half-life, accidental and intentional human exposures continue to be important concerns.

In the early years after plutonium was discovered, data on the possible long-term health effects in humans were absent. Therefore, numerous studies of the dosimetry and health effects of internally deposited ^{239}Pu were conducted in laboratory animals since its discovery more than 60

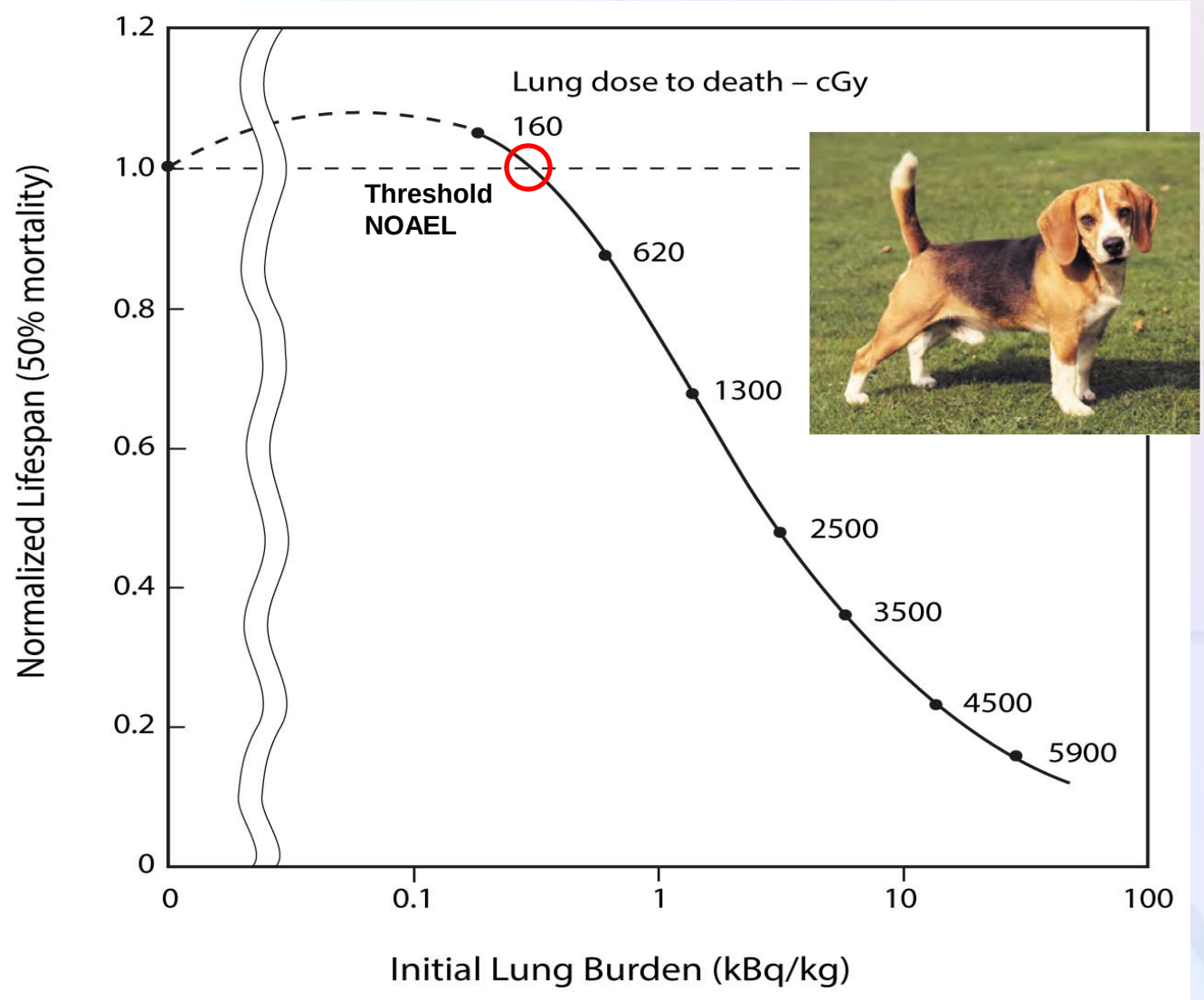
Lifespan versus $^{239}PuO_2$ lung burden

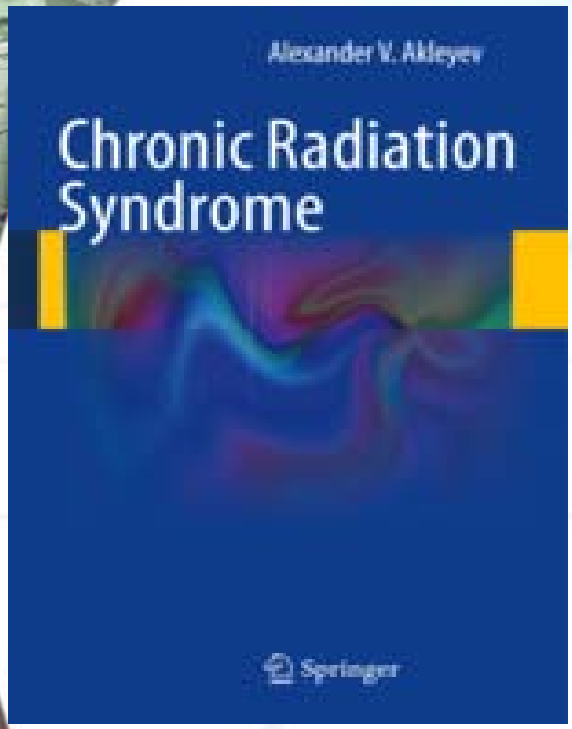


Lifespan versus $^{239}PuO_2$ lung burden

Exposure Level	Initial Lung Burden kBq/kg	Lung Dose to Death cGy	Time to Death days	Normalized Lifespan 50% mortality
Controls	0	0	5150	1.00
1	0.16	160	5316	1.03
2	0.63	620	4526	0.88
3	1.6	1300	3482	0.68
4	3.7	2400	2421	0.47
5	6.4	3500	1842	0.36
6	14	4500	1122	0.22
7	29	5900	807	0.16

Lifespan versus $^{239}PuO_2$ lung burden





Author describes health effects of villagers exposed to radiation from discharges of Mayak nuclear facility into the Techa River in early 1950s. The studies were recognised by United Nations Scientific Committee on Effects of Atomic Radiation as an important opportunity for estimating dose–effect relationships for protracted irradiation.

Incidences of leukemia and cancer mortality for persons with CRS did not exceed those estimated for exposed persons without CRS and in Russia as a whole

Threshold for CRS is an annual dose of 700 to 1000 mGy

Therapeutic Nuclear Medicine
Springer 2012 ISBN 978-3-540-36718-5

Hormesis by Low Dose Radiation Effects: Low-Dose Cancer Risk Modeling Must Recognize Up-Regulation of Protection

Ludwig E. Feinendegen, Myron Pollycove, and Ronald D. Neumann

Contents

Abstract

Ionizing radiation primarily perturbs the basic molecular level proportional to dose, with potential damage propagation to higher levels: cells, tissues, organs, and whole body. There are three types of defenses against damage propagation. These operate deterministically and below a certain impact threshold there is no propagation. Physical static defenses precede metabolic-dynamic defenses acting immediately: scavenging of toxins;—molecular repair, especially of DNA;—removal of damaged cells either by apoptosis, necrosis, phagocytosis, cell differentiation-senescence, or by immune responses,—followed by replacement of lost elements. Another metabolic-dynamic defense arises delayed by up-regulating immediately operating defense mechanisms. Some of these adaptive protections may last beyond a year and all create temporary protection against renewed potentially toxic impacts also from nonradiogenic endogenous sources. Adaptive protections have a maximum after single tissue absorbed doses around 100–200 mSv and

Ludwig Feinendegen et al.

- Studies ignore spontaneous (endogenous) DNA damage rate
- Endogenous rate is very high compared to radiation-induced rate:
  - Natural rate DNA single-strand breaks > 10^6 x SSBs from background radiation
  - Natural rate DNA double-strand breaks > 10^3 x DSBs from background radiation
- Low-dose radiation up-regulates *adaptive* protection systems
- Static defences act immediately to remove toxins, repair molecules (DNA), remove/replace damaged cells and tissue, to restore health
- Dynamic defence: stimulated adaptive systems (> 150 genes), some lasting more than a year, can *protect* against renewed toxic impacts from radiation *and* (non-radiation) endogenous sources, resulting in a lower cancer incidence and a longer life time

Is low radiation really a cancer risk? No

- Spontaneous (natural) DNA damage[1] occurs at very high rate > 1000 x background radiation DNA damage[1] rate
- Organisms have very powerful protection systems against all cell and tissue damage (internal and external)
- Low radiation up-regulates protection → less cancer
- High radiation impairs protection → more damage and harm

---

[1] double-strand breaks

Three lessons from Chernobyl and Fukushima

- Radioactive materials from severely damaged reactors cause radiation levels ~ same as natural high background radiation areas
- Precautionary evacuations cause many deaths and many thousands of distressed victims, due to the fear of radiation
- Radiation exposures, avoided by the evacuations, would not have caused adverse health effects

(Evacuations were needed to address fear, not the hazard)

Peter Sandman: **Risk = Health Hazard + Public Outrage**

(very low) (very high)

Conclusions

- The international consensus ignores the evidence of health benefits and focuses on LNT cancer risk and ALARA
- If radiation protection regulations do not changed to science based, humanity risks losing very important health benefits of low dose radiation and its nuclear energy supply
- If regulations do not change, future releases of radioactivity will lead to more emergency measures and many victims
- Medical radiation treatment to kill cancer cells are approved; treatments to stimulate protection systems are not accepted; ---these are called “alternative treatments”

Recommendations for regulators

- Collect and examine the evidence of radiation-induced beneficial health effects; learn about the mechanisms
- Develop and carry out a public information program to dispel the fear of low radiation
- Learn the lessons of the harm caused by “protecting” people from hypothetical radiation risks
- Change to science-based radiation protection and regulation of nuclear facilities and medical centres
- Stop regulating harmless sources of radiation

Can being cautious do any harm? Fukushima

- Major health problems due to fear of low level radiation and the emergency protective measures:
  - fearful rescue workers abandoned earthquake and flood victims
  - approx 1200 deaths due to evacuation and lack of care
  - more than 100,000 distressed residents for more than 4 years
  - major disruption of farming and food supplies
- 50 reactors shut down; major electricity shortage
- Many hundreds of billions of dollars spent to import coal, oil and gas, to replace lost nuclear electricity generation
- Many other serious social and economic impacts

Rockwell: What's wrong with being cautious?

- When you press them, many regulators will admit there is really no science to support the notion that any amount of radiation, no matter how small, can be harmful. They say:
- "We're not really saying it is harmful; just that it might be"
- "What's wrong with being cautious?"
- "We tell people it might hurt them, and perhaps it won't. "Can that do any harm?"
- The cost of trying to reduce harmless radiation exposures enormous. Predicting cancer deaths from low exposures generates groundless fear and that distorts public policy.

It is time to bring radiation protection policy back into line with the data.

Appendix 7

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1976 HANFORD AMERICIUM EXPOSURE INCIDENT: ORGAN BURDEN AND RADIATION DOSE ESTIMATES

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Abstract—A Hanford worker received an intake of ^{241}Am by skin absorption and inhalation which was later evaluated to be in excess of 1 mCi. The skin was the main pathway for introduction of ^{241}Am into the body; however inhalation was also a significant pathway. Intensive DTPA therapy prevented 99% of ^{241}Am which entered the blood stream from being deposited in the internal organs. Retention and distribution of ^{241}Am in various internal organs and tissues was determined from sequential measurements *in vivo* using several arrangements of externally located scintillation detectors. The organ and tissue retention and distribution have been followed for longer than 5 yr. Excretion patterns and estimates of radiation dose to the lung, liver, bone and skin are described.

INTRODUCTION

INFORMATION is available on the biological behavior of americium, from research in animals and from experience with human exposures (Th83). However, the applicability of the animal data to the prediction of distribution, retention and excretion patterns in man is uncertain, and the data from human exposures is fragmentary at best.

For the ^{241}Am deposition case described in this paper, the magnitude of the exposure (total internal deposition of more than one millicurie) has allowed easy and direct measurement of individual organ burdens using *in vivo* counting techniques (Pa83). Distribution and clearance patterns could be observed directly without reliance on urinary excretion models to predict the systemic burden, or on further modeling to estimate the distribution among internal organs. Extensive data have been obtained from the collection and analysis of excreta and other samples, as well as from *in vivo* measurements, during more than 5 yr following initial exposure.

This paper emphasizes metabolic dosimetric aspects of this exposure incident. Other aspects are considered elsewhere in this volume (Th83; Mc83; Bre83; Bro83; Je83; Be83; Pa83; Ha83; Ka83; Ra83).

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METHODS

An isotopic analysis was obtained on a sputum sample as soon as possible after the accident, using chemical separation procedures and alpha spectrometric techniques to confirm that samples were being analyzed for the correct isotope. The results of the isotopic analysis indicated that > 99% of the activity present was due to ^{241}Am.

