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Attachments

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U.S. Nuclear Regulatory Commission
Washington, DC 20555-0001
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Subject: Wyoming Mining Association (WMA) Comments on the *Advance Notice of Proposed Rulemaking - Radiation Protection* - Federal Register Volume 79, Number 143 Friday, July 25, 2014 FR Doc No: 2014-17252 - Docket ID NRC-2009-0279

To whom it may concern:

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) in-situ uranium recovery operations, one (1) conventional uranium recovery operation (on standby), several companies planning new uranium recovery operations and several companies conducting final reclamation/restoration operations. WMA has reviewed the *Advance Notice of Proposed Rulemaking - Radiation Protection* - Federal Register Volume 79, Number 143 Friday, July 25, 2014 and has the following comments:

Update 10 CFR part 20 to align with ICRP Publication 103 methodology and terminology

Question Q1-4 Should the public dose limit of 0.5 mSv (50 mrem) continue to be the basis for the effluent concentration limits for the radionuclides in 10 CFR Part 20, appendix B, Table 2, Columns 1 and 2? Should it be reduced or otherwise modified?

The WMA believes that no reductions should be made to the public dose limit or effluent concentration limits in 10 CFR part 20, appendix B, Table 2, Columns 1 and 2. Any future reductions especially to the public dose limit or effluent concentrations for Radon-222 in 10 CFR Part 20, appendix B, Table 2, Columns 1 and 2 would create additional compliance determination issues for the uranium recovery industry.

10 CFR Part 2 Appendix B – Table 2 provides Effluent Concentration Limits that "…*are equivalent to the radionuclide concentrations which, if inhaled or ingested continuously over the course of a year, would produce a total effective dose equivalent of 0.05 rem (50 millirem or 0.5 millisieverts).*" The Effluent Concentration Limits for Radon-222 are as follows:

Radon-222

Atomic No.	Radionuclide	Class	Table 1 Occupational Values			Table 2 Effluent Concentrations		Table 3 Releases to Sewers
			Col. 1	Col. 2	Col. 3	Col. 1	Col. 2	
			Oral Ingestion ALI (µCi)	Inhalation		Air (µCi/ml)	Water (µCi/ml)	Monthly Average Concentration (µCi/ml)
				ALI (µCi)	DAC (µCi/ml)			
86	Radon-222	With daughters removed	-	1E+4	4E-6	1E-8	-	-

		With daughters present	-	1E+2 (or 4 working level months)	3E-8 (or 0.33 working level)	1E-10	-	-

The effluent concentration limit with daughters present is 1E-10 microCuries per milliliter which is equivalent to 0.1 pCi/l. In this case 0.1 pCi/l of Radon-222 with daughters present is equivalent to 50 millirems of internal exposure. The problem is that the existing measurement technology (Landauer, Inc. RadTrak detectors) has a minimum level of detection of 0.33 pCi/l based upon a 90 day exposure with reading at conventional resolution and 0.06 pCi/l based upon a 90 day exposure with reading at high resolution. When measuring Radon-222, the high resolution Lower Limit of Detection (LLD) of 0.06 pCi/l based upon a 90 day exposure is very close to the Effluent Concentration Limit of 0.1 pCi/l. In addition, the error estimates for the data provided for RadTrak detectors read at high resolution can vary, with a range of between +/- 0.08 to +/-0.14 pCi/l as documented by a Wyoming uranium recovery licensee. The resolution and Lower Limit of Detection (LLD) of the existing technology for environmental Radon-222 measurement makes it very difficult to precisely measure doses to Radon-222 at the low concentrations encountered around uranium recovery facilities.

In addition, the RadTrak method itself has been known to yield substantially different results for co-located duplicates. This situation was discussed in detail in a presentation given by Oscar Paulson on behalf of the National Mining Association (NMA) at the April 2, 2014 Public Workshop to discuss the March 2014 FSME-ISG-01 Draft Interim Guidance *EVALUATIONS OF URANIUM RECOVERY FACILITY SURVEYS OF RADON AND RADON PROGENY IN AIR AND DEMONSTRATIONS OF COMPLIANCE WITH 10 CFR 20.1301* entitled *Analysis of Data from Co-Located Landauer, Inc. Radtrak Detectors* (ADAMS Accession Number: ML14090A109) which may be found at: http://pbadupws.nrc.gov/docs/ML1409/ML14090A109.pdf

Landauer, Inc. has recently made changes at least in how the environmental RadTrak detectors are shipped in order to attempt to address the problems discussed in the above described presentation.

Given the high Lower Limit of detection (LLD) of the detectors and the documented problems regarding variability in results for collocated detectors, it would not be feasible with present technology to measure Radon-222 doses to members of the general public at compliance levels lower than they are at present.

In addition, in order to accurate assess dose based upon Radon-222 activity in air an equilibrium factor between Radon-222 and its decay products must be calculated. The accuracy of the calculated equilibrium factors is dependent in turn upon the accuracy of the modified Kulsnetz method used to measure radon decay product activities in air. The Statements of Consideration for the final revised 10 CFR Part 20 (Federal Register Volume 56, Number 98 - Tuesday, May 21, 1991 - Rules and Regulations - page 23375) discusses this issue stating:

The Commission is aware that some categories of licensees, such as uranium mills and in situ uranium mining facilities, may experience difficulties in determining compliance with the values in appendix B to Part 20.1001 – 20.2401, Table 2, for certain radionuclides, such as radon-222. Provision has been made for licensees to use air and water concentration limits for protection of members of the general public that are different from those in Appendix B to Part 20.1001 – 20.2401, table 2, if the licensee can demonstrate that the physiochemical properties of the effluent justify such modification and the revised value is approved by the NRC. For example, uranium mill licensees could, under this provision, adjust the table 2 value for radon (with daughters) to take into account the actual degree of equilibrium present in the environment.

Thus the preamble to the current version of 10 CFR Part 20 dated Tuesday, may 21, 1991 already acknowledges that uranium recovery licensees may experience problems in determining compliance with the current dose limits.

The Wma would like to emphasize that compliance with the limits on dose to the general public in *10 CFR § 20.1301 Dose limits for individual members of the public* is not solely required to be demonstrated by measurement but may be demonstrated by calculation (modeling) in accordance with *10 CFR § 20.1302 Compliance with dose limits for individual members of the public* which states:

> *(b) A licensee shall show compliance with the annual dose limit in § 20.1301 by--*
> *(1) Demonstrating by measurement or* ***calculation*** *that the total effective dose equivalent to the individual likely to receive the highest dose from the licensed operation does not exceed the annual dose limit;*

Lower limits would force uranium recovery licenses to perform costly modeling or resort to extreme numbers of measurements in order to demonstrate compliance.

Determining compliance with public dose limits in regard to Radon-222 also involves accurate determination of background Radon-222 as well as the equilibrium factor.

Background Radon-222 activities vary both temporally and spatially in air. The WMA believes that background Radon-222 activities must be measured concurrently with operational monitoring since background Radon-222 activities vary temporally. In winter for example, when the ground is snow covered, background Radon-222 activities in air may be substantially reduced since radon-222 generated in soils upwind of a site are unable to enter the air due to snow. Agricultural activities (plowing) upwind of the facility may elevate background radon-222 activities in air.

Surface mining activities including uranium mining activities, vents from underground uranium mining operations, and other types of earth moving activities are part of background for the area. These activities can contribute to background Radon-222 concentrations in air as well. Because of these factors background Radon-222 activities in air must be measured concurrently with other operational monitoring.

Background monitoring sites must be located upwind of the licensed facility as determined by the predominate prevailing wind direction. For various site specific reasons, background (upwind) Radon-222 activities in air may exceed supposedly impacted downwind radon-222 activities in air. This is known to be true at one uranium recovery site in Wyoming and may be true at others. Background Radon-222 activity in air can vary markedly both temporally and spatially. Radon-222 activity in air, even in air unimpacted by operations, is not homogeneous. Further reductions in effluent concentrations and/or public dose limits would create further problems for licensees in demonstrating compliance with any meaningful reduction in risk since the 0.1 pCi/L effluent concentration limit (with daughters present) would be lost within the variability (noise) of the background concentration in air.

In regards to this issue, NUREG *-1501 - Background as a Residual Radioactivity Criterion for Decommissioning: Appendix A to the Draft Generic Environmental Impact Statement in Support of Rulemaking on Radiological Criteria for Decommissioning of NRC-Licensed Nuclear Facilities* states:

> "*In areas where background is both high and widely variable, the ability to assess facility–related radionuclides becomes increasingly difficult. Even with the application of state-of-the-art measurement techniques and the collection of large amounts of radiological data, radiological dose limits for some radionuclides cannot be measured with sufficient certainty using current survey techniques*."

This raises the issue of the technical feasibility and practicality of measuring facility related radionuclides such as radon when the emissions become lost within the variability of background. The Atomic Energy Act of 1954 as amended (Section 84) clearly states that in the case of sites processing ores primarily for their source material content or used for the disposal of 11(e).2 byproduct material, the licensee may propose alternatives to specific requirements of the act that take into account local (site specific) or regional conditions. The Act states:

c. In the case of sites at which ores are processed primarily for their source material content or which are used for the disposal of byproduct material as defined in section 11e.(2), a licensee may propose alternatives to specific requirements adopted and enforced by the Commission under this Act. Such alternative proposals may take into account local or regional conditions, including geology, topography, hydrology and meteorology. The Commission may treat such alternatives as satisfying Commission requirements if the Commission determines that such alternatives will achieve a level of stabilization and containment of the sites concerned, and a level of protection for public health, safety, and the environment from radiological and non-radiological hazards associated with such sites, which is equivalent to, to the extent practicable, or more stringent than the level which would be achieved by standards and requirements adopted and enforced by the Commission for the same purpose and any final standards promulgated by the Administrator of the Environmental Protection Agency in accordance with section 275.94

Elevated or highly variable background radon would be a local or regional condition that would allow a licensee to propose alternatives to specific requirements.

10 CFR Part 40 Appendix A, *Criteria Relating to the Operation of Uranium Mills and the Disposition of Tailings or Wastes Produced by the Extraction or Concentration of Source Material From Ores Processed Primarily for Their Source Material Content* addresses the issue of practicality as well stating:

All site specific licensing decisions based on the criteria in this Appendix or alternatives proposed by licensees or applicants will take into account the risk to the public health and safety and the environment with due consideration to the economic costs involved and any other factors the Commission determines to be appropriate. In implementing this Appendix, the Commission will consider "practicable" and "reasonably achievable" as equivalent terms. Decisions involved these terms will take into account the state of technology and the economics of improvements in relation to benefits to the public health and safety, and other societal and socioeconomic considerations, and in relation to the utilization of atomic energy in the public interest.

This language clearly allows for consideration of the state of technology (technical feasibility) and whether something is *"practicable"* and *"reasonably achievable"*

NUREG/BR-0184 - *Regulatory Analysis Technical Evaluation Handbook - Final Report* (January 1997) addresses the issue of technical infeasibility. On page 4.4 it states:

Once a broad and comprehensive list of alternatives has been developed, a preliminary analysis of the feasibility, values, and impacts of each alternative is performed. Some alternatives usually can be eliminated based on clearly exorbitant impacts in relation to values, technological infeasibility, severe enforcement or implementation problems, or other fairly obvious considerations. Reduction of the list of alternatives at this point in the analysis will reduce the resources needed to perform detailed evaluation of values and impacts. The regulatory analysis document should list all alternatives identified and considered, and provide a brief explanation of the reasons for eliminating certain alternatives during the preliminary analysis.

This language allows for the elimination of alternatives due to technological infeasibility.

NUREG/BR-0184 - *Regulatory Analysis Technical Evaluation Handbook - Final Report* (January 1997) is a regulatory decision-making guidance document that clearly indicates that technical infeasibility is something to be considered. Also, the language in the Atomic Energy Act of 1954 as amended (Section 84) allows for alternatives in part due to technical infeasibility. The term "practical" appears in Appendix A, which supports the assertion that technical infeasibility must be considered by the staff.

If the effluent release standards and/or the public dose limit are further reduced to the point that the measurement of radioactive effluents or the calculation of dose limits becomes either impracticable, “not

reasonably achievable" or technologically infeasible, licensees will be forced to seek remedies that may be difficult and costly to implement and difficult to manage from the Nuclear Regulatory Commissions' perspective.

Variability of background is discussed in *EPA Review of Standards for Uranium and Thorium Milling Facilities @ 40 CFR Parts 61 and 192* - Comments by Steven H Brown, CHP of SENES Consultants Limited. (Please note that this document is part of the record of comments regarding the Environmental Protection Agency's (EPA's) review of 40 CFR Part 61 Subpart W and may be found at: http://www.epa.gov/radiation/docs/neshaps/subpart-w/senes1.pdf and is included in Appendix 1) In this document he states:

Natural background can vary considerable from place to place across the United States or over relatively small areas within a region. This is due to effects of elevation (higher cosmic radiation exposure at higher elevations), greater levels of naturally occurring radioactive elements in soil and water in mineralized areas (e.g., igneous formations in Rocky Mountains) and other factors like local geology and chemistry. This is depicted in Table 1, which compares average annual background radiation exposure for the US, all of Colorado and Leadville, CO. (high elevation and in mineralized area) as contrasted to coastal areas like Virginia and Oregon. This table shows the major components of natural background radiation including terrestrial radiation (uranium, radium, thorium and a naturally radioactive form of potassium in soil, rocks and water), cosmic radiation (high energy particles and rays from space) and internal radiation (from food, water and radon gas from natural uranium decaying in the ground).

The data in Table 1 demonstrates that the differences in annual background exposure based on where one chooses to live, what one chooses to eat and drink have a much greater impact on public exposure than the regulatory dose limits we discussed above.

Source	US Avg.[1]	Colorado [2]	Leadville, CO. [2]	Virginia [3]	Oregon [3]
Cosmic Radiation	31	50	85	28	28
Terrestrial Radiation	19	49	97	20	27
Radon and Other Internal	260	301	344	182	102
Totals	310	400	526	230	157

TABLE 1: Comparison of average radiation backgrounds in US (units of millirem / yr)
1 National Council on Radiation Protection and Measurements. Report No. 160, Ionizing Radiation Exposure of the Population in the United States. 2009.
2 Moeller D, Sun LSC. Comparison of Natural Background Dose Rates for Residents of the Amargosa Valley, NV, to those in Leadville, CO, and the States of Colorado and Nevada. Health Physics 91:338-353; 2006
3 USEPA. Assessment of Variations in Radiation Exposure in the United States. Contract Number EP-D-05-002 (Revision 1). Washington, DC. 2006

Because background radiation varies significantly across the U.S., it follows that population exposure varies accordingly. As indicated in Table 1, if for example, one chooses to live in Colorado vs. Oregon, the difference in his or her annual radiation dose is more than 240 mrem /yr which is more than twice the Federal public exposure limit for uranium mills of 100 mrem /yr. In other words, if you are a resident of Colorado and leave to visit your

sister for a month in Oregon, you could "save" 20 – 30 mrem of exposure, which is about equal to the EPA 40 CFR 190 limit of 25 mrem /year excluding radon.

The SENES Consultants, Limited document continues by discussing health effects to populations residing near uranium recovery facilities discussing the following three (3) papers:

Cancer and Noncancer Mortality in Populations Living Near Uranium and Vanadium Mining and Milling Operations in Montrose County, Colorado, 1950 2000. Boice, JD, Mumma, MT et al. International Epidemiology Institute, Rockville, MD and Vanderbilt University, Vanderbilt-Ingram Cancer Center, Nashville, TN. Journal of Radiation Research, 167:711-726; 2007: " The absence of elevated mortality rates of cancer in Montrose County over a period of 51 years suggests that the historical milling and mining operations did not adversely affect the health of Montrose County residents"

Cancer Mortality in a Texas County with Prior Uranium Mining and Milling Activities, 1950 – 2001. Boice, JD, Mumma, M et al. International Epidemiology Institute, Rockville, MD and Vanderbilt University, Vanderbilt-Ingram Cancer Center,Nashville, TN Journal of Radiological Protection, 23:247 – 262; 2003 – "No unusual patterns of cancer mortality could be seen in Karnes County over a period of 50 years suggesting that the uranium mining and milling operations had not increased cancer rates among residents".

Cancer Incidence and Mortality in Populations Living Near Uranium Milling and Mining Operations in Grants, New Mexico, 1950–2004. Boice, JD, Mumma, M et al. International Epidemiology Institute, Rockville, MD and Vanderbilt University, Vanderbilt-Ingram Cancer Center, Nashville, TN. Journal of Radiation Research, 174,624–636. 2010 – "With the exception of male lung cancer (in former underground miners), this study provides no clear or consistent evidence that the operation of uranium mills and mines adversely affected cancer incidence or mortality of county residents".

These three (3) papers are includes in Appendices 2 to 4 respectively. The WMA agrees with the findings of these papers.

In addition, determination of dose to the general public from radon involves the calculation of an equilibrium factor which is the ratio of activity of the radon in the air to its decay products. Doses from Radon-222 decay products are generally determined using the modified Kusnetz Method. This method is discussed in *Regulatory Guide 8.30 - HEALTH PHYSICS SURVEYS IN URANIUM RECOVERY FACILITIES:*

> *The modified Kusnetz method for measuring radon daughter working levels is a suitable method for UR facilities. The procedure consists of sampling radon daughters on a high-efficiency filter paper for 5 minutes and, after a delay of 40 to 90 minutes, measuring the alpha counts on the filter during a 1-minute interval. The original Kusnetz method measured the alpha count rate. In the modified Kusnetz method, the rate meter is replaced by a scaler. This improves the sensitivity to a practical lower limit of 0.03 working level for a 1-minute count on a 10-liter (0.01 cubic meter) sample. This is about a factor of 10 lower than that originally obtained using the original Kusnetz method. A 4-minute count gives a lower limit of about 0.003 working level (Ref. 3). High-efficiency membrane or glass fiber filters should be used to minimize loss of alpha counts by absorption in the filter. However, a correction factor to account for alpha absorption in the filter paper should still be used. Care should be taken to avoid contamination of the alpha counter.*

This method is a good one in that testing is performed by the licensee on site and the method can be varied slightly to improve its Lower Limit of Detection (LLD). For example, the volume of air collected in (pumped through) the filter can be increased improving the Lower Limit of Detection (LLD) and reducing the error estimate.

The modified Kusnetz Method must be used in conjunction with Radon-222 RadTrak measurements to calculate equilibrium factors for Radon-222 and its decay products in order to ultimately assess dose to the general public. Lowering the effluent concentration and/or the public dose limit to airborne radionuclides could ultimately

approach the lower limits of detection for this method creating further problems in accurately assessing dose to the general public.

The WMA would also like to point out that doses from uranium recovery facilities are low, specifically doses from in-situ uranium recovery facilities as shown in the tables below from *NUREG-1910 - Generic Environmental Impact Statement for In-Situ Leach Uranium Milling Facilities*:

Table 4.2-2 (Section 4.2.11.2) is included below:

Table 4.2-2. Dose to Offsite Receptors From *In-Situ* Leach Facilities

Facility	Offsite Maximum Dose (mSv/mrem)	Description of Receptor	Reference
Crow Butte	0.317/31.7	0.4 km [0.25 mi] northeast of Central Plant site	Crow Butte Resources, Inc.*
Crow Butte	0.058/5.8	Closest resident downwind of North Trend Satellite Plant	Crow Butte Resources, Inc.*
Smith Ranch/ Sunquest Ranch	0.175/17.5	Nearest resident	NRC, 2007†
Smith Ranch/ Vollman Ranch	0.135/13.5	Nearest resident	NRC, 2007†
Reynolds Ranch	0.04/4	Nearest resident at Reynolds Ranch	NRC, 2006‡
Reynolds Ranch	0.27/27	Unoccupied Mason House	NRC, 2006‡
Gas Hills	0.07/7	Hypothetical individual on eastern boundary	NRC, 2004§
Christensen Ranch	0.006/0.6	Adult nearest resident	NRC, 1998‖
Irigaray	0.004/0.4	Adult nearest resident	NRC, 1998‖

*Crow Butte Resources, Inc. "License Renewal Application: SUA–1534." Crawford, Nebraska: Crow Butte Resources, Inc. 2007.
†NRC. "Environmental Assessment Construction and Operation of *In-Situ* Leach SR–2 Amendment No. 12 to Source Materials License No. SUA–1548 Power Resources, Inc. Smith Ranch-Highland Uranium Project (SR_HUP) Converse County, Wyoming." Docket No. 40-8964. Washington, DC: NRC. 2007.
‡NRC. "Environmental Assessment for the Addition of the Reynolds Ranch Mining Area to Power Resources, Inc.'s Smith Ranch/Highlands Uranium Project Converse County, Wyoming." Source Material License No. SUA–1548. Docket No. 40-8964. Washington, DC: NRC. 2006.
§NRC. "Environmental Assessment for the Operation of the Gas Hills Project Satellite *In-Situ* Leach Uranium Recovery Facility." Docket No. 40-8857. Washington, DC: NRC. 2004.
‖NRC. "Environmental Assessment for Renewal of Source Material License No. SUA–1341. Docket No. 40-8502. Washington, DC: NRC. 1998.

The above doses to members of the public are low, the highest being 27 millirems.

In conclusion, the WMA believes that no reductions should be made to the public dose limit or effluent concentration limits in 10 CFR Part 20, Appendix B, Table 2, Columns 1 and 2. Any future reductions especially to the public dose limit or effluent concentrations for Radon-222 in 10 CFR Part 20, Appendix B, Table 2, Columns 1 and 2 would create additional compliance determination issues for the uranium recovery industry. These issues would arise from limitations on the method (RadTrak detectors) for measuring radon activity in air, problems in assessing background and calculating dose from it, especially in cases when the upwind/background radon activities in air are higher than the downwind activities and limitations in determining radon daughter activities using the modified Kusnetz Method that are required to determine an equilibrium factor.

Also, in the case of uranium recovery, the cited epidemiological literature demonstrates the low risks posed by these operations as does the site specific public dose data for various in-situ uranium recovery facilities.

Dose to the Embryo/Fetus
Q3-1: Are there any significant anticipated impacts associated with reducing the dose limit to the embryo/fetus of a declared pregnant woman, including operational impacts? What are the potential implementation and operational costs?

and

Q3-4: Are there technological implementation issues, such as limits of detection, which would make adoption of the ICRP Publication 103 (2007) recommendation difficult in certain circumstances?

The document discusses reducing the dose limit to the embryo/fetus to 1 mSv (100 mrem). This may not be practical. The current occupational dose limits for Radon-222 are as follows:

Atomic No.	Radionuclide	Class	Table 1 Occupational Values		
			Col. 1	Col. 2	Col. 3
			Oral Ingestion ALI (µCi)	Inhalation	
				ALI (µCi)	DAC (µCi/ml)
86	Radon-222	With daughters removed	-	1E+4	4E-6
		With daughters present	-	1E+2 (or 4 working level months)	3E-8 (or 0.33 working level)

The Derived Air Concentrations (DACs) shown would result in a 5 rem internal dose with a 2,000 hour exposure as per 10 CFR Part 20 Appendix B that states in part:

The derived air concentration (DAC) values are derived limits intended to control chronic occupational exposures. The relationship between the DAC and the ALI is given by: DAC=ALI(in µCi)/(2000 hours per working year x 60 minutes/hour x 2 x 10^4 ml per minute)=[ALI/2.4x10^9] µCi/ml, where 2x10^4 ml is the volume of air breathed per minute at work by "Reference Man" under working conditions of "light work."

and 10 CFR Part 20.1204 Determination of internal exposure that states:

(h)(1) In order to calculate the committed effective dose equivalent, the licensee may assume that the inhalation of one ALI, or an exposure of 2,000 DAC-hours, results in a committed effective dose equivalent of 5 rems (0.05 Sv) for radionuclides that have their ALIs or DACs based on the committed effective dose equivalent.

Reduction of the dose limit to the embryo/fetus to 100 millirems would mean that the Derived Air Concentration (DAC) for Radon-222 (with daughters present) would be (3E-8 µCi/ml)/(50) equaling 6E-10 µCi/ml which equals 6E-07 µCi/L equaling 6E-01 pCi/l (0.6 pCi/L) A Derived Air Concentration (DAC) this low may be difficult to discern from natural variations in background using current measurement technologies such as Landauer, Inc.'s RadTrak units. This issue has been discussed in the prior section regarding doses to the general public. . A Landauer, Inc. RadTrak personal dosimeter is depicted below:

Source: Landauer, Inc.
http://www.landauer.com/uploadedFiles/Radon_Solutions/Radtrak%20Personnel%20DRNP%20Detector.pdf

Their effectiveness at determining radon exposure and ultimately dose is questionable in low concentration environments.

The WMA would also like to state that the proposed dose of 1 mSv (100 rnrem) to the embryo/fetus is very low, in fact unjustifiably so, as per NCRP 174 which states:

> *"There are extensive mammalian studies that support a conclusion that the no-adverse-effect level from acute exposure for birth defects, growth retardation, pregnancy loss, and other tissue reactions (deterministic effects) is - 0.2 Gy (20 rad) (dose to the el11b,yo or fetus) at the most vulnerable stage of pregnancy;" and "Increased risks to the embryo or fetus have not been observed for mental retardation, birth defects, growth retardation, neurobehavioral effects, impaired school performance, convulsive disorders, or embryonic or fetal death below a dose of 0.1 Gy (10 rad)."*

Even ICRP 103, states,

> *"... that risks of malformation after in-utero exposure to doses well below 100 mGy (10 rad) are not expected." (Page 57)*

Individual Protection - ALARA Planning

Q4-1: What are the potential implications of adding specific ALARA planning and implementation requirements to the 10 CFR part 20 regulations? What changes to licensee radiation protection programs could be anticipated? What would be the potential implementation and operational costs?

The document states:

> *In the United States, the majority of occupationally exposed individuals receive less than 20 mSv (2 rem) per year as reported to the NRC.*

and;

> *The NRC notes that its implementation and enforcement of its ALARA principles are generally made through specific license conditions instead of through more detailed regulations. Therefore, the NRC staff questions whether additional regulatory requirements are appropriate to foster a clear and consistent approach for all types of licensees versus relying upon license conditions.*

The WMA believes that a "one size fits all" approach taken by adding specific ALARA planning and implementation requirements to 10 CFR Part 20 is poor practice. Occupational doses in the uranium recovery industry are low. The document states:

> *While nuclear power reactor operators have been successful in reducing individual exposures, such that only a very limited number of individuals exceed 20 mSv (2 rem) in a year,30 this is not the case in other segments of the regulated community. For example, industrial radiographers have a somewhat greater percentage of individuals above the average annual dose level of 20 mSv (2 rem) recommended in ICRP Publication 103 (2007).*

If certain segments of the regulated community have greater percentages of individuals above the annual dose level of 20 mSv (2 rem) recommended in ICRP Publication 103 (2007). then the regulations specifically governing these segments of the regulated community should be modified to include specific ALARA planning and implementation requirements.

Currently 10 CFR Part 20.1101 Radiation Protection Programs states:

(b) The licensee shall use, to the extent practical, procedures and engineering controls based upon sound radiation protection principles to achieve occupational doses and doses to members of the public that are as low as is reasonably achievable (ALARA).

This is the only language that should apply to all licensees. If certain groups have higher exposures to workers than the annual dose level of 20 mSv (2 rem) recommended in ICRP Publication 103 (2007), specific regulatory requirements should be implemented for these groups.

The WMA would like to mention that in *Occupational Radiation Exposure at Commercial Nuclear Power Reactors and Other Facilities 2012: Forty-Fifth Annual Report (NUREG-0713, Volume 34)* occupation doses by licensee types are discussed and the following information is provided:

Table 3.1. Average Annual Exposure Data for Certain Categories of NRC Licensees 2002–2012

NRC License Category * and Program code	Calendar Year	Number of Licensees Reporting	Number of Monitored Individuals	Number of Individuals with Measurable TEDE	Collective TEDE (person-rem)	Average TEDE (rem)	Average Measurable TEDE per Individual (rem)
Industrial Radiography 03310 03320	2002	100	3,420	2,842	1,729.222	0.51	0.61
	2003	118	3,115	2,651	1,584.249	0.51	0.60
	2004	113	3,568	3,014	1,603.591	0.45	0.53
	2005	90	3,009	2,623	1,504.575	0.50	0.57
	2006	79	2,395	1,985	1,109.466	0.46	0.56
	2007	75	2,615	2,228	1,315.590	0.50	0.59
	2008	62	2,976	2,593	1,461.405	0.49	0.56
	2009	65	2,662	2,307	1,317.982	0.50	0.57
	2010	57	2,377	2,034	1,297.300	0.55	0.64
	2011	64	2,545	2,210	1,608.821	0.63	0.73
	2012	64	2,601	2,226	1,495.388	0.57	0.67
Manufacturing and Distribution 02500 03211 03212 03214	2002	29	1,437	1,052	328.092	0.23	0.31
	2003	33	2,372	1,796	436.660	0.18	0.24
	2004	28	2,539	1,787	347.258	0.14	0.19
	2005	23	2,566	1,557	388.547	0.15	0.25
	2006	22	1,256	795	273.028	0.22	0.34
	2007	23	2,106	1,463	291.326	0.14	0.20
	2008	18	1,934	1,341	222.123	0.11	0.17
	2009	16	1,933	1,386	179.222	0.09	0.13
	2010	17	970	670	146.365	0.15	0.22
	2011	15	901	700	111.748	0.12	0.16
	2012	21	1,055	711	118.427	0.11	0.17
Independent Spent Fuel Storage 23100 23200	2002	2	75	67	6.013	0.08	0.09
	2003	2	55	46	2.791	0.05	0.06
	2004	1	37	27	1.257	0.03	0.05
	2005	2	59	30	0.769	0.01	0.03
	2006	2	59	26	2.108	0.04	0.08
	2007	2	57	26	1.697	0.03	0.07
	2008	2	53	21	1.248	0.02	0.06
	2009	2	72	34	1.465	0.02	0.04
	2010	2	73	39	1.337	0.02	0.03
	2011	2	54	25	1.449	0.03	0.06
	2012	2	42	15	1.099	0.03	0.07
Fuel Cycle Licenses - Fabrication Processing and Uranium Enrichment and UF_6 Production Plants 11400 21200 21210	2002	9	8,270	4,209	820.442	0.10	0.19
	2003	9	8,103	3,986	676.082	0.08	0.17
	2004	9	8,060	4,263	657.799	0.08	0.15
	2005	10	8,215	3,839	643.631	0.08	0.17
	2006	10	8,097	4,017	677.025	0.08	0.17
	2007	10	8,402	4,007	588.837	0.07	0.15
	2008	10	7,807	3,424	538.201	0.07	0.16
	2009	11	8,918	3,738	533.721	0.06	0.14
	2010	11	9,362	4,212	541.876	0.06	0.13
	2011	11	9,535	4,361	607.202	0.06	0.14
	2012	9	7,388	3,541	438.729	0.06	0.12
Commercial Light Water Reactors (LWRs) ** 41111	2002	104	149,512	73,242	12,126.190	0.08	0.17
	2003	104	152,702	74,813	11,955.570	0.08	0.16
	2004	104	150,322	69,849	10,367.897	0.07	0.15
	2005	104	160,701	78,127	11,455.807	0.07	0.15
	2006	104	164,823	80,265	11,021.186	0.07	0.14
	2007	104	164,081	79,530	10,120.013	0.06	0.13
	2008	104	169,324	79,450	9,195.940	0.05	0.12
	2009	104	176,381	81,754	10,024.804	0.06	0.12
	2010	104	179,648	75,010	8,631.384	0.05	0.12
	2011	104	191,538	81,321	8,771.326	0.05	0.11
	2012	104	193,977	79,549	8,035.393	0.04	0.10
Grand Totals and Averages	2002	244	162,714	81,412	15,009.959	0.09	0.18
	2003	266	166,347	83,292	14,655.352	0.09	0.18
	2004	255	164,526	78,960	12,977.802	0.08	0.16
	2005	229	174,550	86,176	13,993.329	0.08	0.16
	2006	217	176,630	87,088	13,082.813	0.07	0.15
	2007	214	177,261	87,254	12,317.463	0.07	0.14
	2008	196	182,094	86,829	11,418.917	0.06	0.13
	2009	198	189,966	89,219	12,057.194	0.06	0.14
	2010	191	192,430	81,965	10,618.262	0.06	0.13
	2011	196	204,573	88,617	11,100.546	0.05	0.13
	2012	200	205,063	86,042	10,089.036	0.05	0.12

* These categories consist only of NRC licensees required to submit an annual report (see Section 2).

Fuel cycle licensees (which include uranium recovery) have lower Total Effective Dose Equivalents (TEDEs) that Industrial Radiographers or Manufacturing and Distribution. and represent the fourth smallest group of licensees.

Given the documented low doses to the maximally exposed worker, specific ALARA planning and implementation requirements at least for uranium recovery facilities should not be added to the 10 CFR Part 20.

Included in Appendix 5 is a paper entitled *Mortality among a cohort of uranium mill workers: an Update* by L E Pinkerton, T F Bloom, M J Hein, and E M Ward. The paper states:

Mortality from all causes was less than expected, which is largely accounted for by fewer deaths from heart disease than expected. Mortality from all malignant neoplasms was also less than expected.

This study included a cohort of 1,484 men who worked at least one year in a uranium mill beginning on January 1, 1940 which is over fifty (50) years prior to the May 21, 1991 promulgation the version of 10 CFR Part 20 currently in use. Given the low risk demonstrated by this study, specific ALARA planning and implementation requirements should not be added to the 10 CFR Part 20 at least for the uranium recovery industry.

Given the low risks to workers I the uranium recovery industry as documented in the paper entitled, *Mortality Among a Cohort of Uranium Mill Workers,* do the uranium recovery industry should not be subject to specific ALARA planning and implementation requirements in 10 CFR Part 20. If required ALARA planning and implementation requirements can be included in regulations specific to a particular industry or as license conditions in a specific license.

Q4-8: Should the Agreement States be allowed to use more restrictive or prescriptive requirements if the NRC decides to use a performance-based approach? What are the benefits and impacts of the various methodologies discussed in the preceding section on Agreement State regulatory programs and Agreement State licensees? If the NRC issues a proposed rule, this information will be important in establishing an appropriate Agreement State compatibility level for any proposed regulatory requirements.

Agreement states should not be permitted to use more restrictive or prescriptive requirements than the Nuclear Regulatory Commission (NRC). Uranium recovery licensees do not have the luxury of choosing in which state to site their facilities. The location of the minable uranium deposit makes that selection for them. Uranium recovery operators should not be penalized because their uranium deposit lies within an agreement state that chooses to be more restrictive or prescriptive than the Nuclear Regulatory Commission (NRC). Allowing agreement states to use more restrictive or prescriptive requirements than the Nuclear Regulatory Commission (NRC) could create an uneven playing field for uranium recovery operators.

Metrication - Units of Radiation Exposure and Dose.

Q5-1: Will promulgation of amendments to the 10 CFR part 20 regulations with dose limits and other measurements shown in dual units, with the SI units shown first, followed by the traditional units in parentheses, cause an undue burden or hardship upon any licensee or class of licensees? If so, please explain and provide examples, including any potential implementation or operational costs.

Q5-2. Should 10 CFR 20.2101(a) be revised to allow licensees the option of providing records in SI units or in traditional units? Should licensees be allowed to provide reports in the units used in licensee records? Should licensees be required to record and report in both sets of units? Please provide reasons why or why not.

Q5-3. Should the NRC amend the appendices for 10 CFR part 20 to show values in SI units only, in traditional units only, or in both sets of units? If both SI and traditional units are provided, which set of units should be considered as the regulatory standard? If only one set of units is specified, what would be the most effective means to provide the other set of units (e.g., in a separate guidance publication)? Please provide reasons why or why not.

The Wyoming Mining Association (WMA) opposes any metrification and requests that the currently used units of activity, radiation exposure and dose in 10 CFR Part 20 be left as they are. The uranium recovery industry is a small segment of the licensed community that can ill afford the training and other efforts required to enable its employees to switch to or use other units of measurements. Changing to other units will only create an undue burden and confusion.

Reporting of Occupational Exposure

Q6-1: What criteria should the NRC use to identify additional categories of licensees that should be required to submit annual occupational exposure reports under 10 CFR 20.2206(a)?