The accuracy and sensitivity for measurement of ^{241}Am by direct counting of photons is better than for most other transuranics because of the presence of a 59.6 keV γ which is emitted in 36% of the disintegrations. The amount of ^{241}Am in each voiding of urine and feces was analyzed separately, by direct counting, so results might be obtained as quickly as possible.

Approximately the first 100 samples were assayed with a lithium-drifted germanium, Ge(Li), detector because the high count-rate would have overriden the memory on the subsequently employed sodium iodide system as it was calibrated for routine counting. The detector (60 cm^3, active volume) was cooled with a dipstick cryostat and coupled to a preamplifier and amplifer with a baseline restorer. Pulses from the detector were fed through a mixer-router to one-fourth of the memory of a

4096-channel Canberra, Model 8100, pulse-height analyzer.

After the first 100 samples, subsequent samples were analyzed by adding a known amount of urine or feces to a 500-ml capacity plastic bottle which conforms to the well of a sodium iodide crystal. The crystal was a Harshaw NaI(Tl) which was 9-3/8 in. diam by 8 in. deep (with a 3 in. diam by 5 in. deep well. The crystal had a low background base assembly and was optically coupled to seven 2 in. photomultiplier tubes. These were in turn coupled to a Packard preamplifier incorporated between the detector and main amplifier. The main amplifier was interfaced to a Canberra, Model 8100, pulse-height analyzer.

Both the NaI(Tl) and the Ge(Li) systems were calibrated with radionuclide sources whose calibration values are traceable to the National Bureau of Standards. This direct counting technique produced results sooner than more time-consuming chemical separation procedures and avoided a high potential for laboratory contamination.

The amount of ^{241}Am in whole blood and serum was also determined by direct counting after the samples were alternately dry-ashed and wet-ashed with nitric acid to rid them of organic material. The resulting solution was added to a scintillation vial containing a toluene-based scintillation fluid, mixed thoroughly, and counted in a Packard, Model 3320, Tri-Carb Liquid Scintillation Spectrometer.

When the ^{241}Am activity in blood fell to levels that were too low to be determined by liquid scintillation counting, a chemical separation procedure similar to that described by Butler (Bu70) was used. This procedure involved an initial dry-ashing step followed by a dissolution of the ash in acid and co-precipitation of ^{241}Am with calcium hydroxide. The precipitate was then dissolved and the ^{241}Am co-precipitated with calcium fluoride. The calcium fluoride co-precipitate was then dissolved in 12 N nitric acid and the ^{241}Am was further isolated by extraction into the bidentate extractant DDCP (dibutyl N,N-diethylcarbamylphosphonate). The ^{241}Am was then back-extracted from the DDCP into 2 N HNO_3, and this solution was evaporated to near dryness and quantitatively transferred to a disc for counting in a low-background, gas-flow α proportional counter.

In vivo measurements were utilized to assess the principal organ burdens and related distribution and retention parameters. Clearance pathways were assessed using excreta and blood as well as *in vivo* measurement data. The *in vivo* measurements were initially performed in the presence of large amounts of external skin contamination, but were nevertheless invaluable in early assessments of the severity of the intake. The *in vivo* measurement techniques and procedures are described in detail elsewhere (Pa83).

EARLY EVALUATIONS

Data on the ^{241}Am content of blood, and cumulative ^{241}Am excretion via urine and feces through Day 6 post-exposure are listed, together with the schedule of early DTPA (diethylenetriaminepentaacetic acid) administration, in Table 1. A total of 527 μCi was excreted via the urine through Day 6. The total amount of ^{241}Am excreted via the feces for the first 6 days was 176 μCi; the highest daily total during this period was 71 μCi (found in the first sample of feces, collected on Day 2). The total excretion via urine and feces through Day 6 was $\sim$ 700 μCi. The total amount of ^{241}Am excreted per day decreased with a half-time of about 2 days for the first week; the daily level of ^{241}Am in feces decreased somewhat more rapidly and the levels in urine somewhat more slowly.

Early estimates of the systemic burden were based on the excretion of ^{241}Am via the urine. The interpretation of these data was based on Rosen's excretion model for adult baboons (Ro72). In this model, 5% of the injected dose is excreted during the first day; thereafter, excretion in urine is expressed by the equation:

$$E_u = q_0(0.036t^{-1.3}) \qquad (1)$$

where E_u = ^{241}Am excretion via urine in μCi on day t; q_0 = initial systemic burden in μCi; and t = day post intake, $t > 1$. Application of this model was, of course, complicated by the fact that Rosen's baboons were not treated with DTPA and their systemic burden resulted from a single intravenous injection of ^{241}Am. The patient in the present case received intensive DTPA therapy (Table 1), starting about $2\frac{1}{2}$ hr following exposure, and ^{241}Am was continuing to enter the blood stream from depositions in the lung and skin.

Table 1. Early ^{241}Am content of blood and excreta

Days post-exposure	DTPA injected (grams/salt/time)	Estimated ^{241}Am in total blood volume (μCi/time)	Daily excretion (μCi) Via urine	Via feces	Cumulative total excretion (μCi)
0	1 g/Ca/0530	6.4/1820	130	0	130
1	1 g/Ca/0900	--	150	0	280
2	1 g/Ca/0900	--	70	71	~420
3	1 g/Ca/0900	2.0/0300	57	55	~530
	1 g/Ca/2100				
4	1 g/Ca/0900	1.5/0225	52	24	~610
	1 g/Ca/2100				
5	1 g/Ca/0900	1.1/0105	42	26	~680
	1 g/Zn/2100				
6	1 g/Zn/0900	0.64/0830	26	0	~700
	1 g/Zn/2100				

Nevertheless, an early attempt was made to estimate the ^{241}Am that might be deposited in bone. To do this, it was necessary to make several assumptions based on previous experience at Hanford with workers exposed to plutonium. These assumptions were as follows:

(1) The amount of ^{241}Am excreted in urine during the first few days would be enhanced by a factor of 100 as a result of the DTPA therapy.

(2) The systemic burden would be approximately equally divided between the bone and liver, i.e. ~45% in bone, ~45% in liver (ICRP79).

(3) At least 50% of the ^{241}Am would be chelated and merely passed through the blood, in chelated form, on its way from the skin and lungs to the urine.

On Day 2 the enhanced level of ^{241}Am excreted in urine was 70 μCi. Based on the first assumption, had DTPA not been administered, only 0.7 μCi of americium would have been excreted in urine on Day 2. Using this assumed value in equation (1) the systemic burden would have been 48 μCi *had DTPA not been administered.* Based on the second assumption, 45% of this or 22 μCi would have deposited in bone. However, *DTPA was administered* and based on the third assumption (that DTPA will reduce the actual systemic burden by a factor of at least two), it was assumed only half or about 10 μCi of ^{241}Am would deposit in bone for long-term clearance.

Very soon, of course, these early estimates based on urinary excretion data were supplemented by *in vivo* measurement data. However, *in vivo* measurements obtained prior to Day 3 were seriously compromised by the external contamination present. The measurements on Day 3 indicated: ~25 μCi in the lungs, a liver burden of ~40 μCi, and a bone burden of ~15 μCi. The organ distribution based on *in vivo* counting data through Day 21 post-exposure is given in Table 2. The initial, extrapolated values given in Table 2 were estimated, taking into account later measured data and material balance.

Based on the analysis of ^{241}Am in the liquid and solid wastes generated from the decontamination of the patient's body at the emergency decontamination facility, and on excretion data, 5–6 mCi of ^{241}Am was estimated to be on, and in, the dermal layer of the skin about $2\frac{1}{2}$ hr after the accident. Not included in this

Table 2. Early estimates of organ distribution based on in vivo *measurements*

Days post-exposure	^{241}Am in organs (μCi)			
	Lungs	Liver	Bone	Facial Skin
0	~50[a]	~150[a]	~20[a]	~900[a]
3	26	38	13[a]	~700[a]
4	20	27	12[a]	--
5	14	16	9.9	--
6	12	19	8.7	--
7	15	16	7.9	--
8	11	16	8.3	--
9	9.3	17	8.3	--
10	7.7	16	8.7	~400[a]
12	8.1	16	7.7	--
14	5.7	16	7.5	--
16	6.6	13	7.5	--
18	5.2	13	6.9	--
21	5.5	11	6.7	280

[a]Value estimated by extrapolation from later data.

estimate were curie amounts of ^{241}Am removed by initial decontamination efforts at the scene of the accident (Je83). *In vivo* measurements taken over the face and neck, 12 hr after the accident, indicated that in excess of 3 mCi remained on, and in, the dermal layer of the skin at that time. Subsequent *in vivo* measurements of the face and neck are given in Table 2.

LONG-TERM CLEARANCE AND RADIATION DOSE

Excretion

Nearly half of the ^{241}Am excretion via the urine occurred during the first 3 days post-exposure (Table 3). A plot of the daily excretion rate of ^{241}Am via urine and feces for the first 5.3 yr post-exposure is shown in Fig. 1. Data points beyond 1000 days post-exposure are based on analysis of samples collected less frequently. The ratio of ^{241}Am excreted in the urine to excretion via feces was approx 2.5 for the first 6 days post-exposure. Thereafter, this ratio increased to about 30:1 as the liver became depleted of ^{241}Am by DTPA therapy.

The lower early ratio reflects the rapid clearance (via feces) of ^{241}Am swallowed during the initial exposure and following escalation from the lungs and upper respiratory tract, as well as rapid clearance from the liver.

The excretion of americium was, of course, greatly influenced by the DTPA therapy. One to two g of the calcium salt of DTPA was administered daily for the first 5 days following exposure. On Day 5, the zinc salt of DTPA was substituted, to prevent depletion of essential trace metals in the body (Bre83; Ka83). The daily administration of 2–3 g of Zn-DTPA was continued through Day 15 when the initial supply of Zn-DTPA was exhausted. The administration of Ca-DTPA was resumed on Day 16 and continued through Day 25 when a new supply of Zn-DTPA became available. The

Table 3. Summary of tissue distribution and excretion of ^{241}Am

Time post-exposure	Organ burden (μCi)				Cumulative excretion (μCi)	
	Skin	Lungs	Bone	Liver	Urine	Feces
Day 0	5000+	--	--	--	130	0
Day 3	∿700	26	13	38	405	126
Day 10	∿400	7.7	8.7	16	603	184
Day 60	150	2	6.7	4	837	189
1 year	35	2	6.3	0.04	896	189
2 years	20	1.5	6.0	(a)	898	189
3 years	13	(a)	6.2	0.1[b]	899	189
4 years	8.4	(a)	7.5	0.25[b]	899	189
5 years	5.3	(a)	7.5	0.26[b]	899	189

[a] Not detectable.

[b] The increase in liver burden of ^{241}Am is due to interruption in the administration of DTPA.

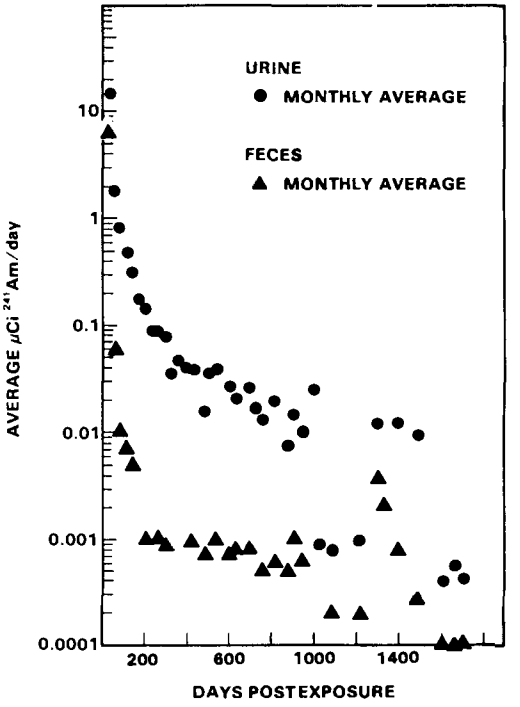

FIG. 1. Excretion rate of ^{241}Am via urine and feces.

Table 4. Summary of DTPA administration

Days postexposure	DTPA salt injected	Frequency of 1-gram doses
0 to 5	Ca	1 to 2 per day
5 to 15	Zn	2 to 3 per day
16 to 25	Ca	1 to 2 per day
26 to 332	Zn	1 per day
333 to 849	Zn	2 to 3 per week
850 to 884	None	--
885 to 933	Zn	2 per month
934 to 1282	None	--
1283 to 1325	Zn	2 per month
1326 to 1465	Zn	1 per month
1466 to 1540	Zn	2 per month
1540 to 1949	None	--

complete schedule of DTPA administration is given in Table 4.

A total of 584 g of DTPA (both forms) was administered through Day 1540, after which time no DTPA has been administered. During one period of about a year (Days 934 to 1282), no DTPA was administered, and ^{241}Am levels in excreta decreased during this period. Treatment was resumed when a significantly increased ^{241}Am level was observed in liver scans (Pa83).

The ^{241}Am in blood was essentially all in the serum as determined from separate analyses of serum and whole blood. The level of ^{241}Am in blood serum as a function of time is shown in Fig. 2. The ratios of the daily amount of ^{241}Am excreted via the urine to the calculated amount

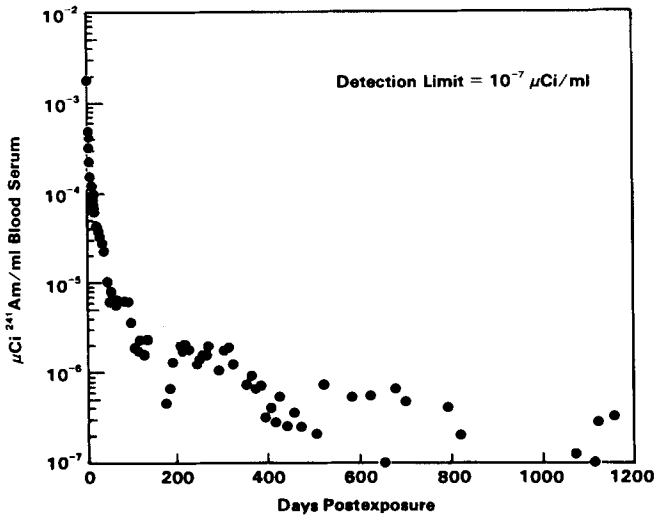

FIG. 2. Clearance of ^{241}Am from blood.

of ^{241}Am present in the total volume of blood (at the time of blood sample collection) averaged 45 during the first 100 days post-exposure, indicating a clearance time of about 30 min.

Estimates of absorbed dose

The equations outlined below were used to estimate the dose from ^{241}Am deposited in various body organs. The complete derivation of the equations used, together with the assumptions usually employed, are given elsewhere (ICRP60; ICRP67; Hi56).

The dose rate, in rad/day, was calculated using the following equation:

$$D_r(t) = 51.15 \frac{q(t)}{m} \times E \qquad (2)$$

where $D_r(t)$ = dose rate in rad per day on day t; $q(t) = \mu$Ci in the organ on day t; m = mass of the organ in g; and E = effective energy per disintegration = 5.7 MeV.

The organ weights used for the calculations (Table 5) were estimated for the worker's age and weight from reference information given in *ICRP Publication* 23 (ICRP75). The absorbed-dose rate and integrated dose to the lungs, bone, liver and dermal layer of skin (in the area of the face and neck) were considered to be of primary interest. All doses are calculated as average doses to the total tissue.

The estimated dose rates in rad/day to lungs, liver and bone for the first day after exposure, based on extrapolated data as shown in Table 2, were: lung, 12; liver, 24; bone, 0.8. The dose rate to the lung, liver and bone dropped to 6.2, 6.0 and 0.5 rad/day, respectively, by Day 3.

Figure 3 portrays the rapidly decreasing dose rate to lung, as a function of time post-exposure. Also shown in Fig. 3 is a 3-term exponential equation, which describes the fractional retention, $R(t)$, as a function of time, as derived from measurements taken after 3 days post-exposure. The overall retention is not greatly different from that predicted by the ICRP lung model for Class W materials (ICRP79).

The dose-rate to the liver decreased even more rapidly than that to lung, reflecting a clearance half-time of ~ 20 days as shown in Fig. 4. The initial clearance from liver, was, of course, greatly accelerated by the DTPA treatment. A retention equation for ^{241}Am in the liver is not given, since deposition and clearance from liver is so clearly influenced by the pattern of DTPA administration. The increased ^{241}Am levels beyond Day 850 reflect the infrequent administration of DTPA beyond that date.

The dose rate to bone decreased to 0.28 rad/day by Day 20 and has since remained essentially unchanged (Fig. 5). The apparent slight build-up beyond about 1000 days post-exposure was apparently due to discontinued DTPA therapy.

An average estimated dose rate to the skin of the face and neck, as it varied with time, is shown in Fig. 6. This dose rate, of course, varied greatly between different areas of skin. Also shown in Fig. 6 is a 3-term exponential equation, which describes the fractional retention, $R(t)$, as a function of time, as derived from measurements taken 21 days or more post-exposure.

The cumulative organ dose from time t_0 to t_1

Table 5. Summary of absorbed dose accumulated over 5.3 yr *post-exposure*

Organ	Assumed Weight of organ (g)	Absorbed dose (rads)
Lungs	1200	∿130
Liver	1740	∿160
Bone	7000	∿550
Skin	20	∿880,000

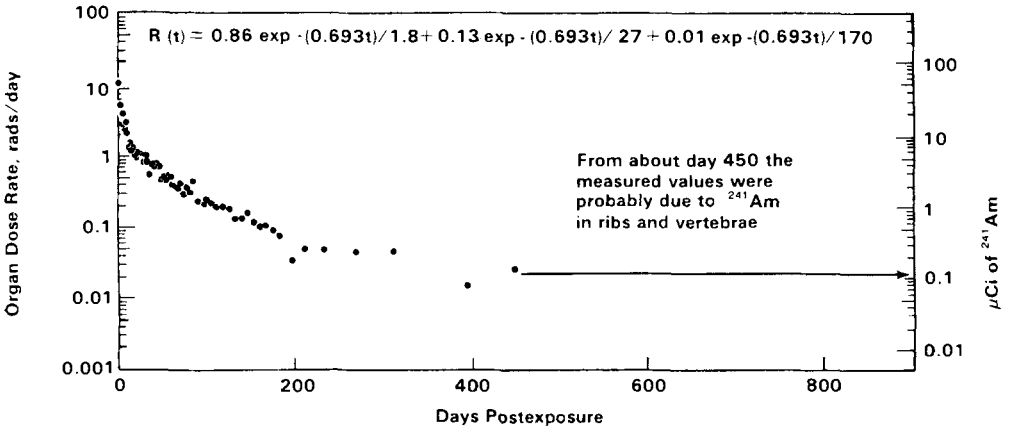

FIG. 3. Dose rate to lungs from ^{241}Am.

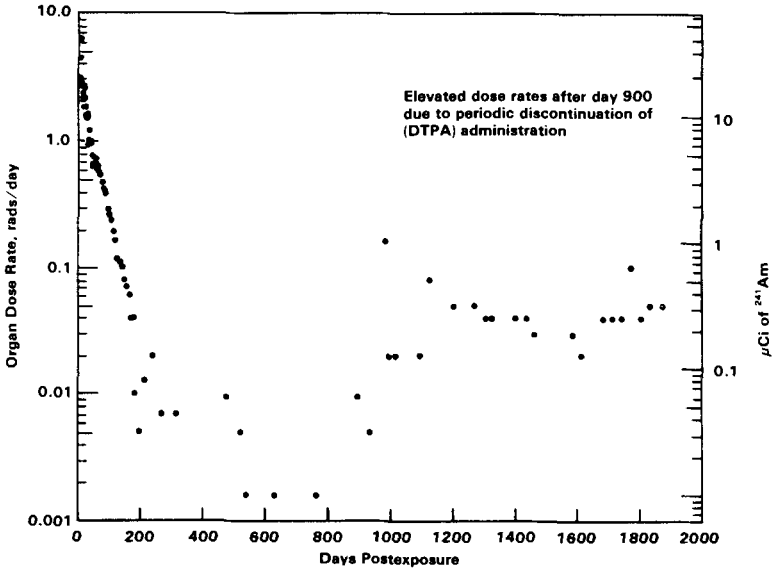

FIG. 4. Dose rate to liver from ^{241}Am.

is equal to the integral of the dose rate over that period of time. Assuming exponential retention, equation (1) can be integrated to give:

$$D_{t_0}^{t_1} = 51.15 \frac{q_0}{m\lambda} E(e^{-\lambda t_0} - e^{-\lambda t_1}) \qquad (3)$$

where $D_{t_0}^{t_1}$ = the total integrated dose in rads for the time interval from t_0 to t_1; q_0 = organ burden at t_0 in μCi; λ = fractional change in organ burden per day; m = mass of organ in grams; and E = effective energy per disintegration = 5.7 MeV.

When n exponential segments (each extending from t_{n-1} to t_n) are employed to describe the

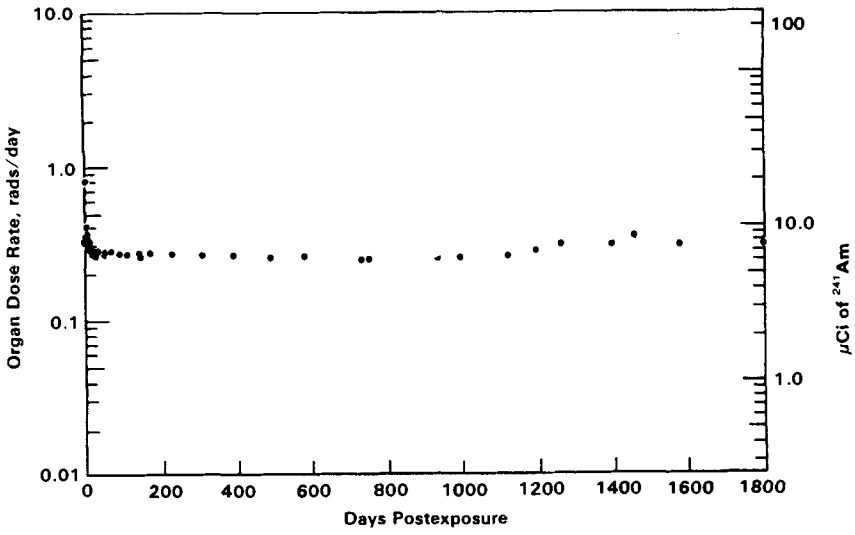

FIG. 5. Dose rate to bone from ^{241}Am.

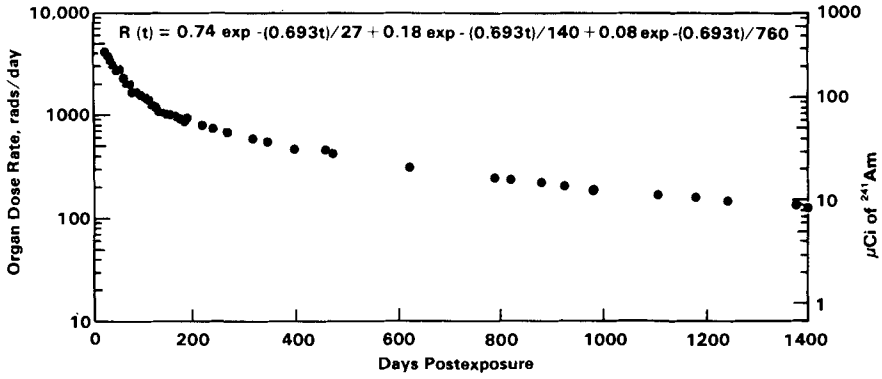

FIG. 6. Average dose rate to skin of face and neck from ^{241}Am.

retention curve, equation (3) becomes:

$$D_{t_0}^{t_n} = \frac{51.15E}{m} \sum_{n=1}^{n} q_{n-1} \times \frac{(e^{-\lambda_n t_{n-1}} - e^{-\lambda_n t_n})}{\lambda_n}. \quad (4)$$

In general, the larger the number of exponential segments employed to describe the retention curve, the greater the accuracy with which the total dose can be estimated. Because of the nature of the data available in the present case, and the length of time during which these data were obtained, from 6 to 8 components were fitted and summed to estimate the total dose to lungs, liver and skin. These doses, from data of intake (30 August 1976) through 31 December 1981—a total of 1949 days (5.3 yr)—are summarized in Table 5.

DISCUSSION

The ~ 900 μCi of ^{241}Am excreted in the urine of this patient plus some fraction of the ~ 190 μCi excreted in the feces (the fraction contributed by biliary excretion), must have been present at some time in the blood, from whence it would have been expected to deposit largely in bone and liver were it not for the DTPA treatment.

The ICRP metabolic model for ^{241}Am (ICRP79) predicts that only 10% of ^{241}Am entering the bloodstream would be excreted in the absence of DTPA; the remaining 90% being deposited half in bone, where it would be retained with a half-time of 100 yr; and half in liver, where it would be retained with a half-time of 40 yr. In the present case, no more than 1% of the ^{241}Am that had been present in blood was retained in bone and liver after 5.3 yr. The DTPA was therefore effective in blocking 99% of the predicted deposition of ^{241}Am in the internal organs.

There was no apparent difference in the effectiveness of Ca-DTPA and Zn-DTPA in preventing deposition of ^{241}Am in internal organs. This finding is in agreement with animal studies. For example, Seidel (Se73; Se75) has shown that beyond 24 hr post-exposure, there is virtually no difference in the effectiveness of the zinc and calcium forms of DTPA, when single or repeated doses are administered to rats. Both Zn-DTPA and Ca-DTPA have characteristics that make their combined use appropriate for the decorporation of ^{241}Am. Calcium-DTPA is more effective than Zn-DTPA for early use (within ~ 2 hr after intake); however, Zn-DTPA is preferred for protracted administration because Ca-DTPA can deplete the body of essential trace metals (Ka83).

The observed clearance of ^{241}Am from the lung was in good agreement with the clearance half-time of 50 days predicted for long-term clearance by the ICRP (ICRP79). The ^{241}Am had essentially all cleared from the lungs by about Day 450.