The requirement to submit annual occupational reports should remain as they are now and as stated in *10 CFR Part § 20.2206 Reports of individual monitoring* which states:

(a) This section applies to each person licensed by the Commission to--

(1) Operate a nuclear reactor designed to produce electrical or heat energy pursuant to § 50.21(b) or § 50.22 of this chapter or a testing facility as defined in § 50.2 of this chapter; or

(2) Possess or use byproduct material for purposes of radiography pursuant to Parts 30 and 34 of this chapter; or

(3) Possess or use at any one time, for purposes of fuel processing, fabricating, or reprocessing, special nuclear material in a quantity exceeding 5,000 grams of contained uranium-235, uranium-233, or plutonium, or any combination thereof pursuant to part 70 of this chapter; or

(4) Possess high-level radioactive waste at a geologic repository operations area pursuant to part 60 or 63 of this chapter; or

(5) Possess spent fuel in an independent spent fuel storage installation (ISFSI) pursuant to part 72 of this chapter; or

(6) Receive radioactive waste from other persons for disposal under part 61 of this chapter; or

(7) Possess or use at any time, for processing or manufacturing for distribution pursuant to parts 30, 32, 33 or 35 of this chapter, byproduct material in quantities exceeding any one of the following quantities:

Radionuclide	***Quantity of radionuclide in curies***
Cesium-137	*1*

Cobalt-60	*1*
Gold-198	*100*
Iodine-131	*1*
Iridium-192	*10*
Krypton-85	*1,000*
Promethium-147	*10*
Technetium-99m	*1,000*

Reporting requirements should not be arbitrarily expanded. Reporting requirements in and of themselves do not enhance radiation protection or reduce doses.

Applicability of Linear No Threshold

The *Advance Notice of Proposed Rulemaking (ANPR)* discusses updating 10 CFR Part 20 to align with ICRP Publication 103 and specifically considers lowering existing dose limits to the general public and to the embryo/fetus. These considerations are based on the application of Linear No Threshold (LNT) which is the current risk model used as the basis for regulation and radiation protection in the United States. The Linear No Threshold (LNT) model that assumes that for each incremental amount of exposure above zero there is a proportional amount of risk.

This model is not accepted worldwide. Included in Appendix 6 is a letter entitled *REPORT OF THE FRENCH ACADEMY OF SCIENCES, "THE DOSE-EFFECT RELATIONSHIP AND ESTIMATING THE CARCINOGENIC EFFECTS OF LOW DOSES OF IONIZING RADIATION* prepared by the Advisory Committee on Nuclear Waste. This letter discusses the French Academy of Sciences Report 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).

The WMA requests that the Commission consider new data including information from the French Academy of Sciences that is showing that Linear No Threshold (LNT) may not be valid at low doses such as those that might be received by a member of the general public from a licensed facility such as a licensed fuel cycle facility including a licensed uranium recovery facility.
In addition, the Commission should consider the following information from the United States that demonstrates the low risks form radiation exposure that would be applicable to radiation from any source within the nuclear fuel cycle:

- *Nuclear shipyard worker study (1980–1988): a large cohort exposed to low-dose-rate gamma radiation Sponsler, R and Cameron, J.R, 2005 - Int. J. Low Radiation, Vol. 1, No. 4, 2005*
  - The Abstract states: *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.

- This paper included in Appendix 7 examines a large cohort of workers exposed to low dose gamma radiation and concludes that the exposed workers demonstrated lower mortality than unexposed workers. This undermines the Linear No Threshold (LNT) model and the assumption that for each incremental amount of exposure there is an associated risk. .

- *Integrated Molecular Analysis Indicates Undetectable DNA Damage in Mice after Continuous Irradiation at ~400-fold Natural Background Radiation Olipitz, W et al 2012 ENVIRONMENTAL HEALTH PERSPECTIVES*
- This paper concludes, *" 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.* "
- This paper included in Appendix 8 presents detailed research that examines potential damage on the molecular level in cells from radiation and again casts doubt on the basic assumptions of Linear No Threshold (LNT).

The Commission should also consider the following papers that are specific to the licensed uranium recovery industry that show the inherent low risks related to radiation from that portion of the nuclear fuel cycle:

- *Mortality among a cohort of uranium mill workers: an update Pinkerton, L.E., et al 2003 Occupational and Environmental Medicine 2004;61:57–64*
- This paper concludes, "*Mortality from all causes was less than expected, which is largely accounted for by fewer deaths from heart disease than expected. Mortality from all malignant neoplasms was also less than expected."*
- This paper included in Appendix 5 examines a cohort of 1484 uranium mill workers who as mill workers would comprise a group subject to exposures higher that members of the general public.

- *Cancer and Noncancer Mortality in Populations Living Near Uranium and Vanadium Mining and Milling Operations in Montrose County, Colorado, 1950-2000, Boice, J.D. et al 2007 Radial. Res. 167.711-726*
- This paper concludes, "*Between 1950 and 2000, a total or 1,877 cancer deaths occurred in the population residing in Montrose County, compared with 1,903 expected based on general population rates for Colorado (SMRn • 0.99). there were 11,837 cancer deaths in the five comparison counties during the same 51-year period compared with 12,135 expected (SMRco 0.98). There was no difference between the total cancer mortality rates in Montrose County and those in the comparison counties (RR = 1.01; 95% CI 0.96-1.06)."*
- This paper included in Appendix 2 discusses mortality among members of the general public/residents in Montrose County, Colorado the home of the Uravan Uranium Mill and concludes that there was no difference in cancer mortality between Montrose County and its neighbors.

- *Cancer mortality in a Texas county with prior uranium mining and milling activities, 1950–2001 Boice, J.D., et al 2003 J. Radiological . Protection **23** (2003) 247–262*
- This paper concludes, "*Overall, 1223 cancer deaths occurred in the population residing in Karnes County from 1950 to 2001 compared with 1392 expected based on general population rates for the US. There were 3857 cancer deaths in the four control counties during the same 52 year period compared with 4389 expected. There was no difference between the total cancer mortality rates in Karnes County and those in the control counties (RR = 1.0; 95% confidence interval 0.9–1.1). There were no significant increases in Karnes County for any cancer when comparisons were made with either the US population, the State of Texas or the control counties. In particular, deaths due to cancers of the lung, bone, liver and kidney were not more frequent in Karnes County than in the control counties. These are the cancers of a priori interest given that uranium might be expected to concentrate more in these tissues than in others. Further, any radium intake would deposit primarily in the bone and radon progeny primarily in the lung. Deaths from all cancers combined also were not increased in Karnes County and the RRs of cancer mortality in Karnes County before and in the early years of operations (1950–64), shortly after the uranium activities began (1965–79) and in two later time periods (1980–89, 1990–2001) were similar, 1.0, 0.9, 1.1 and 1.0, respectively. No unusual patterns of cancer mortality could be seen in Karnes*

County over a period of 50 years, suggesting that the uranium mining and milling operations had not increased cancer rates among residents."

- Karnes County, Texas hosted three (3) uranium mills being the Deweeseville (Falls City) Mill, the Conoco Conquista Mill and the Chevron Pannamaria Mill. This paper included in Appendix 3 concludes that these operations did not increase cancer mortality among members of the public in Karnes County, Texas as compared to those in four (4) control counties. .

- *A cohort study of uranium millers and miners of Grants, New Mexico, 1979–2005 Boice, J.D., et al, 2008 JOURNAL OF RADIOLOGICAL PROTECTION*
  - This paper concludes, "No statistically significant elevation in any cause of death was seen among the 904 non-miners employed at the Grants uranium mill. Among 718 mill workers with the greatest potential for exposure to uranium ore, no statistically significant increase in any cause of death of *a priori* interest was seen, i.e., cancers of the lung, kidney, liver, or bone, lymphoma, non-malignant respiratory disease, renal disease or liver disease. Although the population studied was relatively small, the follow-up was long (up to 50 yrs) and complete.
  - This paper included in Appendix 4 examined among other things a cohort of 718 uranium millers, a maximally exposed group, concluding that there was no statistically significant increase in cancers of *a priori* interest. This area contained a number of licensed uranium recovery facilities including the Bluewater, L-Bar, Homestake/United Nuclear Partners, United Nuclear - Churchrock and Ambrosia Lake Mills.

The WMA also requests that the Commission also consider the following paper included in Appendix 9:

- *Five-Hundred Life-Saving Interventions and Their Cost-Effectiveness Tengs, T.O., 1995 Risk .Analysis. Vol. 15, No. 3. I995*
  - This paper included in Appendix 8 discusses the cost effectiveness of various life saving interventions in terms of dollars per year of life saved. This paper shows that radionuclide emission controls at Nuclear Regulatory Commission (NRC) licensed and uranium fuel cycle facilities are among the highest cost interventions per year of life saved as shown below:

881	Radionucfide emission control at NRC-licensed and non-DOE facilities	$2,600,000,000
881	Radionuclide emission control at uranium fuel cycle facilities	$34,000,000,000

Regulatory interventions to further reduce exposures, and resulting dose and risk are very costly. Such monies would yield greater improvements in the quality of life and longevity if spent elsewhere.
In conclusion, the evidence as presented in these above described appendices show that the risks from radiation in general and in particular from licensed uranium recovery operations are low.

In conclusion, the WMA believes that:

- Further lowering of effluent limits and/or public dose limits may especially in regard to radon, set limits that cannot be accurately measured with existing technology and be indistinguishable from background.
- In regard to uranium recovery operations the three (3) papers included in Appendices 2 to 4 clearly show an absence of health effects in uranium recovery areas.
- Regarding the dose to the embryo/fetus the WMA believes that further reductions especially in regard to radon may not be accurately measureable and may not be distinguishable from background.
- Specific ALARA planning and implementation requirements should not be added "across the board" to the 10 CFR Part 20 regulations, but should only be required of the highest dose licensee groups and not all of them. This is because the uranium recovery industry has had historically low doses to workers and members of the general public and associated low risks. Uranium recovery is the lowest risk portion of the nuclear fuel cycle.
- Agreement states should not be allowed to use more restrictive or prescriptive requirements than the Nuclear Regulatory Commission (NRC). Uranium recovery licensees do not have the luxury of choosing in which state to site their facilities. The location of the minable uranium deposit makes that selection for them. Uranium recovery operators should not be penalized because their uranium deposit lies within an agreement state that chooses to be more restrictive or prescriptive than the Nuclear Regulatory Commission (NRC). Allowing agreement states to use more restrictive or prescriptive requirements than the Nuclear Regulatory Commission (NRC) could create an uneven playing field for uranium recovery operators.

- The Wyoming Mining Association (WMA) opposes any metrification and requests that the currently used units of activity, radiation exposure and dose in 10 CFR Part 20 be left as they are.
- The requirement to submit annual occupational reports should remain as they are now and as stated in *10 CFR Part § 20.2206 Reports of individual monitoring*
- Reductions in allowable dose are not justified especially given recent evidence refuting the applicability of Linear No Threshold (LNT) at low doses and the doubts concerning its applicability at low doses raised by the French Academy of Sciences.

The Wyoming Mining Association (WMA) appreciates the opportunity to comments on this *Advance Notice of Proposed Rulemaking*. If you have any questions please do not hesitate to contact me.

Sincerely yours,

Jonathan Downing
Executive Director

cc: Katie Sweeney - National Mining Association (NMA)

Appendix 1

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EPA Review of Standards for Uranium and Thorium Milling Facilities @ 40 CFR Parts 61 and 192.

Comments by Steven H Brown, CHP
Revised November 7, 2010

I am Steven Brown from Centennial Colorado. I appreciate the opportunity to provide these comments for EPA's consideration regards to review of EPA standards for Uranium and Thorium Milling Facilities @ 40 CFR Parts 61 and 192.

I have been a practicing health physicist for over 40 years. I am certified by the American Board of Health Physics and a Diplomat of the American Academy of Health Physics. I am a past president of Central Rocky Mountain Chapter of the Health Physics Society.

The Health Physics Society, formed in 1956, is a scientific organization of professionals who specialize in radiation safety. Its mission is to support its members in the practice of their profession and to promote excellence in the science and practice of radiation safety. Today its nearly 6,000 members represent all scientific and technical areas related to radiation safety including academia, government, medicine, research and development, analytical services, consulting, and industry in all 50 states and the District of Columbia.

I would like to provide EPA with some broad scientific perspectives related to the adequacy of existing public exposure standards for uranium mills and in situ recovery facilities that are promulgated in 40 CFR Parts 61, 190 and 192. Specifically, these are the 20 picocuries per meter squared per second (pCi / m2-sec) radon flux criteria for uranium mill tailings impoundments specified in Part 61 Subpart W and Part 192, Subpart D as well as the 25 mrem /year public exposure standard in Part 190 as referenced in Part 192.

My remarks will address the following seven questions:

1. Are the existing radiation dose limits in the regulations (Federal and Agreement States) for uranium milling facilities (including in situ recovery plants) adequate to protect the public from additional radiation exposure above our natural background exposure?
2. Is the existing 20 picocuries per meter squared per second (pCi/meter^2 – sec) radon flux (emission) standard in 40 CFR Parts 61, Subpart W and 192, Subpart D adequate to protect the public from additional radiation exposure above our natural background exposure?
3. What do we know about radon releases from water impoundments?
4. What do we know about radon emissions from ISRs?
5. What are current practices and results in estimating doses to the public from uranium recovery facilities?
6. What is known about the potential health effects to populations living in the vicinity of uranium mines and mills?
7. What is known about the health impacts (e.g., lung cancer) to many uranium miners who worked underground in the 1950s and 1960s?

1. Are the existing regulations (Federal or USNRC Agreement States) for uranium milling facilities (including in situ recovery plants) adequate to protect the public from additional radiation exposure above our natural background exposure?

Our lifestyles, where we choose to live, what we eat and drink, has a much larger impact on our radiation exposure than exposure at current regulatory limits. The basic regulatory limits that operating uranium mills and ISRs must comply with are 100 millirem* per year from all sources including radon and 25 millirem / year excluding radon** (US Nuclear Regulatory Commission: 10 CFR 20 and 10 CFR 40 Appendix A; US Environmental Protection Agency: 40 CFR 190; Texas Department of State Health Services, Title 30 of the Texas Administrative Code, Chapter 336; Colorado Department Health of Public and Environment, 6 CCR 1007 - 1, Part 4)

*NOTE: a millirem is a unit of effective radiation dose. It is related to the amount of energy absorbed by human tissue and other factors. 1,000 millirem = one rem.

** Radon is a naturally occurring radioactive gas, which is released into the atmosphere at the Earth's surface from the decay of radium. Both radium and radon are daughter products of uranium.

Now lets compare these numbers to the annual radiation doses we receive as citizens of planet Earth. Figure 1 below depicts the typical components of human exposure in the US to ionizing radiation.

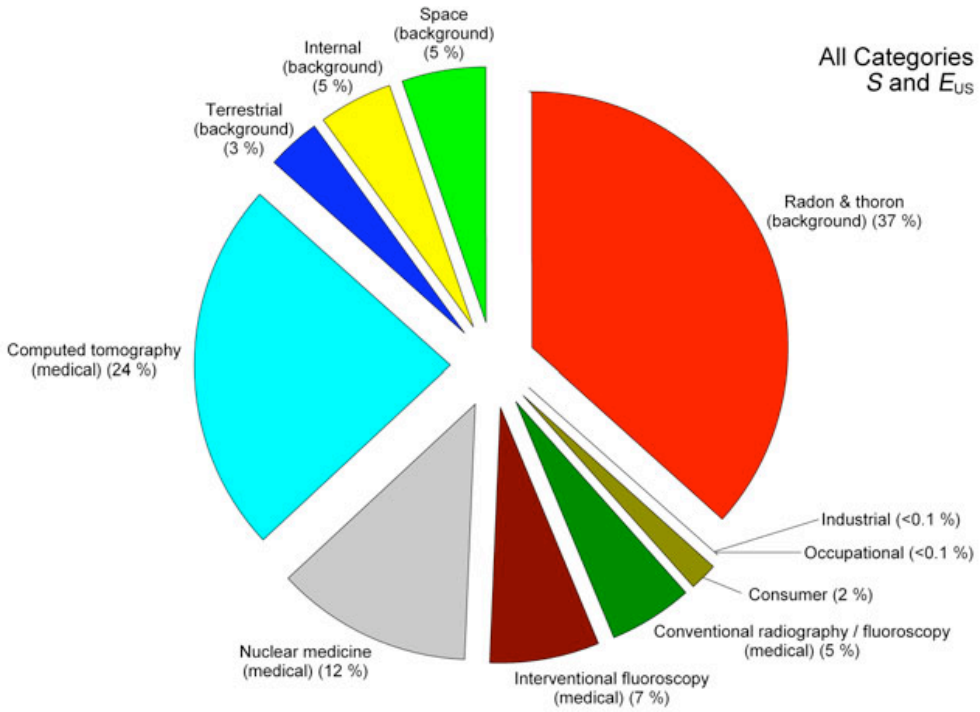

Figure 1: Percent contribution of various sources of exposure to the total radiation dose of a typical resident in the US. Reproduced from National Council on Radiation Protection and Measurements. Report No. 160, *Ionizing Radiation Exposure of the Population in the United States.* 2009.

As can be seen from figure 1, background radiation exposure is about 50% of the total exposure; the other 50% is primarily from medical exposures. Consumer products we use everyday that contain radioactive materials (e.g., smoke detectors, luminous watches, etc) contribute about 2 % of our dose. Other man made sources of radiation, including the nuclear industry, contribute < 0.1% of our annual dose.

Natural background can vary considerable from place to place across the United States or over relatively small areas within a region. This is due to effects of elevation (higher cosmic radiation exposure at higher elevations), greater levels of naturally occurring radioactive elements in soil and water in mineralized areas (e.g., igneous formations in Rocky Mountains) and other factors like local geology and chemistry. This is depicted in Table 1, which compares average annual background radiation exposure for the US, all of Colorado and Leadville, CO. (high elevation and in mineralized area) as contrasted to coastal areas like Virginia and Oregon. This table shows the major components of natural background radiation including terrestrial radiation (uranium, radium, thorium and a naturally radioactive form of potassium in soil, rocks and water), cosmic radiation (high energy particles and rays from space) and internal radiation (from food, water and radon gas from

natural uranium decaying in the ground).

The data in Table 1 demonstrates that the differences in annual background exposure based on where one chooses to live, what one chooses to eat and drink have a much greater impact on public exposure than the regulatory dose limits we discussed above.

Source	US Avg.[1]	Colorado [2]	Leadville, CO. [2]	Virginia [3]	Oregon [3]
Cosmic Radiation	31	50	85	28	28
Terrestrial Radiation	19	49	97	20	27
Radon and Other Internal	260	301	344	182	102
Totals	310	400	526	230	157

TABLE 1: Comparison of average radiation backgrounds in US (units of millirem / yr)

[1] National Council on Radiation Protection and Measurements. Report No. 160, *Ionizing Radiation Exposure of the Population in the United States.* 2009.
[2] Moeller D, Sun LSC. *Comparison of Natural Background Dose Rates for Residents of the Amargosa Valley, NV, to those in Leadville, CO, and the States of Colorado and Nevada.* Health Physics 91:338-353; 2006
[3] USEPA. Assessment of Variations in Radiation Exposure in the United States. Contract Number EP-D-05-002 (Revision 1). Washington, DC. 2006

Because background radiation varies significantly across the U.S., it follows that population exposure varies accordingly. As indicated in Table 1, if for example, one chooses to live in Colorado vs. Oregon, the difference in his or her annual radiation dose is more than 240 mrem /yr which is more than twice the Federal public exposure limit for uranium mills of 100 mrem /yr. In other words, if you are a resident of Colorado and leave to visit your sister for a month in Oregon, you could "save" 20 – 30 mrem of exposure, which is about equal to the EPA 40 CFR 190 limit of 25 mrem /year excluding radon.

2. Is the existing 20 picocurie/meter^2 – second (pCi/m2-sec) radon flux /emission standard in 40 CFR Parts 61, Subpart W and 192, Subpart D adequate to protect the public from additional radiation exposure above our natural background exposure ?

Specifically regarding natural background exposure to radon, note that Figure 1 and Table 1 demonstrate that radon can contribute much more than 50 % of our total background exposure and almost 300 mrem / yr in the Rocky Mountain States (due to higher levels of natural uranium and radium in the soil and rocks than, e.g., the coastal plains of the US).

It is recognized that EPA's public exposure criteria for radon in 40 CFR 61, Subpart W and Part 192, Subpart D is expressed as a "flux" (emission rate from a surface) of 20 pCi/m2-

sec. This limit however includes natural background, which is typically 1-2 pCi/m^2-sec almost anywhere on the earth's surface and can be several times higher than this in mineralized areas. So in some places, the EPA radon flux limit could be just a few times the existing background rate.

It is also recognized that 40 CFR Subpart W also imposes work practice requirements @ 61.252(b)(1) limiting the operator to two tailings impoundments of no more than 40 acres each. Accordingly, if it is assumed that the entire 80- acres are emitting radon at the limit of 20pCi/m2 -sec, the annual "source term" can be directly calculated to be about 200 Curies. This is approximately equal to the "source term" from 2-3 square miles of the earth, almost anywhere, at a typical planet wide background flux of 1 - 2 pCi/m2- sec.

However, the quantity or emission rate of a radionuclide from a source within the restricted area of a licensed facility is not the primary criteria for public radiation protection. This is routinely achieved by demonstrating compliance with the fundamental public dose limit of 100 mrem /year including radon (e.g., @ 10 CFR 20.1301 and commensurate sections of Agreement State regulations) and in demonstrating compliance to concentrations of radionuclides permitted to be released to unrestricted areas (e.g., at the site boundary) specified in 10 CFR 20, Appendix B, Table 2 (for radon = 1 X 10^{-8} uCi/ml w/o progeny; 1 X 10^{-10} with progeny).

It is at the site boundary and/or locations where people actually live, not at a somewhat arbitrary* location within the restricted area inaccessible to the public, that public radiation protection criteria should be applied. Although the historical need is understood for establishment of the radon flux criteria to limit radiological impact to a future public who may have access to formerly decommissioned uranium tailings sites, for licensed operating facilities, other mature regulatory controls as referenced here provide much greater assurances that exposure of the public is maintained ALARA in support of optimizing the risk vs. benefit relationship.

* "Arbitrary" relative to the most likely pathways of exposure to a member of the pubic including considerations of local meteorology and demography

3. What Do We Know About Radon Releases from Water Impoundments?

In response to concerns regards to radon releases from the decay of its radium parent contained in water impoundments (e.g., evaporation ponds) associated with uranium recovery facilities, two recent reports provide some valuable insight:

(1) SENES Consultants Ltd, *Evaporation Pond Radon Flux Analysis, Piñon Ridge Mill Project, Montrose County, Colorado*. August 2010 for Energy Fuels Resources Corporation; included as Appendix D of Energy Fuels' *Application for Approval for Construction, Pinon Ridge Mill, Montrose County,* Colorado as *s*ubmitted to US EPA Region VIII, Denver, Colorado August 31 2010. This report is posted along with the complete application on the EPA Subpart W web

site under "Applications", *Pinon Ridge Mill: Application for Approval of Construction of Tailings Facility.*

This study provided estimates of radon flux from and concentrations above proposed water impoundments (evaporation ponds containing raffinate solution) with a specified radium concentration and compared results to other existing models. Conservative estimates of radon flux indicates that the emissions are low and less than or similar to the pre-operational average background radon flux of 1.7 pCi m^{-2} s^{-1} observed at various locations within the proposed tailings areas on the site. The estimated radon flux levels from the evaporation ponds is also a small fraction (less than 10%) of the 20 pCi m^{-2} s^{-1} limit for pre-1989 uranium tailings that has been assumed here for context. This conservative estimate was based on the Nielson and Rogers model *.

* Nielson, K.K. and V.C. Rogers 1986. *Surface Water Hydrology Considerations in Predicting Radon Releases from Water-Covered Areas of Uranium Tailings Ponds.* Proc. Eighth Annual Symposium on Geotechnical & Hydrological Aspects of Waste Management, Geotechnical Engineering Program, Colorado State University & A.A. Balkema, Fort Collins, CO, USA, February 507, PP:215-222.

The model assumes that the emission rates are enhanced by the turbulence at the top layer of the water column where all the radon in the top one-meter of water is assumed to be released to air instantaneously. For comparison purposes, the same parameters were used to estimate the radon emissions using an on-line program that is available on the World Information Services on Energy (WISE) website. The on-line model, which is attributed to the Rogers and Nielson model, produced identical results.

The results of this assessment also indicated that the radon emissions associated with the evaporation of the raffinate solution and the emissions due to the operation of sprinkler systems are extremely low and insignificant compared to the radon flux from the ponds due to diffusional and turbulence processes.

Finally, the calculations indicated that the incremental air concentration due to the emission of radon from the evaporation ponds is very small (on the order of 3%) relative to the assumed background radon concentration.

(2) K.R. Baker and A.D. Cox 2010. *Radon Flux from Evaporation Ponds*. Presented at National Mining Association (NMA) / Nuclear Regulatory Commission (NRC) Uranium Recovery Workshop 2010, Denver, CO, May 26-27.

A presentation by Baker and Cox at the most recent NMA/NRC workshop in Denver (May 2010) and subsequently at the National Health Physics Society Annual Meeting in Salt Lake City (June 2010) considers the situation where appreciable concentrations of radon are present in the ponded water, as may arise for example from elevated levels of Ra-226 dissolved in the pond water. Baker and Cox, reporting on a stagnant film model and some

measurement data*, suggest a radon flux of the order of 1 pCi m^{-2} s^{-1} per 100 pCi/L of dissolved radon in the ponded water.

* A modified version of EPA Method 115 was used to measure radon flux from the pond surface

4. What do we know About Radon Emissions from ISRs?

Regarding radon evolution from in situ uranium recovery facilities, the majority of radon, which is released at the surface is not (as at a conventional mill) a result of on-surface decay of radium over time in tailings impoundments since ISRs do not generated conventional tailings as a radon source. At ISRs, the radon is brought to the surface dynamically, dissolved in the lixiviant returning from underground. Just as dynamically, that portion of the total dissolved radon that is above the solution's saturation value is released when encountering atmospheric pressures and temperatures.

Modern ISR uranium recovery processes are operated under "closed loop' conditions. The circulating lixiviant goes directly from well field header houses thru the ion exchange process and is then reconstituted and returned directly to the well field as an essentially closed system. Atmospheric conditions are initially encountered during resin transfer at the shaker screens. Accordingly, the vast majority of the "radon source term" for these facilities is associated with small releases from the well heads and header houses in the well fields and from the IX - resin – elution system interface where the process is first opened to atmospheric pressure. For facilities that have water retention ponds at the back end of the process (barren lixiviant bleeds, restoration wastes, etc), only a small percentage of the radon originally dissolved in the pregnant lixiviant initially returning from the well fields would be expected to remain. ISRs in Texas are currently operating without these "surge ponds" and send liquid wastes directly to a permitted deep disposal well.*

* For general discussions of the radiological characteristics of ISRs, including mechanisms of radon evolution, see: National Mining Association. *Generic Environmental Report in Support of the Nuclear Regulatory Commission's Generic Environmental Impact Statement for In Situ Uranium Recovery Facilities,* K Sweeney, NMA to L Camper, USNRC November 30, 2007; Brown, S. *The New Generation of Uranium In Situ Recovery Facilities: Design Improvements Should Reduce Radiological Impacts Relative to First Generation Uranium Solution Mining Plants*. Proceedings of the 2008 Waste Management Symposium, Phoenix. ASME Press, New York, NY, ISBN # 978160560422. 2008.

For more on mechanisms of ISR radon source terms see: Brown**,** S. and Smith, R., 1982. *A Model for Determining the Radon Loss (Source) Term for a Commercial In Situ Leach Uranium Facility.* In: M. Gomez (Editor), Radiation Hazards in Mining-Control, Measurement, and Medical Aspects. Soc. Min. Eng., pp. 794—800; Marple, M.L and Dziuk, T, Texas Department of Health, Bureau of Radiation Control. *Radon Source Terms at In Situ Uranium Extraction Facilities in Texas.* Proceedings of the Sixth Annual Uranium Seminar, South Texas Minerals Section of AIME. Corpus Christi. September 11-14, 1982

5. What are Current Practices and Results in Estimating Doses to the Public from Uranium Recovery Facilities?

Calculations performed in accordance with existing NRC guidance are used to estimate source terms and calculate off-site dose to the public. For example, USNRC Regulatory Guide 3.59, Section 2.6 provides methods acceptable to NRC for estimating the radon source term during ISR operations. Additionally, USNRC NUREG 1569, Appendix D, provides the MILDOS – AREA computer code methodology acceptable to the NRC, which includes expressions for calculating the annual Rn-222 source terms from various aspects of ISR operations which is then used by MILDOS to calculate off-site public dose and demonstrate compliance with dose limits of 10 CFR 20.1301.

See e.g.: U.S. Nuclear Regulatory Commission, NUREG-1569, *Standard Review Plan for In Situ Leach Uranium Extraction License Applications*, June 2003. Yuan, Y.C., J.H.C. Wang and A. Zielen. 1989. *MILDOS-AREA: An Enhanced Version of MILDOS for Large-area Sources.* Argonne National Laboratory (ANL) report ANL/ES-161. June 1989; U.S. Nuclear Regulatory Commission (NRC), 1987. *Methods for Estimating Radioactive and Toxic Airborne Source Terms for Uranium Milling Operations*. Regulatory Guide 3.59.

Regards to historical estimates of offsite radon concentrations and public dose from ISRs as reported by its licensees, the U.S. Nuclear Regulatory Commission, in NUREG-1910, *Generic Environmental Impact Statement for In-Situ Leach Uranium Milling Facilities (*2009), Chapter 4.2 indicates:

- Quarterly and biannual measurements of downwind concentrations of radon at an operational ISR facility boundary from 1991 to early 2007 were below 74 Bq/m3 [2.0 pCi/liter] with a majority of measurements below 37 Bq/m3 [1 pCi/liter]. For comparison, these measured values are well below the NRC effluent limit for radon at 10 CFR Part 20, Appendix B of 370 Bq/m3 [10 pCi/liter] and in fact, are probably just background values.

- Argonne National Laboratory's MILDOS-AREA computer code (Argonne National Laboratory, 1989 – see above) is typically used to calculate radiation doses to individuals and populations from releases occurring at operating uranium recovery facilities. The code is capable of modeling airborne radiological effluent releases applicable to both conventional mills and ISR facilities (including radon gas from well fields and processing facilities and yellowcake particulates from thermal drying operations)

- All reported doses have been well within the 10 CFR Part 20 annual radiation dose limit for the public of 1 mSv [100 mrem/yr] including dose from radon and its progeny and within the EPA fuel cycle annual limit (40 CFR 190) of 0.25 mSv [25 mrem], which does not include dose due to radon and its progeny.

6. What is known about the potential health effects to populations living in the vicinity of uranium mines and mills?

Uranium is a heavy metal and acts similarly to other heavy metals in the body (like molybdenum, lead, mercury). Accordingly, for natural uranium, national and international human exposure standards are based on the possible *chemical toxicity* of uranium (e.g., effect on kidney—nephrotoxicity), not on radiation and possible "cancer effects" (radiotoxicity). However, there has never been a death or permanent injury to a human from uranium poisoning*.

* See e.g.: (1) U.S. Nuclear Regulatory Commission. *Standards for Protection Against Radiation*; 10 CFR 20, Appendix B., Table 1. 1992. (2) International Commission on Radiological Protection. *Limits for Intakes of Radionuclides by Workers*. ICRP Publication 30, 1979. (3) US Dept. of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. *Toxicological Profile for Uranium.* 1999. *(4) Acute Chemical Toxicity of Uranium.* Kathryn, RL and Burkin, RK. Health Physics, 94(2), pp 170-179, February 2008)

Regarding ionizing radiation in general, the health effects are well understood. No health effects have been observed in human populations at the exposure levels within the range and variability of natural background exposures in the US. An official position of the National Health Physics Society is that below 5,000 – 10,000 millirem (which includes the range of both occupational and environmental exposures), risks of health effects are either to small to be observed or non- existent (see *Radiation Risks in Perspective* @hps.org/hpspublications/positionstatements). International and national authorities that establish exposure standards for workers and the public rely on the work of scientific committees of the highest professional standing for their evaluations of the scientific information on the health effects of ionizing radiation. These scientific committees include the United Nations Scientific Committee on the Effects of Ionizing Radiation (UNSCEAR); the International Commission on Radiological Protection (ICRP); the National Academy of Science's Biological Effects of Ionizing Radiation (BEIR) Committee, the National Council on Radiation Protection and Measurements (NCRP) and others.

But what about the specific concerns regarding health effects to populations living close to uranium recovery facilities? Despite much confusion and misunderstanding, possible health effects in populations living near uranium mines and mills have been well studied. No additional effects have been observed when compared to the health status of other similar populations not living nearby. A few sources providing the scientific evidence that supports this conclusion include:

- US Department of Health and Human Services, Public Health Services, Agency for Toxic Substance and Disease Registry, *Toxicological Profile for Uranium*, 1999. Chapter 1: Public Health Statement for Uranium, Section 1.5: How Can Uranium Effect My Health? – " No human cancer of any type has ever been seen as a result of exposure to natural or depleted uranium" (Available at:

http://www.atsdr.cdc.gov/toxprofiles/tp150.html)

- *Cancer and Noncancer Mortality in Populations Living Near Uranium and Vanadium Mining and Milling Operations in Montrose County, Colorado, 1950 -2000*. Boice, JD, Mumma, MT et al. International Epidemiology Institute, Rockville, MD and Vanderbilt University, Vanderbilt-Ingram Cancer Center, Nashville, TN. Journal of Radiation Research, 167:711-726; 2007: " The absence of elevated mortality rates of cancer in Montrose County over a period of 51 years suggests that the historical milling and mining operations did not adversely affect the health of Montrose County residents"

- *Cancer Mortality in a Texas County with Prior Uranium Mining and Milling Activities, 1950 – 2001.* Boice, JD, Mumma, M et al. International Epidemiology Institute, Rockville, MD and Vanderbilt University, Vanderbilt-Ingram Cancer Center, Nashville, TN Journal of Radiological Protection, 23:247 – 262; 2003 – "No unusual patterns of cancer mortality could be seen in Karnes County over a period of 50 years suggesting that the uranium mining and milling operations had not increased cancer rates among residents".

- *Cancer Incidence and Mortality in Populations Living Near Uranium Milling and Mining Operations in Grants, New Mexico, 1950–2004.* Boice, JD, Mumma, M et al. International Epidemiology Institute, Rockville, MD and Vanderbilt University, Vanderbilt-Ingram Cancer Center, Nashville, TN. Journal of Radiation Research, 174, 624–636. 2010 – "With the exception of male lung cancer (*in former underground miners*), this study provides no clear or consistent evidence that the operation of uranium mills and mines adversely affected cancer incidence or mortality of county residents".

7. But what about the known health impacts (e.g., lung cancer) to many uranium miners who worked underground in the 1950s and 1960s?

These miners worked in conditions that by today's standards we would consider unacceptable. They were exposed to very high levels of radon progeny (which are decay products of uranium) in poorly ventilated underground mines. Many of these miners also had severe smoking habits, which enhanced the ability of the radon daughters to deliver radiation dose to the lung. Follow up of 68,000 former miners over many years indicated the occurrence of about 2700 lung cancers in this population; much higher than the expected incidence. This is an incidence rate of about 4%. As a point of comparison, the baseline incident rate of lung cancer in non-smoker, Caucasian males today is about 0.4 % (Dr. John Boice, International Epidemiology Institute, Vanderbilt University – personal communication)

These conditions existed before we had Federal Agencies (Occupational Safety and Health

Administration - OSHA, Mine Safety and Health Administration - MSHA, US Nuclear Regulatory Commission - NRC) and laws to better protect workers throughout American industry (construction, manufacturing, farming, mining, etc). Based on the best scientific information available, we consider as safe the occupational exposure standards we have today as enforced by these agencies. The level of exposure of some of these early uranium miners was 100 – 1000 times higher than our current Federal standards.

As just one of many possible historical comparisons regards to working conditions in American industry decades ago, it is of note that almost 100 men died from construction and related accidents in the building of the Hoover Dam in the 1920s, long before Federal regulations were in place to protect workers. These circumstances would of course also be unacceptable today

Conclusions:

(1) The existing public radiation exposure criteria for uranium mills and in situ recovery facilities in 40 CFR Parts 61, 190 and 192 are adequately protective since they represent small fractions of the natural radiation background variation across the US. Our lifestyles, where we choose to live, what we eat and drink, has a much larger impact on our radiation exposure than exposure at these very low regulatory limits.

(2) Regarding ionizing radiation in general, the health effects are well understood. No health effects have been observed in human populations at the exposure levels within the range and variability of natural background exposures in the US.

(3) Radon emission rates (flux) from water impoundments (evaporation ponds) at licensed conventional mills and ISRs are not expected to be significantly different than that from typical background radon emission associated with land surfaces almost anywhere due to the very poor diffusion of radon through water.

(4) Historical environmental measurements made in the vicinity of uranium recovery facilities and public dose assessment performed and reported to the USNRC indicate radon concentrations at site boundary locations and doses to the public are consistently well below Federal limits.

(5) The possibility of health effects in populations living near uranium mines and mills over 50 years have been well studied by national scientific bodies of the highest professional standing. No additional effects have been observed when compared to the health status of other similar populations not living nearby.