The observed clearance half-time from the liver was much shorter than would normally be expected, i.e. ~ 20 days as opposed to the 40 yr conservatively estimated by ICRP (ICRP79), owing to the continuing administration of DTPA. Essentially all of the ^{241}Am initially deposited had cleared from the liver by Day 400 (Fig. 4), although significant redeposition in liver occurred subsequent to cessation of DTPA treatment (Pa83).

The clearance of ^{241}Am from bone appeared to be unaffected by the DTPA treatment, except for some possible effect during the first week of treatment.

It is interesting to note that while large amounts of ^{241}Am entered the body from deposits in the skin, lesser but significant amounts were also leaving the body via the skin. Mechanisms for loss via the skin included: scabs, extruded glass and other foreign objects, and whiskers (Je83). The total amount of activity removed by these pathways subsequent to Day 2 is estimated to be 3 μCi.

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Appendix 8

TOWARD IMPROVED IONIZING RADIATION SAFETY STANDARDS

Otto G. Raabe*

Abstract—**Ionizing radiation safety standards developed by the International Commission on Radiological Protection (ICRP) during the past 50-plus years have provided guidance for effective protection of workers and the public from the potentially harmful effects of exposure to ionizing radiation, including cancer. Earlier standards were based primarily on radiation dose rate to organs of the body. More recent recommendations have calculated cancer risk as a function of cumulative dose using a linear no-threshold cancer risk model based on the acute high dose rate exposures received by the Japanese atomic bomb survivors. The underlying assumption in these current recommendations is that risk of radiation-induced cancer is proportional to cumulative dose without threshold. In conflict with this position are the studies of protracted exposures from internally-deposited radionuclides in people and laboratory animals that have demonstrated that cancer induction risk is a function of average dose rate for protracted exposures to ionizing radiation. At lower average dose rates, cancer latency can exceed natural lifespan leading to a virtual threshold. This forum statement proposes that the conflict of these two cancer risk models is explained by the fact that the increased risk of cancer observed in the atomic bomb survivor studies was primarily the result of acute high dose rate promotion of ongoing biological processes that lead to cancer rather than cancer induction. In addition, ionizing radiation-induced cancer is not the result of a simple stochastic event in a single living cell but rather a complex deterministic systemic effect in living tissues. It is recommended that the ICRP consider revising its position in light of this important distinction between cancer promotion and cancer induction.**
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Key words: analysis, risk; cancer; radiation, ionizing; radiation effects

INTRODUCTION

THE CURRENTLY accepted methodology for estimation of solid cancer induction risk associated with human exposure to ionizing radiation is based primarily on the detailed lifespan studies of about 80,000 Japanese atomic-bomb survivors of the nuclear weapons detonations at Hiroshima and Nagasaki in 1945 (ICRP 1977; BEIR VII Phase 2 2006; NCRP 2001). However, there is also a body of evidence showing that the underlying linear no-threshold (LNT) dose-response model associated with these studies as reported by the Radiation Effects Research Foundation (RERF) is not appropriate for protracted ionizing radiation exposures from radionuclides internally deposited in the human body (Evans 1974; Raabe et al. 1980, 1990; Raabe 2010). By analogy, it is also inappropriate for other protracted or fractionated ionizing radiation exposures. An understanding of the source of this conflict of data interpretation is essential for sound estimates of cancer risk associated with exposures to ionizing radiation.

About 50 years ago, the International Commission on Radiological Protection (ICRP) developed a systematic model of "permissible dose" for radiation protection based primarily on observed effects associated with acute external x-ray and gamma ray exposures and internal exposures to radium. Based on this model, ICRP-2 provided an extensive set of recommendations for so-called maximum permissible dose and maximum permissible body and organ burdens for radionuclides (ICRP 1959). Those recommendations were sound and practicable.

However, the perspective on which ICRP-2 was based was markedly altered by the developing studies of the Japanese survivors showing a linear dose-response pattern that was interpreted to show that cancer induction increased linearly with exposure, possibly starting near zero dose (the LNT model). In contrast, the studies of the radium workers and others with intakes of isotopes of radium showed a marked threshold at quite high skeletal doses from alpha radiation (Evans 1943, 1974). Other studies of internal emitters have shown similar threshold-like responses (Raabe et al. 1980, 1990; Raabe 2010). However, the common practice of fitting simple LNT cumulative dose models to imprecise grouped data has perpetuated the linear dose-risk model for internal emitters and other protracted or fractionated exposures (Mays and Lloyd 1972; Lloyd et al. 1994; Lubin et al. 1995).

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ICRP-30 (ICRP 1979) developed a well-crafted system for combining all radiation-induced cancer risks into one coherent approach, but it may be based on a faulty premise. Radiation promotion of existing biological processes that eventually lead to cancer depends on the background (so-called "natural" or base level) risks of cancer development. This promotion is primarily what was observed for solid tumors in the Japanese atomic-bomb survivors. In contrast, true radiation induction of cancer is independent of and additive to or preemptive of the background spontaneous cancer cases (Raabe 2010).

The brilliance of Evans and other early radiation safety scientists was in applying the developing radium study results to a set of safety limits of internal emitters as well as the use of the protracted and fractionated exposure concepts for setting safety limits for external exposures. Where the atomic bomb survivor data become important is in the cases of brief high dose-rate exposures, as occurred during the atomic bomb detonations where the total dose was delivered in only about 1 min. Even a dose of only 1 mSv delivered in 1 min is at a high dose rate and may alter cellular processes too quickly to allow for some naturally protective biological responses to occur.

The adjective "stochastic" has been used by the ICRP and many others to describe the nature of radiation-induced cancer. In statistics, the adjective "stochastic" implies randomness. The idea is that a few random isolated events associated with a single cell can result in a neoplastic or genetic transformation. Typical models of stochastic effects are based on one or more individual events in a selected cell, such as cellular mutations. In such a stochastic model, the more radiation dose the greater the likelihood of a neoplastic transformation in a cell in a manner proportional to the total dose. According to ICRP 26, "'Stochastic' effects are those for which the probability of an effect occurring, rather than its severity, is regarded as a function of dose, without threshold" (ICRP 1977). As implied by this definition, radiation-induced cancer is independent of any so-called naturally-occurring or spontaneous cancer cases. Also, the development of a radiation-induced malignant tumor is presumed to be initiated by a single random interaction of the ionizing radiation with an isolated cell. Hence, the LNT theory is part of the definition and conceptual model of the ICRP.

RADIATION CANCER RISK

Radiation-induced cancer from protracted or fractionated exposure to ionizing radiation

Based on the human radium studies of Evans, in 1959 the ICRP established a maximum permissible skeletal content safety recommendation of 3.7 kBq (0.1 μCi) for ^{226}Ra and extended the dosimetric implications for recommended maximum permissible values for a whole range of radionuclides (ICRP 1959). Evans showed that the induction of cancer from radium in the skeleton was a non-linear function with an observed threshold at a cumulative dose of about 10 Gy, calculated to be about an equivalent dose of 200 Sv with a quality factor of 20 for alpha radiation (Fig. 1; Evans 1972). Later Raabe (Raabe et al. 1980) found that the three-dimensional dose-response relationship for radium-induced bone cancer is properly described as a function of lifetime average dose rate to target tissues rather than of cumulative dose. This relationship demonstrated a lifespan virtual threshold for cancer induction when the cancer latency exceeds the normal lifespan (Fig. 2). Also the response of various mammalian species depends on cell division rates that are inversely related to normal lifespan (Raabe et al. 1980, 1990; Raabe 2010).

In 1974, Evans showed definitively that no linear cumulative dose model of radiation-induced bone cancer is consistent with the U.S. data on radium in people (Evans 1974). He used linear plots and statistical tests of several hypothetical linear models. His analysis demonstrated that it is highly unlikely that these data can be explained by any linear dose-response model and that all of the linear dose-response models were "strongly rejected by the chi-square test for goodness of fit." In terms of lifetime cumulative dose, radiation-induced bone sarcoma and head carcinoma associated with internally-deposited radium in people display a non-linear effective threshold dose-response relationship. Other studies have confirmed these findings and elucidated them (Raabe et al. 1980, 1990; Raabe 2010).

Three-dimensional analyses have been performed of the human radium cases and of 25 internal-emitter laboratory studies with beagles for injected ^{226}Ra, ^{228}Ra, ^{224}Ra, ^{228}Th, ^{239}Pu, ^{249}Cf, ^{252}Cf, ^{241}Am, ^{90}Sr, inhaled ^{239}Pu, ^{238}Pu, ^{90}Y, ^{91}Y, ^{90}Sr,^{144}Ce, and ingested ^{90}Sr (Raabe 2010). These radionuclides have principle emissions that include low linear-energy transfer (LET) beta radiation

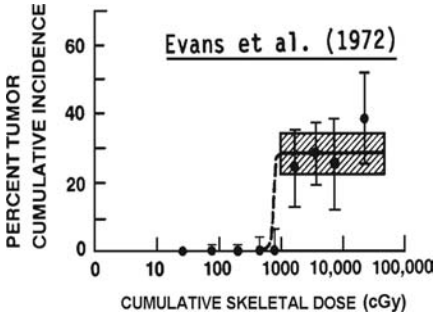

Fig. 1. Cumulative bone sarcoma incidence in people exposed to ^{226}Ra as a function of cumulative dose to the skeleton as reported by Evans et al. (1972).

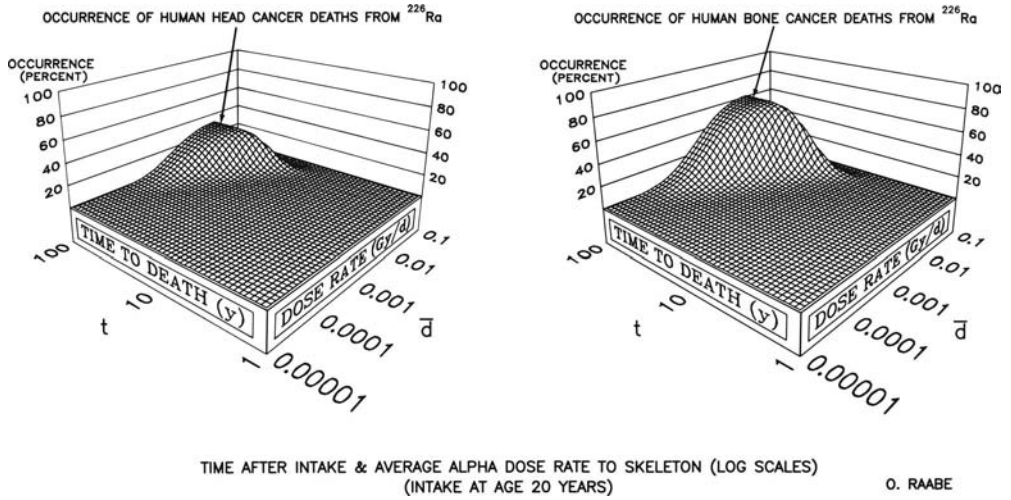

Fig. 2. Three-dimensional representation of the average-dose-rate/time/response relationships for people after intake of ^{226}Ra showing the occurrence of deaths from alpha radiation-induced head carcinoma and bone sarcoma (Raabe 2010) .

or high-LET alpha radiation. These studies show that cancer induction risk associated with a protracted ionizing radiation exposure is a non-linear function of lifetime average dose rate to the affected tissues. Cumulative dose was found to be an imprecise and unreliable indicator of cancer induction risk. Cells in bone and lung appeared equally sensitive to cancer induction either by high-LET or low-LET radiation. No tissue-weighting factors are involved.

Cancer induction associated with protracted exposures to ionizing radiation is a three-dimensional average dose rate, time, response process that depends on the parameter, K_m, controlling the time to cancer induction as a function of average dose rate to the exposed organ (Fig. 3 and Fig. 4). The other parameters depend on radiation type and characteristic temporal distribution (lognormal for alpha radiation, Weibull for beta radiation). For bone cancer, these relationships reduce to a pair of three-dimensional functions, one for alpha radiation and one for beta radiation, after adjustment for potency in irradiation of sensitive cells at bone surfaces. Likewise, for lung cancer these relationships reduce to a pair of three-dimensional functions, one for alpha radiation and one for beta radiation, after adjustment for potency in irradiation of sensitive bronchiolar cells. The resulting cancer occurrence displays a remarkably narrow and consistent range with a long latency and lifetime virtual thresholds below lifetime cumulative organ or sensitive tissue equivalent doses of about 10 Sv (Fig. 5). For lifetime cumulative skeletal equivalent doses below 10 Sv from ingested ^{90}Sr in beagles (Fig. 6), the risk of bone sarcoma was found to be significantly lower than for controls with $p < 0.047$ (Raabe 2010).

The precision and time-delay of the cancer induction phenomenon indicate an underlying gradual biological process involving many altered cells associated with cellular deoxyribonucleic acid (DNA) mutations, clonal development depending on cell division cycles, cellular maturation, and average ionizing radiation dose rate over long latency periods. An important finding is that two beta particles were found to equal one alpha particle in the radiation induction process (Raabe 2010). This finding suggests that double-strand damage to DNA is involved in the cancer induction process.