(6) However, given that 40 CFR 192 was released in 1983, changes and updates have been made in the basic dosimetry models and science we use today to estimate radiological doses and risks. Accordingly, EPA should consider reassessing exposure terminology and criteria (e.g., as used in 40 CFR 190) to be consistent with current national and international methods and models, e.g., (1) International Commission on Radiological

Protection, 2008. “Publication 103 Recommendations of the ICRP, Annals of the ICRP.” 2008 and (2) National Research Council, 2006. “Health Risks for Exposure to Low Levels of Ionizing Radiation; BEIR VII, Phase II.”

Appendix 2

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Cancer and Noncancer Mortality in Populations Living Near Uranium and Vanadium Mining and Milling Operations in Montrose County, Colorado, 1950–2000

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Boice, J. D., Jr., Mumma, M. T. and Blot, W. J. Cancer and Noncancer Mortality in Populations Living Near Uranium and Vanadium Mining and Milling Operations in Montrose County, Colorado, 1950–2000. *Radiat. Res.* 167, 711–726 (2007).

Mining and milling of uranium in Montrose County on the Western Slope of Colorado began in the early 1900s and continued until the early 1980s. To evaluate the possible impact of these activities on the health of communities living on the Colorado Plateau, mortality rates between 1950 and 2000 among Montrose County residents were compared to rates among residents in five similar counties in Colorado. Standardized mortality ratios (SMRs) were computed as the ratio of observed numbers of deaths in Montrose County to the expected numbers of deaths based on mortality rates in the general populations of Colorado and the United States. Relative risks (RRs) were computed as the ratio of the SMRs for Montrose County to the SMRs for the five comparison counties. Between 1950 and 2000, a total of 1,877 cancer deaths occurred in the population residing in Montrose County, compared with 1,903 expected based on general population rates for Colorado (SMR_{CO} 0.99). There were 11,837 cancer deaths in the five comparison counties during the same 51-year period compared with 12,135 expected (SMR_{CO} 0.98). There was no difference between the total cancer mortality rates in Montrose County and those in the comparison counties (RR = 1.01; 95% CI 0.96–1.06). Except for lung cancer among males (RR = 1.19; 95% CI 1.06–1.33), no statistically significant excesses were seen for any causes of death of *a priori* interest: cancers of the breast, kidney, liver, bone, or childhood cancer, leukemia, non-Hodgkin lymphoma, renal disease or nonmalignant respiratory disease. Lung cancer among females was decreased (RR = 0.83; 95% CI 0.67–1.02). The absence of elevated mortality rates of cancer in Montrose County over a period of 51 years suggests that the historical milling and mining operations did not adversely affect the health of Montrose County residents. Although descriptive correlation analyses such as this preclude definitive causal inferences, the increased lung cancer mortality seen among males but not females is most likely due to prior occupational exposure to radon and cigarette smoking among underground miners residing in Montrose County, consistent with previous cohort studies of Colorado miners and of residents of the town of Uravan in Montrose County.

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INTRODUCTION

Uranium and vanadium oxides were extracted from carnotite ore as early as 1900 in Montrose County, CO (*1*). In 1912, carnotite ore was mined and radium was extracted at one of the first mills in what later became the town of Uravan, Montrose County, on the Western Slope of Colorado (*2, 3*). By 1919, the mining of uranium was well established as an ongoing industry in Montrose Country (*1*). Between 1925–1945, carnotite ore was mined to extract vanadium for use as a hardening component of steel. Some uranium was also extracted for use in ceramic and chemical industries. In the mid to late 1930s, the U.S. Vanadium Corporation built a mill at Uravan, named from the first three letters of the elements uranium and vanadium. During the 1940s ore was mined and milled in Montrose County to extract uranium for use in the Manhattan Project to produce the first atomic weapons (*2*). According to the U.S. Geological Survey (*5*), there were more uranium mines located in Montrose County (n = 223) than in any other county in Colorado. The average density of about one mine per 10 square miles was also the highest in Colorado. Mining and milling activities were substantially curtailed by the 1980s for economic reasons (*2, 4*).

The extraction of uranium from ore produced solid and liquid wastes, called tailings. The wastes contained the naturally occurring radionuclides present in the ore, including thorium, radium and other decay products. Tailing piles, runoff collection ponds, ore transport, and airborne and liquid effluents from the mills (extraction facilities) were potential sources of environmental exposure to humans (*6*). Historical milling and mining activities have raised questions over the years about possible increased exposure of milling and mining communities to ionizing radiation from

uranium and its decay products, possible contamination of groundwater and vegetation, and possible increased levels of indoor radon.

The primary occupational exposures in uranium mills were to airborne uranium, silica and vanadium. NIOSH conducted a comprehensive study of 1,484 men who worked at one of seven uranium mills on the Colorado Plateau on or after January 1, 1940 (*7*). Increased numbers of deaths were found for nonmalignant respiratory diseases, lung cancer, lymphoma and kidney disease. The authors were unable to show conclusively whether these deaths resulted from working in the mills because length of employment was not associated with increased risks. Studies of other "non-mining" uranium workers have provided little to no evidence of increased cancer risks among occupationally exposed workers (*8–10*). Environmental studies of populations residing in areas near uranium mining, milling or processing facilities similarly have not shown increased cancer risks (*11–13*). Studies of populations with increased levels of uranium, radium, radon and other radionuclides in drinking water also have not found associations with any cancers, overt kidney disease or bone disease (*14–19*).

An earlier cohort study of over 3,500 residents of the town of Uravan in Montrose County (which contained one of the earliest uranium and vanadium mills in the country) found no statistically significant increases in cancer mortality or cancer incidence except for male lung cancer, which was attributed to prior employment of some residents in underground uranium mines and increased tobacco use (*20*). This explanation was plausible since underground miners working on the Colorado Plateau are known to have been exposed to high cumulative levels of radon gas and radon decay products during their working careers and to have been heavy smokers (*21, 22*). While underground miner studies have linked radon exposures and tobacco use to increased lung cancer risks, no other cancer has been reported to be significantly linked to radon concentrations among underground miners (*23–25*). Studies of underground miners of the Colorado Plateau, however, have reported significant elevations of noncancer deaths from tuberculosis, nonmalignant respiratory disease and accidents (*24*).

Radium (which naturally occurs in carnotite ore but is not extracted during the milling of uranium and vanadium) is a component of mill tailings. Excessive ingestion of radium has been linked to bone cancer in occupational studies, although only at extraordinarily high levels, and no other cancer excesses were observed except for a rare carcinoma of the paranasal sinuses (*26, 27*). Radium decays into radon, and radon levels are increased near mill tailings. Case-control studies of indoor radon suggest increased lung cancer rates in long-term residents of homes with high radon concentrations (*25, 28, 29*) but have not found increased rates of childhood leukemia or childhood cancer (*30–32*). Radium also decays by emitting γ radiation, and excessive exposure to such external penetrating radiation is a known cause of breast cancer, leukemia and other malignancies (*33–35*). Cohort studies of uranium processors, millers and miners, however, have revealed no significant increases in leukemia, nor have descriptive studies of communities living near uranium milling and processing facilities revealed significant increases (*7, 8, 11, 12, 25*). Some ecological studies have reported correlations between radon levels and leukemia, but results are not consistent, and some studies appeared methodologically flawed (*25, 36*). Two cohort studies of underground miners have reported increases in leukemia, but the risks were not significant, nor were they correlated with cumulative radon exposures (*37, 38*). A recent case-control study of leukemia among Czech uranium miners reported a significant association with radon concentrations for chronic lymphocytic leukemia, a cancer that is not considered inducible by radiation (*39*), suggesting that aspects in the mining environment other than radon might be involved (*37, 40*).

Vanadium also was extracted from carnotite ore and is another source of potential exposure. No human study has linked vanadium to increased cancer rates (*41*), but recent animal experiments have found significant elevations of lung cancer in rats (*42*).

An earlier cancer mortality study of counties in the Western Slope of Colorado by the National Cancer Institute revealed no unusual patterns of death compared to the rest of Colorado (*43*). A later tabulation of county cancer mortality rates for 1950–1979 suggested increased rates of male lung cancer in Montrose County compared to the state of Colorado, but female lung and breast cancer rates were decreased, as were leukemia rates (*44*). Because of the long history of uranium and vanadium milling and mining activities and the large number of uranium mines in Montrose County, we extended the previous county cancer mortality studies by 20 years and compared the mortality risks in Montrose County with the mortality risks seen in demographically similar counties in Colorado as well as with the state of Colorado and the United States. Further, we evaluated noncancer causes of death in Montrose County, which had not previously been done.

METHOD

Cancer and noncancer mortality rates among Montrose county residents were compared with rates among residents in five other counties in Colorado that were selected because of similar demographic and socioeconomic characteristics. Mortality rates in Montrose County also were compared to the mortality rates in the general populations of Colorado and the United States, and standardized mortality ratios (SMRs) were computed. Following an approach taken by the National Cancer Institute (NCI) in a nationwide study of cancer mortality in counties with nuclear installations, relative risks were estimated as the ratio of the SMRs for Montrose County to the SMRs for the comparison counties (*45*). Similar approaches have been used to evaluate cancer risk in communities living in areas near uranium mining, milling and processing operations in Colorado, Pennsylvania and Texas (*11, 13, 43*).

TABLE 1
Demographic and Socioeconomic Characteristics of Montrose County, the Comparison Counties[a] and the State of Colorado

County	Total score[a]	Total persons	Area (square miles)	Population density	Percentage							Median household income ($)
					Male	White	Rural	High school graduate	Age 65+	Employed	Below poverty	
Study county												
Montrose	—	24,423	2,242	10.9	48.4	96.0	63.7	73.4	16.4	57.2	14.0	22,610
Comparison counties[a]												
Montezuma	177	18,672	2,040	9.2	48.6	85.1	61.0	73.6	12.3	57.3	20.0	22,491
Delta	181	20,980	1,148	18.4	49.1	96.0	81.9	72.4	22.3	45.3	17.4	18,532
Yuma	186	8,954	2,369	3.8	48.9	98.5	69.6	77.7	16.8	59.9	13.1	22,249
Logan	204	17,567	1,845	9.6	48.5	95.8	41.0	79.1	15.4	64.1	14.5	22,065
Mesa	214	93,145	3,341	28.0	48.4	94.9	18.4	79.0	14.4	58.2	14.8	23,698
Total comparison counties	—	159,318	10,743	14.9	48.5	94.2	37.1	77.4	15.4	57.1	15.6	22,570
State of Colorado		3,294,394	103,718	31.8	49.5	88.3	17.6	83.8	10.0	66.4	11.4	30,140

[a] As described in the Methods, a simple rank-sum algorithm was applied to all Colorado counties contrasting demographic and socioeconomic characteristics with those of Montrose County. A low score signifies close similarity to Montrose County. The five counties most similar to Montrose County (i.e., with the lowest scores) were selected as comparison counties.

Mortality Data

Counties are the smallest areas for which both population estimates and annual counts of the number of deaths from specific causes are readily available back to 1950 from the National Center for Health Statistics (*46*). Cancer mortality data for all counties in the state of Colorado from 1950 to 2000 were obtained from the National Cancer Institute (*46*). Noncancer mortality rates for counties in Colorado from 1960 to 1999 were obtained from the University of Pittsburgh (*47*). The number of deaths from noncancer causes was not available and was estimated by multiplying the cause-specific mortality rates by the corresponding age, sex, race and calendar year population data available from the National Cancer Institute (*46*).

Selection of Comparison Counties

Mining and milling activities in Montrose County began in the early 1900s; this county had many more uranium mines and mills than any other Colorado county (*5*). Accordingly, Montrose County was chosen as the study county. Comparison counties were selected based on similar population characteristics. All 62 of Colorado's other counties were eligible for selection as comparison counties. Census Bureau demographic data on nine socioeconomic variables were obtained for all counties, i.e., population density (total residents divided by county area), percentage male, percentage white, percentage rural, percentage high school graduate, percentage over age 64 years, percentage employed, percentage below poverty, and median household income (*48*). For each of these characteristics, counties were sorted and ranked based on their similarity to Montrose County. The rank values for the nine socioeconomic variables were then summed, with a low sum (or score) representing more similarity to Montrose than a high sum (or score). The five counties with the lowest scores (Montezuma, Delta, Yuma, Logan and Mesa) were chosen as the comparison counties (Table 1, Fig. 1). The determination of a socioeconomic score based on area-level characteristics is similar to that done in other studies (*49*). Data on diet, smoking and other potential risk factors for disease are not readily available at the county level, but use of comparison counties in proximity to Montrose County (Montezuma, Delta and Mesa) should help minimize differences in these unknown factors, assuming that factors such as diet would be similar in neighboring areas. Montrose County had the highest number of uranium mines (n = 223) of any county in Colorado. Delta and Yuma Counties did not have any uranium mines, Logan had one, Montezuma had eight, and Mesa had 55 (*5*). The average density of mines in the five comparison counties was about six per 1000 square miles or 600 times less than Montrose County. Montrose County had two operating uranium mills, Mesa Country had one, and the other comparison counties had none. Supplemental analyses excluding Mesa County were conducted to reduce the likelihood that these mining and milling activities had affected the mortality rates in the comparison counties.

Statistical Analyses

Mortality rates for the general populations of Colorado and the United States were used for calculating expected numbers of deaths and SMRs among the Montrose County and comparison county populations. Counts of cancer deaths by cause, sex, race and 5-year age group were obtained for Montrose County and the five comparison counties for each year from 1950 to 2000. For each type of cancer and each county, the expected number of deaths, based on concurrent Colorado and U.S. experience, was calculated for the 51-year study period (*46, 47*). Expected numbers were obtained by multiplying annual Colorado and U.S. cancer death rates by the estimated populations, stratified by 5-year age group, race and sex. Counts of observed and expected deaths were then summed over the periods 1950–1969, 1970–1984 and 1985–2000. These intervals were selected to be of similar size, and consideration was given to the fact that practically all milling and mining activities had ceased by 1985.

The standardized mortality ratio was calculated by dividing the number of deaths observed among the Montrose County population by the number of deaths that would be expected using U.S. (SMR_{US}) or Colorado (SMR_{CO}) rates. Relative risks (RRs) were computed as the ratios of the SMRs for Montrose County to the comparison counties, and 95% confidence intervals were calculated following the methods applied in the NCI nationwide study of nuclear facilities (*45*). A 95% confidence interval that contains 1.00 means that chance cannot be ruled out as a possible explanation for any observed differences in mortality rates between Montrose County and the comparison counties. When a 95% confidence interval does not contain 1.00, the difference in mortality rates is called "statistically significant" and means that chance is not a likely explanation for the observed results (*50*).

SMRs and RRs for noncancer deaths between 1960 and 1999 were computed in a similar manner as for cancer deaths. Although counts of noncancer deaths were not available, they could be estimated accurately

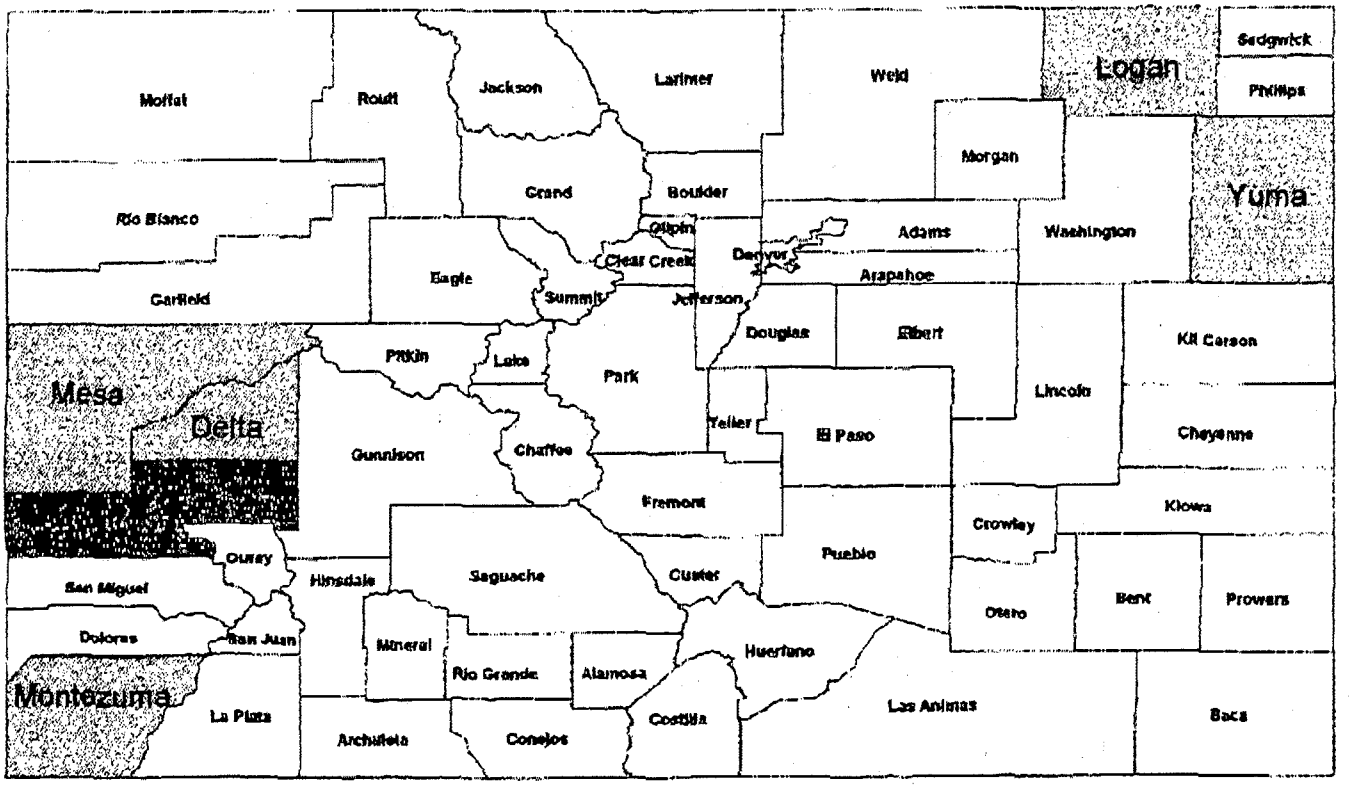

FIG. 1. County map of Colorado indicating the study county (Montrose) and the comparison counties (Mesa, Delta, Montezuma, Logan and Yuma) selected to be similar to Montrose County on demographic and socioeconomic characteristics.

by multiplying the age, calendar year, sex, race and site-specific mortality rates times the corresponding population data obtained from the NCI. This procedure was validated by comparing the estimated counts for cancer deaths with the actual counts of cancer deaths available from the NCI data files (*46*).

While the study uses existing databases that contain no identifying information, strata containing two or fewer deaths are not presented but are listed as LT3 to denote "less than three". This is to abide by the confidentiality requirements for using the NCI and National Center for Health Statistics databases. The concern is the possibility that individuals with certain characteristics might be identified if the number of deaths were small.

RESULTS

The number of residents in Montrose County and the five comparison counties totaled 24,423 and 159,318, respectively, in 1990 (Table 1). Residents in the comparison counties were similar to residents in Montrose County with regard to demographic indicators of cancer risk such as age, race and various accepted measures of socioeconomic status such as educational level and median household income. Most of the population studied was white with few black or Asian citizens; 15.4% of the comparison county residents were older than 64 years compared to 16.4% for Montrose County residents; most graduated from high school (77.4% compared to 73.4%), and most were employed (57.1% compared to 57.2%). The median household incomes of Montrose County ($22,610) and the comparison counties ($22,570) were also similar. Comparison counties were less rural (37.1% compared to 63.7%) than Montrose County, but residents were similar with regard to poverty level (15.6% compared to 14.0%). Montrose and the comparison counties differed from the state of Colorado in being more rural, less educated, older and much less affluent. Because certain diseases are known to be associated with low socioeconomic status (*51, 52*), any differences in mortality risks based on Colorado comparisons may be related in part to differences in socioeconomic factors and not environmental factors. Any bias associated with differences in socioeconomic status would be in the direction of producing higher SMRs. Some variations in characteristics were also seen among the comparison counties (e.g., Yuma has a relatively low population density and Mesa has a high population density). Such differences, however, are balanced by closer similarities in other characteristics (e.g., Yuma is similar to Montrose in rural characteristics and Mesa is similar in poverty characteristics).

Table 2 presents the total number of cancer deaths, SMRs based on Colorado and U.S. rates, and RRs comparing Montrose County with the comparison counties, for all cancers and for specific cancers, during 1950–2000. There were no significantly increased or significantly decreased RRs for any cancer or combination of cancers. No significant differences were seen for all cancers (RR 1.01; 95% CI 0.96–1.06), lung cancer (RR 1.08; 95% CI 0.98–1.19),

kidney and liver cancer (RR 0.92; 95% CI 0.74–1.15), breast cancer (RR 0.86; 95% CI 0.71–1.03), non-Hodgkin lymphoma (RR 1.05; 95% CI 0.82–1.34), leukemia (RR 0.78; 95% CI 0.60–1.01), or childhood cancer (RR 0.73; 95% CI 0.43–1.25).

Overall, results based on Colorado population rates were generally similar to results based on the comparison counties (e.g., the SMR_{CO} for all cancer deaths was 0.99 based on Colorado rates, whereas the RR was 1.01 contrasting cancer rates in Montrose with the comparison counties). There were 1,877 cancer deaths in Montrose County (SMR_{CO} 0.99) and 11,837 cancer deaths in the comparison counties (SMR_{CO} 0.98). The most frequent causes of death in Montrose County and the comparison counties were cancer of the lung (SMR_{CO} 1.14 compared to. 1.06), breast (SMR_{CO} 0.80 compared to 0.93), colon and rectum (SMR_{CO} 0.88 compared to 0.93), and prostate (SMR_{CO} 1.07 compared to 1.00). Leukemia deaths occurred below expectation in both Montrose County and the comparison counties (SMR_{CO} 0.73 compared to 0.94). There were five childhood leukemia deaths in Montrose County and 58 in the comparison counties (SMR_{CO} 0.57 compared to 1.14). The SMRs based on U.S. rates were generally lower than those based on Colorado rates (e.g., the all-cancer SMR_{US} of 0.85 was significantly lower than the all-cancer SMR_{CO} of 0.99 based on Colorado rates). Similarly, the lung cancer SMR_{US} of 0.85 based on U.S. rates was significantly low, whereas the SMR_{CO} of 1.14 based on Colorado rates was significantly high.

Contrasting cancer rates in Montrose with the comparison counties revealed no significantly high or significantly low relative risks for any cancer of *a priori* interest. Slight elevations were seen for cancers of the lung (RR 1.08; 95% CI 0.98–1.19), bone (RR 1.36; 95% CI 0.63–2.91), and non-Hodgkin lymphoma (RR 1.05; 95% CI 0.82–1.34). Slight deficits were seen for cancers of the kidney (RR 0.80; 95% CI 0.56–1.14), breast (RR 0.87; 95% CI 0.72–1.04), thyroid (RR 0.82; 95% CI 0.32–2.07), leukemia other than CLL (RR 0.80; 95% CI 0.61–1.06), and childhood cancer (RR 0.73; 95% CI 0.43–1.25).

Of the 28 relative risks presented, 16 were less than 1.00 and 12 were greater than 1.00, a distribution about the overall value of 1.01 for all cancers combined that is consistent with the play of chance when evaluating so many individual cancers. SMRs based on comparisons with the Colorado population were similar to the RRs in magnitude and direction (i.e., above or below 1.00). For all cancers taken together, the SMR_{CO} for men and women combined was 0.99 (95% CI 0.94–1.03) based on Colorado rates and similar to the RR of 1.01 (95% CI 0.96–1.06) based on the comparison counties.

With regard to sex-specific risks, there were no significantly high or significantly low RRs for female residents of Montrose County (Table 3). Overall, female cancer mortality rates in Montrose County were the same as those in the comparison counties (RR 1.00; 95% CI 0.93–1.08). Lung cancer (RR 0.83; 95% CI 0.67–1.02) and breast cancer (RR 0.86; 95% CI 0.72–1.04) risks were notably low, with the deficits approaching statistical significance. The overall cancer rates for males in Montrose County were also similar to those in the comparison counties (RR 1.02; 95% CI 0.95–1.09). Lung cancer, however, was significantly increased (RR 1.19; 95% CI 1.06–1.33), whereas kidney cancer (RR 0.60; 95% CI 0.37–0.99), liver and kidney cancer (RR 0.70; 95% CI 0.50–0.97), and leukemia (RR 0.63; 95% CI 0.44–0.90) were significantly decreased. The SMRs based on Colorado rates were extremely similar to the RRs based on the comparison counties, indicating that the choice of the referent made little difference.

Table 4 presents, for both sexes combined, the SMRs and RRs of mortality for selected cancers in Montrose County for three periods during 1950–2000. Overall, cancer rates in Montrose County were similar to those in the comparison counties. No RR for any cancer was significantly above or below expectation for any time interval. There were no increasing patterns of risk over the 51-year period of observation. There was a tendency for the SMRs and the RRs to be lower in the last interval, 1985–2000.

Table 5 presents SMRs and RRs for noncancer causes of death for the years 1960–1999. A slightly increased RR for all causes of death (RR 1.03; 95% CI 1.01–1.06) compared to the five comparison counties was due largely to a significant increase in deaths from accidents other than automobile accidents (RR 1.15; 95% CI 1.02–1.30). Deaths due to tuberculosis were also significantly increased (RR 1.89; 95% CI 1.10–3.48). Significantly low RRs were seen for hypertension but not for heart disease. Of the 23 RRs presented in Table 5, 10 were below, 11 were above, and two were equal to the central value of 1.03, which is consistent with the play of chance when many comparisons are made.

SMRs based on U.S. rates tended to be lower than those based on Colorado rates. The all-causes-of-death SMR_{US} for Montrose County residents based on U.S. rates, for example, was significantly low. Lower SMRs based on U.S. rates were also seen for heart disease and cerebrovascular disease, but significantly higher mortality rates were seen for nonmalignant respiratory disease, accidents and suicides. These differences were also apparent among residents of the five comparison counties and may reflect differences in socioeconomic factors between the study counties and the general populations of the state of Colorado and the United States (52).

Table 6 presents, for both sexes combined, the SMRs and RRs for selected noncancer causes of death in Montrose County for three periods during 1960–1999. There was little tendency for any cause of death to increase over time. The RRs tended to be higher in the earliest interval, 1960–1969, than in any other interval. The all-cause RR was significantly high during 1960–1969 (RR 1.14) whereas it was close to expectation during 1970–1984 (RR 1.02) and 1985–1999 (RR 1.01). The significantly high all-cause RR during 1960–1969 was due to significantly high risks for

TABLE 2
Observed (Obs) and Expected (Exp)[a] Numbers of Cancer Deaths and Standardized Mortality Ratios (SMRs) for Montrose County and the Five Comparison Counties during 1950–2000, and the Estimates of Relative Risk (RR)[b]

	Montrose County				
Cancer (ICD 9)	Obs	Exp_{US}	Exp_{CO}	SMR_{US}	SMR_{CO}
All cancers (140–208)	1,877	2,201.4	1,903.2	0.85*	0.99
Esophagus (150)	22	39.4	31.3	0.56*	0.70
Stomach (151)	87	88.6	80.3	0.98	1.08
Colon/rectum (153, 154)	207	279.7	234.0	0.74*	0.88
Pancreas (157)	121	111.8	107.0	1.08	1.13
Lung (162)	454	531.0	397.5	0.85*	1.14*
Skin (172, 173)	37	38.0	37.7	0.97	0.98
Malignant melanoma of the skin (172)	25	26.7	27.7	0.94	0.90
Breast (174)	126	175.5	158.2	0.72*	0.80*
Cervix uteri (180)	15	26.8	25.0	0.56*	0.60
Corpus uteri (182)	34	29.7	24.4	1.15	1.39
Ovary (183)	49	56.2	54.0	0.87	0.91
Prostate (185)	148	136.3	138.2	1.09	1.07
Urinary bladder (188)	44	57.1	48.4	0.77	0.91
Kidney (189)	34	45.1	41.9	0.75	0.81
Liver and kidney (155, 189)	88	106.3	95.9	0.83	0.92
Bone (170)	8	8.4	6.4	0.95	1.25
Connective tissue (171)	12	11.9	12.0	1.01	1.00
Brain & CNS (191, 192)	44	52.1	49.3	0.84	0.89
Thyroid (193)	5	5.7	5.6	0.88	0.89
Non-Hodgkin lymphoma (200, 202)	75	76.4	72.6	0.98	1.03
Hodgkin lymphoma (201)	15	12.8	11.1	1.17	1.35
Multiple myeloma (203)	33	32.3	32.9	1.02	1.00
Leukemia (204–208)	65	91.4	88.6	0.71*	0.73*
Leukemia, CLL (204.1)[c]	10	13.3	13.1	0.75	0.76
Leukemia, not CLL	55	77.3	74.8	0.71*	0.74*
Childhood leukemia (<20 years)	5	9.0	8.8	0.55	0.57
Childhood cancer (<20 years)	15	21.9	20.1	0.68	0.75

[a] Expected numbers based on U.S. rates (Exp_{US}) and on Colorado rates (Exp_{CO}).
[b] RR is taken as the SMR_{CO} for Montrose County divided by the SMR_{CO} for the comparison counties.
[c] CLL denotes chronic lymphocytic leukemia.
* $P < 0.05$.

tuberculosis (RR 3.07), diabetes (RR 1.90), cerebrovascular disease (RR 1.22), cirrhosis of the liver (RR 1.91), and all external causes of death (RR 1.20). Except for tuberculosis, none of these causes of death were significantly elevated overall or during 1970–1984 or 1985–1999. For the interval 1970–1984, the RR (1.04) and estimated number of all-cancer deaths ($n = 508$) were the same as those computed in Table 4 based on exact cancer counts; this concordance supports the validity of the approach used to estimate RRs for the noncancer deaths.

DISCUSSION

Cancer and noncancer mortality rates among residents of Montrose County were similar to those of residents in the state of Colorado as well as residents in five comparison counties in Colorado selected as comparable based on a wide range of demographic and socioeconomic characteristics. Notably, no significant increases were seen for either men or women for all cancers combined, kidney cancer or kidney disease, liver cancer or bone cancer, leukemia, lymphoma or nonmalignant respiratory disease. These causes of death were of an *a priori* interest because of associations reported previously in studies of uranium mill workers and uranium miners of the Colorado Plateau (*7, 24*) or because they are the most biologically plausible tissues to be affected by any deposition of uranium and its decay products after possible ingestion or inhalation (*53, 54*). Significant increases among men but not women, however, were seen for lung cancer, tuberculosis and accidental injuries. These causes of death were also previously reported to be significantly increased among male miners of the Colorado Plateau (*24*) and suggest that the mortality rates in Montrose County were influenced by occupational rather than environmental factors since it is implausible that environmental exposures would affect the mortality rates of these three causes of death in one sex but not in the other. Tobacco use likely contributed to this risk of lung cancer since miners of the Colorado Plateau are known to be heavy smokers (*22*). Although there were increases and decreases in other causes of death over time, there were no consistent patterns to suggest that living in Montrose County increased the risk

TABLE 2
Extended

Comparison counties						
Obs	Exp_{US}	Exp_{CO}	SMR_{US}	SMR_{CO}	RR[a]	95% CI
11,837	13,981.4	12,135.3	0.85*	0.98	1.01	0.96–1.06
196	247.1	195.4	0.79*	1.00	0.70	0.45–1.09
496	581.0	527.4	0.85*	0.94	1.15	0.92–1.45
1,416	1,814.8	1,519.7	0.78*	0.93	0.95	0.82–1.10
705	715.3	685.6	0.99	1.03	1.10	0.91–1.33
2,612	3,282.0	2,472.7	0.80*	1.06	1.08	0.98–1.19
218	237.0	235.3	0.92	0.93	1.06	0.75–1.50
171	164.5	171.4	1.04	1.00	0.90	0.59–1.38
951	1,133.7	1,025.9	0.84*	0.93	0.86	0.71–1.03
136	176.5	165.6	0.77*	0.82	0.73	0.43–1.24
168	197.4	163.4	0.85	1.03	1.35	0.94–1.96
337	363.6	350.3	0.93	0.96	0.94	0.70–1.27
881	865.6	882.1	1.02	1.00	1.07	0.90–1.28
281	369.2	312.9	0.76*	0.90	1.01	0.74–1.39
270	282.8	264.9	0.95	1.02	0.80	0.56–1.14
613	679.8	615.2	0.90	1.00	0.92	0.74–1.15
38	53.9	41.3	0.70	0.92	1.36	0.63–2.91
58	73.9	75.6	0.78	0.77	1.30	0.70–2.42
291	320.0	302.7	0.91	0.96	0.93	0.68–1.28
40	37.2	36.7	1.07	1.09	0.82	0.32–2.07
451	479.9	457.4	0.94	0.99	1.05	0.82–1.34
55	80.9	70.0	0.68*	0.79	1.72	0.97–3.04
217	204.0	209.5	1.06	1.04	0.97	0.67–1.39
530	578.9	560.9	0.92	0.94	0.78	0.60–1.01
90	84.1	83.2	1.07	1.08	0.71	0.37–1.36
434	489.8	473.8	0.89	0.92	0.80	0.61–1.06
58	52.3	50.7	1.11	1.14	0.50	0.20–1.24
120	128.8	117.6	0.93	1.02	0.73	0.43–1.25

of cancer or other fatal diseases other than those related to employment as an underground miner and increased tobacco use. This is one of the few descriptive county mortality studies that included both cancer and noncancer mortality, and the male excess of specific cancer and noncancer diseases that have been associated with underground mining (i.e., lung cancer, tuberculosis and accidental deaths) strengthens the inference made that occupational exposures and cigarette smoking were responsible for the observed county excesses.

Lung Cancer

Given the statistically significant increase in lung cancer rates among men living in Montrose County, we considered the possibility that environmental exposures from uranium and vanadium milling and mining activities might be contributing factors. This is unlikely, however, because the risk of lung cancer was decreased in women (RR 0.82), and it is implausible that an environmental exposure would increase the risk of lung cancer among men and decrease the risk of lung cancer among women. Further, it has been known for some time that working as an underground miner in the Colorado Plateau is associated with an increased rate of lung cancer due to high-level exposure to radon and its decay products, increased tobacco use and possibly other mine exposures such as silica, diesel exhaust and blasting fumes (*21, 22, 24*). It has also been reported that radon exposures and cigarette smoking among underground miners of the Colorado Plateau have interacted in a synergistic or nearly multiplicative fashion to increase lung cancer risks. It is noteworthy that a previous study of persons living in the town of Uravan in Montrose County found a significant increase in lung cancer among men but not women, which was also attributed to employment in underground mines and smoking and not to environmental exposures (*20*).

Because workers with a specific occupation usually make up only a small percentage of all persons residing in a county, it is often difficult to identify occupational risks based on county mortality studies. However, there are notable examples where this has been possible [e.g., occupational exposure to asbestos from shipyard work during World War II was identified as a risk factor for lung cancer based on county mortality data and later confirmed in analytic studies (*55*)]. Indirect support for the likelihood that our county mortality study identified an occupational rather than environmental cause of male lung cancer also comes from the similarities in other causes of death that were elevated both

TABLE 3
Observed (Obs)[a] Numbers of Cancer Deaths and Standardized Mortality Ratios (SMRs) for Montrose County for Males and Females during 1950–2000, and the Estimates of Relative Risk (RR)[b]

	Males					Females				
Cancer (ICD 9)	Obs[a]	SMR_{US}	SMR_{CO}	RR[b]	95% CI	Obs[a]	SMR_{US}	SMR_{CO}	RR[b]	95% CI
All cancers (140–208)	1,068	0.85*	1.02	1.02	0.95–1.09	809	0.85*	0.95	1.00	0.93–1.08
Esophagus (150)	16	0.52*	0.65	0.63	0.37–1.05	6	0.69	0.87	1.01	0.43–2.38
Stomach (151)	63	1.10	1.21	1.30	0.99–1.70	24	0.77	0.85	0.89	0.58–1.37
Colon/rectum (153, 154)	108	0.72*	0.90	0.97	0.79–1.19	99	0.76*	0.86	0.93	0.75–1.14
Pancreas (157)	64	1.02	1.08	0.99	0.76–1.28	57	1.16	1.20	1.26	0.95–1.67
Lung (162)	353	0.94	1.27*	1.19*	1.06–1.33	101	0.66*	0.84	0.83	0.67–1.02
Skin (172, 173)	24	0.98	1.00	1.06	0.69–1.64	13	0.96	0.95	1.05	0.59–1.89
Malignant melanoma of the skin (172)	16	0.97	0.94	0.97	0.57–1.64	9	0.90	0.84	0.81	0.40–1.62
Breast (174)	—	—	—	—	—	126	0.72*	0.80*	0.86	0.72–1.04
Cervix uteri (180)	—	—	—	—	—	15	0.56*	0.60*	0.73	0.43–1.24
Corpus uteri (182)	—	—	—	—	—	34	1.15	1.39	1.35	0.94–1.96
Ovary (183)	—	—	—	—	—	49	0.87	0.91	0.94	0.70–1.27
Prostate (185)	148	1.09	1.07	1.07	0.90–1.28		—	—	—	—
Urinary bladder (188)	29	0.70	0.84	0.97	0.65–1.43	15	0.97	1.09	1.12	0.65–1.93
Kidney (189)	17	0.58*	0.64	0.60*	0.37–0.99	17	1.08	1.10	1.16	0.69–1.94
Liver and kidney (155, 189)	39	0.63*	0.72*	0.70*	0.50–0.97	49	1.11	1.17	1.23	0.91–1.67
Bone (170)	6	1.19	1.55	1.74	0.71–4.29	LT3	0.60	0.79	0.82	0.19–3.56
Connective tissue (171)	5	0.80	0.79	1.06	0.41–2.75	7	1.27	1.23	1.55	0.68–3.53
Brain and CNS (191, 192)	23	0.76	0.81	0.83	0.54–1.29	21	0.96	1.00	1.06	0.67–1.69
Thyroid (193)	LT3	0.44	0.46	0.42	0.06–3.15	4	1.19	1.16	1.07	0.37–3.08
Non-Hodgkin lymphoma (200, 202)	32	0.75	0.82	0.81	0.56–1.18	43	1.28	1.29	1.33	0.96–1.85
Hodgkin lymphoma (201)	7	0.89	0.98	1.49	0.65–3.41	8	1.63	2.00	1.99	0.90–4.40
Multiple myeloma (203)	18	1.00	0.99	0.92	0.56–1.50	15	1.05	1.02	1.03	0.60–1.78
Leukemia (204–208)	32	0.59*	0.61*	0.63*	0.44–0.90	33	0.89	0.92	1.01	0.70–1.46
Leukemia, CLL (204.1)[c]	6	0.73	0.72	0.61	0.26–1.41	4	0.80	0.84	0.91	0.32–2.59
Leukemia, not CLL	26	0.57*	0.59*	0.64*	0.43–0.96	29	0.92	0.94	1.03	0.70–1.53
Childhood leukemia (<20 years)	LT3	0.19	0.20	0.19	0.03–1.37	4	1.07	1.05	0.86	0.30–2.45
Childhood cancer (<20 years)	6	0.47	0.52	0.51	0.22–1.17	9	0.97	1.06	1.03	0.51–2.10

[a] Observed number of cancer deaths in Montrose County. LT3 denotes less than 3 deaths.
[b] RR is taken as the SMR_{CO} for Montrose County divided by the SMR_{CO} for the comparison counties.
[c] CLL denotes chronic lymphocytic leukemia.
* $P < 0.05$.

among miners of the Colorado Plateau and among Montrose County residents (i.e., tuberculosis and accidental deaths were significantly increased among miners and also among male, but not female, residents of Montrose County).

Smoking

Cigarette smoking is the predominant cause of lung cancer and is responsible for more than 87% of all lung cancers diagnosed in the United States (*56*). It is thus possible that men in Montrose County used tobacco products to a greater extent than men who lived in other counties in Colorado. This supposition seems possible since miners of the Colorado Plateau are known to be heavy smokers (*22*). Females residing in Montrose County had a lower risk of lung cancer than females residing in the comparison counties or the state of Colorado. Although this suggests that they may have smoked proportionally less than females in the comparison counties, the lower risk was not significant and thus chance cannot be ruled out. Further, the risk of other smoking-related sites among females, such as the bladder and pancreas, was slightly elevated and in the opposite direction expected if they were infrequent smokers.

External Radiation

The potential for environmental exposures to penetrating radiation, such as γ rays, to have contributed to the risk of cancer in Montrose County residents is also unlikely because of the deficits seen for leukemia, female breast cancer and childhood cancer. Leukemia and female breast cancer are the cancers most frequently observed to be increased in comprehensive epidemiological studies of populations exposed to excessive amounts of ionizing radiation, and, in addition, children are considered to be at higher risk of radiation-induced cancers than adults (*33–35*). Living in areas of high natural background radiation, which primarily would include exposure to external radiation, also has not been convincingly linked to elevations in cancer risk or thyroid disease (*57, 58*).

Uranium Ingestion

Uranium from the environment can enter the body by ingestion of food and water or by inhalation of uranium

TABLE 4
Standardized Mortality Ratios (SMR) and Relative Risks (RRs) for Selected Cancer Deaths in Montrose County for Three Times during 1950–2000 for Both Sexes Combined

	1950–1969			1970–1984			1985–2000		
Cancer (ICD 9)	Obs[a]	SMR_{co}	RR[b]	Obs[a]	SMR_{co}	RR[b]	Obs[a]	SMR_{co}	RR[b]
All cancers (140–208)	470	1.03	1.10	508	0.99	1.04	899	0.96	0.94
Esophagus (150)	5	0.94	1.04	6	0.87	1.15	11	0.58	0.51
Stomach (151)	45	1.22	1.23	23	1.18	1.47	19	0.80	0.81
Colon/rectum (153, 154)	55	0.89	1.03	53	0.78	0.81	99	0.94	0.98
Pancreas (157)	33	1.27	1.04	25	0.86	0.88	63	1.21	1.27
Lung (162)	67	1.14	1.28	133	1.22*	1.18	254	1.11	0.98
Skin (172, 173)	16	2.07*	1.96	8	0.83	0.87	13	0.64	0.71
Malignant melanoma of the skin (172)	11	2.49*	1.97	4	0.52	0.50	10	0.64	0.71
Breast (174)	35	0.91	1.08	32	0.71	0.72	59	0.79	0.84
Cervix uteri (180)	9	0.69	0.91	3	0.51	0.63	3	0.49	0.50
Corpus uteri (182)	7	0.86	0.75	10	1.50	2.07	17	1.77*	1.52
Ovary (183)	14	1.05	1.15	14	0.94	0.91	21	0.82	0.85
Prostate (185)	36	1.14	1.04	44	1.26	1.32	68	0.95	0.96
Urinary bladder (188)	12	0.87	1.01	12	0.92	0.92	20	0.93	1.08
Kidney (189)	6	0.63	0.54	9	0.79	0.91	19	0.90	0.86
Liver and kidney (155, 189)	28	1.07	0.89	22	0.89	1.10	38	0.84	0.86
Bone (170)	3	1.06	0.98	LT3	1.14	1.19	3	1.64	2.65
Connective tissue (171)	LT3	0.91	2.16	3	0.97	1.02	7	1.04	1.29
Brain and CNS (191, 192)	4	0.36*	0.41	13	0.95	0.91	27	1.10	1.15
Thyroid (193)	LT3	1.03	0.86	LT3	1.53	1.49	LT3	0.42	0.41
Non-Hodgkin lymphoma (200, 202)	14	0.95	0.89	16	0.92	1.04	45	1.11	1.11
Hodgkin lymphoma (201)	7	1.28	1.70	3	0.94	1.06	5	2.01	2.81
Multiple myeloma (203)	3	0.59	0.73	13	1.48	1.49	17	0.89	0.79
Leukemia (204–208)	21	0.83	0.87	14	0.58*	0.60	30	0.77	0.84
Leukemia, CLL (204.1)	0	0.00	0.00	LT3	0.50	0.53	8	0.93	0.81
Leukemia, not CLL	21	0.85	0.89	12	0.59	0.61	22	0.74	0.88
Childhood leukemia (<20 years)	LT3	0.39	0.30	LT3	0.85	0.89	LT3	0.81	0.89
Childhood cancer (<20 years)	7	0.65	0.57	6	1.06	1.17	LT3	0.56	0.66

Notes. SMRs based on rates in Colorado population. RRs based on comparison counties.
[a] Observed number of cancer deaths in Montrose County. LT3 denotes less than three deaths.
[b] RR is taken as the SMR_{co} in Montrose County divided by the SMR_{co} in the comparison counties.
* $P < 0.05$.

containing dust. Uranium is ubiquitous and is distributed throughout the Earth's crust. Environmental exposures to uranium, however, have not been linked to any detrimental effects (*59*), and the IARC has concluded that there is inadequate evidence to classify uranium as a human carcinogen (*27*). Because uranium has such a long half-life, it is not very radioactive. Chemical toxicity (especially of the kidney) is considered more important for human health than the risk of cancer from uranium's radioactive properties (*59*). Nevertheless, even with respect to chemical toxicity, studies of workers exposed to uranium have failed to demonstrate overt kidney disease (*24, 60*) including end stage renal disease (*7*). Among Montrose County residents, deaths associated with kidney disease were not significantly increased, again suggesting that any environmental exposures to uranium milling products were likely too low to result in toxic effects.

Occupational Studies

Workers exposed to uranium dust during milling, processing and manufacturing have not shown significant or consistent increases in lung cancer, kidney cancer or any other cancer in large-scale occupational studies (*8–10, 27, 61, 62*), so it is not surprising that lower-level environmental exposures are not found to increase cancer risks. One study of uranium processing reported a significant dose response for kidney cancer based on four high-dose cases, but the SMR for kidney cancer was not significantly increased, and the authors concluded that chance was a possible explanation (*63*). Studies of uranium mill workers have reported significant increases of nonmalignant respiratory disease and nonsignificant increases of lymphoma, but the associations were not considered causal because increased risks were not seen among the workers who were employed for the longest time (*7*). Residents of Montrose County were not found to be at significant risk of dying from nonmalignant respiratory disease or from lymphoma.

Radon and Radium

While occupational exposures to high radon levels in underground mines have been shown to increase lung cancer risks, employment in underground mines has not been con-

TABLE 5
Observed (Obs) and Expected (Exp)[a] Numbers of Noncancer Deaths and Standardized Mortality Ratios (SMRs) for Montrose County and the Five Comparison Counties during 1960–1999, and the Estimates of Relative Risk (RR)[b]

Cause of death (ICD 9)	Montrose County				
	Obs[c]	Exp_{US}	Exp_{CO}	SMR_{US}	SMR_{CO}
All causes of death (001–999)	8,617	8,941.7	8,330.3	0.96*	1.03*
Tuberculosis (010–018)	15	12.1	10.7	1.24	1.40
All malignant neoplasms (140–208)	1,610	1,888.0	1,620.1	0.85*	0.99
Diabetes mellitus (250)	152	173.9	139.8	0.87	1.09
Cerebrovascular disease (430–438)	720	755.2	659.2	0.95	1.09*
All heart disease (390–398, 404, 410–429)	2,638	3,316.8	2,705.9	0.80*	0.97
Hypertension with heart disease (402, 404)	58	104.4	71.7	0.56*	0.81
Hypertension without heart disease (401, 403, 405)	23	38.1	35.3	0.60*	0.65*
Non-malignant respiratory disease (460–519)	897	708.5	903.0	1.27*	0.99
Influenza and pneumonia (480–487)	318	300.2	356.7	1.06	0.89
Bronchitis, emphysema, asthma (490–493)	188	133.3	181.3	1.41*	1.04
Bronchitis (490, 491)	37	34.5	43.3	1.07	0.85
Emphysema (492)	126	83.7	116.3	1.51*	1.08
Asthma (493)	25	15.1	21.7	1.65*	1.15
Ulcer of stomach and duodenum (531–533)	44	33.1	39.1	1.33	1.12
Cirrhosis of liver (571)	97	114.7	109.2	0.85	0.89
Nephritis and nephrosis (580–589)	68	69.8	59.7	0.97	1.14
All external causes of death (800–999)	810	572.6	667.8	1.41*	1.21*
Accidents (850–949)	595	399.7	446.7	1.49*	1.33*
Motor vehicle accidents (810–825)	270	186.6	197.9	1.45*	1.36*
All other accidents (800–807, 826–949)	325	213.1	248.8	1.53*	1.31*
Suicides (950–959)	174	115.7	162.6	1.50*	1.07
Homicides and other external causes (960–978, 980–999)	41	57.2	58.5	0.72*	0.70*

[a] Expected numbers based on U.S. rates (Exp_{US}) and on Colorado rates (Exp_{CO}).
[b] RR is taken as the SMR_{CO} for Montrose County divided by the SMR_{US} for the comparison counties.
[c] The observed numbers were estimated by applying the age, calendar year, sex and cause-specific mortality rates for Montrose County for 1960–1999 to the corresponding Montrose County population data. All cancer deaths were accurately known and comparison with these known values validated the estimation procedure. Slight differences might occur, however, due to rounding.
* $P < 0.05$.

vincingly associated with any other cancer (*23, 25*). Again, were environmental (as opposed to occupational) radon exposure the cause of elevated lung cancer rates observed in males living in Montrose County, a corresponding increase should have been observed in females, but it was not. Risk of leukemia has been investigated in case-control studies of residential radon exposures, but no significant associations were found (*27, 30, 31*). Leukemia and childhood leukemia did not occur at elevated rates among Montrose County residents in the current or previous county mortality studies (*43, 44*).

Vanadium

Carnotite ore also was processed to extract vanadium in addition to uranium and is another source of potential exposure. No human study has linked vanadium to increased cancer rates (*41, 64*), but one animal study recently reported significant elevations of lung cancer in rats, although not mice, after 2 years of continuous inhalation of vanadium pentoxide (*42*). There is some evidence that very large exposures to vanadium could result in kidney damage (*64*). Thus, if vanadium exposures were to result in adverse health effects among residents of Montrose County, they would likely involve damage to the lungs and/or kidney. Similar to the discussion of uranium and radiation exposure, it would be implausible that environmental exposure to vanadium would increase the risk of lung cancer among males while decreasing the risk among females. Further, kidney cancer and kidney disease were not significantly increased among Montrose county residents.

Strengths and Limitations

Strengths of our geographical correlation study include the availability of mortality data that spanned over 50 years, the long history of milling and mining operations in Montrose County from the early 1900s to after 1970, the large number of uranium mines ($n = 223$) and mills ($n = 2$), the availability of several comparison populations, the use of previously accepted methodologies, and the insights provided by previous county, occupational and residential studies of Colorado Plateau populations. Evaluation of both cancer and noncancer mortality is another unique strength of this county investigation.

The minimum latent period for the development of solid cancer after radiation exposure is approximately 5 to 10 years and for leukemia approximately 2 years (*33-35*).

TABLE 5
Extended

Comparison counties						
Obs[a]	Exp_{us}	Exp_{co}	SMR_{us}	SMR_{co}	RR[b]	95% CI
54,125	58,381.1	54,392.5	0.93*	1.00	1.04*	1.02–1.00
51	80.7	71.2	0.63*	0.72*	1.96*	1.10–3.49
10,117	12,004.8	10,315.8	0.84*	0.98	1.01	0.96–1.07
968	1,134.3	910.8	0.85*	1.06	1.02	0.86–1.21
4,600	5,176.4	4,515.5	0.89*	1.02	1.07	0.99–1.16
17,912	21,996.4	18,019.4	0.81*	0.99	0.98	0.94–1.02
557	712.4	495.3	0.78*	1.12*	0.72*	0.55–0.94
240	256.4	238.9	0.94	1.00	0.65*	0.42–0.99
5,548	4,570.2	5,842.4	1.21*	0.95*	1.05	0.97–1.12
2,085	1,990.5	2,386.4	1.05	0.87*	1.02	0.91–1.15
1,128	855.3	1,168.1	1.32*	0.97	1.07	0.92–1.25
262	218.1	273.5	1.20*	0.96	0.89	0.63–1.26
742	540.0	755.1	1.37*	0.98	1.10	0.91–1.33
124	97.2	139.5	1.28*	0.89	1.30	0.84–1.99
242	218.9	261.6	1.11	0.93	1.22	0.88–1.68
540	709.7	676.1	0.76*	0.80*	1.11	0.90–1.38
404	451.1	386.5	0.90*	1.05	1.09	0.84–1.41
5,033	3,662.5	4,249.6	1.37*	1.18*	1.02	0.95–1.10
3,678	2,559.1	2,853.8	1.44*	1.29*	1.03	0.95–1.13
1,866	1,187.7	1,256.2	1.57*	1.49*	0.92	0.81–1.04
1,812	1,371.4	1,597.6	1.32*	1.13*	1.15*	1.02–1.30
1,026	725.5	1,017.8	1.41*	1.01	1.06	0.90–1.25
329	377.8	377.9	0.87*	0.87*	0.80	0.58–1.11

Thus, because uranium and vanadium mining and milling activities in Montrose Country began in the early 1900s, there was ample time for any environmental exposures to accumulate and any effects on resident populations to be detected during 1950–2000. Mortality occurring before 1950 could not be evaluated because county mortality data are not readily available before then.

Comparing the mortality experience of residents of Montrose County with that of demographically similar counties in Colorado followed the methods used by the National Cancer Institute in similar studies (*43, 45*). The use of local comparison populations rather than the state of Colorado or the entire United States minimizes biases possibly associated with different demographic and socioeconomic features that cannot be easily controlled for in analyses. For example, an early report of an excess of chronic renal disease among miners of the Colorado Plateau based on comparisons with U.S. rates was not apparent when comparisons were made based on rates in the corresponding four-state area (*24*). Finally, the Montrose County mortality analyses could be interpreted in light of findings from previous studies; e.g., the excess of lung cancer in men but not women was consistent with an occupational exposure to radon and tobacco use in underground mines previously reported in Uravan and Montrose County (*20, 44*). The excess of tuberculosis and accidental deaths among men but not women was similarly consistent with findings from studies of underground miners of the Colorado Plateau (*24*).

Common to all ecological or geographic correlation studies, however, our study could not assign exposure levels to individuals or directly control for potential confounding factors such as cigarette smoking (*65*). However, because the milling and mining operations in Montrose County began many years before 1950, and because there were many more uranium mines in Montrose County than any other county in Colorado, it is reasonable to assume that the residents of Montrose County experienced more environmental exposures over time than residents of other counties, albeit at presumably low levels. The comparison counties were selected to have similar demographic and socioeconomic characteristics so that personal habits such as use of tobacco products and diet or other potentially confounding factors might be as similar as possible to those of residents of Montrose County. The slightly lower socioeconomic status among Montrose Country residents than the comparison county residents and Colorado state residents suggests that this selection process was not perfect. However, the lower measures of socioeconomic status would act in the direction of increasing the SMRs and RRs in Montrose County, and no consistent increases were seen.

Common to all geographical correlation studies, the comparison counties also could not be perfectly matched on all characteristics. Mesa County, for example, had a higher population density than Montrose County and included some residents who had engaged in uranium mill and mine activities, which might have reduced the magnitude of any

TABLE 6
Standardized Mortality Ratios (SMRs) and Relative Risks (RRs) for Selected Noncancer Deaths in Montrose County for Three Time Periods during 1960–1999 for Both Sexes Combined

Cause of death (ICD 9)	1960–1969			1970–1984			1985–1999		
	Obs[a]	SMR_{co}	RR[b]	Obs[a]	SMR_{co}	RR[b]	Obs[a]	SMR_{co}	RR[b]
All causes of death (001–999)	1,816	1.10*	1.14*	2,817	1.01	1.02	3,984	1.03	1.01
Tuberculosis (010–018)	11	1.89	3.07*	LT3	0.66	0.76	LT3	1.11	1.39
All malignant neoplasms (140–208)	255	1.05	1.12	508	0.99	1.04	846	0.98	0.97
Diabetes mellitus (250)	47	2.24*	1.90*	43	1.01	1.01	62	0.81	0.76*
Cerebrovascular disease (430–438)	215	1.31*	1.22*	265	1.14	1.05	239	0.91	1.00
All heart disease (390–398, 404, 410–429)	599	1.01	1.05	890	0.89*	0.94	1,149	1.03	0.97
Hypertension with heart disease (402, 404)	28	1.05	0.77	17	0.97	0.93	13	0.47*	0.52*
Hypertension without heart disease (401, 403, 405)	8	1.00	1.31	7	0.80	0.76	8	0.43*	0.39*
Non-malignant respiratory disease (460–519)	119	0.83*	0.96	295	1.13	1.24*	483	0.97	0.97
Influenza and pneumonia (480–487)	56	0.67*	0.94	123	1.13	1.39*	139	0.85	0.84
Bronchitis, emphysema, asthma (490–493)	45	1.04	0.95	48	0.88	0.89	95	1.14	1.30*
Bronchitis (490, 491)	9	1.43	1.95	8	0.84	0.95	20	0.73	0.70
Emphysema (492)	28	0.86	0.73	36	0.90	0.87	61	1.40*	1.84*
Asthma (493)	8	1.82	2.00	4	0.81	0.99	13	1.05	1.16
Ulcer of stomach and duodenum (531–533)	18	1.39	1.66	16	1.32	1.21	10	0.71	0.83
Cirrhosis of liver (571)	26	1.17	1.91*	30	0.72	0.94	42	0.92	1.00
Nephritis and nephrosis (580–589)	13	1.52	1.30	27	1.65*	1.52	28	0.81	0.81
All external causes of death (800–999)	205	1.34*	1.20*	290	1.16*	0.92	315	1.19*	1.03
Accidents (850–949)	170	1.50*	1.23*	212	1.27*	0.90	213	1.29*	1.07
Motor vehicle accidents (810–825)	77	1.55*	1.09	104	1.34*	0.83	89	1.27*	0.91
All other accidents (800–807, 826–949)	93	1.45*	1.37*	108	1.21	0.96	124	1.30*	1.22*
Suicides (950–959)	29	0.91	1.16	58	0.99	0.98	87	1.21	1.09
Homicides and other external causes (960–978, 980–999)	5	0.62	0.75	20	0.82	1.08	15	0.58*	0.58*

Notes. SMRs based on rates in the Colorado population. RRs based on comparison counties.

[a] Observed deaths of deaths in Montrose County. See footnote 3 in Table 5 for explanation of estimation procedure. LT3 denotes less than 3.

[b] RR is taken as the SMR_{co} for Montrose County divided by the SMR_{co} for the comparison counties.

* $P < 0.05$.

observed associations. Analyses excluding Mesa County (and also Yuma and Logan counties) produced similar results as those based on all five comparison counties (Table 7). Comparisons with the general populations of Colorado and the United States also yielded similar results [e.g., based on Colorado rates, significant increases in lung cancer mortality among men (but not women) were seen only among residents of Montrose County and not the residents of the comparison counties]. The advantages of the five-county analyses over the two-county analyses include statistical precision due to larger numbers and likely validity given the closer similarity of essentially all cancer rates with those of the state of Colorado.

While the fact of death within the study counties is known with certainty, length of residence and migration into and from the counties are not known for individuals. There was in general population growth throughout the years, although there may have been some migration out of Montrose County when the uranium industry became less active in the 1980s. Nonetheless, there would have been ample opportunity for any environmental exposures from milling or mining activities to occur and accumulate from the late 1930s to the 1970s in Montrose County so that any increase in mortality from 1950 to about 1984 related to such exposures could have been observed. Further, there was little evidence that Montrose County experienced population changes different from those of the comparison counties over the years 1950 to 2000. The percentage increase in population growth, for example, was essentially the same for each decade over this period [e.g., the population of Montrose County grew from 15,220 in 1950 to 24,423 in 1990 (or 60%), whereas the population growth in the comparison counties was from 94,341 to 159,318 (or 68%)]. Although immigration of "nonexposed" persons might be expected to reduce somewhat the magnitude of the risk associated with possible environmental exposures, much of the increase in Montrose County was related to employment opportunities in the uranium industry and associated occupational and environmental exposures.

Our study is of mortality and not incidence. However, because reporting of deaths is likely to be similar within Montrose County and the comparison counties, and many of the diseases of interest (e.g., lung cancer), have a high fatality rate, mortality would be expected to reflect incidence fairly closely. The current 5-year survival rate for

TABLE 7
Observed (Obs) and Expected (Exp)[a] Numbers of Cancer Deaths and SMRs Occurring in the Two Most Similar Comparison Counties (Delta and Montezuma) during 1950–2000, and the Estimates of Relative Risk (RR)[b] Comparing Montrose County with These Two Counties

	Delta and Montezuma						
Cancer (ICD 9)	Obs	Exp_{us}	Exp_{co}	SMR_{us}	SMR_{co}	RR[b]	95% CI
All cancers (140–208)	3,254	3,981.4	3,467.5	0.82*	0.94*	1.05	0.99–1.11
Esophagus (150)	45	71.3	56.8	0.63*	0.79	0.89	0.53–1.48
Stomach (151)	142	168.6	153.0	0.84*	0.93	1.17	0.89–1.52
Colon/Rectum (153, 154)	384	518.6	435.0	0.74*	0.88*	1.00	0.85–1.19
Pancreas (157)	195	204.6	196.8	0.95	0.99	1.14	0.91–1.43
Lung (162)	710	940.8	713.6	0.75*	0.99	1.15*	1.02–1.29
Skin (172, 173)	79	66.0	65.6	1.20	1.20	0.82	0.55–1.21
Malignant melanoma of the skin (172)	60	45.3	47.3	1.33*	1.27	0.71	0.45–1.13
Breast (174)	240	312.9	284.3	0.77*	0.84*	0.94	0.76–1.17
Cervix uteri (180)	47	48.8	45.9	0.96	1.02	0.58	0.33–1.05
Corpus uteri (182)	60	55.3	45.8	1.08	1.31	1.06	0.70–1.62
Ovary (183)	92	100.9	97.4	0.91	0.94	0.96	0.68–1.36
Prostate (185)	264	255.2	261.7	1.03	1.01	1.06	0.87–1.30
Urinary bladder (188)	61	106.7	90.6	0.57*	0.67*	1.35	0.92–1.99
Kidney (189)	68	80.5	75.7	0.84	0.90	0.90	0.60–1.36
Liver and kidney (155, 189)	178	195.0	176.4	0.91	1.01	0.91	0.70–1.17
Bone (170)	6	14.9	11.2	0.40*	0.54	2.33	0.81–6.73
Connective tissue (171)	10	20.4	21.1	0.49*	0.47*	2.10	0.91–4.87
Brain and CNS (191, 192)	97	88.4	83.8	1.10	1.16	0.77	0.54–1.10
Thyroid (193)	5	10.6	10.5	0.47	0.48	1.86	0.54–6.43
Non-Hodgkin lymphoma (200, 202)	111	135.3	129.4	0.82*	0.86	1.20	0.90–1.61
Hodgkin lymphoma (201)	12	21.9	19.0	0.55*	0.63	2.14	0.99–4.57
Multiple myeloma (203)	75	58.3	60.4	1.29*	1.24	0.81	0.54–1.21
Leukemia (204–208)	133	162.7	158.1	0.82*	0.84	0.87	0.65–1.17
Leukemia, CLL (204.1)[c]	20	24.0	23.9	0.83	0.84	0.91	0.43–1.95
Leukemia, not CLL	111	137.2	133.1	0.81*	0.83	0.88	0.64–1.22
Childhood leukemia (<20 years)	15	13.8	13.5	1.08	1.11	0.51	0.19–1.42
Childhood cancer (<20 years)	24	33.9	31.2	0.71	0.77	0.97	0.51–1.85

[a] Expected numbers based on U.S. rates (Exp_{us}) and on Colorado rates (Exp_{co}).
[b] RR is taken as the SMR_{co} for Montrose County divided by the SMR_{co} for the two comparison counties (see Table 2 for the observed numbers of cancer deaths and SMR_{co} for Montrose County).
[c] CLL denotes chronic lymphocytic leukemia.
* $P < 0.05$.

lung cancer is 17% (*66*), whereas in years past, survival was much worse; e.g., in 1960–1973, the median survival time was only 5.4 months (*67*). Diseases that have a low fatality rate can also be evaluated, although the statistical power to identify an effect would be lower than for an incidence survey because of the smaller number of events. Improvement in treatment would also be expected to be similar between Montrose and the comparison counties so that it is unlikely that study findings would reflect differences in medical care over time. Cancer incidence data exist for Colorado for recent years, 1990–2002. Similar to the patterns for cancer mortality, there were essentially no differences in cancer incidence rates for all cancers over this 13-year period among the residents of Montrose County, the five comparison counties, and the State of Colorado (Fig. 2). Comparable findings are seen for childhood leukemia in that cancer incidence between 1990 and 2002 gave a similar picture as the mortality data [i.e., the rate of leukemia (2.6 per 100,000) was lower than the state of Colorado (4.0 per 100,000) and the difference was not statistically significant].

Finally, the entire county rather than smaller areas in the immediate vicinity of specific mining or milling facilities was used as the geographic unit for analysis. This was necessitated because mortality data extending back to 1950 are available only at the county level. However, mining and milling facilities were widespread throughout large parts of western Montrose County so that the potential for environmental exposure was not limited to any single area. There were 223 uranium mines and two uranium mills in Montrose County, and the average density of about one uranium facility per 10 square miles was much greater than that for the state of Colorado or the comparison counties. Further, a comprehensive cohort study of residents of the town of Uravan from 1937 and followed through May 1984 reached similar conclusions based on both cancer incidence and mortality data (i.e., there was no significant increase in any cancer or disease except lung cancer among men attributed

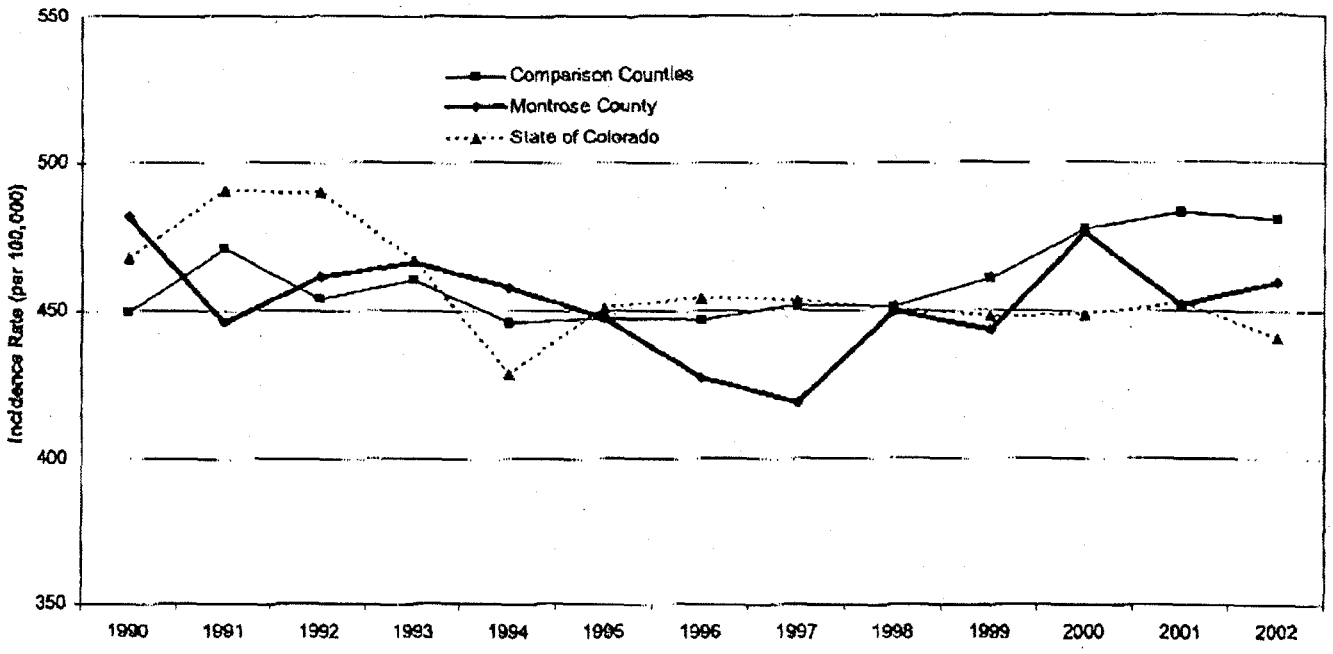

FIG. 2. Age-adjusted cancer incidence rates for all cancers in Montrose County, the five comparison counties, and the state of Colorado from 1990–2002. Except for the first 2 calendar years, 3-year moving averages are presented to smooth fluctuations in rates due to relatively small numbers of cancer cases occurring in a single year for Montrose County and the five comparison counties. Source: Colorado Department of Public Health and Environment (http://www.cdphe.state.co.us/cohid/agreement.html).

to documented employment in underground mines and tobacco use (*20*)].

Summary

In summary, there is no evidence that residents of Montrose County experienced an increased risk of dying of cancer or other diseases because of environmental exposures associated with uranium and vanadium milling and mining activities. Although descriptive correlation analyses such as this preclude definitive causal inferences on their own, an occupational risk of lung cancer due to underground mining exposure to radon and smoking is suggested among males and consistent with previous cohort studies of underground miners of the Colorado Plateau and of residents of a milling and mining community in Montrose County.

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Appendix 3

INSTITUTE OF PHYSICS PUBLISHING JOURNAL OF RADIOLOGICAL PROTECTION

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Cancer mortality in a Texas county with prior uranium mining and milling activities, 1950–2001

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Abstract

Uranium was discovered in Karnes County, Texas, in 1954 and the first uranium mill began operating in 1961 near Falls City. Uranium milling and surface and *in situ* mining continued in Karnes County until the early 1990s. Remediation of uranium tailings ponds was completed in the 1990s. There were three mills and over 40 mines operating in Karnes County over these years and potential exposure to the population was from possible environmental releases into the air and ground water. From time to time concerns have been raised in Karnes County about potential increased cancer risk from these uranium mining and milling activities. To evaluate the possibility of increased cancer deaths associated with these uranium operations, a mortality survey was conducted. The numbers and rates of cancer deaths were determined for Karnes County and for comparison for four 'control' counties in the same region with similar age, race, urbanisation and socioeconomic distributions reported in the 1990 US Census. Comparisons were also made with US and Texas general population rates. Following similar methods to those used by the National Cancer Institute, standardised mortality ratios (SMRs) were computed as the ratio of observed numbers of cancers in the study and control counties compared to the expected number derived from general population rates for the United States. Relative risks (RRs) were computed as the ratios of the SMRs for the study and the control counties. Overall, 1223 cancer deaths occurred in the population residing in Karnes County from 1950 to 2001 compared with 1392 expected based on general population rates for the US. There were 3857 cancer deaths in the four control counties during the same 52 year period compared with 4389 expected. There was no difference between the total cancer mortality rates in

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Karnes County and those in the control counties (RR = 1.0; 95% confidence interval 0.9–1.1). There were no significant increases in Karnes County for any cancer when comparisons were made with either the US population, the State of Texas or the control counties. In particular, deaths due to cancers of the lung, bone, liver and kidney were not more frequent in Karnes County than in the control counties. These are the cancers of *a priori* interest given that uranium might be expected to concentrate more in these tissues than in others. Further, any radium intake would deposit primarily in the bone and radon progeny primarily in the lung. Deaths from all cancers combined also were not increased in Karnes County and the RRs of cancer mortality in Karnes County *before* and in the early years of operations (1950–64), shortly after the uranium activities began (1965–79) and in two later time periods (1980–89, 1990–2001) were similar, 1.0, 0.9, 1.1 and 1.0, respectively. No unusual patterns of cancer mortality could be seen in Karnes County over a period of 50 years, suggesting that the uranium mining and milling operations had not increased cancer rates among residents.

1. Introduction

In Karnes County, Texas, concern has been expressed that cancer rates might be greater than expected due to uranium mining and milling activities that began in the 1950s (Brender 1987, 1989). The concerns were related to potential environmental releases into the air and ground water from operating the three mills and over 40 uranium mines, including the transport of uranium ore. The activities associated with uranium extraction from ore would produce solid and liquid wastes. The wastes, called tailings, contain most of the radionuclides present in the ore, including thorium, radium and other decay products. Radon and radon progeny are a secondary source of possible exposure in mines, mills and tailings ponds. The tailings ponds, surface mines, runoff collection ponds, ore transport and the mills (extraction facilities) are the potential exposure pathways to humans (NCRP 1993).

A small cytogenetic study in Karnes County (Au *et al* 1995) and a recent exploratory geographical correlation study in Spain (López-Abente *et al* 2001) have suggested that uranium operations might increase cancer risk, but both investigations had methodologic deficiencies that limited interpretation. Studies of cancer mortality (1979–88) and cancer incidence (1976–80) conducted previously by the Texas Department of Health, provided no indication of unusually high cancer rates in populations living in Karnes County (Brender 1987, 1989) but it is possible that the time between potential exposure and occurrence of disease may have been too short to demonstrate an effect. To provide additional information over a longer time period than previously possible, we conducted a county mortality study contrasting cancer rates in Karnes County before, during and after the uranium operations began. The current investigation includes more calendar years than previously possible, over 50 years, and incorporates a comparison with nearby counties with similar demographic characteristics. The investigative methods followed are similar to those used by the National Cancer Institute in a study of nuclear installations throughout the United States (Jablon *et al* 1990, 1991).