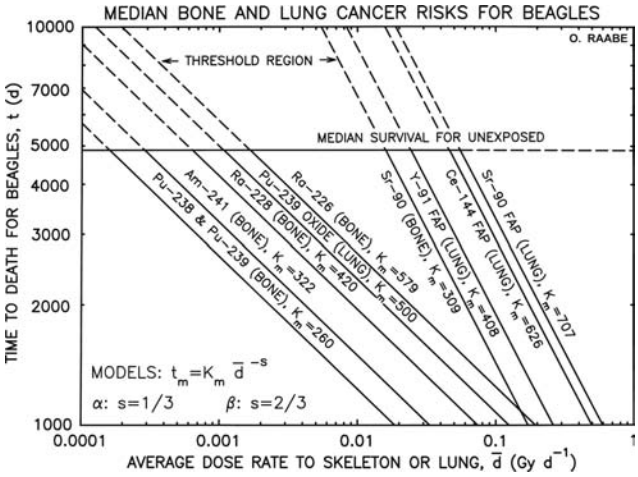

Fig. 3. Illustration of bone sarcoma and lung carcinoma risk functions for beagles demonstrating similar target organ average dose-rate/time/response patterns with lifespan virtual thresholds at low dose rates (Raabe 2010). The positions of the lines vary because of inherent differences in irradiation of the target cells by the different radionuclides and forms. FAP refers to inhaled insoluble fused aluminosilicate particles containing the specified radionuclide.

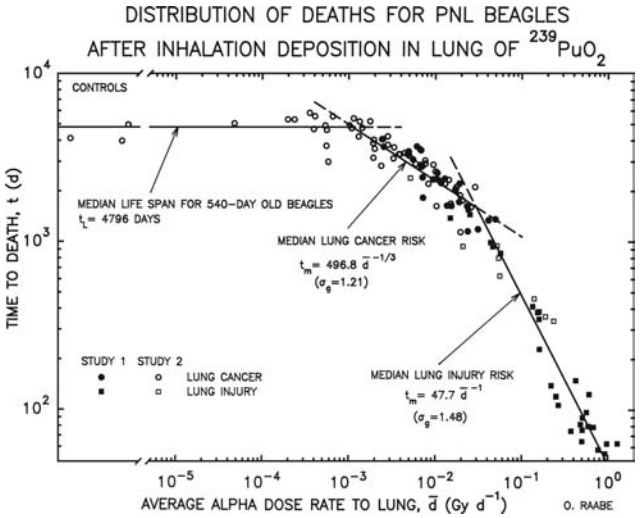

Fig. 4. Distribution of deaths in two lifespan studies of beagles inhaling $^{239}PuO_2$ at Pacific Northwest Laboratory (PNL) showing the lung carcinoma and lung injury risk distributions (Raabe 2010).

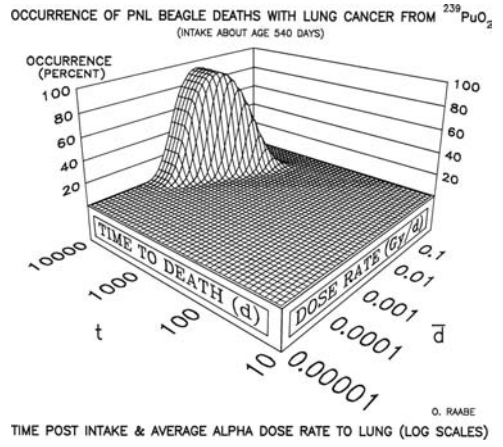

Fig. 5. Three-dimensional representation of the average-dose-rate/time/response relationships for beagles at Pacific Northwest Laboratory (PNL) after inhalation of ^{239}Pu showing the occurrence of deaths from radiation-induced lung carcinoma (Raabe 2010).

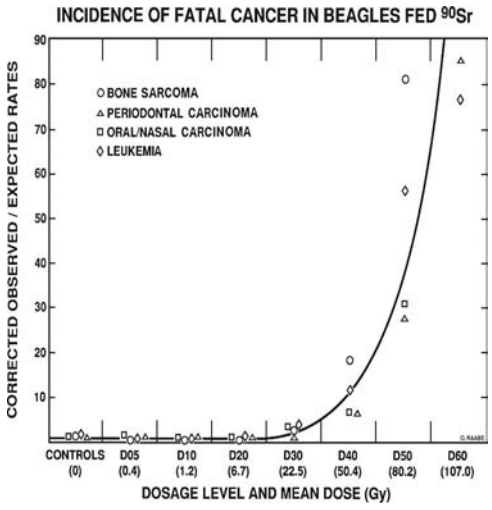

Fig. 6. Statistical evaluation by survival analysis of the incidence of fatal bone sarcoma, periodontal carcinoma, oral/nasal carcinoma and myeloid leukemia in beagles fed ^{90}Sr from before birth to adulthood at the University of California, Davis, as a function of dosage group (with mean cumulative beta radiation dose to the skeleton). The absence of bone sarcoma cases in the lowest three dosage groups is significantly less than those found in the controls ($p < 0.047$) (Raabe 2010).

Because of the long latency that may exceed the natural lifespan, the radiation-induced cancer risk associated with protracted exposures to ionizing radiation involves a lifespan virtual threshold when the lifetime average dose rate is low and the cumulative equivalent dose to sensitive tissues is below about 10 Sv. Lifespan virtual thresholds for radiation-induced cancer risk should exist for other types of protracted and fractionated exposures including radon inhalation and external exposures associated with background levels of ionizing radiation from environmental radionuclides.

An important conclusion is that the current risk assessment practice of adding so-called committed ionizing radiation effective dose from internally-deposited radionuclides to acute dose from high dose rate external radiation exposures is not appropriate. Risk from the protracted exposure is a function of the lifetime average dose rate to the sensitive tissues without use of a tissue-weighting factor. The lifetime average dose rate per day to an irradiated body organ or tissue can be estimated from published ICRP dosimetry information as the uncorrected 50-y committed equivalent dose (without tissue-weighting factor, w_T) divided by18,262 d.

These results should be expected to apply to all forms of protracted or fractionated ionizing radiation exposure including external exposures, since the individual cells of the body do not distinguish between internally- or externally-originated ionizing radiation. For example, dose-response relationships for high-LET proton radiation associated with external exposures to neutrons should be similar to the observed high-LET alpha radiation internal dose rate response relationships. Likewise, dose response relationships for external low-LET gamma radiation exposures should be similar to the observed low-LET beta radiation internal dose rate response relationships.

In studies of 64,172 tuberculosis patients, of whom 39% were exposed externally to highly fractionated x-ray chest fluoroscopies, lung cancer deaths showed no evidence of cancer risk associated with the x-ray exposures, with the relative risk at a cumulative equivalent dose of 1 Sv being 1.00 [95% confidence interval 0.94–1.07] (Howe 1995). Also studies of people exposed to unusually high levels of protracted external ionizing radiation

associated with natural background (up to 260 mSv y^{-1}) have not detected increased cancer risks (Ghiass-nejad et al. 2002).

Radiation-promoted cancer from acute exposure to ionizing radiation

The principle basis of current radiation safety standards is the study by the Radiation Effects Research Foundation (RERF) and its predecessor organizations of the development of solid malignant tumors in about 80,000 survivors of the 1945 Japanese atomic bomb detonations in Hiroshima and Nagasaki (Pierce and Preston 2000; Preston et al. 2003, 2007). These about 1-min exposures involved high-energy gamma radiation and some neutrons. Myeloid leukemia from bone marrow exposures followed a different response course and is usually considered separately from the solid tumor incidence. The traditional approach is to assume that the solid tumors are the result of stochastic initiating events in individual cells that occurred during that about 1-min exposure.

The stochastic model of ionizing-radiation-induced cancer is based on the simple idea that a single cell is randomly altered by a unique ionizing radiation event causing a unique pre-malignant mutation in that cellular DNA (Moolgavkar et al. 1988; Heidenreich et al. 1997). This single stochastic event then ultimately leads to a clone of similar pre-malignant cells. Later, usually much later, a second random DNA alteration occurs in one of the clonal pre-malignant cells that produces a malignant cell that develops into a monoclonal malignant tumor. These processes began with the single cellular event. They can be advanced by promoter agents including ionizing radiation that presumably affect the clonal development, quantity, and maturation of the pre-malignant clonal cells. A cancer promoter is anything that advances the development of a malignancy other than a directly carcinogenic agent or an intrinsic component of the carcinogenesis process (Casarett 1968). Mathematical models are readily constructed with unknown parameters, hypothetical modifying factors and process lag times designed to fit the data associated with acute ionizing radiation exposures (Heidenreich et al. 1997).

Simple mathematical stochastic models are fit to summary data by estimating values of the various parameters of the models. They assume a unique stochastic individual start for each cancer case followed by the development of a clone of altered cells. Much later one altered cell is randomly converted to a neoplastic cell that may have delayed response but ultimately produces the monoclonal malignant tumor. Those models that incorporate radiation promotion assume that pre-cancerous cells already exist that are unrelated to the radiation exposure and that these are nudged along in a conversion to a malignant cell by the radiation exposure. Hence, the promotion effect occurs on existing pre-cancerous processes and may involve numerous cells in a non-stochastic fashion. Versions of this model that consider a promotional component along with stochastic induction have been applied to acute low-LET ionizing radiation exposures (Heidenreich et al. 2007; Shuryak et al. 2010).

The internal emitter studies discussed above strongly suggest that double-strand DNA damage or a related phenomenon is involved in the cancer induction process associated with ionizing radiation. In particular, two low-LET beta particles were found to be required to match the radiation induction process associated with each alpha particle (Raabe 2010). Since the exposure of the Japanese atomic bomb survivors was primarily associated with low-LET gamma radiation and associated energetic electrons, two hits at the same region of DNA in a target cell would be expected to be required for the induction of cancer. The resulting increase in cancer by induction in this two-hit process would follow a sharply increasing curvilinear power function of increasing cumulative absorbed dose. In fact, the increase in cancer among the atomic bomb survivors tended to follow a linear pattern. Deterministic cancer promotion rather than stochastic cancer induction better explains the increase of solid cancers in the atomic bomb survivor studies.

Another historic conceptual issue that affects the traditional interpretation of radiation carcinogenesis stems from the work of Muller (1927) and Oliver (1930) showing a linear dose-response relationship for simple mutations in the male germ cells of fruit flies (*Drosophila)*. These simple events are stochastic, but they are not themselves related to carcinogenesis. Recently, Koana et al. (2004) pointed out that fruit fly somatic cells respond to radiation exposure differently than germ cells and that germ cells are not an appropriate model. They showed that an impressive threshold exists in the dose-response relationship for somatic cell mutation frequency in *Drosophila*. There was no significant effect until doses exceeded about 1 Gy. They attributed the absence of any effect at lower doses to efficient DNA repair processes.

The studies of the atomic bomb survivors demonstrate a linear dose-response promotional effect related to the natural or existing biological processes that may eventually lead to cancer in the exposed population (Fig. 7). These processes involve years of cellular division, clonal expansion, and cellular maturation. The exposure to a sudden high dose of ionizing radiation delivered in about 1 min at the time of the nuclear detonations may have advanced or stimulated the cellular changes that led eventually to various typical types of cancer. Hence, some cancers may have appeared at an earlier time than

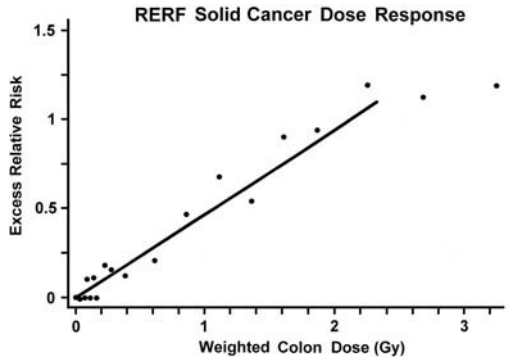

Fig. 7. Linear dose-response relationship of Excess Relative Risk for the promotion of solid cancer in Japanese survivors of the atomic bomb detonations at Hiroshima and Nagasaki in 1945 with respect to survivors who received low radiation exposures as reported by the Radiation Effects Research Foundation (RERF) (Preston et al. 2007).

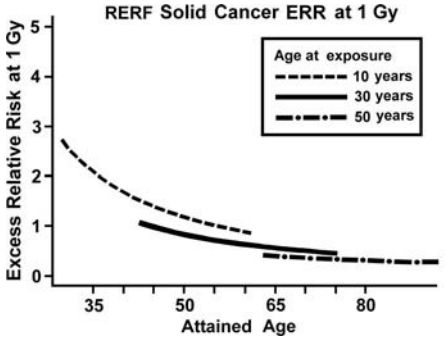

Fig. 9. Observed gender-averaged Excess Relative Risk (ERR) of promoted solid cancer at 1 Gy weighted colon absorbed dose vs. attained age at exposure for highly irradiated Japanese atomic bomb survivors compared to survivors who received low radiation exposure as reported by the Radiation Effects Research Foundation (RERF) (Preston et al. 2007).

otherwise would have occurred based on the existing underlying cellular and tissue processes (Fig. 8). This promotional effect was observed to advance cancer rates not only relatively soon after exposure but throughout the lives of the exposed individuals (Fig. 9). This behavior is proportional to the instantaneous dose just as would be expected for any phenomenon that involves augmentation of existing processes rather than a few random or "stochastic" changes in a few select cells (Fig. 7). However, the resulting cancer promotion phenomena should not be expected to describe the effects of similar exposures delivered uniformly or fractionated over a relatively long period of time. Since promotion is a relative process rather than an absolute process, it is not meaningful to try to create absolute risk estimates from relative response information.

Concerning the solid tumor incidence in the atomic bomb survivor studies, Pierce and Mendelsohn (1999) pose the question, "How could it be that the excess cancer rate might depend only on age and not on time since exposure or age at exposure?" Fig. 10 shows that the increase in malignant solid tumors in the atomic bomb survivors associated with their radiation exposure follows the same lifetime pattern irrespective of the age at exposure. The simple answer is that the normal progression of cancer incidence in the population was somewhat promoted by the radiation exposure without the actual independent induction of cancer. This promotion is not a stochastic process, but rather the result of the almost instantaneous delivery of ionizing charged electrons produced in all the tissues by ionizing radiation from the atomic bombs. The tissues' response is complex and unfocused. The cells of the tissue communicate

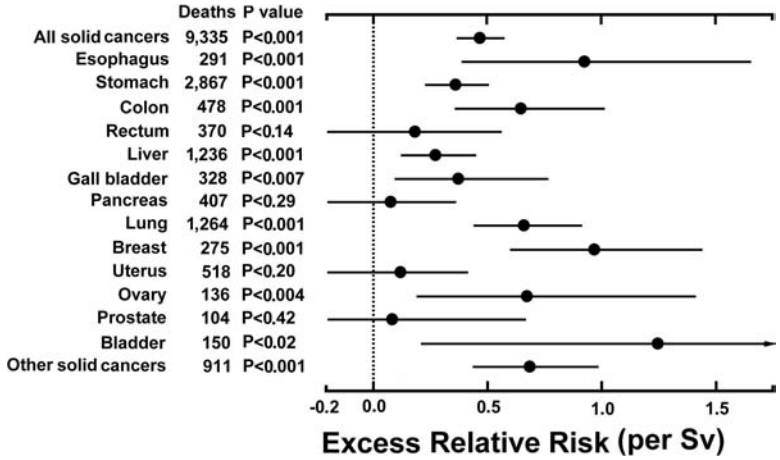

Fig. 8. Observed Excess Relative Risk by body organ for promoted solid cancer observed per Sv of equivalent ionizing radiation dose in highly irradiated Japanese atomic bomb survivors compared to survivors who received low radiation exposure as reported by the Radiation Effects Research Foundation (RERF) (Preston et al. 2003).

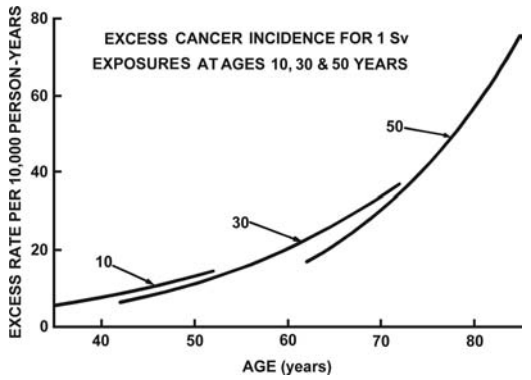

Fig. 10. Observed gender-averaged, age-specific excess incidence rates at 1 Sv equivalent dose for most major solid cancers over the 1958–1987 follow-up period for ages at exposure 10 y, 30 y, and 50 y for the Japanese atomic bomb survivors (Pierce and Mendelsohn 1999). The excess rates appear to depend only on age rather than on time since exposure or age at exposure as might be expected for radiation-induced promotion of the cancer types normally found in this population.

among themselves as a result of the exposure in a process called bystander effect, with various responses evoked even among the cells in those tissues that were not directly impacted (Hall 2003). Tissues respond to sudden ionizing radiation exposure with up-regulation of various genes and down-regulation of others (Snyder and Morgan, 2004; Coleman et al. 2005). This imprint is apparently not lost and carries forward throughout life, promoting the existing biological processes that may lead to cancer in the exposed atomic bomb survivor population. This complex process suggests a systems biology phenomenon rather than a unique stochastic response (Barcellos-Hoff 2008).

The atomic bomb survivor data are unique because they do not in any way predict the observed carcinogenesis associated with protracted exposures as occur in the case of internal emitters. In fact, the acute gamma ray exposures clearly represent a completely different mechanism of carcinogenesis from that which occurs with protracted exposure as with long-lived internal emitters.

The tissue-weighting factors (w_T) developed by the ICRP to calculate the so-called effective dose are actually a reflection of the convolution of the underlying incidences of different types of cancer in the control population and the relative promotional effect of the whole body exposure to gamma rays and some neutrons in the Japanese atomic bomb lifespan studies (ICRP 1977, 1979, 1991). Cancers that were somewhat rare in this Japanese population, such as bone cancer, were assigned relatively low tissue weighting factors relative to the whole body cancer or assumed genetic risk (such as $w_T = 0.01$ for bone surfaces). Cancers that were somewhat common in this Japanese population, such as lung cancer, were assigned relatively high ratio values relative to the whole body cancer or genetic risk (such as $w_T = 0.12$ for whole lung). These tissue-weighting factors can be related to observed cancer promotion but are unrelated to the cancer induction associated with protracted or fractionated exposure to ionizing radiation. The use of tissue-weighting factors recommended by the ICRP is inappropriate for protracted or fractionated exposures.

The elaborate Radiation Effects Research Foundation (RERF) studies of the atomic bomb survivors have investigated in rigorous detail the effect of whole body irradiation by high-energy gamma rays (and some neutrons) delivered in about one minute. The atomic bomb RERF lifespan study clearly describes a meaningful linear dose model of promotion of ongoing biological processes that lead to increased cancer rates for brief high dose rate exposure to ionizing radiation. The relative risk values might be applicable to other brief high dose-rate ionizing radiation exposures, as may occur in occupational exposures or in medical diagnosis and treatment (Hall and Brenner 2008). However, there is still considerable uncertainty for acute doses less than about 0.05 Sv. Small acute doses may be beneficial as they may promote or stimulate DNA repair or other defensive cellular phenomena that reduce promotional cancer risks associated with ongoing cellular processes that might otherwise lead to cancer (Feinendegen 2005).

DISCUSSION

Failure to realize the fundamental differences between cancer promotion and cancer induction has been the source of scientific misunderstandings. A wall of separation has stood between the LNT model of cancer promotion in the acute exposures associated with the Japanese survivors and the virtual threshold associated with induction of cancer associated with protracted exposures as received from long-lived internally-deposited radionuclides in humans or animals. Further, it has led to a systematic overestimation of cancer induction risk from protracted exposures to ionizing radiation.

The LNT model does not predict the observed effects or lack thereof for protracted exposures to ionizing radiation exposure (Jaworowski 2010). Neither does the LNT model readily predict the results of a cumulative set of fractionated medical diagnostic x-ray exposures of the lung where there was no indication of increased lung cancer with the observed relative risk at a cumulative doses of 1 Sv being 1.00 [95% confidence interval 0.94–1.07], contrasting with the high expected relative risk based on the atomic bomb survivors being 1.60 [95% confidence interval 1.27–1.99] (Howe 1995). Also, the large population exposures to long-term protracted ionizing

radiation associated with the 1986 Chernobyl reactor accident in the Ukraine were predicted with LNT to result in a virtual epidemic of long term radiation-induced cancer (Anspaugh et al. 1988). Instead, there was no apparent major effect of this widespread protracted exposure to ionizing radiation except for thyroid disease associated with very high acute radiation doses from short-lived ^{131}I in milk (WHO 2006; Jaworowski 2010).

Based on the linear relative risk relationship observed for acute exposure in the RERF studies of the atomic bomb survivors, the ICRP developed an absolute risk model for radiation-induced cancer as a function of absorbed cumulative ionizing radiation dose that was believed to apply to all forms of exposures to ionizing radiation. In recognition that protracted or fractionated exposures have been observed to be less carcinogenic than the RERF data directly suggest, the ICRP reduced the calculated risk using a dose and dose-rate effectiveness factor (DDREF) of two, but the assumed lifetime LNT linearity of cancer induction was maintained (ICRP 2007). DDREF is a factor used to divide the calculated risk for high dose or high dose rates to obtain the risk for low dose or low dose rates. This approach has led to simplistic cancer induction risk factors such as "5% per Sv" (ICRP 1991, 2007).

The idea that such a risk factor is valid rests on the assumption that each ionizing-radiation-induced malignancy is the result of an isolated random or "stochastic" initial event that is equally probable in any exposed person. Although each malignant tumor is monoclonal, the biological processes that lead to that first tumor (and successive tumors) are apparently deterministic systemic processes rather than simple isolated stochastic events.

It has been assumed that the linear model obtained from the RERF atomic bomb survivor studies can predict this stochastic cancer induction after applying hypothetical DDREF correction factors for protracted, fractionated, or low dose exposures. Others have also adopted similar linear cancer induction risk models as a function of person-Sievert based on the RERF studies. However, as discussed above, these cancer induction models do not apply to non-acute exposures that depend on lifetime average dose rate rather than simply on cumulative dose.

None of the following examples of linear-model (LNT) estimates of cancer risk should be applied to protracted, fractionated, or long-lived internal emitter exposures:

- UNSCEAR: A risk of 0.11 fatal radiation-induced cancers per person-Sievert for high doses (comparable to those experienced by the survivors of the Hiroshima and Nagasaki bombings). For protracted or fractionated exposures, "no single figure can be quoted" for a risk-reduction factor relative to the Japanese LSS, "but it is clear that the factor is small. The data from the Japanese studies suggest a factor (DDREF) not exceeding 3" (UNSCEAR 1993);
- BEIR V, 1990: A total of 0.08 fatal radiation-induced cancers per person-Sievert based on Hiroshima and Nagasaki survivor data (National Research Council 1990);
- ICRP, 1991: A total of 0.05 fatal radiation-induced cancers per person-Sievert for the entire population and 0.04 fatal induced cancers per person-Sievert for adult workers, with both estimates being for low dose rates and incorporating a DDREF of 2 (ICRP 1991);
- U.S. EPA: A risk of 0.06 radiation-induced cancer cases per person-Sievert. Because the cancer incidence rate is about 50 percent greater than the cancer fatality rate, the implied risk is about 0.04 fatal radiation-induced cancers per person-Sievert (U.S. EPA 1993);
- BEIR VII Phase 2, 2006: The RERF Japanese atomic bomb survivor data were used along with expanded linear models and separate parameters associated with gender, age at exposure, and attained age. The committee recommended that linear risk estimates obtained from the these data be reduced using a DDREF of 1.5 (confidence range from 1.1 to 2.3) for cancer induction (National Research Council 2006); and
- U.S. EPA Federal Guidance Report No. 13 (Eckerman et al. 1999) uses ICRP cancer induction linear risk models along with cumulative doses to human organs from internal emitters to calculate the so-called radiation-induced cancer risk per Bq for a numerous selection of radionuclides (Eckerman 1999). The resulting cancer induction risk estimates per Bq are not meaningful.

These cancer induction risk models are not valid because of the confusion of cancer promotion associated with brief high dose-rate exposures and cancer induction associated with protracted exposures. Unfortunately, these misleading cancer induction risk values may be used to implement expensive cleanup standards for environmental radioactivity.

Radiation cancer induction is not a stochastic process in the sense that it is not the result of a few random radiation events in a single cell that converts it into a neoplastic cell. In reality, both radiation-promoted and radiation-induced cancers are the result of complex biological processes involving multiple cellular events. These events include but are not limited to intercellular communication in irradiated tissues, up-regulation and down-regulation of genes, DNA mutations, clonal expansion of altered cells, and various responses to numerous specific radiation events such as DNA double-strand breaks. Induced cancer risk from protracted radiation

exposures of body organs depends on the lifetime average dose rate to the irradiated organs rather than on some function of cumulative dose.

CONCLUSION

Clearly the development of a radiation-induced malignant tumor from either protracted ionizing radiation exposures or acute exposures is not the result of a single random interaction of the ionizing radiation with an isolated cell. Hence, the term stochastic as used by the ICRP is not appropriate. The following conclusions indicate that major revisions of the ICRP methodology and standards are needed, and other currently accepted ionizing radiation risk models should be improved to provide more meaningful and realistic estimates of ionizing radiation cancer risk:

- Cancer *induction* risk associated with protracted or fractionated ionizing radiation exposure is a non-linear function of *lifetime average dose rate to the affected tissues* and exhibits a virtual threshold at low lifetime average dose rates;
- Cumulative radiation dose is neither an accurate nor an appropriate measure of cancer *induction* risk for protracted or fractionated ionizing radiation exposure except for describing the virtual threshold for various exposures; and
- Cancer *promotion* risk for ongoing lifetime biological processes is a relative process as seen in the RERF studies of the Japanese atomic bomb survivors for brief high dose-rate exposures to ionizing radiation. It cannot be used to estimate cancer *induction* risk from protracted or fractionated ionizing radiation exposures over long times and at low dose rates.