2. Methods

2.1. Uranium mining, transportation, milling and waste disposal activities

Karnes County is south of San Antonio, Texas, in the central coastal plain area in the southern part of the state. The uranium mining activities around Karnes County began in 1959 and the

first uranium mill began operating in 1961. The uranium ore was transported from surface mines to mills where the uranium concentrate U_3O_8 (yellowcake) was produced. There were three conventional uranium mills and over 40 *in situ* and surface mines operating in Karnes County for several decades. *In situ* or solution mining is a method where a leaching solution is injected through wells into the ore body to dissolve the uranium. Production wells are then pumped to bring the uranium-bearing solution to the surface for eventual extractions. There were no underground mines. After the uranium ore was processed, the waste material, called tailings, was placed in tailings piles or ponds. The tailings contain unrecovered uranium and amounts of other radionuclides including thorium and radium (Ruttenber *et al* 1984, Eisenbud 1987, Ibrahim *et al* 1990, Veska and Eaton 1991, Thomas 2000). Radon gas released from the decay of radium would be dispersed and diluted into the atmosphere. Remediation of the Falls City mill site was completed in 1994 (DoE 2002). The Conquista mill was decommissioned in the early 1980s and the tailings pond was capped and closed by the early 1990s. The Panna Maria mill was decommissioned in the early 1990s and the tailings pond was capped and closed in the late 1990s.

Because the uranium mining and milling processes in Karnes County did not involve any uranium enrichment, workers and the public were not exposed to enriched radioactive materials or wastes. Natural uranium ores are not generally considered to present an external radiation hazard (NCRP 1993, Priest 2001). Exposure to airborne ore dust is a principal source of potential exposure. The Texas Department of Health began monitoring the environment around uranium mines and recovery facilities in 1961 and in 1988–89 instituted a sampling programme in response to public concerns about possible exposure to radioactive materials from the uranium recovery activities (Meyer 1990). The sampling programme included private water supplies, radon in homes, radon in schools and radioactivity in milk and meat. There was no evidence for increased levels of radioactive materials in Karnes County compared with other parts of Texas; if anything, the average radon concentrations in homes (0.8 pCi l^{-1}) was lower than in other parts of the state. The concentration of uranium in milk samples was also below the minimum detectable level of the measurement equipment.

2.2. Cancers considered in the study

After ingestion or inhalation, uranium distributes within the body to tissues depending on its chemical properties and route of intake (ICRP 1995a, 1995b). Inhalation of uranium would result in deposition within the lung and pulmonary lymph nodes. The bone, kidney and liver are the other most probable sites of deposition and exposure, albeit at a lower level than for the lung. In general, the solubility of natural uranium is very high (ICRP 1995a, 1995b, Priest 2001) which implies a relatively short residence time within the body before being eliminated by normal processes. The kidney is also an organ of interest because of possible damage related to the chemical properties of uranium, a heavy metal.

The following kinds of cancer were studied on the basis of the likely deposition of uranium in body tissue mentioned above: cancers of the lung, bone, liver and kidney. In addition, it is known that substantial ingestion of radium has increased the risk of bone cancer among dial painters (Fry 1998) and extensive exposure to radon and its progeny has increased the risk of lung cancer among underground miners (Lubin *et al* 1995, NRC 1999). On the basis of the knowledge of cancers found increased after high dose and high dose rate external exposures to gamma or x-rays, cancers of the stomach, colon, female breast and thyroid gland and leukemia were studied (Boice *et al* 1996, UNSCEAR 2000). For completeness, other cancers were included, including those not frequently found to be increased in exposed populations, such as cancers of the oesophagus, pancreas, cervix uteri and corpus uteri and prostate, malignant melanoma of the skin, Hodgkin's disease, non-Hodgkin's lymphoma and multiple myeloma.

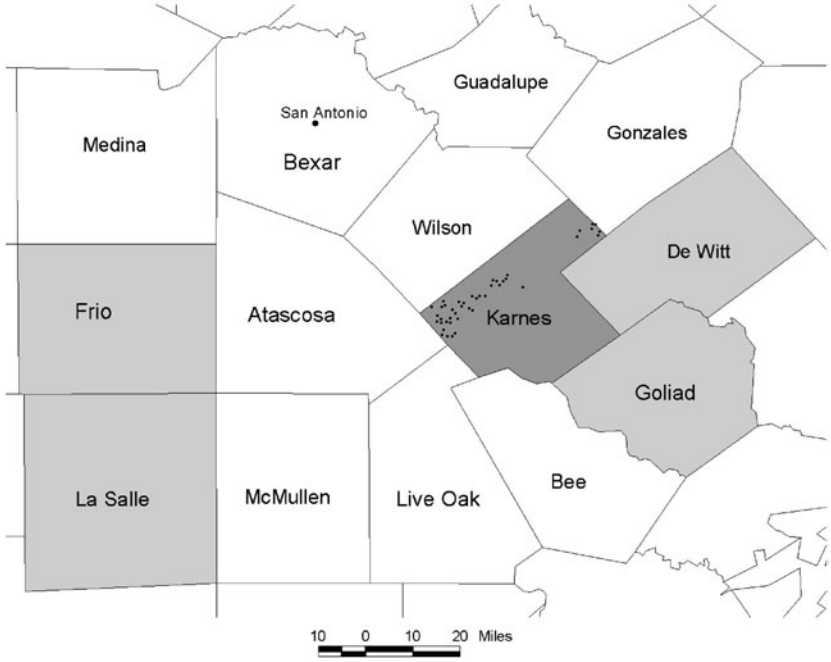

Figure 1. A map of South Texas containing Karnes County and the four control counties (Frio, La Salle, DeWitt and Goliad). The dots in Karnes County represent the prior location of 43 mines and 3 mills (Railroad Commission of Texas, Surface Mining and Reclamation Division map).

2.3. Mortality data

Counties are the smallest areas for which both population estimates and annual counts of the number of deaths for specific causes are readily available back to 1950 from the National Center for Health Statistics and the US Census Bureau (NCI 1999). Cancer mortality data for Texas at the county level were available from the National Cancer Institute from 1950 to 1995 (NCI 1999) and from the Texas Department of Health from 1996 to 2001 (TDH 2002).

2.4. Study county (figure 1)

Karnes County constituted the study county where the residing population had the potential for exposure to uranium ore and its decay products from the surface and *in situ* mining and milling activities, including transportation and any possible exposures from tailings ponds.

2.5. Control counties

Four comparison counties were selected (table 1). Control counties were matched to Karnes County by the following characteristics: percentages of persons in the population that were white, Hispanic, urban, rural, employed in manufacturing, below the poverty level, over age 64, and high school graduates, and mean family income and population size. Data were obtained from the 1990 census (USDC 1992). Data on diet, smoking and other potential cancer risk factors are not readily available at the county level, but choosing control counties from the same region as the study counties, i.e., South Central Texas, helps minimise differences in these and other factors.

Table 1. Selected characteristics of residents in Karnes County and in four control counties in South Central Texas.

County	Total population 1990	Percentages (%)									Median household income ($10 000)
		Male	White	Black	Hispanic	Rural	>64 y	Below poverty	High school graduate	Employed	
Study county											
Karnes	12 455	48	97	3	47	46	16	36	51	50	16.2
Control counties											
DeWitt	18 840	47	89	11	24	53	19	25	55	49	18.0
Frio	13 472	49	98	1	72	29	10	38	50	53	14.1
Goliad	5 980	48	93	7	36	100	16	18	63	53	21.4
La Salle	5 254	50	99	0	75	29	14	37	45	51	15.6
All control											
	43 546	48	93	6	47	49	15	29	56	51	18.5

2.6. Statistical analyses

Counts of deaths by cause, sex, race and five year age group were obtained for each of the five selected counties for each year from 1950 to 2001. Estimated annual county populations by sex, race and age group were obtained by interpolation in census counts for 1950–69 and for later years decennial censuses prepared by the Bureau of the Census (NCI 1999, Jablon *et al* 1990). Population data for counties in Texas were also available from the Texas Department of Health (TDH 2002). For each type of cancer and each county the 'expected' number of deaths, based on concurrent US experience, was calculated for the 52 year study period (NCI 1999, Marsh *et al* 1998). The expected numbers were obtained by multiplying annual US cancer death rates by the estimated populations, stratified by five year age group and sex. Counts were then summed for Karnes County and for all four of the corresponding control counties. Counts of observed and expected deaths were then summed over the following time periods: 1950–64 (before and just after the uranium operations began), 1965–79, 1980–89 and 1990–2001, thus producing numbers of deaths observed and expected generally *before, during* and *after* uranium activities began. This approach is the same as what was done previously in the United States by the National Cancer Institute (NCI) using similar databases and statistical programs (Jablon *et al* 1990, NCI 1999). Comparisons with Texas cancer death rates were also made but are not presented because computed RRs, described below, did not differ appreciably from those based on US general population rates.

The ratio of the actual number of deaths observed to the number expected at US rates is the standardised mortality ratio (SMR). Ratios of the SMRs for the study and control counties were called RRs. The difference between each RR and 1.00 was assessed by calculation of the probability that a difference of the observed magnitude, or larger, might have arisen by chance (Breslow and Day 1987, Jablon *et al* 1990, Mantel and Ederer 1985). A 95% confidence interval that contains 1.00 indicates that chance is a likely explanation for any observed differences in cancer mortality rates between Karnes County and the control counties.

Strata containing three or fewer cancer deaths are not presented but are listed as LT4 to denote 'less than four'. This is to abide by the confidentiality requirements for using the NCI and National Center for Health Statistics database. The concern is the possibility that individuals with certain characteristics might be identified if the number of deaths were small.

Table 2. The number of cancer deaths occurring in Karnes County and in the four control counties in South Central Texas, 1950–2001. 'LT4' denotes 'less than 4'.

	Number of deaths	
Cancer (ICD-9)	Karnes County	Control counties
Oesophagus (150)	20	58
Stomach (151)	72	207
Colon/rectum (153, 154)	168	456
Pancreas (157)	69	217
Lung (162)	224	653
Melanoma/skin (172)	21	58
Female breast (174)	79	246
Cervix uteri (180)	18	72
Corpus uteri (182)	5	27
Ovary (183)	28	97
Prostate (185)	76	257
Urinary bladder (188)	17	87
Kidney/renal pelvis (189)	19	105
Liver (155)	27	109
Bone (170)	11	23
Connective tissue (171)	LT4	15
Brain and CNS (191, 192)	24	78
Thyroid (193)	LT4	20
Non-Hodgkin's lymphoma (200, 202)	38	121
Hodgkin's disease (201)	12	22
Multiple myeloma (203)	22	52
Leukemia (204–8)	59	161
All cancers (140–208)	1223	3857

3. Results

In 1990, the total number of residents within Karnes County and the four control counties were 12 455 and 43 546, respectively. During the 52 years of study, 1950–2001, nearly 650 000 person-years of observation were accrued by people living in Karnes County and just over 2260 000 person-years among people living in the control counties. The control counties were similar to the study counties with regard to demographic indicators of cancer risk such as age, race and various measures of socioeconomic status (table 1). Over 90% of the population studied were listed on the census as white, including 47% Hispanic, just over 15% were older than 64 years and over 51% had graduated from high school. The median household income in 1990, about $16 200 per year, for the study population was somewhat lower than that for the control population. Both study and control counties were about 50% rural.

Table 2 shows the number of cancer deaths occurring in Karnes County and the control counties over the years 1950–2001. There were 1223 cancer deaths within Karnes County (1392 expected; SMR = 0.88) and 3857 cancer deaths within the four control counties (4389 expected; SMR = 0.88). The RR for total cancer mortality in Karnes County compared to the control counties was 1.00 (95% CI 0.9–1.1). The most frequent cancer deaths were of the lung, colon and rectum, female breast, prostate and stomach. There were 224 lung cancer deaths, 11 bone cancer deaths, 19 kidney cancer deaths, 27 liver cancer deaths, 59 leukemia deaths and 79 deaths due to female breast cancer in Karnes County.

Table 3 shows the SMRs for all types of cancer combined for the time periods 1950–64, 1965–79, 1980–89 and 1990–2001. The SMRs comparing study and control counties

Table 3. Mortality due to all types of cancer, all ages and sexes combined over four time periods, 1950–2001, in Karnes County and in the four control counties. ('Obs' stands for 'Observed'.)

	Calendar years of death									
	1950–64		1965–79		1980–89		1990–2001		All	
	Obs	SMR[a]	Obs	SMR[a]	Obs	SMR[a]	Obs	SMR[a]	Obs	SMR[a]
Karnes County	267	0.9[c]	331	0.9[c]	279	0.9	346	0.9[c]	1223	0.88[c]
Control counties	799	0.8[c]	1102	0.9[c]	818	0.8[c]	1138	0.9[c]	3857	0.88[c]
RR[b]	1.0		0.9		1.1		1.0		1.0	

[a] SMR is the observed number of cancers divided by that expected based on rates within the general population of the United States.
[b] Estimated RR taken as the ratio of the SMR in Karnes County with that in the four control counties.
[c] $p < 0.05$.

with the general population of the United States were slightly below 1.00 for each of the four time periods. The RRs contrasting total cancer mortality in Karnes County with that in control counties before and after uranium operations began were similar and varied between 0.9 and 1.1.

Table 4 concerns specific causes of death for both children and adults and shows very little difference in cancer mortality rate between study and control counties over the four time periods. There were three statistically significant RRs. Colon and rectal cancer was increased significantly overall (RR 1.17) which was due to a significant elevation (RR 1.6) in 1950–64 and prior to the major onset of uranium operations. Cancer of the kidney was significantly low (RR 0.58). Lung cancer (RR 1.08), leukemia (RR 1.15), bone cancer (RR 1.35), female breast cancer (RR 1.01), liver cancer (RR 0.81) and non-Hodgkin's lymphoma (RR 1.04) occurrences were close to expectation and were not statistically distinguishable from no risk (RR 1.0). Of the 23 RRs presented in table 4 for 1950–2001, nine were slightly above 1.0, ten were slightly below 1.0 and four were essentially equal to 1.0—a distribution consistent with the random variations commonly seen in population statistics. There was no suggested pattern for increasing risks over time for any specific cancer.

For childhood cancer mortality, including leukemia, the RR comparing Karnes County with the control counties was 1.2 ($n = 7$) before most uranium operations began (1950–64) and 1.3 ($n = 8$) after the onset of the mining and milling activities (1965–2001) (data not shown). Overall in Karnes County, there were 6 deaths due to leukemia in children versus 5.1 expected based on general population rates. Based on a total of 59 leukemia deaths, there were no significant elevations in any time interval or overall (RR 1.15; 95% CI 0.9–1.1). Only 2 deaths from thyroid cancer were observed versus 2.7 expected.

4. Discussion

Compared to similar counties in South Central Texas, no increase in cancer mortality was found in Karnes County where there was potential for radiation exposures from uranium mining and milling activities, including potential exposures from transportation of ore and from tailings ponds. No significant excess deaths were found for cancers of the lung, bone, liver or kidney, or non-Hodgkin's lymphoma, i.e., in those tissues where deposition of uranium might have been anticipated had there been intake (ICRP 1995a, 1995b). Any intake of radium would have lodged primarily in bone and radon decay products would have deposited primarily in lung.

Table 4. RR of mortality due to selected cancers in Karnes County versus the four control counties for four time periods during 1950–2001. ('Obs' denotes the observed cancer deaths within Karnes County, 'LT4' denotes that the observed number of deaths is less than 4 and 'RR' denotes the estimated relative risk taken as the ratio of the SMR in Karnes County to that in the four control counties.)

	Calendar year of death											
	1950–64		1965–79		1980–89		1990–2001		Total 1950–2001			
Cancer (ICD-9)	Obs	RR	Obs	RR	Obs	RR	Obs	RR	Obs	RR	95% CI	
Oesophagus (150)	5	1.4	4	0.7	LT4	1.1	9	1.1	20	1.06	(0.6–1.8)	
Stomach (151)	29	1.3	19	1.0	11	0.9	13	1.0	72	1.08	(0.8–1.4)	
Colon/rectum (153, 154)	45	1.6[a]	40	0.9	35	1.1	48	1.2	168	1.17[a]	(1.0–1.4)	
Pancreas (157)	14	1.0	22	1.1	20	1.3	13	0.7	69	1.01	(0.8–1.3)	
Lung (162)	0	0.0	59	1.0	73	1.2	92	1.0	224	1.08	(0.9–1.3)	
Melanoma/skin (172)	5	2.0	9	1.7	LT4	0.8	4	0.7	21	1.23	(0.7–2.0)	
Female breast (174)	21	1.3	21	0.9	14	0.9	23	1.0	79	1.01	(0.8–1.3)	
Cervix uteri (180)	9	1.1	4	0.5	LT4	0.8	LT4	0.6	18	0.76	(0.5–1.3)	
Corpus uteri (182)	0	0.0	0	0.0	4	1.8	LT4	0.3	5	0.72	(0.3-1.9)	
Ovary (183)	LT4	0.3	13	1.7	4	0.7	8	1.0	28	0.90	(0.6–1.4)	
Prostate (185)	15	0.9	15	0.7	16	1.0	30	1.2	76	0.95	(0.7–1.2)	
Urinary bladder (188)	5	0.7	4	0.5	4	1.1	4	0.6	17	0.64	(0.4–1.1)	
Kidney/renal pelvis (189)	LT4	0.4	6	0.6	5	0.9	5	0.5	19	0.58[a]	(0.4–1.0)	
Liver (155)	0	0.0	11	1.0	6	0.8	10	0.7	27	0.81	(0.5–1.2)	
Bone (170)	5	2.2	LT4	0.3	LT4	—	LT4	0.9	11	1.35	(0.7–2.8)	
Connective tissue (171)	LT4	0.7	0	0.0	0	0.0	LT4	1.2	LT4	0.44	(0.1–1.5)	
Brain and CNS (191, 192)	5	0.8	5	0.6	8	1.8	6	0.9	24	0.92	(0.6–1.4)	
Thyroid (193)	0	0.0	LT4	0.4	0	0.0	LT4	0.8	LT4	0.31	(0.1–1.3)	
Non-Hodgkin's lymphoma (200, 202)	LT4	0.7	13	0.9	8	1.2	14	1.1	38	1.00	(0.7–1.4)	
Hodgkin's disease (201)	4	1.8	5	1.5	LT4	—	0	0.0	12	1.79	(0.9–3.6)	
Multiple myeloma (203)	LT4	0.7	4	1.0	6	1.1	11	2.0	22	1.37	(0.8–2.3)	
Leukemia (204–208)	9	0.7	20	1.3	17	1.7	13	1.0	59	1.15	(0.9–1.6)	
All cancers (140–208)	267	1.0	331	0.9	279	1.1	346	1.0	1223	1.00	(0.9–1.1)	

[a] $p < 0.05$.

Knowledge about radiation carcinogenesis has accumulated during the past 50 years and is helpful in interpreting the study findings (UNSCEAR 1994, 2000, IARC 2000, 2001). Although radiation-induced leukemia may occur as soon as two years after exposure, other cancers such as those of the lung and breast develop more slowly and are unlikely to be identified in mortality data for ten years or more after radiation exposures. Because mortality data were available for over 40 years after the uranium mining activities began in 1959, residents of the surrounding area could be evaluated for a long enough period of time to accumulate sufficient exposure to detect any increase in mortality due to cancer if one were present. Comparing Karnes County with the four nearby control counties, the RR for all cancer mortality ranged from 0.9 to 1.1 over the 52 years of study. The fact that significant differences were not found in our survey for the periods *before, during* or *after* the uranium mining and milling activities

began provides evidence that the mining and milling operations have not adversely affected the occurrence of cancer among County residents. Our survey is thus consistent with other studies of persons living near uranium processing facilities in the US (Jablon *et al* 1990, Boice *et al* 2003a, 2003b), and also with studies of workers heavily exposed to uranium during processing activities (CRS 2001) where no increased cancer risks were observed.

Because many workers involved in uranium mining and milling activities lived in Karnes County, their inclusion within the study population probably enhances our power to detect a radiation association given that worker exposures would be expected to be much greater than residential exposures. Studies of over 120 000 workers at uranium milling, fabrication and processing facilities, however, have not found any consistent links between uranium exposures and increases in any cancer or leukemia (McGeoghegan and Binks 2000a, 2000b, CRS 2001, IOM 2001, IARC 2001). Specifically, no increases in cancers of the lung, liver or bone or lymphoma were observed among these uranium workers, i.e., in those tissues where the probable distribution of uranium was highest (ICRP 1995a, 1995b, IARC 2001). Uranium, similar to radium or plutonium, would deposit primarily in bone and not bone marrow, minimising the likelihood of a leukemogenic exposure to the uncommitted stem cells that reside more centrally in the marrow (Priest 1989, 2001). Thus the absence of a leukemia risk is not surprising. A recent geographical correlation study in Finland also found no evidence for increased leukemia rates among communities with high levels of uranium in their water supplies (Auvinen *et al* 2002). Radon and its decay products have caused lung cancer among underground miners (Lubin *et al* 1995, NRC 1999) but no other cancer or leukemia has been found elevated among the over 64 000 heavily exposed miners studied (Darby *et al* 1995). Substantial intake of radium has caused excess bone cancers among dial painters, but no risk was seen at low to moderately high doses (<10 Gy skeletal dose) and no other cancers were associated with radium intake except a rare carcinoma of the sinuses attributable to the build-up of radon from the radium decay (Rowland *et al* 1978, Polednak *et al* 1978, Fry 1998, Priest 2001).

Reports of small clusters of childhood leukemia around nuclear installations in the United Kingdom in the 1980s prompted several large scale systematic surveys around the world (UNSCEAR 1994). Subsequent surveys in other counties failed to confirm a link between childhood leukemia or any other cancer and proximity to nuclear installations (Doll *et al* 1994, Doll 1999). Several geographical correlation studies around nuclear installations in Spain have been published recently suggesting an increase in cancer mortality in areas containing uranium processing facilities, including one that also contained a nuclear waste storage facility, but not in areas with nuclear power plants (López-Abente *et al* 1999, 2001). However, the cancer mortality rates in the towns near the uranium operations were below expectation based on general population rates (SMR 0.88) and it was the even lower rates among the more distant towns (50–100 km) used as control that produced the apparent elevation. The areas with uranium facilities, then, did not experience elevated cancer rates but rather the control areas experienced unusually low cancer rates. This suggests that the residents of the control areas may not have been similar to the residents of towns near uranium processing facilities and such non-comparability tempers interpretation (Laurier *et al* 2002). Further, cancer risks overall and for lung cancer and kidney cancer in particular were lower in the towns nearest (<15 km) to the uranium facilities than in the towns located further away (15–30 km), which is just the opposite to what would be expected if radiation were a contributing factor. In addition, the elevated mortality rates were gender specific in that lung cancer increases were seen only in males and not females, whereas kidney cancer increases were seen only in females and not males. Such differences are also not consistent with a possible effect of environmental exposures, because any exposures common to both sexes would be expected to affect both males and

females and not just one or the other. Similarly, a slight increase in leukemia reported in the Spanish study (López-Abente *et al* 1999) is not in accord with what is known about the distribution of uranium in the body after intake, i.e., exposure to the leukemia-producing cells is minuscule (Bender *et al* 1988, Priest 1989). Further a radiation link between leukemia and living near nuclear installations has been discounted after extensive epidemiologic study (UNSCEAR 1994, Laurier *et al* 2002). Finally, uranium processing facilities in the US have not been correlated with increased cancer mortality (Jablon *et al* 1990, Boice *et al* 2003a) or cancer incidence in nearby populations (Boice *et al* 2003b). Thus the exploratory correlation studies in Spain must be interpreted with caution, since the mortality excesses and deficits may be attributable to bias if control area residents were not comparable to study area residents in terms of cancer risk factors or, as mentioned by the authors, to chance when so many hundreds of comparisons are made (11 different cancers, 8 installations and 3 distances).

A cross-sectional cytogenetic analysis has also been conducted among a small number of Karnes County residents to investigate whether living near uranium mining and milling activities might be associated with chromosome aberrations in circulating lymphocytes and also with abnormal DNA repair processes (Au *et al* 1995). Bloods were analysed for 24 persons, primarily women, potentially exposed to uranium and other radionuclides and for 24 persons presumably non-exposed. The participation rate was very low, about 30% of those initially selected, and only 6 of the 48 participants were males, indicating the possibility of selection bias. Although the frequency of all types of chromosome aberration combined was slightly increased among those presumably exposed to radiation, the difference was not statistically significant. Further, dicentrics, a type of unstable chromosome aberration found to be increased in populations continuously exposed to environmental radioactivity (Wang *et al* 1990, Upton 1990), was actually higher among the presumed non-exposed and this difference approached statistical significance ($p = 0.06$). Thus there was no evidence that radiation exposure from uranium mining and milling operations resulted in increased levels of chromosome breakage among residents of Karnes County.

An abnormal DNA repair response was also reported among the exposed subjects based on a 'challenge assay' developed by the authors who concluded that prior radiation exposure caused these DNA repair problems (Au *et al* 1995). In addition to the substantial uncertainties associated with small numbers, poor participation rates and the potential for selection bias, the study has other serious deficiencies. First, there was no attempt to estimate radiation exposure to any group, so it is uncertain whether the exposed group actually received more exposure than the non-exposed. Second, the assay, which apparently has not been validated by other laboratories, appears to have been misapplied. The potential exposure is from uranium, an alpha particle emitting radionuclide that deposits energy mainly in the lung and bone. Because alpha particles have little penetrating power, circulating lymphocytes would be expected to demonstrate little if any damage since the stem cells within the bone marrow would not be reached (Bender *et al* 1988, Priest 1989, Lloyd *et al* 2001). Third, the results are not internally consistent. It is not logical that chromosomal aberrations would not be increased in a radiation-exposed group characterised by an abnormal DNA repair processes (somehow associated with this same radiation). For example, in patients with severely defective DNA repair mechanisms, such as ataxia telangiectasia, exposure to radiation results in substantial elevations in chromosome aberrations (IARC 2000). Fourth, cytogenetic studies are substantially limited in their ability to detect any effect from low protracted environmental exposures. In addition, several experimental cellular studies have found that low dose radiation can enhance the repair capabilities of cellular DNA subsequently exposed to higher doses (adaptive response) (UNSCEAR 1994); and not damage them as postulated by (Au *et al* 1995). Finally the authors' claim that their assay results indicate that residents have increased health risks from uranium

exposures (Au *et al* 1998) is speculative and unproven. Chromosome aberrations, including dicentrics, have been reported to be increased in areas of high natural background radiation due to thorium contaminated soil (similar to the postulated exposure conditions associated with the uranium mining and milling activities), yet no health effects have been identified in large populations residing their entire lives in such areas in China (Wang *et al* 1990, Wei *et al* 1997, Boice 2002). Thus radiation-associated damage in circulating lymphocytes is considered a marker of prior exposure but has not been linked to increased health risks (Upton 1990). The Au *et al* (1995) cytogenetics study thus provides no evidence for either increased radiation exposure or adverse health effects among residents of Karnes County.

4.1. Strengths and limitations

This community study covered a long time frame, over 50 years, which enabled detailed analyses of several specific cancers. For Karnes County, comparisons of cancer rates before and after uranium mining and milling activities began could be made. Further comparisons with similar control counties in South Central Texas and with the entire United States were possible. The numbers of total cancer deaths between 1950 and 2001, over 1200, was such that any differences between Karnes County and the control counties could be identified, if they were present. The methodology used was the same as that employed by the National Cancer Institute in a similar, but larger scale investigation of mortality in counties throughout the United States with nuclear facilities: electrical utilities, uranium processing plants and weapons production laboratories (Jablon *et al* 1990, 1991). Like us, the National Cancer Institute concluded that increased cancer risks were not associated with living in counties with nuclear facilities and associated radiation activities.

The cancer data reported herein resulted from routinely collected mortality statistics, but were not from an experimental study where individuals would be randomly assigned exposures and followed forward in time. Information on uranium or other radionuclide exposures, if any, was not known for individuals countywide. Although counties were matched using available data concerning racial composition, urban–rural mix, income and other factors, it is not possible to choose control counties that are exactly comparable with the study county. Counties, for example, can vary with respect to industries, occupations, and lifestyle. Cancer deaths in each county were also compared with the numbers expected on the basis of concurrent US and Texas mortality rates. However, the similarity in cancer rates between Karnes County and the proximal control counties and the Texas and US population for practically all cancers suggest very little incompatibility. The absence of any significant trends in cancer risk over time indirectly addresses the possibility of differences arising solely from inadequate comparison populations.

This study relied mainly on mortality data. Although the accuracy of the cause of death information on death certificates is variable, this inaccuracy is less for cancer than other causes even during the early years of this study (Percy *et al* 1981). Further, the quality of death certificate information would be expected to be similar for Karnes County and the neighbouring counties which comprised the comparison population. Mortality data, however, are not optimal for monitoring such cancers as those of the thyroid or childhood leukemia, for which improved therapy has markedly lowered death rates in recent years while not affecting incidence. The numbers of deaths due to thyroid cancer ($n = 2$) and childhood leukemia ($n = 6$) did not differ from expectation but were too small to be informative in the current study other than to indicate a low mortality risk for these cancers. On the other hand, mortality and incidence rates are highly correlated and mortality nearly equals incidence for many cancers which have high fatality rates, such as cancers of the lung, stomach, bone, connective tissue and liver and

adult leukemia. Further, the mortality data are consistent with the available incidence data from 1976 to 1980 in finding no significant increases for these or any other cancers in Karnes County (Brender 1987). These findings are also consistent with a study of cancer incidence in small geographical areas around two uranium processing facilities in the US which also found no increased cancer rates (Boice *et al* 2003a, 2003b).

Mortality rates have changed over time for a number of reasons including improvements in treatment and changes in lifestyle. For example, mortality rates for childhood leukemia have decreased in the entire United States during the study time period, whereas mortality rates for lung cancer have increased (Jemal *et al* 2003). Our study compares mortality rates in Karnes County with those in nearby control counties by calendar year to account for such changes over time to the extent possible. The increases in lung cancer rates in Karnes County, for example, were similar to the increases seen in the control counties and throughout the nation. The absence of lung cancer deaths in the 1950s reflects both the low death rate during these years and the small numbers at risk of dying.

Data were available only for counties and some residents may have lived at some distance from the uranium mining and milling operations. Local effects might be difficult to detect using county death rates because of any dilution resulting from the inclusion of the populations living far from the uranium mining and milling activities. However, over the years there were over 40 uranium mines, mills and tailings piles and ponds in Karnes County (figure 1) and it also has been suggested that the transport of ore on various county roads might have resulted in some population exposure. Thus, the potential for population exposure was greater than in counties with only one operating facility. Further, the county residents also included workers who probably received higher exposures than were possible from environmental circumstances and their inclusion would probably have increased the chance of finding an effect had there been one.

This was an 'ecological' survey in which the exposures, if any, of individuals are not known. Persons who lived in particular counties at the time of death may not have been long term residents. Some residents will have moved elsewhere and died in another part of the country. Although there have been population changes within Karnes County over the years, e.g., with young people going to college and seeking employment elsewhere or with some workers leaving the area when the mining and milling activities ceased, there has been some relative stability as suggested by the population census. In 1960, for example, the population was 14 995 in contrast to 12 455 in 1990 and 15 446 in 2000 (Website, US Census Bureau).

Despite the limitations inherent in an ecological study of cancer mortality in the counties with and without uranium operations, the methods used have been applied effectively in the past to identify environmental carcinogens when exposures were high and long term. For example, on the basis of findings from the 'cancer maps' constructed from county mortality statistics by the National Cancer Institute (Devesa *et al* 1999a, 1999b), counties with shipyard industries were found to have elevated lung cancer death rates, particularly among men. Subsequent case-control studies in the high risk areas linked the excess lung cancer deaths to occupational exposures to asbestos (Blot *et al* 1978). It might be noted that the NCI cancer maps, similar to our community study, do not indicate that cancer mortality in Karnes County is higher than in the rest of the US or that changes in cancer rates over time differ from those of the rest of the US (Devesa *et al* 1999b).

5. Conclusions

The cancers that might possibly be increased following high exposures to uranium and its decay products, i.e., cancers of the lung, bone, kidney and liver, were not elevated, nor was leukemia, a sensitive indicator of excessive exposure to external gamma radiation. This survey

then provides no evidence that the mining and milling activities increased the rate of any cancer in Karnes County. The ecological nature of the study design, however, tempers the strength of these conclusions.

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Résumé

De l'uranium fut découvert en 1954 dans le comté de Karnes, Texas. Le premier broyeur d'uranium commença à fonctionner en 1961, près de Falls City. Le broyage de l'uranium, son extraction en surface et *in situ* continuèrent, dans ce comté, jusqu'au premières années 90. Dans les années 90, on élimina les dépôts de résidus de broyage. Il existait trois usines de broyage et plus de 40 mines, fonctionnant dans le comté de Karnes, durant ces années; l'irradiation potentielle de la population venait de rejets possibles dans l'environnement, air et eaux souterraines. De temps à autre, il naissait, dans le comté de Karnes, le souci d'une augmentation potentielle du risque de cancers, venant de ces activités d'extraction et de broyage d'uranium. On a établi le relevé de la mortalité pour évaluer la possibilité d'une augmentation des décès par cancer, associée aux opérations sur l'uranium. On a déterminé le nombre et le taux de décès par cancer, pour le comté de Karnes, et on les a comparés aux valeurs pour quatre comtés 'de contrôle' de la même région, présentant des âges, des races, une urbanisation et des distributions socio-économiques semblables, données dans l' US Census de 1990. On fit aussi des comparaisons avec les taux pour la population générale des Etats Unis et du Texas. Par des méthodes semblables à celles employées par l'Institut national du cancer, on a calculé les rapports normalisés de mortalité (SMR); il s'agit du rapport du nombre de cancers dans les comtés, étudié ou de contrôle, au nombre attendu, déduit du taux pour la population globale des Etats Unis. Les risques relatifs (RR) calculés, sont les rapports des SMR pour le comté étudié à celui pour les comtés de contrôle. Au total, il y a eu 1223 décès par cancer dans la population résidant dans le comté de Karnes, entre 1950 et 2001; le nombre attendu en partant de la population générale des Etats Unis était de 1392. Il y eut 3857 décès par cancers dans les quatre comtés de contrôle durant la même période de 52 ans, à comparer aux 4389 attendus. Il n'y a pas de différence entre les taux totaux de mortalité par cancer, dans le comté de Karnes et ceux dans les comtés de contrôle (RR = 1,0; probabilité de 95% pour l'intervalle 0,9–1,1). Quand on a comparé à la population des Etats Unis, à celle du Texas, à celle des comtés de contrôle, on n'a observé aucune augmentation significative dans le comté de Karnes. En particulier, les décès dus à des cancers du poumon, des os, du foie et du rein n'étaient pas plus fréquents dans le comté de Karnes que dans les comtés témoins. Ce sont les cancers à prendre en compte, *à priori*, compte tenu que l'on peut penser que l'uranium se concentre plus dans ces tissus que dans les autres; De plus, toute absorption de radium se déposerait principalement dans les os, et son descendant, le radon, principalement dans les poumons. Les décès venant de l'ensemble de tous les cancers n'avaient pas augmenté dans le comté de Karnes; les RR de mortalité par cancer dans le comté de Karnes *avant* et dans les premières années des opérations (1950–64), peu de temps après que ne commencent les activités sur l'uranium (1965–79) et dans les deux dernières périodes de temps (1980–95, 1990–2001) étaient semblables; 1,0, 0,9, 1,1, 1,0, respectivement. On n'a vu aucun schéma inhabituel de mortalité par cancer dans le

comté de Karnes, sur une période de 50 ans; cela suggère que les opérations d'extraction et de broyage d'uranium n'ont pas augmenté les taux de cancers chez les résidents.