Recommendations

The current ICRP radiation protection recommendations certainly provide a high level of safety and protection for radiation workers and the public. Radiation safety has been the most important goal of the ICRP, and their recommendations have met that goal with distinction. However, the ICRP risk estimates and response models for protracted or fractionated ionizing radiation exposures and long-lived internal emitters seriously overestimate the risks of low doses. Reasonably accurate cancer induction risk estimates are needed to avoid expensive over-regulation and to bolster the scientific foundation of radiation safety regulations and analysis. Many of the current environmental radiation safety standards are inappropriately low and prohibitively expensive to enforce.

The current ICRP models of radiation carcinogenesis can be misleading. Revision of the radiation safety standards is needed that clearly distinguishes between radiation cancer promotion as observed in the atomic bomb survivor studies and radiation cancer induction as observed for long-lived internal emitters. In particular, the ICRP needs to revisit and revise the standards currently recommended for ionizing radiation-induced cancer. Recommended standards should be considered that are based on lifetime average dose rate to sensitive tissues in the case of internally-deposited, relatively long-lived radionuclides and other protracted or fractionated exposures rather than on cumulative or committed dose.

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Appendix 9

August 22, 2015

Secretary
U. S. Nuclear Regulatory Commission
Washington, D. C. 20555-0001
Attn: Rulemakings and Adjudications Staff

Subject: **Nancy A. Standler, MD PhD Comments on *Petition for Rulemaking - Linear No-Threshold Model and Standards for Protection Against Radiation* Federal Register Volume 80, Number 120 - Tuesday, June 23, 2015 pages 35870 to 35872**

Gentlemen:

Mr. Oscar Paulson of Rio Tinto and of the Wyoming Mining Association thought that it might be of help to your staff to have another physician's input on the question of the validity of the Linear No-Threshold hypothesis that is used as a basis for radiation protection regulations. He specifically asked me to review recent petitions for rulemaking submitted by Carol S. Marcus, PhD MD (PRM-20-28), Mark Miller, CHP (PRM-20-29) and Dr. Mohan Doss (PRM-20-30). These petitions challenge the use of the Linear No-Threshold hypothesis, and they ask that the NRC amend 10 CFR Part 20, Standards for Protection Against Radiation, to remove the dependence of the standards on a hypothesis that the supporters of these petitions believe to be erroneous.

If I were a member of your staff, I would like to have a feel for who was writing the letters that I was reading, so I am taking the liberty of offering you some information about myself before I make my comments about the Linear No-Threshold hypothesis. I am a practicing board certified pathologist who normally works as a hospital pathologist. My MD and residency training are from the University of Pittsburgh. Prior to entering medical school, I completed a PhD in biophysics from what was then the Department of Radiation Biology and Biophysics (now part of the Biochemistry Department) at the University of Rochester.

As part of my course work at the University of Rochester, I took virtually all of the available coursework on radiation biology in the department. In later years, I have written broadly in medicine, having published two textbooks of pathology for medical students, and also having been heavily involved with the Kaplan Medical course that many medical students use for their Board examinations. As part of that work, I have written over roughly 7500 medical scenario questions (over 4000 pages of text). That work has been used by over 100,000 medical students to prepare for the required national boards examination taken after the second year of medical school.

I have been involved with the specific problem of uranium toxicity and the regulatory issues related to ground water uranium standards since about 2002 when Mr. Paulson contacted me because I had both a PhD with training in radiation biology and an MD degree. At the time, New Mexico was considering altering ground water standards for uranium. I looked critically at the uranium toxicology literature for Mr. Paulson at that time, and since then have from time to time been involved with uranium issues in several Western states.

Let me stress, if I may, that while I was contacted to review material by Mr. Paulson, I am not now, never have been, and never will be an employee of the uranium industry. I make enough money as a hospital pathologist that I can choose to do this work as a public service. My interest is in the general good, because I think that we need good law, which balances medical and economic needs realistically. I have stressed in all of my contacts with the broader uranium community that I will write the truth as best I understand it, and if I think that we really do have a problem with uranium, I will say so publically.

However, I also recognize the danger of producing bad law that is based on a panicky reaction to something that is perceived as a problem but in reality is not.

Before specifically discussing the petitions for rulemaking PRM-20-28, PRM-20-29, and PRM-20-30, I would like to offer an anecdotal story that may contribute to the discussions of the Linear No-Threshold hypothesis. Early in my PhD work at the University of Rochester in the Department of Radiation Biology and Biophysics, in approximately 1981, I knew a PhD pathologist in radiation biology, Dr. George W. Casarett. He was a distinguished man with a multi-decade history of studying the tissue effects of radiation. He had written textbooks on Clinical Radiation Biology and Radiation Histopathology. I knew him over the period of my PhD candidacy. At the time that I knew him, Dr. Casarett was very heavily involved at the national and international level with successive U. S. National Academy of Sciences Committee on Biological Effects of Ionizing Radiation (BEIR) studies. Dr. Casarett was also a member of the group that first wrote the discussion of the Linear No-Threshold model that was used in the U.S. National Academy of Sciences Committee on Biological Effects of Atomic Radiation (BEAR I)/Genetics Panel in 1956.

While I was in my first year of graduate school in approximately 1981, I had a discussion of this early work with Dr. Casarett, during which he explained to me the context in which the work was done. At that point, which was when the Linear No-Threshold hypothesis was introduced, and which was about ten years after the end of World War II, the experiences of Hiroshima and Nagasaki were still extremely fresh in all of the committee members' minds. The study of radiation damage was in its infancy, and almost no real data was available. The leukemia cases in the populations of Hiroshima and Nagasaki that had been exposed to the radiation from the atomic bombs were new cases, and were poorly understood. Per Dr. Casarrett, the members of the BEAR I committee on which he was on (I am not sure exactly which one it was) specifically had no low dose information at all. Techniques for delivering low doses of radiation had not yet been worked out, and close to none of the biology of radiation damage was at that time understood, so the available research was not even close to identifying accurate markers for radiation damage.

While it is easy to criticize this early work now, I think we owe them the dignity of recognizing that they were trying to make good decisions in the near complete absence of information which we would consider credible now. The scientists involved in the decision making in 1956 were apparently very distressed about the overall situation, particularly so because there was international concern about radiation toxicity, which was at its peak at that time, because radiation appeared so bizarre and dangerous to most lay people. So the committee felt obligated to act, before the science that they needed really existed. What they did was ingenious, and I believe that it was truly that best that anybody could have done at that time, given the enormous scarcity of pertinent data. They had one factual piece of information, the number of cancers, primarily leukemias, seen in the survivors of the Hiroshima and Nagasaki nuclear explosions, and they used that to go as far as they could.

The committee decided to make the assumption, in the complete lack of any other available information, that each little unit of radiation had the same potential for causing cancer risk. What they were essentially saying was that it didn't matter what the total dose of radiation received was, nor the route of exposure used, nor the timing of the exposures used to give the radiation dose. No matter what, each little unit of radiation carried exactly the same radiation risk.

This is the basis of the Linear No-Threshold model or hypothesis. Specifically, the idea is that if 1 little radiation exposure had a chance of 1 in whatever large number of causing a cancer, then 10 little radiation exposures of the same size had a chance of 10 in the same whatever large number of causing a cancer. The curve produced from this sort of assumption is a straight line that intercepts at the origin of the graph, point (0,0).

This assumption looks very unrealistic to many who know radiation biology now that there has been a great deal more research. If there is any circumstance in which it is not true that one tiny dose of radiation causes exactly the same risk as another tiny dose the same size, then the Linear No-Threshold hypothesis is just plain wrong. Examples of ways in which this could conceivably be wrong include the

possibility that there was any ability for cells to heal from tiny radiation doses by rebuilding their DNA, as is known to happen, or if a very heavily damaged cell actually has less risk of causing a cancer because it just dies, as happens in radiation therapy of cancers.

To see intuitively why it was always highly unlikely that the Linear No-Threshold hypothesis was correct, I find it helpful to think about an example from another, imaginary, setting. Suppose that we start with the (imaginary) fact that eating 5 apples in a row gives 1 in 10 kids a stomach ache. Does that automatically mean that eating 1/5 as many apples, or 1 apple, will give 1/5 as many kids a stomach ache, or give 1 in 50 kids a stomach ache? Or eating 1/10 of an apple will give 1 in 500 kids a stomach ache? We know things don't typically scale that simply with apples, and many of us who have looked at the literature don't think that the effects of radiation doses scale that simply either.

Per my discussion in about 1981 with Dr. Casarett, what we often don't realize is that the only reason the Linear No-Threshold hypothesis was initially used was that it was better to use a hypothesis that the people who made the estimate knew to be wrong, but for which they had no decent replacement at that time because the science was too new, rather than do nothing at all in a setting in which a great many people across the United States were feeling very panicky.

To find a line for the Linear No-Threshold calculations, you need the following:

1. *Assumption* that you will use a straight line with a slope and an intercept.
2. *Assumption* that the line passes through the origin of the graph, point (0,0).
3. A single point known to be on the line.

The first of these assumptions, the use of a straight line to relate radiation dose to radiation effect, specifically cancer risk, is equivalent to the verbal assumption that any little piece of radiation has exactly the same effect on cancer risk as any other little piece of radiation of the same size. A trivial, obviously true, counterexample from the radiation literature is to point out that in a patient who dies immediately after a nuclear explosion, none of the very large number of little radiation doses the person received ever cause a cancer, since the person died first. The silly, but obvious once said, conclusion is that extremely large radiation doses carry a markedly decreased cancer risk since the person doesn't live long enough to get cancer. I am obviously not really suggesting that people avoid cancer by killing themselves with radiation, but it does illustrate that the Linear No-Threshold hypothesis cannot be an adequate hypothesis for the entire range of values from 0 to infinity of radiation doses. This means that it really is appropriate for us to ask whether the Linear No-Threshold hypothesis is valid at low doses, where it is being used for regulatory reasons. The possibility of this low dose variation from Linear No-Threshold prediction is the subject of most of the petitions about Linear No-Threshold reasoning that are being presented to your staff.

If you have assumed a (0,0) origin for your straight line relating dose to cancer risk, as is done in the Linear No-Threshold model, then you can use the origin together with a single data point to construct the line. This was what was done in 1956, and per Dr. Casarett, the single "real" data point that was used to obtain the number used by the BEAR I to develop a number for a safe exposure level to radiation, was based in part on the average radiation dose that the people in Nagasaki and Hiroshima received. The BEAR I committee also figured out how many of the Nagasaki and Hiroshima survivors had developed cancers (notably leukemias), so that they had the ratio of cancers to population at a single average radiation dose to the individuals in those cities. Per Dr. Casarett, the original BEAR committee members then used the Linear No-Threshold idea (which they knew was likely to be wrong , but they didn't have any information about a better guess) to extrapolate what the dose would be (by that Linear No-Threshold model) that would produce less than 1 cancer death per year in the entire United States. This is a very conservative estimate, which was specifically designed to alleviate fear.

At the time that I had the conversation about the Linear No-Threshold idea with Dr. Casarett (about 1981), he mentioned that he was pleased that the work with low dose radiation effects were finally beginning to have enough depth that he thought that it would soon be feasible to develop better models

that would lead to more accurate standards. I think he would have been surprised that we have to this date still had trouble switching over to using more modern information for setting acceptable doses.

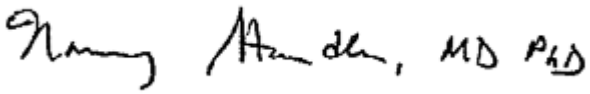
My personal reaction is that the BEAR I work, even though it has been criticized, was remarkable for its time, and that it made sense then. It is just time now, and has been for a while, to use more accurate modeling to develop numbers for appropriate radiation exposure limits. The information collected and referenced by the three petitions PRM -20-28, PRM-20-29, and PRM-20-30, and also additional material that you receive from other sources, are likely to be helpful in these efforts.

I have included as appendices specific commentary on the three petitions for rulemaking pertaining to the Linear No-Threshold hypothesis that are being considered at this time. I have also included as an appendix a brief discussion of several papers presented in the Wyoming Mining Association's discussion of the three petitions.

The term "hormesis" is important in these documents. This term should be understood as conveying the idea that something poisonous at high doses may sometimes actually be helpful at lower doses, often because tiny amounts of a stressor may turn on strong biological mechanisms, probably developed over millions to billions of years of evolution, that counteract damage so effectively that an organism actually benefits from rather than is harmed by tiny amounts of the stressors. Any time that hormesis is demonstrated, you have of course also demonstrated a failure of the Linear No-Threshold model.

I strongly believe that it is time to revise our current radiation standards to reflect the information that has been obtained about radiation damage over the last nearly 60 years.

Sincerely yours,
Nancy A. Standler, MD PhD



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APPENDIX 1
COMMENTARY ON PRM-20-28, SUBMITTED BY CAROL S. MARCUS
Nancy Standler MD PhD

This petitioner requests that the NRC amend 10 CFR Part 20, *Standards for Protection Against Radiation*, based on new science and evidence that contradicts the Linear No-Threshold (LNT) hypothesis, which has been used as the basis for radiation protection regulations.