Zusammenfassung

Uran wurde in Karnes County, Texas im Jahre 1954 entdeckt und das erste Uranwerk nahm 1961 in der Nähe von Falls City den Betrieb auf. Uranverarbeitung sowie Tagebau und *in situ* Bergbau wurden in Karnes County bis in die frühen 1990iger fortgesetzt. Die Beseitigung der Uranabfälle in Teichen wurde in den 1990igern abgeschlossen. In diesen Jahren waren drei Werke und mehr als 40 Zechen in Karnes County in Betrieb und die potenzielle Bestrahlung der Bevölkerung wurde durch mögliche Freisetzungen umweltschädlicher Stoffe in die Luft und das Grundwasser verursacht. Von Zeit zu Zeit wurden in Karnes County Bedenken über ein mögliches erhöhtes Krebsrisiko aufgrund dieser Uranabbau- und Verarbeitungsaktivitäten zum Ausdruck gebracht. Zur Bewertung der Möglichkeit einer erhöhten Zahl von Krebstoten aufgrund dieser Uranverarbeitung wurde eine Sterblichkeitsstudie durchgeführt. Die Anzahl der Krebstode wurde für Karnes County ermittelt und im US-Census 1990 verglichen mit vier 'Kontroll'-Counties in derselben Region mit Personen ähnlichen Alters, Rasse, Urbanisierung und soziökonomischen Verteilungen. Weitere Vergleiche wurden angestellt mit allgemeinen Bevölkerungsraten in den USA und Texas. Unter Verwendung ähnlicher Methoden, wie sie vom National Cancer Institute eingesetzt werden, wurden standardisierte Sterblichkeitsverhältnisse (SMRs) berechnet, d.h. die beobachteten Zahlen von Krebsfällen im Studien-und in den Kontroll-Counties wurden mit der Anzahl der zu erwartenden Anzahl verglichen, die aus den allgemeinen Bevölkerungsraten in den USA abgeleitet wurden. Die relativen Risiken (RR) wurden berechnet als Verhältnisse der SMRs für die Studien- und Kontroll-Counties. Insgesamt gab es zwischen 1950 und 2001 1223 Krebstote in der Bevölkerung in Karnes County, verglichen mit 1392, die auf der Grundlage der allgemeinen Bevölkerungsraten in den USA erwartetet worden waren. In den vier Kontroll-Counties gab es im selben Zeitraum über 52 Jahre 3857 Krebstote, verglichen mit 4389 erwarteten. Es gab keinen Unterschied zwischen den gesamten Krebssterblichkeitsraten in Karnes County und denen in den Kontroll-Counties (RR = 1,0; 95% Konfidenzintervall 0,9–1,1). Es gab keine signifikante Zunahme in Karnes County für irgendeine Krebsart, als Vergleiche entweder mit der US-Bevölkerung, dem Staat Texas oder den Kontroll-Counties angestellt wurden. Insbesondere waren Todesfälle aufgrund von Lungen-, Knochen-, Leber- und Nierenkrebs in Karnes County nicht häufiger als in den Kontroll-Counties. Diese Krebsarten sind deshalb von besonderem Interesse, weil sich Uran in diesen Geweben stärker konzentriert als in anderen. Außerdem würde sich jede Radiumaufnahme primär im Knochen ablagern und Radon-Folgeprodukte primär in der Lunge. Die Zahl der Toten aus allen Krebsarten kombiniert lag in Karnes County ebenfalls nicht höher. Die RRs der Krebssterblichkeit in Karnes County *vor* und in den ersten Jahren des Betriebs (1950–64), kurz nach Beginn der Uranaktivitäten (1965–79) und in den beiden Zeiträumen (1980–89, 1990–2001) waren ähnlich: 1,0, 0,9, 1,1 bzw. 1,0. Keine ungewöhnlichen Muster der Krebssterblichkeit wurden in Karnes County über einen Zeitraum von 50 Jahren beobachtet; dies deutet darauf hin, dass Uranabbau und—verarbeitung nicht zu einer Zunahme der Krebsraten unter den Bewohnern führte.

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Appendix 4

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A cohort study of uranium millers and miners of Grants, New Mexico, 1979–2005

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Abstract

A cohort mortality study of workers engaged in uranium milling and mining activities near Grants, New Mexico, during the period from 1955 to 1990 was conducted. Vital status was determined through 2005 and standardised mortality ratio (SMR) analyses were conducted for 2745 men and women alive after 1978 who were employed for at least six months. Overall, mortality from all causes (SMR 1.15; 95% CI 1.07–1.23; $n = 818$) and all cancers (SMR 1.22; 95% CI 1.07–1.38; $n = 246$) was greater than expected on the basis of US mortality rates. Increased mortality, however, was seen only among the 1735 underground uranium miners and was due to malignant (SMR 2.17; 95% CI 1.75–2.65; $n = 95$) and non-malignant (SMR 1.64; 95% CI 1.23–2.13; $n = 55$) respiratory diseases, cirrhosis of the liver (SMR 1.79; $n = 18$) and external causes (SMR 1.65; $n = 58$). The lung cancer excess likely is attributable to the historically high levels of radon in uranium mines of the Colorado Plateau, combined with the heavy use of tobacco products. No statistically significant elevation in any cause of death was seen among the 904 non-miners employed at the Grants uranium mill. Among 718 mill workers with the greatest potential for exposure to uranium ore, no statistically significant increase in any cause of death of *a priori* interest was seen, i.e., cancers of the lung, kidney, liver, or bone, lymphoma, non-malignant respiratory disease, renal disease or liver disease. Although the population studied was relatively small, the follow-up was long (up to 50 yrs) and complete. In contrast to miners exposed to radon and radon decay products, for uranium mill workers exposed to uranium dusts and mill products there was no clear evidence of uranium-related disease.

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Abbreviations

CI	Confidence interval
ICD-9	Ninth revision of the international classification of diseases
NDI	National death index
NIOSH	National Institute of Occupational Health and Safety
SMR	Standardised mortality ratio
SSA	Social security administration

1. Introduction

Underground uranium miners exposed to high levels of radon and radon decay products are at increased risk of lung cancer but apparently no other cancer (Wagoner *et al* 1965, Lundin *et al* 1971, Whittemore and McMillan 1983, Hornung and Meinhardt 1987, Samet *et al* 1991, Lubin *et al* 1995, Darby *et al* 1996, NRC 1999). Several non-cancer causes of death (i.e., tuberculosis, non-malignant respiratory disease and accidents), however, were increased among early miners in the United States (Archer *et al* 1976, Roscoe 1997).

Uranium mill workers, however, have not been consistently found to be at increased risk for cancer. The National Institute for Occupational Health and Safety (NIOSH) conducted a study of 1484 men who worked at one of seven uranium mills on or after January 1, 1940 and reported a statistically significant increase in non-malignant respiratory disease mortality (SMR 1.43; $n = 100$) and non-statistically significant increases in mortality from lung cancer, lymphoma, and kidney disease (Pinkerton *et al* 2004). The authors were cautious in interpreting their findings, however, because increased length of employment (and assumed increased exposure to uranium compounds) was not associated with increased mortality from any of these conditions. A recent study of 450 uranium mill workers at Uravan, Colorado followed through 2004 revealed no statistically significant excess deaths from any cause, including non-malignant respiratory disease (SMR 0.99; $n = 24$) and lung cancer (SMR 1.26; $n = 24$) (Boice *et al* 2007b). Some of the uranium millers in the Uravan study were also included in the NIOSH study.

Although there have been many studies of underground uranium miners, few studies have been conducted of uranium millers. Exposures among these two groups differ appreciably, with underground miners being exposed primarily to radon and radon decay products, and millers being exposed primarily to uranium ore dust and mill products but not radon. Other than the recent study of Uravan uranium workers, there have been few studies of a workforce that includes both miners and millers. We report here such a study of workers employed by a large milling and mining company in Grants, New Mexico.

1.1. Exposure potential

The Grants, New Mexico uranium belt is an area of 100 by 25 miles in Cibola, McKinley and Sandoval Counties. In the 1950s and 1960s, 60 mines and five mills were in operation and New Mexico led the nation in uranium production (Samet *et al* 1983). The chief mining districts were Laguna, Ambrosia Lake and Church Rock.

The heyday of New Mexico mining and milling activities began in the mid to late 1950s and after the hazards of underground mining had been recognised in studies by the US Public Health Service (Lundin *et al* 1971). As such, state and federal regulations limited radon progeny exposures and New Mexico miners experienced generally lower cumulative exposures than for

other miners of the Colorado plateau (Morgan and Samet 1986). Nonetheless, a statistically significant risk of lung cancer (SMR 4.0; $n = 68$) was reported among 3469 male miners from New Mexico with a mean cumulative exposure concentration of 111 WLM (Samet *et al* 1991). An increase in external causes of death (SMR 1.5; $n = 173$) was also statistically significant. The mortality data also supported an association between pneumoconiosis and exposure to silica and other dusts (Samet *et al* 1984b, 1991). Increased mortality due to lung cancer, tuberculosis and non-malignant respiratory disease has also been reported among Navajo miners from New Mexico (Wagoner *et al* 1975, Samet *et al* 1984a, Roscoe *et al* 1995)

The Grants uranium mill was located in Cibola County, New Mexico, about 5.5 miles northwest of the Village of Milan and about seven miles northeast of the Town of Grants. Uranium milling began in 1958 and continued through 1990. Radon and radon decay product exposures are relatively insignificant among mill workers due to the aboveground nature of their work. However, there is the potential for exposure to other radioactive substances such as uranium-238, uranium-234 and thorium-230, as well as exposure from uranium ore dust, vanadium pentoxide, yellowcake, ammonium diuranate, silica and slight traces of radium-226 (Waxweiler *et al* 1983).

Uranium milling involves ore crushing and grinding; ore leaching, i.e., removing and dissolving uranium; uranium recovery from leach solutions; and drying and packaging of yellowcake (uranium oxide, U_3O_8)—the final product of the milling process. Crushing and grinding of ore and yellowcake drying and packaging are dusty operations where inhalation potential is highest. The solid and liquid wastes remaining after uranium is extracted from ore are called tailings, and contain the same radionuclides found in the ore, i.e., uranium, thorium, radium and other decay products. Potential sources of environmental exposures around uranium milling operations include these tailings piles, in addition to runoff collection ponds, ore transport and airborne and liquid effluents (NCRP 1993). There are two tailings piles covering about 200 acres near the Grants uranium mill (EPA 2007).

Radium, a component of mill tailings, occurs naturally in uranium ore but generally is not extracted during the milling process. Ingestion of large amounts of radium by dial painters during the early part of the last century resulted in excesses of bone cancer and a rare carcinoma of the paranasal sinuses, but no other cancer was significantly increased (Fry 1998, IARC 2001). Radium decays into radon gas, a known cause of lung cancer, and also emits gamma radiation, which at sufficiently high levels can cause leukaemia, breast cancer and other malignancies (UNSCEAR 2000, NRC 2006). Leukaemia, however, has not been found to be significantly increased in studies of uranium processors, millers or miners (Harley *et al* 1999, IOM 2001, Pinkerton *et al* 2004, Darby *et al* 1996, NRC 1999, Boice *et al* 2007b, Canu *et al* 2008). Descriptive studies of communities living near uranium milling or processing facilities in Texas (Boice *et al* 2003a), Pennsylvania (Boice *et al* 2003b, 2003c) and Colorado (Boice *et al* 2007a) also provide little evidence for elevated rates of leukaemia or other cancers associated with penetrating external radiation.

The route of intake and the biological solubility of a given uranium compound influences the potential for chemical or radiological toxicity (ATSDR 1999, IOM 2001). Natural uranium, i.e., uranium ore, is largely soluble and passes through the body rather quickly whether inhaled or ingested (Harley *et al* 1999, Priest 2001). Yellowcake and other mill products are largely insoluble uranium oxides that, if inhaled, would accumulate in the lung and tracheobronchial lymph nodes (ATSDR 1999, Pinkerton *et al* 2004); the tracheobronchial lymph nodes, however, do not appear radiosensitive and are not considered a target for uranium toxicity (Eidson 1994). Different uranium ore processing schemes involve different uranium compounds with different dissolution rates so that workers could be exposed to mixtures of both soluble and insoluble forms of uranium (Eidson and Mewhinney 1980, Eidson 1994). Chemical toxicity, primarily

renal dysfunction, may be a consequence of high intakes of soluble uranium. Lung injury may occur after high intakes of insoluble uranium. In general, ingested uranium is poorly absorbed from the intestinal tract and retention in the body would be low (ATSDR 1999, IOM 2001).

Based on associations reported in previous studies of uranium millers and miners and knowledge of the likely distribution of uranium within body tissues after inhalation or ingestion (Leggett 1989, ATSDR 1999, IARC 2001), we focused our attention on cancers of the lung, kidney, liver and bone, lymphoma and non-malignant respiratory, non-malignant renal and non-malignant liver diseases.

2. Material and methods

A retrospective cohort mortality study was conducted of uranium miners and millers of Grants, New Mexico. Institutional Review Board approval of the research protocol was received from Independent Review Consulting, Inc. (www.irb-irc.com).

2.1. Population identification

All uranium miners and millers who worked for a large uranium mining and milling company in Grants, New Mexico were eligible for study. The study population was identified from computerised listings of 3390 company personnel (1955–1991) and from overlapping job history records for 5606 workers (1955–2001). Duplicates were removed and persons without identifying information excluded (figure 1). We also excluded persons who worked less than 6 months.

2.1.1. Demographic information. Available demographic information included name, date of birth, social security number, sex, marital status and current address.

2.1.2. Work histories. Available work history information included year of hire, year of termination, pay type (hourly, salaried) and job history (job location, department, job title). Employment at uranium mines and mills was readily determined on the basis of job location (mine or mill) and job title (e.g., miner, underground labourer, driller, shaftman, tailings pile operator, yellowcake filter and dryer operator, crusher operator). Everyone who worked underground was classified as a 'miner' regardless of job classification. A sample of 19 millers was submitted to NIOSH to learn of any additional uranium work that was not known from the existing company records. Similarly, linkages of worker rosters were made with a Colorado milling and mining study (Boice *et al* 2007b). NIOSH had conducted health studies of uranium millers (Pinkerton *et al* 2004) and Colorado plateau uranium miners (Roscoe 1997). The NIOSH records often included detailed occupational histories, questionnaires with smoking information, and pathology evaluations for many of the workers. The Grants uranium mill was not one of the seven mills included in the NIOSH study (Pinkerton *et al* 2004), but some of the Grants underground miners were likely included in previous studies of miners in New Mexico (Samet *et al* 1991).

2.1.3. Exposure to ore or uranium processing. Workers who had not worked as an underground miner were classified as to the likelihood that they worked with uranium ore or with the processing of uranium ore at the mill. The assignment of exposure potential was based on job titles (e.g., accountants and clerks were assumed to be unlikely or infrequently exposed to ore or uranium processing activities, whereas crusher operators, yellowcake filter and dryer

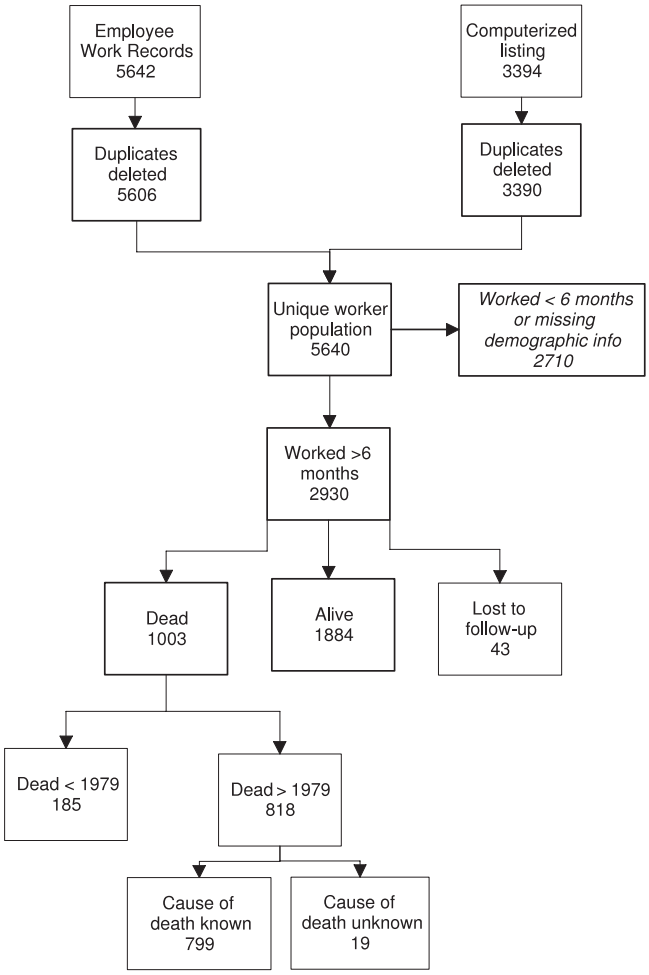

Figure 1. Identification of workers engaged in uranium milling and mining activities near Grants, New Mexico, and vital status as of December 31, 2005. Eligible subjects worked for 6 or more months with sufficient identifying information for tracing; duplicates were removed. Study subjects were assumed alive if NDI and Social Security Administration linkages failed to provide a death or vital status match ($n = 43$).

operators and tailings pond operators were assumed to have had the potential for exposure to ore and uranium dust). Interviews with employees were helpful in resolving uncertainties in specific job titles and work responsibilities. Some employees also lived in Milan and in areas close to the uranium mill.

2.1.4. Length of employment. Persons were categorised as to their length of employment as follows: <6 months (excluded); 6 months to 1.9 yrs; 2–4.9 yrs; ⩾5 yrs. Based on the sample of records submitted to NIOSH, it was learnt that some workers had also been employed at different facilities in other parts of the country. Unfortunately our records of such employment were incomplete and we were unable to incorporate subsequent work histories into the analyses.

2.2. Follow-up

Mortality and vital status were determined from various linkages of the study roster with national databases including the National death index (NDI), the Social security administration (SSA) Death Master File and other SSA files, credit bureaus and Comserv, a computer services firm specialising in locating persons. SSA files confirmed that 1750 persons were alive in 2004. Searches with credit bureau records and LexisNexis, an online information service provider (www.lexisnexis.com), confirmed that 177 of the 220 persons without an SSA or NDI match were alive sometime after 1979. The remaining 43 persons (1.5%) without a SSA or NDI mortality match were assumed to be alive. Of the 818 deaths occurring after 1978, cause of death was not obtained for 19 (2.3%) including one person who died outside the United States. Deaths prior to 1979 ($n = 185$) were excluded from the SMR analyses (figure 1, table 1) because cause of death information from the National Death Index is not available before 1979 and attempts to obtain death certificates for these early deaths were in large part unsuccessful. Of the 185 deaths occurring before 1978, death certificates were sought but not obtained for 80 (43.2%) which precluded a meaningful cause of death analysis.

2.3. Analysis

Person-years of follow-up began on January 1, 1979 or the date of first employment (plus 6 months), whichever came later (except for those first employed July 1, 1978 to December 31, 1978 for whom follow-up began 6 months after hire date). Follow-up ended on the date of death, December 31, 2005 or age 95, whichever came earlier. There were 6 persons who were withdrawn from follow-up once they reached the age of 95. Standardised mortality ratios (SMR) were computed as the ratio of the observed numbers of deaths to the number of deaths that would have been expected using the mortality rates of the general population of the United States. Observed numbers of deaths from cancers and all other diseases were categorised by sex, age and calendar year for all workers and for subgroups defined by duration of employment and work experience at a uranium mine or uranium mill. Expected numbers of deaths were computed based on age-, calendar year and sex-specific rates in the general population of the United States. SMR analyses based on mortality rates of the general population of New Mexico were also conducted using race weightings of 90% white and 10% non-white. White rates included Hispanics and non-Hispanic whites, and non-white rates included primarily Navajo and other Native Americans. There were very few black workers. SMRs and 95% confidence intervals (95% CI) were calculated using OCMAP software for 41 causes of death categories (Marsh *et al* 1998).

3. Results

Computerised company records and imaged work history records were used to identify 2930 workers (2682 men and 248 women) who worked at least 6 months between 1955 and 2004 (table 1). The average length of time between the date of first employment and the date when follow-up was completed was 36.4 years. Over 28% of the workers had been employed for 5 or more years, and 38% of the workers were followed for more than 40 years after first employment. Just over one-third (34.2%) of the workers were found to have died, 64% were confirmed to be alive at the end of follow-up (December 31, 2005) and 1.5% were assumed to be alive.

After excluding 185 persons who died before 1979, 2745 workers remained for inclusion in the SMR analyses. Nearly 45% of the 818 deaths observed between 1979 and 2005 occurred

Table 1. Demographic and occupational characteristics of uranium millers and miners, Grants, New Mexico, 1955–2005.

	Miners ($N = 1867$)		Millers[a] ($N = 759$)		Other/Unk ($N = 304$)		Total ($N = 2930$)	
Characteristic	*N*	%	*N*	%	*N*	%	*N*	%
Gender								
Male	1813	97.1	692	91.2	177	58.2	2682	91.5
Female	54	2.9	67	8.8	127	41.8	248	8.5
Marital status								
Married	820	43.9	304	40.1	144	47.4	1268	43.3
Single	521	27.9	315	41.5	102	33.6	938	32.0
Unknown	306	16.4	133	17.5	51	16.8	490	16.7
Missing	220	11.8	7	0.9	7	2.3	234	8.0
Pay type								
Hourly	1168	62.6	366	48.2	82	27.0	1616	55.2
Salary	521	27.9	315	41.5	102	33.6	938	32.0
Unknown	178	9.5	78	10.3	120	39.5	376	12.8
Year of birth								
<1900	2	0.1	9	1.2	2	0.7	13	0.4
1900–1919	142	7.6	95	12.5	27	8.9	264	9.0
1920–1929	323	17.3	94	12.4	38	12.5	455	15.5
1930–1939	440	23.6	205	27.0	74	24.3	719	24.5
1940–1949	517	27.7	190	25.0	95	31.3	802	27.4
1950–1959	420	22.5	151	19.9	65	21.4	636	21.7
⩾1960	23	1.2	15	2.0	3	1.0	41	1.4
Calendar year of first employment								
1955–1964	603	32.3	339	44.7	99	32.6	1041	35.5
1965–1974	518	27.8	185	24.4	75	24.7	778	26.6
1975–1984	720	38.6	187	24.6	124	40.8	1031	35.2
1985–1989	26	1.4	48	6.3	6	2.0	80	2.7
Years since first employed								
<20	26	1.4	48	6.3	6	2.0	80	2.7
20–29	659	35.3	175	23.1	115	37.8	949	32.4
30–39	543	29.1	175	23.1	75	24.7	793	27.1
40–49	639	34.2	361	47.6	108	35.5	1108	37.8
Year of termination								
Prior to 1960	71	3.8	40	5.3	7	2.3	118	4.0
1960–1969	585	31.3	255	33.6	91	29.9	931	31.8
1970–1979	657	35.2	224	29.5	86	28.3	967	33.0
1980–1989	521	7.9	193	25.4	100	32.9	814	27.8
1990–2004	33	1.8	47	6.2	20	6.6	100	3.4
Duration of employment								
6 months–1.9 yrs	872	46.7	315	41.5	126	41.5	1313	44.8
2–4.9 yrs	489	26.2	216	28.5	73	24.0	778	26.6
5–9.9 yrs	287	15.4	111	14.6	53	17.4	451	15.4
⩾10 yrs	219	11.7	117	15.4	52	17.1	388	13.2
Work with ore or uranium processing[b]								
Likely	0	0.0	759	100	0	0.0	759	25.9
Unlikely	0	0.0	0	0.0	194	63.8	194	6.6
Missing/Not applicable[c]	1867	100.0	0	0.0	110	36.2	1977	67.5

Table 1. (Continued.)

Characteristic	Miners ($N = 1867$)		Millers[a] ($N = 759$)		Other/Unk ($N = 304$)		Total ($N = 2930$)	
	N	%	*N*	%	*N*	%	*N*	%
Vital status as of 12/31/2005								
Alive (confirmed)	1165	62.4	490	64.6	229	75.3	1884	64.3
Alive (assumed)	25	1.3	8	1.1	6	2.0	43	1.5
Dead after 1978	541	29.0	220	29.0	57	18.8	818	27.9
Dead before 1979	132	7.1	41	5.4	12	4.0	185	6.3

[a] Mill workers with job titles associated with uranium ore or processing activities (e.g., yellowcake dryer).
[b] Tabulations are only for the 953 workers at the Grants mill not known to have worked at a mine.
[c] Miners were not classified as to whether they worked at a uranium mill.

in New Mexico with over 55% occurring in 38 other states, indicating the appropriateness of using US mortality rates for the SMR analyses.

Most of the workers were male (92%) and paid hourly wages (55%), 50% were born before 1940 (average 1938), 62% were hired before 1975 (average 1969) and 69% terminated their employment before 1980 (average 1973) (table 1). There were 1867 (or 64%) workers known to have worked at a uranium mine at some time during their career. There were 1063 workers employed at the uranium mill or proximal facilities with no known mining experience; personnel job history records indicated that 759 of these workers held jobs that were likely to have involved working directly with uranium ore or with uranium processing activities (e.g., yellowcake drying).

Information requested from NIOSH to learn of subsequent employment at other uranium mines and mills was found for 8 (42%) of the 19 mill workers; 3 of the 11 workers without information had been hired after the NIOSH studies had been initiated in 1970. Of the 8 mill workers, one had worked at another uranium mill in Arizona, two as surface workers at uranium mines and two as underground miners. Three had also worked at a mine but details were not available. Linkages of worker rosters had also revealed that 9 of the 904 mill workers had been employed at the Uravan mill in Colorado (Boice *et al* 2007b).

Table 2 presents the observed and expected number of deaths and SMRs for the 2745 workers at uranium mines or mills who were alive in 1979 and followed through 2005 by sex. There were 63 395 person-years of observation (average 23.1 yrs). Overall, 818 workers were found to have died compared with 713.7 expected (SMR 1.15; 95% CI 1.07–1.23). Statistically significant increased numbers of deaths were found for lung cancer (SMR 1.65; 95% CI 1.36–1.97; $n = 117$), diseases of the nervous system (SMR 1.60; 95% CI 1.01–2.39; $n = 23$), non-malignant respiratory disease (SMR 1.42; 95% CI 1.14–1.76; $n = 84$), accidents (SMR 1.44; 95% CI 1.05–1.92; $n = 46$) and suicides (SMR 1.61; 95% CI 1.04–2.37; $n = 25$). The only cause with statistically significant decreased numbers of deaths was AIDS (SMR 0.0; expected number 7.2). Lung cancer was increased only among males. There were no statistically significant findings among the small number of 245 female workers.

The observed numbers of deaths were not statistically different from the expected numbers in the general population for cancers of the kidney (SMR 1.11; 95% CI 0.41–2.42; $n = 6$) and liver (SMR 1.70; 95% CI 0.78–3.23; $n = 9$) or for non-Hodgkin lymphoma (SMR 0.75; 95% CI 0.28–1.64; $n = 6$), leukaemia other than CLL (SMR 1.36; 95% CI 0.59–2.68; $n = 8$), heart disease (SMR 0.93; 95% CI 0.81–1.06; $n = 218$), liver cirrhosis (SMR 1.47; 95% CI 0.93–2.21; $n = 23$) or non-malignant kidney disease (SMR 0.86; 95% CI 0.32–1.87; $n = 6$).

Table 2. Observed and expected numbers of deaths and standardised mortality ratios (SMRs) among employees at uranium mills or mines near Grants, New Mexico, followed 1979–2005, by sex.

Sex	Males				Females				Total			
No. of persons	2500				245				2745			
Person-years	57 284				6110				63 395			
Cause of death (ICD9)	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI
All causes of death (001–999)	789	689.3	1.15[b]	1.07–1.23	29	24.4	1.19	0.80–1.70	818	713.7	1.15[b]	1.07–1.23
All malignant neoplasms (140–208)	235	192.2	1.22[b]	1.07–1.39	11	9.3	1.18	0.59–2.11	246	201.5	1.22[b]	1.07–1.38
Buccal cavity and pharynx (140–149)	1	4.1	0.25	0.01–1.37	1	0.1	10.9	0.27–60.8	2	4.2	0.48	0.06–1.73
Oesophagus (150)	4	6.0	0.67	0.18–1.71	0	0.1	0.00	—	4	6.1	0.66	0.18–1.69
Stomach (151)	5	5.1	0.99	0.32–2.30	0	0.1	0.00	—	5	5.2	0.96	0.31–2.24
Colon (153)	11	15.9	0.69	0.35–1.24	0	0.6	0.00	—	11	16.5	0.67	0.33–1.19
Rectum (154)	1	3.1	0.33	0.01–1.82	0	0.1	0.00	—	1	3.2	0.32	0.01–1.76
Biliary passages and liver (155, 156)	9	5.1	1.76	0.80–3.34	0	0.2	0.00	—	9	5.3	1.70	0.78–3.23
Pancreas (157)	7	9.6	0.73	0.29–1.50	2	0.4	5.01	0.61–18.1	9	10.0	0.90	0.41–1.71
Bronchus, trachea, and lung (162)	114	68.8	1.66[b]	1.37–1.99	3	2.4	1.27	0.26–3.72	117	71.1	1.65[b]	1.36–1.97
Breast (174, 175)	0	0.2	0.00	0.00–15.9	2	2.0	1.00	0.12–3.62	2	2.2	0.90	0.11–3.25
All uterine (179–182)	—	—	—	—	0	0.4	0.00	0.00–8.35	0	0.4	0.00	0.00–8.35
Other female genital organs (183–184)	—	—	—	—	2	0.6	3.17	0.38–11.5	2	0.6	3.17	0.38–11.5
Prostate (185)	13	14.6	0.89	0.47–1.52	—	—	—	—	13	14.6	0.89	0.47–1.52
Kidney (189.0–189.2)	6	5.3	1.14	0.42–2.49	0	0.2	0.00	0.00–24.3	6	5.4	1.11	0.41–2.42
Bladder and other urinary (188, 189.3–189.9)	3	4.9	0.61	0.13–1.80	1	0.1	13.1	0.33–72.7	4	5.0	0.81	0.22–2.07
Melanoma of skin (172)	6	3.7	1.63	0.60–3.54	0	0.1	0.00	—	6	3.8	1.57	0.57–3.41
Brain and CNS (191–192)	5	5.4	0.93	0.30–2.16	0	0.3	0.00	—	5	5.7	0.88	0.29–2.06
Thyroid and other endocrine glands (193–194)	1	0.6	1.82	0.05–10.1	0	0.0	0.00	—	1	0.6	1.71	0.04–9.52
Bone (170)	0	0.4	0.00	0.00–10.3	0	0.0	0.00	—	0	0.4	0.00	0.00–9.87
All lymphatic, haematopoietic tissue (200–208)	23	18.8	1.22	0.78–1.84	0	0.8	0.00	0.00–4.87	23	19.6	1.18	0.75–1.77
Non-Hodgkin lymphoma (200, 202)	6	7.6	0.79	0.29–1.71	0	0.3	0.00	—	6	8.0	0.75	0.28–1.64
Hodgkin lymphoma (201)	1	0.7	1.52	0.04–8.48	0	0.0	0.00	—	1	0.7	1.45	0.04–8.08
Leukaemia and aleukaemia (204–208)	12	7.1	1.69	0.87–2.95	0	0.3	0.00	—	12	7.4	1.62	0.84–2.83

Table 2. (Continued.)

Sex	Males				Females				Total			
No. of persons	2500				245				2745			
Person-years	57 284				6110				63 395			
Cause of death (ICD9)	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI
Chronic lymphocytic leukaemia (204.1)	4	1.5	2.71	0.74–6.93	0	0.0	0.00	—	4	1.5	2.65	0.72–6.79
Leukaemia other than CLL	8	5.6	1.42	0.61–2.80	0	0.2	0.00	—	8	5.9	1.36	0.59–2.68
Multiple myeloma (203)	4	3.2	1.24	0.34–3.16	0	0.1	0.00	—	4	3.4	1.19	0.32–3.04
Pleura and peritoneum (158.8, 158.9, 163) and mesothelioma (ICD10 C45)[a]	2	0.7	2.71	0.33–9.80	0	0.0	0.00	—	2	0.8	2.66	0.32–9.61
AIDS (042–044, 795.8)	0	7.1	0.00[b]	0.00–0.52	0	0.1	0.00	—	0	7.2	0.00[b]	0.00–0.51
Diabetes (250)	19	15.9	1.20	0.72–1.87	1	0.8	1.31	0.03–7.29	20	16.6	1.20	0.74–1.86
Mental and behavioural disorders (290–319)	9	8.0	1.13	0.52–2.14	0	0.2	0.00	—	9	8.2	1.10	0.50–2.08
Diseases of the nervous system (320–389)	21	13.8	1.52	0.94–2.32	2	0.6	3.29	0.40–11.9	23	14.4	1.60[b]	1.01–2.39
Cerebrovascular disease (430–438)	30	31.4	0.95	0.64–1.36	2	1.2	1.61	0.20–5.81	32	32.7	0.98	0.67–1.38
All heart disease (390–398, 404, 410–429)	212	228.9	0.93	0.81–1.06	6	5.2	1.16	0.43–2.53	218	234.0	0.93	0.81–1.06
Non-malignant respiratory disease (460–519)	83	57.1	1.45[b]	1.16–1.80	1	1.9	0.52	0.01–2.91	84	59.1	1.42[b]	1.14–1.76
Bronchitis, emphysema, asthma (490–493)	35	18.8	1.86[b]	1.30–2.59	0	0.9	0.00	0.00–4.28	35	19.7	1.78[b]	1.24–2.48
Cirrhosis of liver (571)	22	15.1	1.46	0.91–2.20	1	0.5	2.02	0.05–11.3	23	15.6	1.47	0.93–2.21
Nephritis and nephrosis (580–589)	6	6.7	0.89	0.33–1.94	0	0.2	0.00	0.00–15.1	6	7.0	0.86	0.32–1.87
All external causes of death (800–999)	77	52.1	1.48[b]	1.17–1.85	1	1.8	0.56	0.01–3.10	78	53.9	1.45[b]	1.14–1.81
Accidents (850-949)	46	30.9	1.49[b]	1.09–1.99	0	1.1	0.00	0.00–3.40	46	32.0	1.44[b]	1.05–1.92
Suicides (950-959)	24	15.1	1.59[b]	1.02–2.37	1	0.5	2.20	0.06–12.3	25	15.5	1.61[b]	1.04–2.37
Unknown causes of death	18				1				19			

[a] Mesothelioma was not a codeable cause of death until 1999: ICD10 (C45). Before 1999, cancers of the pleura and peritoneum (ICD9 158.8, 158.9, 163) have been used to approximate mesothelioma mortality.

[b] $p < 0.05$.

No deaths were observed for bone cancer (0.4 expected) and only one death occurred from cancer of the thyroid (0.6 expected).

Table 3 presents the observed and expected number of deaths and SMRs by employment at a uranium mine. Among the 1735 miners, the total number of deaths, 541, was statistically higher than expected, 426.4 (SMR 1.27; 95% CI 1.16–1.38). The excess number of deaths among workers with mining experience arose primarily from five causes: lung cancer (SMR 2.17; 95% CI 1.75–2.65; $n = 95$); non-malignant respiratory diseases (i.e., bronchitis, emphysema and asthma combined, influenza and pneumonia) (SMR 1.64; 95% CI 1.23–2.13; $n = 55$), cirrhosis of the liver (SMR 1.79; 95% CI 1.06–2.83; $n = 18$), accidents (SMR 1.50; 95% CI 1.02–2.13; $n = 31$) and suicides (SMR 2.06; 95% CI 1.28–3.15; $n = 21$). Among men with mining experience, heart disease occurred as expected (SMR 0.96; 95% CI 0.80–1.14; $n = 133$).

The overall SMR for the 106 workers whose mining experience was unknown was 0.95 (95% CI 0.61–1.42; $n = 24$) and their total-cancer SMR was 0.58 (95% CI 0.16–1.47; $n = 4$).

There were no statistically significant high or low SMRs among the 904 workers not known to have worked at a uranium mine. Their overall SMR for all causes of death was 0.97 (95% CI 0.85–1.09) and their total-cancer SMR was 0.89 (95% CI 0.69–1.14). Lung cancer was not increased (SMR 0.85; 95% CI 0.52–1.29; $n = 21$), nor was non-malignant respiratory disease (SMR 1.07; 95% CI 0.69–1.58; $n = 25$). Deaths from heart disease occurred below expectation (SMR 0.84; 95% CI 0.66–1.05; $n = 73$).

Table 4 presents the observed and expected numbers of deaths and SMRs for the 904 workers at the uranium mill who were not known to have worked at a mine. Among the 718 millers with the highest potential for exposure to uranium ore, there were no statistically significant increased causes of death. The all-cause SMR was 1.00 (95% CI 0.87–1.14; $n = 220$), the total-cancer SMR was 0.94 (95% CI 0.71–1.22; $n = 56$), the lung cancer SMR was 0.88 (95% CI 0.52–1.38; $n = 18$), the SMR for non-malignant respiratory disease was 1.22 (95% CI 0.78–1.81; $n = 24$), the SMR for non-malignant kidney disease was 1.30 (95% CI 0.27–3.79; $n = 3$) and the SMR for heart disease was 0.84 (95% CI 0.65–1.08; $n = 63$).

SMR analyses were conducted for uranium millers not known to have worked at an underground mine by duration of employment (data not shown). There were no statistically significant increased SMRs for any cause of death for those employed for the longest time. The all-cause SMR for the 209 persons who worked for more than 5 yrs (SMR 0.87; 95% CI 0.70–1.07; $n = 88$) was slightly lower than for all 718 mill workers combined (SMR 1.00), as were the SMRs for total cancer (0.72; $n = 19$), lung cancer (0.56; $n = 5$) and non-malignant respiratory disease (0.68; $n = 7$), although the numbers were small. A decreased risk of heart disease (SMR 0.77; 95% 0.51–1.11; $n = 28$) was consistent with the low SMR (0.84) seen for all millers.