Dr. Carol S. Marcus, the petitioner, is an MD PhD radiation oncologist who is a professor at the David Geffen School of Medicine at UCLA. Her scientific training was from Cornell University, where she took a Bachelor of Science degree in biology (1960), Master of Science in Radiation Biology (1961), and Doctor of Philosophy in Physical Biology (1963). Her medical training was initially at the University of Southern California, where she took a Doctor of Medicine (1977) and an Internal Medicine Residency (1980). She then went to the V.A. Wadsworth Medical Center, where she took a Nuclear Medical Residency (1982). She has been a Professor at the David Geffen School of Medicine at UCLA in Los Angeles for the past 33 years. She has served on the NRC Advisory Committee in the Medical Uses of Isotopes from 1990 to 1994.

In her petition, Dr. Marcus gives general context for the possibility of hormesis, in which low doses of potential stressful agents may be protective rather than noxious. She points out that "Biological organisms are exceedingly complex, and have evolved in a world full of stressors, particularly oxygen, and also by low dose background radiation from above, below, and within our own bodies." She notes that more than 150 different genes are involved in protection from noxious agents, and that this protective system is consequently very complex. Typically, this is a range of fairly low, but not extremely low doses, at which the hormesis effect is most potent, with overall damage at higher levels. In general, this implies that while we need in the case of toxins to protect against high doses, protection again lower doses may not be warranted.

Dr. Marcus goes on to express the high level of frustration that she feels, which I also feel, and which I believe that many people familiar with the issue feel, with the very high level of dependency that numerous regularatory agencies, both nationally and internationally, have on the Linear No-Threshold Assumption. She believes that there are literally thousands of papers in which more detailed analyses of specific problems show results other than the Linear No-Threshold assumption. She also believes that the dependence on this Linear No-Threshold assumption is in part based on fraudulent data, and she specifically cites three papers by Professor Edward J. Calabrese of the University of Massachusetts that document early problems within the United States (US) National Academy of Sciences (NAS) Biological Effects of Atomic Radiation (BEAR I) Genetics Panel.

Incidentally, the BEAR I panel is the same one that Dr. George Casarett discussed with me, in which he said that the committee was doing its best to make a reasonable guess in a time in which public concern was very high, because Hiroshima and Nagasaki had occurred only about ten years before, and only the very earliest radiation induced cancer data was available. Dr. Marcus also refers to a recent critique of the 2001 NCRP report no. 136 entitled "Evaluation of the Linear-Nonthreshold Dose-Response Model for Ionizing Radiation. The critique, published in 2003 by Zbigniew Jaworski of the United nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and Michael Waligorski, demonstrated what Dr. Marcus calls "an astonishing expose of scientific misconduct".

Dr. Marcus goes on to list specific papers showing hormesis (protective) effects at low does. These include the following examples:

1. Japanese atomic bomb survivors "show a hermetic effect for all solid cancers in the 0.3-0.7 Gy (30-70 rad) dose range."

2. Leukemia rates in the 96,000 Japanese atomic bomb survivors also “showed hormesis at low doses with a threshold at about 500 mSv (50 rem).”
3. Over 400,000 nuclear power industry workers in 154 facilities in 15 countries had a decrease in the risk of all cancers including leukemia.
4. The BEIR VII report notes that most of the nuclear industry worker studies show mortality from all cancers and all causes is substantially lower than in the reference population. Dr. Marcus suggests that the cause of the decreased mortality may be hormesis.
5. 31,710 female patients with tuberculosis who were being treated in Canadian sanatoriums were followed with multiple fluoroscopies. In this population, “patients who received a total radiation absorbed dose in the range from 5-30 cGy (5-30 rads) had a breast cancer incidence up to one third less than the background incidence.”
6. In an important historical case, 900 young women who were radium dial watch painters who were ingesting radium when they sharpened their paintbrushes with their tongues developed 54 bone sarcomas and 25 carcinomas of the mastoids and paranasal sinus. However, Dr. Marcus points out that none of these malignancies occurred at a radiation dose to bone less than 10Gy (1000 rads), suggesting that there was a very high threshold for induction of bone cancer.
7. In 36,000 hyperthyroid patients treated following World War II, Dr. Marcus notes that “the age-adjusted leukemia incidence rate was 11/100,000 patient years in the I-131 treated patients and 14/100,000 patient years in patients treated by surgical removal of the thyroid gland”. Dr. Marcus further notes that “the 22% decrease in I-131 treated patients suggests a possible hermetic effect.”
8. The Russian “Mayak” nuclear fuel reprocessing facility exploded in 1957 releasing radioactive waste. When occupants of nearby villages were studied, “the cancer death rate in the 50 rem group was 29% lower than controls, and in the 12 rem group was 39% lower than controls,” suggesting radiation hormesis.
9. In Taiwan, 7271 people representing 101,560 person-years were at risk from exposure to several orphan cobalt-60 sources that were recycled into 20,000 tons of steel that were used to construct 200 residential, industrial, and school buildings. These people who were exposed to an average of about 5 cGy (5 rads) had standardized incidence ratios of 0.8 for all cancers (confidence interval 0.7 to 1.0), 0.8 for all cancers except leukemias (confidence interval 0.6 to 0.9), and 0.7 (confidence interval 0.6 to 0.9) for solid cancers, suggesting radiation hormesis.
10. Dr. Marcus cites papers by Bernard Cohen in the United States that “show increasing levels of residential radon were associated with decreasing levels of lung cancer.” She notes that Klaus Becker has found similar results in Central Europe.
11. Dr. Marcus refers to an analysis of the Chernobyl area thyroid cancer cases by Jaworski, who points out that “the natural incidence of occult thyroid cancer is approximately 1000 times higher in the countries with the greatest fallout from the Chernobyl accident.” The thyroid cancers that were found in the area were most likely found because of the intense screening, and are not likely to be the result of the Chernobyl accident.

Dr. Marcus also gives a number of examples in which the same or similar data are used to draw different conclusions by different regulating agencies.

Dr. Marcus asks that allowable worker doses for radiation remain at up to 100 mSV (10 rem) effective dose, and that this same limit be used with public doses, including those to pregnant women, embryos and fetuses, and children less than 18 years of age. I agree with her recommendations. I also agree with Dr. Marcus’ recommendation that the concept of “as low as reasonably achievable” (ALARA) be discarded, as it introduces steadily increasing cost to no advantage in a setting where hormesis is operating.

APPENDIX 2
COMMENTARY ON PRM-20-29, SUBMITTED BY MARK L. MILLER
Nancy Standler MD PhD

Mark L. Miller is a certified health physicist associated with Sandia National Laboratories. He has a M.S. in Radiologic Health Physics, and has 8 papers listed on Research Gate. Mark Miller is also one of the signers of PRM-20-30, which was by members of the Scientists for Accurate Radiation Information. Like Dr. Carol Marcus, he is challenging the Linear No-Threshold hypothesis.

Overall, Mark Miller's petition follows the same general lines as Dr. Carol Marcus' petition (PRM-20-28). His information and sources closely overlaps with those used by Dr. Marcus, and I will consequently not discuss it further, to avoid additional repetition.

APPENDIX 3
COMMENTARY ON PRM-20-30, SUBMITTED BY 24 SIGNERS
FROM SCIENTISTS FOR ACCURATE RADIATION INFORMATION (SARI)
Nancy Standler MD PhD

The organization whose members are submitting the commentary in this petition is an international one. The majority of the signers are from the United States. Other countries that are represented in the signatures , which would not necessarily have much legal standing in the United States, but which tend to indicate the international importance of United States leadership, include the United Kingdom, Canada, Saudi Arabia, Poland, Germany, and Japan.

The signers are writing to support Dr. Marcus' petition, PRM-20-28. They use 32 references, all but one of which are in addition to those that Dr. Marcus chose to present.

Some of the references look at cancer risk in patients exposed to medical radiation, particular computed tomography. This literature is complex, and the SARI signers of the petition PRM-20-30 point out that the credibility of recent studies that appeared to show increased risks of cancers following computed tomography exposure has been challenged.

With respect to the question of radiation hormesis, in which low doses of radiation reduce cancer risks, the SARI authors offer supporting references on the following topics, which are different from those offered by Dr. Marcus:

1. A radiation dose of around 4 cGy in nuclear shipyard workers was associated with significantly lower cancer mortality rates in comparison to workers in the same shipyard with no occupational radiation dose.
2. Second cancers per kg of exposed tissue in children who were cancer survivors treated with radiation therapy at a dose of around 20cGy were decreased compared to regions of the body that had received no cancer dose.
3. Whole body low-dose radiation given repeatedly over a 5 week period showed a cancer therapeutic effect with similar to or better than chemotherapy on patient survival, with no observable side effects.
4. Low-dose radiation treatment given to whole body or half body between standard radiotherapy of the tumor improved patient survival.

The above material illustrates that there is a clearly developing interest in the use of low dose radiation as a therapeutic modality to supplement the usual forms of radiation therapy and chemotherapy. This would have been unexpected in a traditional Linear No-Threshold model.

APPENDIX 4
POTENTIALLY USEFUL PAPERS REFERENCED IN WYOMING MINING ASSOCIATION (WMA) COMMENTS ON PETITIONS PRM-20-28, PRM-20-29, AND PRM-20-30
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Some of these papers are discussed in the submitted petitions PRM-20-28, PRM-20-29, and PRM-20-30. I am including them here to draw your attention to specific quotations and figures.

TD Luckey, KS Lawrence. Radiation hormesis: the good, the bad, and the ugly. *Dose Response* 4(3): 169-2006. A copy of this paper is present in Appendix 1 of the WMA comments on the petitions. Selections from the paper:

> p. 172: "Over 3000 scientific research papers how that low dose irradiation is stimulatory and/or beneficial in a wide variety of microbes, plants, invertebrates, and vertebrates".
> p. 172: "The good is acceptance of radiation hormesis by the French Academy of Sciences… That thorough and exemplary document makes it very clear that the Linear No Threshold (LNT) concept is not tenable."
> p. 175: Figure 3 in the paper demonstrates that between 0.5 and 5 pCi/liter home radon dose, lung cancer deaths per 10,000 person years *decrease* from around 7 to around 4.5 (about 64% of the 0.5 pCi/liter dose).
> p. 185: Figure 7 in the paper shows the data for the breast cancer deaths in Canadian women treated for tuberculosis and monitored repeated fluoroscopy. The lowest death rate was 4 deaths per 10,000 women at a dose of 1bout 15 cGy; nearly 6 deaths per 10,000 women were seen at about 4 cGy and nearly 9 deaths per 10,000 women were seen at 500 cGy.

A Aurengo et al. Dose-effect relationships and estimation of the carcinogenic effects of low doses of ionizing radiation. Academie des Sciences- Academie nationale de Medecine. March 30, 2005. A copy of this paper is present in Appendix 2 of the WMA comments on the petitions. This paper has a detailed discussion of why the French authors have concluded that common justifications for use of a Linear No Threshold hypothesis are not as strong as they might initially appear.

LE Feinendegen. Evidence for beneficial low level radiation effects and radiation hormesis. JAERI-Conf 2005-001. A copy of this paper is present in Appendix 3 of the WMA comments on the petitions. This paper gives a theoretical base for the types of processes that can cause hormesis.
Selections from the paper:

> p. 165: Figure 1. Schematic summary of categories of adaptive protection. This is an overview figure to introduce protective mechanisms in cellular biology.
> p. 167: Figure 3. Dual effect of low dose radiation. This presents a model for the complex interactions between tissue and ionizing radiation.
> p. 167-8: The summary part of this paper describes the varying physiologic processes that occur with radiation.

W Olipitz et al. Integrated molecular analysis indicates undetectable DNA damage in Mice after continuous irradiation at ~400-fold natural background radiation. National Institute of Environmental Health Sciences. National Institutes of Health. 2012. A copy of this paper is present in Appendix 4 of the WMA comments on the petitions. This paper uses an important, unique method for assaying very low levels of radiation damage. They use a mouse model in which the mice have been genetically modified so that cells within the mice that have undergone recombination events will fluoresce under microscopy. This method is strikingly sensitive and removes most of the subjective bias in the measuring. By this technique, the authors were unable to detect DNA damage after 5 weeks of exposure of the mice to radiation doses approximately 400x background.

R Sponsler and JR Cameron. Nuclear shipyard worker study (1980-1988): a large cohort exposed to low-dose-rate gamma radiation. *Int. J. Low Radiation,* Vol. 1, No. 4, 2005. A copy of this paper is presented in Appendix 5 of the WMA comments on the petitions.
Selection from the paper:

> p. 469: Table 2 demonstrates standardized mortality ratios less than 1 for exposed cohorts compared to controls.

JM Cutler. Future of radiation protection regulation. Talk given at Health Risks from Ionizing Radiation, 60th Annual Meeting of Health Physics Society, Indianapolis, Indiana, July 12-16, 2015. The slides from this talk are presented in Appendix 6 of the WMA comments on the petitions. The talk is a long one that covers a wide range of topics.
Of particular note are the following slides:

> Nasopharyngeal Radium Irradiation (NRI) and Cancer: Fact Sheet: "At this time, worldwide studies have not confirmed a definite link between NRI exposure and any disease."
> Spontaneous Lung Metastasis vs. Total Body Dose: Total body dose around 0.15 Gy has 0.4 times the number of lung colonies of that with no added radiation
> Hiroshima Atomic Bomb Survivor Leukemia: Demonstrates decreased numbers of leukemia cases at about 1 rem dose compared to those expected from the LNT model