SMR analyses were conducted using general population rates for the state of New Mexico and the mortality patterns were generally similar to those using rates for the United States. The all-cause SMR among all workers was 1.19 (95% CI 1.11–1.28) and similar to the SMR of 1.15 (95% CI 1.07–1.23) based on US rates. The total-cancer SMR was somewhat higher based on New Mexico rates (SMR 1.49; 95% CI 1.30–1.68) compared with US rates (SMR 1.22; 95% CI 1.07–1.38)—mainly due to the somewhat higher lung cancer SMR based on New Mexico rates (SMR 2.56; 95% CI 2.12–3.07) compared with US rates (SMR 1.65; 95% CI 1.36–1.97). Non-malignant respiratory disease mortality was nearly identical based on New Mexico rates (SMR 1.38) compared with US rates (SMR 1.42). Deaths due to external causes were lower based on New Mexico rates (SMR 0.87; 95% CI 0.69–1.08) compared with US rates (SMR 1.45; 95% CI 1.14–1.92). Other than for external causes of death, there were no appreciable differences in the SMRs.

Table 3. Observed and expected numbers of deaths and standardised mortality ratios (SMRs) among employees at uranium mills or mines near Grants, New Mexico, followed 1979–2005, by mining experience.

Mining experience	Yes				No			
No. of persons	1735				904			
Person-years of observation	40 027				20 937			
Cause of death (ICD9)	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI
All causes of death (001–999)	541	426.4	1.27[b]	1.16–1.38	253	262.1	0.97	0.85–1.09
All malignant neoplasms (140–208)	177	121.6	1.46[b]	1.25–1.69	65	73.0	0.89	0.69–1.14
Buccal cavity and pharynx (140–149)	1	2.6	0.38	0.01–2.13	1	1.4	0.71	0.02–3.98
Oesophagus (150)	2	3.8	0.52	0.06–1.89	2	2.0	0.99	0.12–3.57
Stomach (151)	5	3.2	1.58	0.51–3.68	0	1.9	0.00	0.00–1.99
Colon (153)	9	9.9	0.91	0.42–1.73	2	6.1	0.33	0.04–1.19
Rectum (154)	1	1.9	0.52	0.01–2.90	0	1.1	0.00	0.00–3.26
Biliary passages and liver (155, 156)	6	3.2	1.85	0.68–4.02	3	1.9	1.62	0.33–4.72
Pancreas (157)	4	6.1	0.66	0.18–1.68	4	3.6	1.12	0.31–2.87
Bronchus, trachea, and lung (162)	95	43.8	2.17[b]	1.75–2.65	21	24.9	0.85	0.52–1.29
Breast (174, 175)	0	0.5	0.00	0.00–7.59	2	1.7	1.20	0.15–4.32
All uterine (179–182)	0	0.1	0.00	—	0	0.3	0.00	0.00–10.6
Other female genital organs (183–184)	0	0.1	0.00	—	2	0.5	3.94	0.48–14.2
Prostate (185)	9	8.3	1.08	0.49–2.05	4	5.8	0.69	0.19–1.76
Kidney (189.0–189.2)	3	3.4	0.89	0.18–2.61	3	1.9	1.61	0.33–4.71
Bladder and other urinary (188, 189.3–189.9)	0	2.9	0.00	0.00–1.26	4	1.9	2.15	0.59–5.50
Melanoma of skin (172)	6	2.4	2.49	0.91–5.41	0	1.3	0.00	0.00–2.87
Brain and CNS (191–192)	2	3.6	0.56	0.07–2.03	3	1.9	1.57	0.32–4.59
Thyroid and other endocrine glands (193–194)	1	0.4	2.80	0.07–15.6	0	0.2	0.00	0.00–17.8
Bone (170)	0	0.2	0.00	0.00–15.9	0	0.1	0.00	0.00–28.8
All lymphatic, haematopoietic tissue (200–208)	18	11.9	1.51	0.90–2.39	4	7.0	0.57	0.16–1.47
Non-Hodgkin lymphoma (200, 202)	4	4.9	0.82	0.22–2.11	1	2.8	0.36	0.01–1.98
Hodgkins lymphoma (201)	1	0.4	2.28	0.06–12.7	0	0.2	0.00	0.00–16.3
Leukaemia and aleukaemia (204–208)	9	4.5	2.01	0.92–3.82	3	2.7	1.12	0.23–3.28
Chronic lymphocytic leukaemia (204.1)	2	0.9	2.23	0.27–8.05	2	0.6	3.58	0.43–12.9
Leukaemia other than CLL	7	3.6	1.96	0.79–4.04	1	2.1	0.47	0.01–2.64
Multiple myeloma (203)	4	2.0	1.97	0.54–5.05	0	1.2	0.00	0.00–3.02
Pleura and peritoneum (158.8,158.9,163) and mesothelioma (ICD10 C45)[a]	1	0.5	2.14	0.05–11.9	1	0.3	3.85	0.10–21.5
AIDS (042-044, 795.8)	0	5.0	0.00[b]	0.00–0.74	0	2.0	0.00	0.00–1.86
Diabetes (250)	11	10.0	1.10	0.55–1.97	9	6.1	1.48	0.68–2.81
Mental and behavioural disorders (290–319)	8	4.9	1.65	0.71–3.25	1	3.1	0.33	0.01–1.81
Diseases of the nervous system (320–389)	14	8.3	1.69	0.92–2.83	9	5.6	1.60	0.73–3.03
Cerebrovascular disease (430–438)	16	18.3	0.88	0.50–1.42	14	13.3	1.06	0.58–1.77
All heart disease (390–398, 404, 410–429)	133	138.6	0.96	0.80–1.14	73	87.1	0.84	0.66–1.05
Non-malignant respiratory disease (460–519)	55	33.6	1.64[b]	1.23–2.13	25	23.4	1.07	0.69–1.58
Bronchitis, emphysema, asthma (490–493)	25	11.6	2.16[b]	1.40–3.19	8	7.4	1.08	0.47–2.12
Cirrhosis of liver (571)	18	10.1	1.79[b]	1.06–2.83	3	5.0	0.60	0.12–1.75
Nephritis and nephrosis (580–589)	3	4.0	0.76	0.16–2.21	3	2.8	1.08	0.22–3.17
All external causes of death (800–999)	58	35.1	1.65[b]	1.26–2.14	20	16.8	1.19	0.73–1.84
Accidents (850–949)	31	20.6	1.50[b]	1.02–2.13	15	10.1	1.48	0.83–2.45
Suicides (950–959)	21	10.2	2.06[b]	1.28–3.15	4	4.8	0.84	0.23–2.15
Unknown causes of death	12				7			

[a] There were 106 workers with 2431 person-years of follow-up whose mining experience was unknown. Their overall SMR was 0.95 (95% CI 0.61–1.42; $n = 24$) and their total-cancer SMR was 0.58 (95% CI 0.16–1.47; $n = 4$).
[b] $p < 0.05$.

Table 4. Observed and expected numbers of deaths and standardised mortality rates (SMRs) for employees at the uranium mill near Grants, New Mexico, who never worked at an underground mine and followed from 1979–2005, by whether they worked with ore or processed uranium.

Worked with ore or uranium processing activities	Likely[a]				Unlikely[b]			
No. of persons	718				186			
Person-years of observation	16 333				4604			
Cause of death (ICD9)	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI
All causes of death (001–999)	220	220.1	1.00	0.87–1.14	33	42.0	0.79	0.54–1.10
All malignant neoplasms (140–208)	56	59.6	0.94	0.71–1.22	9	13.5	0.67	0.31–1.27
Buccal cavity and pharynx (140–149)	1	1.2	0.84	0.02–4.69	0	0.2	0.00	0.00–17.4
Oesophagus (150)	2	1.7	1.15	0.14–4.16	0	0.3	0.00	0.00–12.8
Stomach (151)	0	1.6	0.00	0.00–2.35	0	0.3	0.00	0.00–13.0
Colon (153)	2	5.0	0.40	0.05–1.44	0	1.0	0.00	0.00–3.55
Rectum (154)	0	0.9	0.00	0.00–3.90	0	0.2	0.00	0.00–19.8
Biliary passages and liver (155, 156)	3	1.5	1.94	0.40–5.67	0	0.3	0.00	0.00–11.9
Pancreas (157)	4	2.9	1.37	0.37–3.49	0	0.6	0.00	0.00–5.80
Bronchus, trachea, and lung (162)	18	20.6	0.88	0.52–1.38	3	4.3	0.70	0.14–2.04
Breast (174, 175)	0	0.5	0.00	0.00–7.13	2	1.2	1.73	0.21–6.26
All uterine (179–182)	0	0.1	0.00	0.00–36.3	0	0.2	0.00	0.00–14.9
Other female genital organs (183–184)	0	0.1	0.00	0.00–27.0	2	0.4	5.39	0.65–19.5
Prostate (185)	3	5.1	0.59	0.12–1.71	1	0.7	1.47	0.04–8.18
Kidney (189.0–189.2)	3	1.6	1.92	0.40–5.62	0	0.3	0.00	0.00–12.3
Bladder and other urinary (188, 189.3–189.9)	4	1.6	2.50	0.68–6.40	0	0.3	0.00	0.00–14.1
Melanoma of skin (172)	0	1.1	0.00	0.00–3.46	0	0.2	0.00	0.00–16.9
Brain and CNS (191–192)	3	1.6	1.93	0.40–5.63	0	0.4	0.00	0.00–10.4
Thyroid and other endocrine glands (193–194)	0	0.2	0.00	0.00–22.3	0	0.0	0.00	—
Bone (170)	0	0.1	0.00	0.00–34.7	0	0.0	0.00	—
All lymphatic, haematopoietic tissue (200–208)	4	5.8	0.69	0.19–1.77	0	1.2	0.00	0.00–3.03
Non-Hodgkin lymphoma (200, 202)	1	2.3	0.43	0.01–2.40	0	0.5	0.00	0.00–7.40
Hodgkin lymphoma (201)	0	0.2	0.00	0.00–19.7	0	0.0	0.00	—
Leukaemia and aleukaemia (204–208)	3	2.2	1.35	0.28–3.96	0	0.5	0.00	0.00–8.13
Chronic lymphocytic Leukaemia (204.1)	2	0.5	4.21	0.51–15.2	0	0.1	0.00	0.00–44.2
Leukaemia other than CLL	1	1.7	0.57	0.01–3.20	0	0.4	0.00	0.00–9.95
Multiple myeloma (203)	0	1.0	0.00	0.00–3.68	0	0.2	0.00	0.00–17.0
Pleura and peritoneum (158.8,158.9,163) and mesothelioma (ICD10 C45)	1	0.2	4.60	0.12–25.6	0	0.0	0.00	—
AIDS (042-044, 795.8)	0	1.8	0.00	0.00–2.08	0	0.2	0.00	0.00–17.9
Diabetes (250)	8	5.0	1.62	0.70–3.18	1	1.1	0.89	0.02–4.98
Mental and behavioural disorders (290–319)	1	2.6	0.38	0.01–2.12	0	0.4	0.00	0.00–8.30
Diseases of the nervous system (320–389)	8	4.6	1.73	0.75–3.40	1	1.0	1.00	0.03–5.54
Cerebrovascular disease (430–438)	12	11.2	1.07	0.55–1.87	2	2.0	0.98	0.12–3.54
All heart disease (390–398, 404, 410–429)	63	74.8	0.84	0.65–1.08	10	12.4	0.81	0.39–1.49
Non-malignant respiratory disease (460–519)	24	19.7	1.22	0.78–1.81	1	3.7	0.27	0.01–1.51
Bronchitis, emphysema, asthma (490–493)	8	6.0	1.34	0.58–2.64	0	1.5	0.00	0.00–2.53
Cirrhosis of liver (571)	3	4.2	0.72	0.15–2.09	0	0.8	0.00	0.00–4.58
Nephritis and nephrosis (580–589)	3	2.3	1.30	0.27–3.79	0	0.5	0.00	0.00–8.15
All external causes of death (800–999)	17	14.3	1.19	0.69–1.90	3	2.4	1.23	0.25–3.59
Accidents (850–949)	13	8.6	1.51	0.80–2.58	2	1.5	1.36	0.16–4.90
Suicides (950–959)	3	4.1	0.73	0.15–2.14	1	0.7	1.47	0.04–8.19
Unknown causes of death	6				1			

[a] Mill worker with potential exposure to uranium ore and/or uranium processing activities, e.g., yellowcake drying.
[b] Workers employed at mill but with unlikely or minimal exposure to uranium ore or uranium processing activities, e.g., clerk or accountant.

4. Discussion

Underground uranium miners in the vicinity of Grants, New Mexico were found to be at statistically significant increased risk of dying from lung cancer, non-malignant respiratory disease, cirrhosis of the liver and external causes of death, similar to the findings of previous occupational studies of New Mexico and Colorado plateau miners (Samet *et al* 1984a, 1991, Roscoe *et al* 1995, Roscoe 1997). The increase in lung cancer is likely attributable to the high levels of radon and radon decay products in these early mines coupled with heavy smoking habits among miners (Lundin *et al* 1971, Whittemore and McMillan 1983, Hornung and Meinhardt 1987, Samet *et al* 1991). The increase in non-malignant respiratory disease, including pneumoconiosis, may be related in part to high levels of mining dusts, such as quartz (silica) present in the mines (Samet *et al* 1984b, 1991), as well as radon decay products, diesel exhaust and excessive tobacco use (Archer *et al* 1976). Increases in deaths from cirrhosis of the liver may be related to lifestyle factors of the early mining populations such as heavy alcohol consumption. Accidental deaths while on the job were not infrequent. An association with deaths from diseases of the nervous system for all workers combined was of borderline statistical significance and may be a chance finding. Interestingly, a healthy worker effect (Howe *et al* 1988) was not apparent in this miner population as indicated by the near normal rates of heart disease, cerebrovascular disease and most other conditions.

Although there are many studies of uranium miners (Lubin *et al* 1995, NRC 1999), there are few studies of uranium millers (Pinkerton *et al* 2004, Boice *et al* 2007b). Thus it is of interest that the 718 workers with the highest potential for exposure to uranium ore and processing activities were not found to be at increased risk of any of the diseases of *a priori* interest—based on possible associations seen in other studies and on knowledge of the likely distribution of uranium within the body once inhaled or ingested. No statistically significant increases were found for kidney disease, liver disease, non-malignant respiratory disease, lung cancer, bone cancer or non-Hodgkin lymphoma.

Table 5 compares the findings of the current study of uranium mill workers with the two other studies of mill workers at the Uravan mill in Colorado (Boice *et al* 2007b) and at the seven mills included in the NIOSH study of Colorado Plateau workers (Pinkerton *et al* 2004). The latter two studies are not independent since the Uravan mill was included in the NIOSH study. The general patterns of mortality are consistent across the three studies: there is no increase in all-cause mortality or all-cancer mortality, and cancer of the lung is increased in two studies but the increases were not statistically significant. An association between exposure to uranium and lung cancer has not been established in any study of uranium millers or uranium workers (IOM 2001).

No statistically significant associations were seen for cancers of the kidney, liver, bone or lymphoma (table 5). The risk of bladder cancer was increased in our study but was decreased in the other two series. Heart disease was below expectation in all three studies and the decreased risk was statistically significant in two of them. Non-malignant renal disease was not increased in any study at the level of statistical significance. The only statistically significant elevation was for non-malignant respiratory disease observed in the large NIOSH study (SMR 1.43; $n = 100$) but not in the Uravan study (SMR 0.99; $n = 24$) or in the current study (SMR 1.22; $n = 24$). Most (54%) of the uranium mill workers in the NIOSH study had begun work prior to 1955 when the potential for exposure to silica, uranium ore, vanadium and other mill contaminants was assumed higher than in later years. The Grants uranium mill began in 1955 but the Uravan mill began operations in 1936 and 42% were hired prior to 1955. The NIOSH investigators, however, were cautious in concluding that non-malignant respiratory disease was due to milling activities because of the inverse association seen with duration of

Table 5. Observed and expected numbers of deaths and standardised mortality ratios (SMRs) among mill workers near Grants, New Mexico (current study), Colorado (Boice *et al* 2007b), and the Colorado Plateau (Pinkerton *et al* 2004).

Worked with ore or uranium processing	Grants New Mexico Mill[a]				Uravan Colorado Mill[a]				7 Colorado Plateau Mills[b]			
No. of persons	718				450				1484			
Person-years of observation	16 333				9294				49 925			
Calendar years of mill operation	1958–1990				1936–1984				<1940–1970+			
Calendar years of follow-up	1979–2005				1979–2004				1940–1998			
Cause of death (ICD9)	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI
All causes of death (001–999)	220	220.1	1.00	0.87–1.14	186	233.6	0.80[e]	0.69–0.92	810	877.7	0.92[e]	0.86–0.99
All malignant neoplasms (140–208)	56	59.6	0.94	0.71–1.22	48	57.6	0.83	0.62–1.11	184	204.1	0.90	0.78-1.04
Buccal cavity and pharynx (140–149)	1	1.2	0.84	0.02–4.69	1	1.0	0.96	0.02–5.37	2	5.06	0.40	9.05–1.43
Oesophagus (150)	2	1.7	1.15	0.14–4.16	0	1.5	0.00	0.00–2.51	1	5.06	0.20	0.01–1.10
Colon (153)	2	5.0	0.40	0.05–1.44	0	5.3	0.00	0.00–0.70	12	19.0	0.63	0.33–1.11
Rectum (154)	0	0.9	0.00	0.00–3.90	1	0.9	1.06	0.03–5.91	2	4.77	0.42	0.05-1.51
Biliary passages and liver (155,156)	3	1.5	1.94	0.40–5.67	1	1.4	0.71	0.02–3.94	4	5.04	0.79	0.22–2.03
Pancreas (157)	4	2.9	1.37	0.37–3.49	3	2.7	1.10	0.23–3.20	6	10.3	0.58	0.21–1.27
Bronchus, trachea, and lung (162)	18	20.6	0.88	0.52–1.38	24	19.1	1.26	0.81–1.87	78	68.9	1.13	0.89–1.41
Prostate (185)	3	5.1	0.59	0.12–1.71	7	6.9	1.01	0.41–2.08	15[c]	19.7	0.76	0.43–1.26
Kidney (189.0–189.2)	3	1.6	1.92	0.40–5.62	1	1.4	0.74	0.02–4.10	4	4.96	0.81	0.22–2.06
Bladder and other urinary (188, 189.3–189.9)	4	1.6	2.50	0.68–6.40	1	1.9	0.54	0.01–2.99	5[d]	11.0	0.45	0.15–1.06
Bone (170)	0	0.1	0.00	0.00–34.7	0	0.1	0.00	0.00–39.3	Not given			
All lymphatic, haematopoietic tissue (200–208)	4	5.8	0.69	0.19–1.77	3	5.5	0.55	0.11–1.60	21	18.7	1.12	0.69–1.71
Non-Hodgkin lymphoma (200, 202)	1	2.3	0.43	0.01–2.40	1	2.1	0.47	0.01–2.63	4	2.29	1.74	0.48–4.46
Hodgkin lymphoma (201)	0	0.2	0.00	0.00–19.7	1	0.1	6.94	0.17–38.7	4	1.21	3.30	0.90-8.43
Leukaemia and aleukaemia (204–208)	3	2.2	1.35	0.28–3.96	1	2.2	0.46	0.01–2.54	5	7.62	0.66	0.21–1.53
Diabetes (250)	8	5.0	1.62	0.70–3.18	4	4.7	0.86	0.23–2.19	10	14.6	0.68	0.33–1.26

Table 5. (Continued.)

Worked with ore or uranium processing	Grants New Mexico Mill[a]				Uravan Colorado Mill[a]				7 Colorado Plateau Mills[b]			
No. of persons	718				450				1484			
Person-years of observation	16 333				9294				49 925			
Calendar years of mill operation	1958–1990				1936–1984				<1940–1970+			
Calendar years of follow-up	1979–2005				1979–2004				1940–1998			
Cause of death (ICD9)	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI
All heart disease (390–398, 404, 410–429)	63	74.8	0.84	0.65–1.08	65	85.9	0.76[e]	0.58–0.97	293	349.0	0.84[e]	0.75–0.94
Non-malignant respiratory disease (460–519)	24	19.7	1.22	0.78–1.81	24	24.4	0.99	0.63–1.47	100	70.2	1.43[e]	0.65–1.05
Cirrhosis of liver (571)	3	4.2	0.72	0.15–2.09	0	2.9	0.00	0.00–1.27	Not given			
Nephritis and nephrosis (580–589)	3	2.3	1.30	0.27–3.79	3	2.7	1.09	0.23–3.19	9	7.07	1.28	0.59–2.44
All external causes of death (800–999)	17	14.3	1.19	0.69–1.90	7	10.1	0.69	0.28–1.43	47	37.2	1.26	0.93–1.68
Unknown causes of death	6				1				16			

[a] Mill workers with potential exposure to uranium ore and/or uranium processing activities based on job titles, e.g., yellowcake drying. Uravan mill values from table 6 of Boice *et al* (2007b).

[b] Cause of death categories are presented that are as similar as possible to those in the other two mill worker studies. Values from table 2 of Pinkerton *et al* (2004). The Uravan mill was included in the NIOSH study so the results are not independent. The Grants, New Mexico mill was not included in the NIOSH study.

[c] Male genital (ICD9 185–187).

[d] All urinary (ICD9 188–189).

[e] $p < 0.05$.

employment. Similar to lung cancer, non-malignant respiratory disease has not been established as a consequence of uranium exposure in any study (IOM 2001).

Ours is one of the few studies of uranium workers that include both underground miners exposed to radon, and uranium millers exposed to ore and milling products. These two types of uranium exposure showed very different risk patterns. Underground mining, with increased exposure to radon gas and its decay products, was clearly associated with increased risk of lung cancer, but no other cancer, consistent with previous studies of miners (Darby *et al* 1996, NRC 1999). In contrast, uranium milling and exposure to uranium ore was not associated with any cancer or non-malignant condition, also consistent with previous studies (Waxweiler *et al* 1983, Pinkerton *et al* 2004, Boice *et al* 2007b). Uranium is not considered carcinogenic in humans (IARC 2001, ATSDR 1999), in large part because it is not very radioactive given its long half-life of billions of years. The hazard associated with uranium exposure is due primarily to its chemical properties as a heavy metal, and kidney disease is the outcome of most concern following excessive exposure (Leggett 1989, ATSDR 1999). Apparently, such exposure was not sufficient to result in a detectable increase of renal disease among mill workers in our study or the two previous studies, consistent with practically all other studies that find no association between exposure to uranium and clinically important renal dysfunction (IOM 2001). Our findings of excess lung cancer among miners but not among millers are also consistent with a recent study of uranium millers and miners in Colorado (Boice *et al* 2007b).

4.1. Studies of environmental exposure to uranium

Although uranium can enter the body by ingestion of food and water or by inhalation of uranium-containing dust, environmental exposures have not been associated with detrimental health effects (Taylor and Taylor 1997). Epidemiologic studies of the ingestion of high levels of uranium, radium, radon and other radionuclides in drinking water in Finland have provided no evidence for increased rates of cancers of the bladder, kidney or stomach, or of leukaemia (Auvinen *et al* 2002, 2005, Kurttio *et al* 2006b). High intakes of natural uranium in drinking water have been linked to subtle effects on bone formation but only in males and not females and there was no evidence of overt bone disease (Kurttio *et al* 2005). Uranium millers and miners in the current study also were not found to be at increased risk for cancers of the bone, bladder, kidney and stomach or leukaemia.

Several descriptive correlation studies of populations living near uranium milling and mining facilities have been conducted in Texas (Boice *et al* 2003a) and in Colorado (Mason *et al* 1972, Boice *et al* 2007a). No association with any cancer was observed except for lung cancer in the Colorado study which was attributed, and then confirmed, to be most likely due to an occupational exposure to radon among underground miners residing in the area (Boice *et al* 2007b). The extensive uranium milling and mining activities in Texas were not associated with increased lung cancer mortality in all likelihood because only surface and *in situ* mining, and not underground mining, were performed and high exposures to radon were not possible (Boice *et al* 2003a). Similar studies of cancer incidence and mortality in populations residing within about one mile of nuclear fuel processing and uranium fabrication facilities in Pennsylvania have also failed to reveal increased cancer rates (Boice *et al* 2003b, 2003c).

4.2. Kidney disease

The possible chemical toxicity of uranium, a heavy metal, is considered more important for human health than the risk of cancer from its radioactive properties (Taylor and Taylor 1997, Leggett 1989). No statistically significant increase in renal disease, however, was found in

the current study (3 observed versus 2.3 expected) nor in the NIOSH study of uranium millers of the Colorado plateau (9 observed versus 7.07 expected). The NIOSH study also reported that the risk of end-stage renal disease was not increased (Pinkerton *et al* 2004). Consistent with these results, renal disease was not increased among 450 millers in Uravan, Colorado (3 observed versus 2.7 expected) although many of these workers may have been included in the larger NIOSH investigation (Boice *et al* 2007b). Other studies of workers exposed to uranium have not found increases in kidney disease (Roscoe 1997, Russell *et al* 1996). One study of 39 uranium mill workers, however, reported changes in kidney function that suggested mild renal damage and, conversely, other changes that suggested improved glomerular function, but no apparent kidney disease (Thun *et al* 1985). Similarly, high levels of uranium in drinking water in Finland have produced subtle changes in some measures of kidney function but not kidney disease (Kurttio *et al* 2002, 2003, Kurttio *et al* 2006a). Studies of Gulf War veterans exposed to depleted uranium and of workers exposed to enriched uranium also find no evidence of clinically important renal dysfunction (IOM 2001, McDiarmid *et al* 2007). Consistent with these observations, we found no increase in mortality from non-malignant kidney disease among uranium millers and miners of Grants, New Mexico (6 observed deaths versus 7.0 expected).

4.3. Studies of New Mexico underground miners

A previous study of underground miners in New Mexico evaluated cancer and non-cancer mortality (Samet *et al* 1991). The only statistically significant excess was of lung cancer mortality (SMR 4.00; 95% CI 3.1–5.1; $n = 68$) attributed to the high concentrations of radon gas and radon decay products in unventilated underground mines and excessive tobacco use. Lung cancer increases were also seen among Navajo miners (Samet *et al* 1984a, Roscoe *et al* 1995). Increases in non-malignant respiratory diseases may have been partially due to high levels of silica dust causing pneumoconiosis and associated lung conditions (Samet *et al* 1984b). Our study of 1735 uranium miners revealed a statistically significant excess of lung cancer (SMR 2.17; $n = 95$) that was consistent with these previous investigations, as was the statistically significant increase in non-malignant respiratory disease (SMR 1.64; $n = 55$), attributable, perhaps, to silica, radon and other mine exposures and excessive tobacco use (IOM 2001). Statistically significant increases in external causes of death from accidents and suicides were seen in our study (SMR 1.65) and the previous study (SMR 1.5) of miners from New Mexico (Samet *et al* 1991) indicating the hazardous nature of underground mining and, perhaps, the characteristics of persons who choose mining as a profession.

4.4. Studies of cohorts exposed to uranium

During the early years of uranium processing, enrichment, manufacturing and milling, aboveground workers had the potential to inhale or ingest uranium dust with minimal exposure to radon gas (UNSCEAR 2008). Well over 120 000 of these workers have been studied and, overall, no consistent elevations in cancer risk were observed (Harley *et al* 1999, Royal Society 2001, IOM 2001, McGeoghegan and Binks 2000a, 2000b, 2006). Studies of workers with estimates of organ doses from uranium intakes also failed to find clear evidence of dose-response relationships (Dupree *et al* 1995, Boice *et al* 2006a, 2006b). In contrast to these negative studies of cancer risk among workers exposed to uranium dust and compounds, studies of underground uranium miners have revealed consistent and substantial increases in lung cancer attributed to radon gas and its decay products (NRC 1999).

4.5. Strengths and limitations

Strengths of our occupational study include the cohort design, the complete roster of all workers employed by a large uranium milling and mining company, and the long follow-up of the workers of up to 50 yrs. We also were able to distinguish between workers employed as underground miners, uranium millers or in both occupations. Limitations of the study include the relatively small number of workers within specific exposure categories and the lack of measurements of actual radiation exposure. Smoking histories also were not known.

Although the number of workers was relatively small (2930 overall and 2745 alive in 1979), the follow-up was long with 65% followed for more than 30 yrs after date of first employment and 38% followed for more than 40 yrs. Further, the number of deaths was sufficient to reveal increases for several causes of death; for example, among uranium miners we found statistically significant elevations of two-fold or less for lung cancer, non-malignant respiratory disease and cirrhosis of the liver.

For non-miners, the sample size was also sufficient to rule out relatively small increases in risk. For example, the SMR for total cancer, based on 56 deaths, was 0.94 (95% CI 0.71–1.22), indicating that with 95% confidence mortality elevations greater than 1.22 can be excluded. Relatively low SMRs for most diseases of *a priori* interest could be excluded, i.e., the upper 95% confidence limit was 1.38 for lung cancer, 1.81 for non-malignant respiratory disease and 2.09 for liver cirrhosis.

Although there were no measurements of individual exposures to uranium, silica, vanadium, radon, radium or other radionuclides, we could classify workers with regard to type of employment (underground mine and/or uranium mill), length of employment and, based on job title, likely exposure to ore or uranium processing activities. These occupational classifications allowed us to infer risks associated with specific types of exposures. For example, the statistically significant increase in lung cancer was restricted to workers employed as underground miners exposed to radon and radon decay products, whereas the non-mining population was not at statistically significant increased risk of dying from any cause. Thus, our study provides little support for the hypothesis that non-mining jobs may increase cancer risk. Furthermore, there was no evidence that those employed in non-mining jobs for greater than 5 yrs (i.e., for those who might have received the greatest exposure to uranium ore and mill effluents) experienced greater risks than those potentially exposed for shorter times.

Exposure misclassification is possible because employment in other regions of the country was not generally known. Prior work for other companies was not always recorded, and work histories after leaving the Grants, New Mexico area were in large part not available. The sample of worker records sent to NIOSH, for example, indicated that up to 17% of the millers might have had unrecognised employment underground as uranium miners. Such unrecognised underground exposures to radon and radon progeny could be substantial with cumulative concentrations over 100 WLM (Boice *et al* 2007b), compared with the yearly non-occupational exposure to radon of about 0.2 WLM. In addition to work as underground miners, some millers were also found to have worked at other uranium mills in Arizona, Colorado and other states.

Low risks for heart disease and cerebrovascular disease are often reported in occupational studies and ascribed to the 'healthy worker effect' associated with selection for employment and for continued employment (Monson 1986, Howe *et al* 1988). The healthy worker effect often diminishes with time, especially for cancer deaths. While a healthy worker effect was suggested among millers who had a lower risk of death from heart disease compared with the general population, no similar effect was seen among miners.

The study is of mortality and not incidence of disease for which the number of events and quality of diagnoses would be expected to be higher. Most of the diseases of interest, e.g., lung cancer and bone cancer, however, have a high fatality rate so that mortality would reflect incidence fairly closely. Diseases that have a low fatality rate can be evaluated in mortality studies, although the statistical power to identify a significant increase in risk might be lower than for an incidence survey because of the smaller number of events.

Because of the mobility of the workforce, mortality rates for the entire United States were used to compute expected numbers of deaths since use of New Mexico rates likely would have overestimated the SMRs. Many workers after terminating employment left New Mexico and spent substantial portions of their lives living in other states. Just over 55% of the 818 deaths occurring after 1978 happened outside the state of New Mexico. Because New Mexico rates of mortality are generally lower than for the United States as a whole, the computed expected numbers accordingly would be lower and the SMRs higher than if based on comparisons with the United States. The all-cause SMR among all workers based on New Mexico rates was 1.19 compared with the SMR of 1.15 based on United States rates, although there were wider differences for specific cancer sites such as of the lung. A 'true' SMR is likely somewhere between that computed using New Mexico rates and that computed using United States rates. Fortunately, comparisons did not differ greatly and no changes in study conclusions would have resulted had New Mexico mortality rates been used.

Tobacco use was not known for individual workers. This important carcinogenic exposure causes nearly 90% of all lung cancers, and significant percentages of cancers of the kidney, oral cavity and pharynx and non-malignant respiratory disease (Surgeon General 2004, ACS 2008). Previous studies of workers occupationally exposed to uranium in New Mexico indicate that they tend to be heavy smokers (Samet *et al* 1991), although not the Navajo miners (Samet *et al* 1984a, Roscoe *et al* 1995).

The mortality before 1979 from all causes (SMR 1.24 based on US rates and 1.09 based on NM rates, $n = 185$) was similar to that after 1978 (SMR 1.15). However, SMRs for specific causes of death could not be determined because of the incomplete collection of death certificates in the early years before the National Death Index began. Although death certificates were sought for all 185 deaths occurring before 1979, information on state of death was so incomplete that only 105 (or 56.8%) certificates were obtained. Most of the acquired death certificates were from the state of New Mexico (75 or 71.4%); the other certificates resulted from requests made to 26 other states. Most of these early deaths with known causes were due to car and mine accidents, gun shot wounds and homicides ($n = 40$ or 21.6%). Lung cancer deaths were elevated, i.e., 14 lung cancer deaths occurred in contrast to 9.8 expected computed based on the person-years of observation between date of first employment to January 1, 1979. There was only one death each attributed to kidney cancer and leukaemia and there was no deaths from lymphoma. The consistency of the pre-1979 findings with those for deaths after 1978, i.e., no apparent increase overall and only lung cancer being significantly elevated, indicates that the incomplete cause of death information for these early deaths and their exclusion from study is unlikely to have biased study conclusions with regard to late effects from mining or milling exposures.

4.6. Conclusions

Consistent with prior studies of underground miners in New Mexico, the lung cancer excess among miners in our study is likely due to radon and radon decay products. In contrast, exposure to uranium dust and other mill products had little or no effect upon disease rates, consistent with current understanding (ATSDR 1999, IOM 2001, IARC 2001). The absence

of statistically significant excesses of leukaemia is as expected since uranium ore and mill products are not very radioactive and the emission of penetrating gamma radiation is low. This is one of the few studies of both uranium miners and uranium millers within the same workforce and the patterns of cancer clearly differ. Underground uranium miners were exposed to high levels of radon decay products and lung cancer resulted, but no other malignancy. Uranium millers were exposed to uranium dust, ore and mill effluents, but exposure to this heavy metal and mill processes did not increase the number of lung cancers or non-malignant diseases of the respiratory system and urinary tract. Our study adds to the growing body of evidence that uranium ore and uranium compounds are not human carcinogens, and that, in comparison to radon, uranium dust is not a major health hazard.

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Appendix 5

ORIGINAL ARTICLE

Mortality among a cohort of uranium mill workers: an update

L E Pinkerton, T F Bloom, M J Hein, E M Ward

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Aims: To evaluate the mortality experience of 1484 men employed in seven uranium mills in the Colorado Plateau for at least one year on or after 1 January 1940.
Methods: Vital status was updated through 1998, and life table analyses were conducted.
Results: Mortality from all causes and all cancers was less than expected based on US mortality rates. A statistically significant increase in non-malignant respiratory disease mortality and non-significant increases in mortality from lymphatic and haematopoietic malignancies other than leukaemia, lung cancer, and chronic renal disease were observed. The excess in lymphatic and haematopoietic cancer mortality was due to an increase in mortality from lymphosarcoma and reticulosarcoma and Hodgkin's disease. Within the category of non-malignant respiratory disease, mortality from emphysema and pneumoconioses and other respiratory disease was increased. Mortality from lung cancer and emphysema was higher among workers hired prior to 1955 when exposures to uranium, silica, and vanadium were presumably higher. Mortality from these causes of death did not increase with employment duration.
Conclusions: Although the observed excesses were consistent with our a priori hypotheses, positive trends with employment duration were not observed. Limitations included the small cohort size and limited power to detect a moderately increased risk for some outcomes of interest, the inability to estimate individual exposures, and the lack of smoking data. Because of these limitations, firm conclusions about the relation of the observed excesses in mortality and mill exposures are not possible.

In the United States, mining and milling of uranium ores to recover uranium for nuclear weapons began during World War II to support the Manhattan Project. Uranium bearing ores had been mined previously on a small scale, but mainly for the recovery of vanadium. Continued development and expansion of the industry after the war was promoted by a domestic uranium concentrate procurement programme that was established by the Atomic Energy Commission in 1947.[1] As early as 1949, health officials became concerned about the potential health risks associated with uranium mining and milling.[2]

The health risks associated with uranium mining have been extensively studied. Uranium miners have been found to have a substantially increased risk of death from lung cancer, which is associated with cumulative exposure to radon decay products.[3–5] Excess mortality from non-malignant respiratory diseases has also been found.[6] However, existing data concerning the health effects of uranium milling are limited. Waxweiler and colleagues reported a significantly increased risk of ''other non-malignant respiratory disease'' (standardised mortality ratio (SMR) = 2.50; observed (obs) = 39) among 2002 workers at seven uranium mills in the Colorado Plateau.[7] This category included emphysema, fibrosis, silicosis, and chronic obstructive pulmonary disease. Non-significant excesses were observed for lymphatic and haematopoietic malignancies other than leukaemia after 20 years latency (SMR = 2.3; obs = 6) and chronic renal disease (SMR = 1.67; obs = 6). In an earlier overlapping study of 662 uranium mill workers, Archer and colleagues observed an excess risk of mortality from lymphatic and haematopoietic malignancies other than leukaemia (SMR = 3.92; obs = 4).[8] Limited data from morbidity studies suggest that uranium millers may have an increased risk of pulmonary fibrosis[2] and renal tubular injury.[9]

The primary exposures of interest in uranium mills are uranium, silica, and vanadium containing dusts. Inhalation of uranium dust may pose an internal radiation hazard as well as the potential for chemical toxicity. High concentrations of radon and radon decay products, similar to the levels found in underground uranium mines, are not expected in the mills.

Because of continuing concern about the health effects of uranium milling, we extended the follow up of the cohort described by Waxweiler and colleagues.[7] The present report describes the mortality experience of the cohort through 21 additional years of observation. In addition, the risk of end stage renal disease was evaluated among the cohort.

Uranium milling process

The primary function of uranium mills is to extract and concentrate uranium from uranium containing ore to produce a semi-refined product known as yellowcake. Yellowcake is a chemically complex mixture of diuranates, basic uranyl sulphate, and hydrated uranium oxides that contains 80–96% uranium as U_3O_8, UO_3, and/or ammonium diuranate.[10] Yellowcake is used commercially to manufacture nuclear fuel for nuclear power and national defence purposes.

Conventional mills process uranium bearing ores from underground or open-pit mines. Until the mid-1970s, all yellowcake in the United States was produced at conventional uranium mills.[11] The main stages of the process in conventional mills involved: (1) ore handling and preparation; (2) extraction; (3) concentration and purification; and (4) precipitation, drying, and packaging. So-called ''upgrader'' facilities processed virgin ore that was initially too low in uranium content to process economically in a uranium mill. At an upgrader, a series of crushing, grinding, and chemical separation steps were employed to ''upgrade'' the percent

Main messages

- Potential exposures among uranium mill workers that may be associated with adverse health effects include uranium, silica, and vanadium containing dusts.
- We observed a statistically significant increase in mortality from non-malignant respiratory disease and non-significant increases in mortality from lymphatic and haematopoietic malignancies other than leukaemia, lung cancer, and chronic renal disease. These findings were consistent with our a priori hypotheses.
- The SMRs for lung cancer and emphysema among men hired before 1955, when exposures to uranium, silica, and vanadium were presumably higher, were significantly increased and greater than the SMRs observed among men hired in 1955 or later. However, mortality for causes of death observed to be in excess did not increase with employment duration.
- Limitations include a lack of smoking data, small cohort size and limited power to detect a moderately increased risk for some outcomes of interest, and the inability to estimate individual exposures to uranium, silica, and vanadium.

uranium contained in the final product, which was sent to a uranium mill for further processing. Unlike conventional uranium mills, upgrader facilities did not carry out concentration and purification of the uranium, and precipitation, drying, and packaging of yellowcake. In this paper, the term ''mill'' will be used in reference to both conventional uranium mills and upgrader facilities.

METHODS

Cohort description

The cohort was assembled from the personnel records obtained from the companies operating seven uranium mills (five conventional uranium mills and two upgraders). The original cohort described by Waxweiler and colleagues, which is referred to hereafter as the Waxweiler cohort, included 2002 men who had worked for at least one day after 1 January 1940, worked for at least one year in uranium mills, and never worked in underground uranium mines.[7] Because some of the work histories in the Waxweiler cohort were found to be coded inaccurately, we recoded all work histories. We also reviewed documentation from the original study to identify men who met the original cohort criteria, but had been omitted. Personnel records were obtained and work histories updated for cohort members who were still employed in 1971 when the personnel records were originally microfilmed. After re-coding the work histories, we limited the cohort to men who met the original cohort criteria, had never worked in an above-ground or underground uranium mine, and had worked for at least one year in the seven uranium mills before the personnel records were originally microfilmed in 1971 while the mills were operating to recover uranium and/or vanadium concentrates. The final cohort included 1485 men, 1438 (96.8%) of whom were in the Waxweiler cohort. Of the 564 workers not included in the current study, 103 (18.3%) worked in uranium mines, 318 (56.4%) never worked in one of the seven mills comprising the study, 141 (25.0%) worked for less than one year in the seven mills when they were operating, and one (0.2%) was excluded because the work history was incomplete. One woman whose gender was coded incorrectly in the Waxweiler cohort was also excluded.

Follow up

The vital status of all persons in the cohort was determined until 31 December 1998. Follow up included inquiry through the Social Security Administration, Internal Revenue Service, US Postal Service, National Death Index (NDI), and state bureaus of motor vehicles. Death certificates were obtained from state vital records offices for some deceased members of the cohort and coded by a trained nosologist according to the revision of the International Classification of Diseases in effect at the time of death. The causes of death for other deceased members of the cohort were obtained from the NDI.

To identify cohort members with treated end stage renal disease, the cohort was linked with the End Stage Renal Disease (ESRD) Program Management and Medical Information System (PMMIS) by name, social security number, and date of birth. The ESRD PMMIS is maintained by the Health Care Financing Administration (HCFA) and includes all individuals who received Medicare covered renal replacement therapy (dialysis or transplant) in 1977 or later. Approximately 93% of ESRD patients in the United States are included in the ESRD PMMIS.[12]

Analysis

The mortality experience of the cohort was analysed with the use of the National Institute for Occupational Safety and Health (NIOSH) modified life table analysis system (LTAS).[13 14] Each cohort member accumulated person-years at risk (PYAR) for each year of life after 1 January 1940 or completion of the one year eligibility period, whichever was later, until the date of death for deceased cohort members, the date last observed for persons lost to follow up, or the ending date of the study (31 December 1998) for cohort members known to be alive. Cohort members known to be alive after 1 January 1979 (the date that the NDI began) and not identified as deceased were assumed to be alive as of 31 December 1998. The PYAR were stratified into five year intervals by age and calendar time and were then multiplied by the appropriate US gender, race, and cause specific mortality rates to calculate the expected number of deaths for that stratum. The resulting expected numbers were summed across strata to obtain cause specific and total expected number of deaths. The ratio of observed to expected number of deaths was expressed as the standardised mortality ratio (SMR). Ninety five per cent confidence intervals (CI) were computed for the SMRs assuming a Poisson distribution for observed deaths. The mortality analysis was repeated using Colorado, New Mexico, Arizona, and Utah state mortality rates to generate expected numbers of deaths. In addition to analyses of underlying cause of death, all causes listed on the death certificate were analysed using multiple cause mortality methods described by Steenland and colleagues.[15] Multiple cause analyses are particularly important for diseases that may be prevalent at death but that are not the underlying cause of death.[15] In analyses using state or multiple cause mortality rates, person-years at risk started to accumulate on 1 January 1960, when the rates were first available, or completion of the one year eligibility period, whichever was later.

The end stage renal disease experience of the cohort was analysed using methods described by Calvert and colleagues.[16] Briefly, the modified life table analysis system was used to calculate PYAR, expected number of individuals developing ESRD, and standardised incidence ratios (SIRs) for ESRD. Since the ESRD PMMIS is considered incomplete prior to 1977, cohort members who died before this date were excluded from the ESRD analysis. PYAR for cohort members

who were alive on 1 January 1977 began to accumulate on this date. Cohort members accumulated PYAR until the first service date for those with ESRD, the date of death for deceased cohort members, the date last observed for those lost to follow up, or the ending date of the study for those known to be alive. The first service date for ESRD, which generally represents the date on which renal replacement therapy began, was used as a surrogate for the date of onset of ESRD. After the PYAR were stratified into five year intervals by age and calendar time, the PYAR were multiplied by the appropriate US ESRD incidence rates to calculate the expected number of cases for that stratum. The US incidence rates were developed by NIOSH from the HCFA PMMIS data and US census data as described elsewhere.[16] The expected number of treated ESRD cases in all strata were summed to yield the total expected number. The ratio of the observed to expected number of treated ESRD cases was expressed as the standardised incidence ratio (SIR). The SIR for four major categories of ESRD (systemic, non-systemic, other, and unknown) were also calculated.

We stratified SMRs and SIRs by duration of employment (1–2, 3–9, 10+ years), time since first employment (latency) (0–9, 10–19, 20+ years), and year of first employment (<1955, 1955+). In general, the cut points for duration of employment and time since first employment were retained from the original study; however, we lowered the cut point between the lowest and middle duration of employment categories so that the number of deaths in each category would be more similar. The cut point for year first employed was selected a priori based on the assumption that exposures in the earlier years (when there was little emphasis on dust control) would be higher than in later years. Duration of employment was based on employment in the seven cohort mills while they were operating to produce uranium and/or vanadium concentrates and included employment that occurred prior to the start of the follow up period. The analyses were repeated restricting the cohort to those who had worked in a conventional mill and to those who had worked in a conventional mill that produced both vanadium and uranium concentrates. Because of the potential impact of exposures encountered during other employment in the uranium industry, SMRs and SIRs were also conducted restricting the cohort to those without such employment. All analyses were done using the PC version of the LTAS[17] (http://www.cdc.gov/niosh/ltindex.html). Testing for heterogeneity and trend in the SMRs used the methods of Breslow and Day.[18]

Based on previous studies and the known toxic effects of uranium and silica, the a priori outcomes of interest in this study included non-malignant respiratory disease, chronic renal disease, lung cancer, and lymphatic and haematopoietic cancer other than leukaemia. Within the major category of non-malignant respiratory disease, the minor category ''pneumoconiosis and other respiratory diseases'' was of a priori interest.

RESULTS

A total of 1484 men contributing 49 925 person-years were included in the study. Table 1 presents the distribution of the cohort by vital status, plant type (conventional mill, upgrader), duration of employment, time since first employment, and first year of employment. Race was unknown for 642 (43.3%) members of the cohort. Because all workers of known race were white, workers of unknown race were classified as white in the analysis. In the total cohort, 656 (44.2%) men were alive, 810 (54.6%) were deceased, and 18 (1.2%) were lost to follow up. Causes of death were obtained from death certificates or the NDI for 794 (98.0%) of the individuals known to be deceased. Deaths with missing causes of death were included in the other and unknown causes category. The duration of employment of the cohort is relatively short with a median of 3.6 (range 1–36.3) years. Over half of the cohort was first employed prior to 1955. The median time since first employment, based on employment in the seven mills while they were operating, is 37 years.

Table 1 Characteristics of the study population

No. of workers	1485
Excluded from analysis*	1
Person-years at risk	49925
Mill type	
Conventional mill only	1412 (95.1%)
Upgrader only	44 (3.0%)
Both	28 (1.9%)
Vital status as of 31 Dec 1998	
Alive	656 (44.2%)
Dead	810 (54.6%)
Unknown	18 (1.2%)
Year of birth	1921 median
	1872–1951 range
Year of first employment†	
Prior to 1955	799 (53.8%)
1955 or later	685 (46.2%)
Duration of employment†	
1–2 years	634 (42.7%)
3–9 years	547 (36.9%)
10 + years	303 (20.4%)
Time since first employment†	
<10 years	76 (5.1%)
10–19 years	128 (8.6%)
20+ years	1280 (86.3%)

*Missing date of birth.
†Employment in the seven mills while operating to produce uranium and/or vanadium concentrates.

Almost all of the workers and person-years were from conventional uranium mills. Of the 1440 men who were employed at conventional mills, 1263 (87.7%) were employed at mills that recovered vanadium, 145 (10.1%) were employed at mills that did not recover vanadium, and 32 (2.2%) were employed both at mills that recovered vanadium and mills that did not recover vanadium. Among the entire cohort, 83 (5.6%) men had also been employed in other aspects of the uranium industry according to their employment application or other employment records.

Table 2 shows the results of the analysis for all causes of death. Mortality from all causes was less than expected, which is largely accounted for by fewer deaths from heart disease than expected. Mortality from all malignant neoplasms was also less than expected. Among the outcomes of a priori interest, a statistically significant increase in mortality from non-malignant respiratory disease (SMR = 1.43; 95% CI 1.16 to 1.73; obs = 100) and non-significant increases in mortality from trachea, bronchus, and lung cancer (SMR = 1.13; 95% CI 0.89 to 1.41; obs = 78), lymphatic and haematopoietic malignancies other than leukaemia (SMR = 1.44; 95% CI 0.83 to 2.35; obs = 16), and chronic renal disease (SMR = 1.35; 95% CI 0.58 to 2.67; obs = 8) were observed. The excess in mortality from lymphatic and haematopoietic malignancies was due to an excess in mortality from lymphosarcoma and reticulosarcoma (SMR = 1.74; 95% CI 0.48 to 4.46; obs = 4) and Hodgkin's disease (SMR = 3.30; 95% CI 0.90 to 8.43; obs = 4). Within the major category of non-malignant respiratory disease, mortality from emphysema (SMR = 1.96; 95% CI 1.21 to 2.99; obs = 21) and pneumoconioses and other respiratory disease (SMR = 1.68; 95% CI 1.26 to 2.21; obs = 52) was significantly increased. Among outcomes other than those of a priori interest, non-significant increases in mortality from other and unspecified cancers (SMR = 1.59; 95% CI 0.98 to 2.43; obs = 21) and accidents (SMR = 1.26; 95% CI 0.93 to 1.68;

Table 2 Uranium mill workers' mortality (since 1940, US referent rates): update of cohort to 1998

Underlying cause of death (ICD9 code)*	Obs	Exp	SMR	95% CI
All causes	810	877.66	0.92‡	0.86 to 0.99
All cancers (140–208)	184	204.12	0.90	0.78 to 1.04
Buccal and pharyngeal CA (140–149)	2	5.06	0.40	0.05 to 1.43
All digestive CA (150–159)	33	53.18	0.62§	0.43 to 0.87
Oesophagus (150)	1	5.06	0.20	0.01 to 1.10
Colon (152–153)	12	18.96	0.63	0.33 to 1.11
Rectal (154)	2	4.77	0.42	0.05 to 1.51
Liver and biliary (155–156)	4	5.04	0.79	0.22 to 2.03
Pancreas (157)	6	10.30	0.58	0.21 to 1.27
All respiratory CA (160–165)	78	72.29	1.08	0.85 to 1.35
Trachea, bronchus, and lung (162)	78	68.93	1.13	0.89 to 1.41
Male genital CA (185–187)	15	19.67	0.76	0.43 to 1.26
All urinary CA (188–189)	5	11.03	0.45	0.15 to 1.06
Kidney (189.0–189.2)	4	4.96	0.81	0.22 to 2.06
Leukaemia/aleukaemia (204–208)	5	7.62	0.66	0.21 to 1.53
Lymphatic and haematopoietic CA other than leukaemia (200–203)	16	11.08	1.44	0.83 to 2.35
Lymphosarcoma and reticulosarcoma (200)	4	2.29	1.74	0.48 to 4.46
Hodgkin's disease (201)	4	1.21	3.30	0.90 to 8.43
Other lymphatic and haematopoietic CA (202–203)	8	7.57	1.06	0.46 to 2.08
Other/unspecified CA (194–199)	21	13.20	1.59	0.98 to 2.43
Tuberculosis (001–008)	2	3.88	0.52	0.06 to 1.86
Diabetes mellitus (250)	10	14.60	0.68	0.33 to 1.26
Heart disease (390–398, 402, 404, 410–414, 420–429)	293	349.10	0.84§	0.75 to 0.94
Ischemic heart disease (410–414)	236	280.07	0.84§	0.74 to 0.96
Other circulatory disease (401, 403, 405, 415–417, 430–459)	69	83.06	0.83	0.65 to 1.05
Non-malignant respiratory disease (460–519)	100	70.16	1.43§	1.16 to 1.73
Pneumonia (480–486)	25	23.76	1.05	0.68 to 1.55
Chronic and unspecified bronchitis (490–491)	2	2.20	0.91	0.11 to 3.28
Emphysema (492)	21	10.72	1.96§	1.21 to 2.99
Pneumoconioses and other respiratory disease (470–478, 494–519)	52	30.87	1.68§	1.26 to 2.21
Non-malignant digestive disease (520–579)	23	36.91	0.62‡	0.39 to 0.94
Non-malignant genitourinary disease (580–629)	13	13.03	1.00	0.53 to 1.71
Acute renal disease (580–581, 584)	1	1.16	0.86	0.02 to 4.79
Chronic renal disease (582–583, 585–587)	8	5.91	1.35	0.58 to 2.67
Ill defined conditions (780–796, 798–799)	4	8.01	0.50	0.14 to 1.28
Accidents (E800–E949)	47	37.23	1.26	0.93 to 1.68
Violence (E950–E978)	18	17.73	1.02	0.60 to 1.60
Suicide (E950–E959)	15	14.19	1.06	0.59 to 1.74
Homicide (E960–E978)	3	3.54	0.85	0.18 to 2.48
Other and unknown causes	27†	14.04	1.92§	1.27 to 2.80

*International Classification of Disease codes, 9th revision.
†Includes 16 observed deaths with missing death certificates.
‡95% confidence interval excludes the null value (1.0).
§99% confidence interval excludes the null value (1.0).

obs = 47) were observed. The observed other and unspecified cancers were metastatic cancers of unknown primary site. Mortality from all digestive cancers was significantly less than expected (SMR = 0.62; 95% CI 0.43 to 0.87; obs = 33).

An analysis was also conducted (not shown) using US rate files for 1960 to 1999 which have 99 causes of death instead of 92 because these rate files include more detailed categories of non-malignant respiratory disease and slightly different categories of malignancies of the lymphatic and haematopoietic system. Of the 1484 cohort members, 89 (6.0%) were not included in this analysis because they had either died or were lost to follow up before 1960. Only one death from silicosis (SMR = 5.93; 95% CI 0.15 to 32.94) and two deaths from pneumoconioses other than silicosis and asbestosis (SMR = 2.29; 95% CI 0.28 to 8.25) were observed. The remainder of the excess in non-malignant respiratory disease mortality was due to a significant excess in mortality from emphysema (SMR = 1.83; 95% CI 1.10 to 2.86) and other respiratory diseases (SMR = 1.62; 95% CI 1.19 to 2.15). Most of the observed deaths from other respiratory diseases were due to chronic obstructive lung disease. In the category of malignancies of the lymphatic and haematopoietic system other than leukaemia, mortality was significantly increased for Hodgkin's disease (SMR = 4.01; 95% CI 1.09 to 10.25, obs = 4) and non-significantly increased for non-Hodgkin's lymphoma (SMR = 1.25; 95% CI 0.54 to 2.46; obs = 8).

In order to evaluate whether regional variations in mortality rates could explain the findings, analyses were conducted using state rates as the comparison population (table 3). State rates are not available before 1960 so men who had either died or were lost to follow up before 1960 were also excluded from this analysis. The excess in mortality from cancer of the trachea, bronchus, and lung (SMR = 1.51; 95% CI 1.19 to 1.89) based on state rates was statistically significant and greater than the excess based on US rates since 1960 (SMR = 1.13; 95% CI 0.89 to 1.42). In contrast, the excess in mortality from emphysema (SMR = 1.25; 95% CI 0.75 to 1.95) and other respiratory diseases (SMR = 1.35; 95% CI 0.99 to 1.79) was less than the excess based on US rates. Mortality from chronic renal disease was not increased based on state rates (SMR = 1.02; 95% CI 0.33 to 2.39; obs = 5) and was similar to that based on US rates since 1960 (SMR = 1.00; 95% CI 0.32 to 2.35). This is in contrast to the excess in mortality from chronic renal disease observed based on US rates since 1940.

Tables 4 and 5 show mortality according to duration of employment and time since first employment for selected causes of death based on US rates. Overall mortality was highest among those with the shortest duration of employment and lowest among those with the longest duration of employment. Similar trends with duration of employment were observed for mortality from lung cancer, non-malignant

Table 3 Uranium mill workers' mortality (since 1960) from selected causes of death (state referent rates): update of cohort to 1998

Underlying cause of death (ICD9 code)*	Obs	Exp	SMR	95% CI
All respiratory CA (160–165)	75	51.98	1.44‡	1.13 to 1.81
Trachea, bronchus, and lung (162)	75	49.73	1.51‡	1.19 to 1.89
Leukaemia/aleukaemia (204–208)	5	6.51	0.77	0.25 to 1.80
Lymphatic and haematopoietic CA other than leukaemia (200–203)	15	9.58	1.57	0.88 to 2.58
Non-Hodgkin's lymphoma (200, 202)	8	5.71	1.40	0.60 to 2.76
Hodgkin's disease (201)	4	0.94	4.24†	1.15 to 10.84
Myeloma (203)	3	2.93	1.02	0.21 to 3.00
Other/unspecified CA (187, 194–199)	22	11.93	1.84‡	1.16 to 2.79
Non-malignant respiratory diseases (460–519)	94	79.32	1.19	0.96 to 1.45
Chronic and unspecified bronchitis (490–491)	1	2.74	0.36	0.01 to 2.03
Emphysema (492)	19	15.22	1.25	0.75 to 1.95
Asbestosis (501)	0	0.12	0.00	0.00 to 30.62
Silicosis (502)	1	0.45	2.22	0.06 to 12.36
Other pneumoconioses (500, 503, 505)	2	0.40	5.04	0.61 to 18.19
Other respiratory diseases (470–478, 494–499, 504, 506–519)	47	34.86	1.35	0.99 to 1.79
Non-malignant genitourinary disease (580–629)	10	10.51	0.95	0.46 to 1.75
Acute renal disease (580–581, 584)	1	0.79	1.26	0.03 to 6.99
Chronic renal disease (582–583, 585–587)	5	4.89	1.02	0.33 to 2.39

*International Classification of Disease codes, 9th revision.
†95% confidence interval excludes the null value (1.0).
‡99% confidence interval excludes the null value (1.0).

respiratory disease, and emphysema. A positive trend between mortality and duration of employment was not observed for any of the selected causes of death except other and unspecified cancers. The excess in mortality from Hodgkin's disease was confined to 20 years or more since first employment. Mortality from Hodgkin's disease was significantly increased over sevenfold among this group, but the confidence interval around the point estimate was wide (95% CI 1.96 to 18.40).

Mortality was also examined (not shown) by date of hire (pre-1955 versus 1955 or later). There appeared to be a relation between an earlier date of hire and increased mortality from trachea, bronchus, and lung cancer (prior to 1955: SMR = 1.34, 95% CI 1.02 to 1.74; 1955 or later: SMR = 0.79, 95% CI 0.49 to 1.21). Mortality from emphysema was also higher among men hired prior to 1955 (SMR = 2.22; 95% CI 1.29 to 3.56; obs = 17) than among men hired in 1955 or later (SMR = 1.30; 95% CI 0.36 to 3.33; obs = 4), but mortality from pneumoconiosis and other respiratory disease was similar among men hired prior to 1955 (SMR = 1.69; 95% CI 1.17 to 2.36) and men hired in 1955 or later (SMR = 1.68; 95% CI 0.99 to 2.65).

Analyses of multiple causes of death and end stage renal disease incidence were conducted to further evaluate the risk of renal disease among the cohort. The risk of chronic renal disease mortality was not increased (SMR = 1.05; 95% CI 0.69 to 1.54, obs = 26) in the multiple causes of death analysis. The risk of treated end stage renal disease was less than expected overall (SIR = 0.71; 95% CI 0.26 to 1.55, obs = 6). The risk of treated end stage renal disease of unknown aetiology was increased (SIR = 2.73; 95% CI 0.56 to 7.98, obs = 3). This finding was based on three observed cases and the confidence interval was wide. The primary cause of renal failure was missing in the ESRD PMMIS for two of the three observed cases, raising the possibility that these cases were misclassified. Death certificates were available for these cases; renal disease was mentioned on the death certificate for both, but not a specific type or aetiology of renal disease.

Similar results were obtained when the cohort was restricted to men who were employed in conventional mills and when the cohort was restricted to men who were employed in conventional mills that produced both uranium and vanadium concentrates. Results were also similar when

Table 4 Uranium mill workers' mortality (since 1940) from selected causes of death by duration of employment (US referent rates): update of cohort to 1998

	Duration of employment (years)			
Underlying cause of death	1–2 SMR (obs)	3–9 SMR (obs)	⩾10 SMR (obs)	
All deaths	1.01 (352)	0.91 (295)	0.80 (163)†	‡
All cancers	0.94 (75)	0.91 (68)	0.83 (41)	
Trachea, bronchus, and lung CA	1.35 (36)	1.27 (32)	0.58 (10)	‡
Lymphatic and haematopoietic CA other than leukaemia	1.38 (6)	1.22 (5)	1.90 (5)	
Lymphosarcoma and reticulosarcoma	2.15 (2)	1.15 (1)	2.03 (1)	
Hodgkin's disease	1.91 (1)	4.25 (2)	4.57 (1)	
Other lymphatic and haematopoietic CA	1.03 (3)	0.73 (2)	1.56 (3)	
Other/unspecified CA	1.16 (6)	1.65 (8)	2.19 (7)	
Non-malignant respiratory disease	1.99 (53)†	1.12 (29)	1.02 (18)	‡
Emphysema	2.69 (11)†	1.79 (7)	1.11 (3)	
Pneumoconioses and other respiratory diseases	2.53 (29)†	1.07 (12)	1.35 (11)	
Chronic renal disease	1.27 (3)	1.33 (3)	1.53 (2)	

*95% confidence interval excludes the null value (1.0).
†99% confidence interval excludes the null value (1.0).
‡Test for trend p value <0.05.

Table 5 Uranium mill workers' mortality (since 1940) from selected causes of death by length of time since first employment (US referent rates): update of cohort to 1998

	Time since first employment (years)		
Underlying cause of death	<10 SMR (obs)	10–19 SMR (obs)	⩾20 SMR (obs)
All deaths	0.95 (68)	0.87 (125)	0.93 (617)
All cancers	0.62 (7)	0.88 (25)	0.92 (152)
Trachea, bronchus, and lung CA	0.36 (1)	1.45 (13)	1.12 (64)
Lymphatic and haematopoietic CA other than leukaemia	1.35 (1)	0.00 (0)	1.72 (15)
Lymphosarcoma and reticulosarcoma	3.33 (1)	0.00 (0)	2.24 (3)
Hodgkin's disease	0.00 (0)	0.00 (0)	7.19 (4)**
Other lymphatic and haematopoietic CA	0.00 (0)	0.00 (0)	1.18 (8)
Other/unspecified CA	0.00 (0)	1.21 (2)	1.76 (19)*
Non-malignant respiratory disease	1.32 (4)	1.48 (11)	1.42 (85)**
Emphysema	2.39 (1)	2.21 (4)	1.89 (16)*
Pneumoconioses and other respiratory diseases	3.73 (2)	2.24 (4)	1.61 (46)**
Chronic renal disease	3.95 (3)	1.23 (1)	0.92 (4)

*95% confidence interval excludes the null value (1.0).
**99% confidence interval excludes the null value (1.0).

the cohort was restricted to men without known employment in other aspects of the uranium industry.

DISCUSSION

Uranium exposure presents both chemical and radiological hazard potentials. Both the chemical and radiological toxicity are influenced by the biological solubility of a given uranium compound. Poorly soluble uranium compounds are cleared slowly from the lungs and pose a potential internal radiation hazard. More soluble compounds are absorbed rapidly from the lungs, decreasing the radiation hazard, but increasing the potential for renal toxicity.[19 20] In the ore handling and preparation areas of the mills, the uranium in ore dusts consists mostly of insoluble uranium oxides with a relatively small fraction of the more soluble uranium compounds. The potential for exposure to the long lived alpha emitters (uranium-238, uranium-234, thorium-230, radium-226, and lead-210) is greatest in these areas of the mill. In the yellowcake drying and packaging areas of the mill, the uranium in yellowcake consists of a complex mixture of uranium compounds of varying solubility. The composition and solubility of the yellowcake product depends on the drying temperature employed.[19 21] In mills that dry the product at relatively low temperatures (100–150°C), the yellowcake product is high in ammonium diuranate [$(NH_4)_2U_2O_7$] which is highly soluble in lung fluids; in mills that dry the product at relatively high temperatures (370–538°C), the yellowcake is high in uranium oxide (U_3O_8) which is mostly insoluble in lung fluids.[21 22] Based on available data on drying temperatures and drying equipment, four of the five conventional mills in this study used relatively high drying temperatures. The fifth mill did not prepare a dried yellowcake product; rather, it produced filter press cake or a uranium product liquor, depending on the year of operation. Accordingly, most mill workers in this study worked in mills that probably produced yellowcake of relatively low solubility.

Both human and animal data suggest that insoluble uranium compounds and thorium accumulate in the tracheobronchial lymph nodes.[23–26] Because of this, it has been suggested that studies of early uranium workers evaluate the effects on lymphatic tissues.[25] In the previous study of workers at the mills in this study, a significant increase in mortality from lymphatic and haematopoietic malignancies other than leukaemia was observed after 20 years latency, based on six deaths.[7] We also found an excess in mortality from lymphatic and haematopoietic malignancies other than leukaemia but the magnitude of the excess was less than the excess observed in the previous study. The observed excess was due to an excess in both Hodgkin's disease mortality and lymphosarcoma and reticulosarcoma mortality based on four observed deaths each. The ability to evaluate exposure response relations, using duration of employment as a surrogate of exposure, was limited by the small number of observed deaths from these cancers. Of the eight observed deaths due to Hodgkin's disease, lymphosarcoma, and reticulosarcoma in this study, three were observed in the previous study and one was observed in the study by Archer and colleagues.[8]

Hodgkin's disease and non-Hodgkin's lymphoma, a group of lymphomas which includes lymphosarcoma and reticulosarcoma, have not been clearly linked to radiation.[27 28] Data on the risk of death from Hodgkin's disease and non-Hodgkin's lymphoma among uranium or thorium workers are limited. An increased risk of Hodgkin's disease mortality and lymphosarcoma and reticulosarcoma mortality has been observed among uranium processing workers at the Fernald Feed Materials Production Center near Cincinnati, Ohio (SMR = 2.04, 95% CI 0.74 to 4.43, obs = 6; and SMR = 1.67, 95% CI 0.72 to 3.29, obs = 8, respectively)[29] and thorium processing workers (SMR = 1.64, 95% CI 0.33 to 4.79, obs = 3; and SMR = 1.14, 95% CI 0.23 to 3.34, obs = 3, respectively),[30] but not among uranium processing workers at the Y-12 plant at Oak Ridge, Tennessee[31] and Mallinckrodt Chemical Works in St Louis, Missouri[32] or among a combined cohort of uranium and other miners from 11 studies.[33] Hodgkin's disease mortality and incidence and non-Hodgkin's lymphoma incidence was associated with cumulative external radiation dose among workers at the Springsfield uranium production facility; the effects of internal exposures were not evaluated.[34] In general, these studies, like the current study, are limited by the small number of deaths from Hodgkin's disease and non-Hodgkin's lymphoma among exposed workers.

A new finding in this update not previously reported was a small increase in mortality from cancer of the trachea, bronchus, and lung, particularly relative to state rates. We also observed an increased risk of mortality from non-malignant respiratory disease. Mortality from lung cancer was higher based on state rates than US rates, whereas mortality from non-malignant respiratory disease was lower based on state rates than US rates. This is consistent with the relatively low smoking attributable mortality and relatively high chronic obstructive lung disease mortality in Arizona, Colorado, and New Mexico compared to other states.[35] The reason for the discrepancy in smoking-attributable mortality

and chronic obstructive lung disease mortality in many inland western states is unknown. However, the results suggest that regional differences in mortality may explain, in part, the observed excess in non-malignant respiratory disease mortality based on US rates.

The excess in both lung cancer mortality and emphysema mortality was greater among workers hired prior to 1955, when there was little emphasis on dust control and exposures to uranium and silica containing dusts were presumably higher. However, mortality from lung cancer and non-malignant respiratory disease was inversely related to duration of employment. We found no evidence that workers who were hired prior to 1955 were more likely to be short term workers. The inverse relation between lung cancer and emphysema mortality and duration of employment in this study may be a reflection of the healthy worker survivor effect, in which individuals who remain in the workforce over time tend to be healthier than those who leave.[36] Duration of employment may also be a poor surrogate of exposure in this study since exposures are thought to have varied considerably by mill area and over time.

Some data suggest that uranium workers other than miners may be at increased risk of lung cancer[29 31] and non-malignant respiratory disease.[37] Uranium ore dust has been shown to induce pulmonary lesions in animals[23 38 39] and lung cancer in rats.[40] Silica exposure has been reported to lead to the development of silicosis, emphysema, obstructive airways disease, and lymph node fibrosis.[41] Although the carcinogenicity of silica continues to be debated in the scientific community, several investigators have showed an increased risk of lung cancer among workers exposed to silica.[42–44] Vanadium containing compounds have known acute respiratory effects,[45] but it is less clear whether exposure to vanadium can lead to chronic non-malignant respiratory disease.[45 46] In this study, we only observed three deaths from silicosis and unspecified pneumoconioses. The majority of the excess in non-malignant respiratory disease mortality was due to mortality from emphysema and other respiratory disease.

Other potential explanations also exist for the observed excesses in mortality from lung cancer and non-malignant respiratory disease mortality. Smoking data are not available for this cohort, and differences in smoking habits between the cohort and the general population may partially explain the excesses observed. White men in the Colorado Plateau uranium miners cohort were heavy smokers,[6 47] but it is unknown whether the smoking habits of uranium mill workers who never worked underground in uranium mines would be similar to these miners. Even if the mill workers in this study were more likely to smoke than the general population, other investigators have shown that smoking is unlikely to account for SMRs above 1.3 for lung cancer and other smoking related diseases.[48] Other potential factors that may contribute to these excesses include unknown employment in underground uranium mines and employment in other mines with increased levels of radon and radon decay products. It is unlikely that the cohort included many mill workers who also worked as uranium miners. Mill workers who also worked in uranium mines were identified by reviewing the work history records and by matching the cohort to a NIOSH file of over 18 000 uranium miners. All identified uranium miners were excluded from the final cohort. However, members of the cohort may have been more likely to work in other types of mines than the general population.

We found a small non-significant excess in chronic renal disease when using US rates as a comparison; this excess was not apparent when only deaths between 1960 and 1998 were analysed (both underlying cause and multiple cause). Renal effects have been observed among silica exposed workers. Goldminers and industrial sand workers exposed to silica have been found to be at excess risk of death from renal disease and to have increased renal disease incidence.[16 49 50] Low level β_2 microglobulinuria and aminoaciduria has been observed among uranium mill workers exposed to soluble uranium compounds at a mill not in the current study,[9] but little data on chronic renal disease mortality among uranium workers exist. An increase in mortality from chronic nephritis (SMR = 1.88; 95% CI 0.75 to 3.81) was observed among uranium processing workers at Mallinckrodt, based on six observed deaths.[32] An excess in chronic renal disease mortality has been observed among uranium miners (SMR = 1.6; 95% CI 0.7 to 3.0, obs = 9), but the observed excess was not related to duration of employment.[6]

This study may have underestimated the risk of ESRD and renal disease mortality associated with uranium milling. We observed an excess in chronic renal disease mortality during the follow up period 1940–59, but not during the follow up period 1960–98. This suggests that the exclusion of cohort members who died or were lost to follow up prior to 1960 may have been a significant limitation in our ability to evaluate the risk of ESRD and chronic renal disease mortality using multiple cause of death data. Because the cohort is relatively old, approximately 22% of the cohort was excluded from the analysis of ESRD because they died or were lost to follow up before the ESRD PMMIS is first considered complete, which also reduced the statistical power of the ESRD analysis. In addition, the majority of the mill workers in this study were probably exposed to relatively insoluble forms of uranium. The risk of renal disease may be higher in mills using relatively low drying temperatures where the potential for exposure to soluble forms of uranium is greater. The study evaluated chronic renal disease mortality and ESRD and was not able to evaluate the risk of less severe renal effects.

In conclusion, we observed an excess in mortality from haematopoietic and lymphatic malignancies other than leukaemia, trachea, bronchus, and lung cancer, non-malignant respiratory disease, and chronic renal disease. Some of these excesses were based on a small number of deaths and the confidence intervals around the point estimates were wide. Limitations include the lack of smoking data, small cohort size and limited power to detect a moderately increased risk of some of the a priori outcomes of interest, and the inability to evaluate exposure-response relations using individual estimates of exposure to uranium, silica, and vanadium. Because of these limitations and the lack of a positive trend between the observed excesses and duration of employment, firm conclusions about the relation of the observed excesses and mill exposures are not possible.

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The manuscript was written by employees of the US government as part of their official duties; the work is therefore not subject to copyright.

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Appendix 6

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)

Appendix 7

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 8

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

Werner Olipitz, Dominika Wiktor-Brown, Joe Shuga, Bo Pang, Jose McFaline, Pallavi Lonkar, Aline Thomas, James T. Mutamba, Joel S. Greenberger, Leona D. Samson, Peter C. Dedon, Jacquelyn C. Yanch, Bevin P. Engelward

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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 Ng/ml) (National Cancer Institute, Bethesda, MD) and tetrahydrouridine (50 Ng/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 100Nl 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 Rg/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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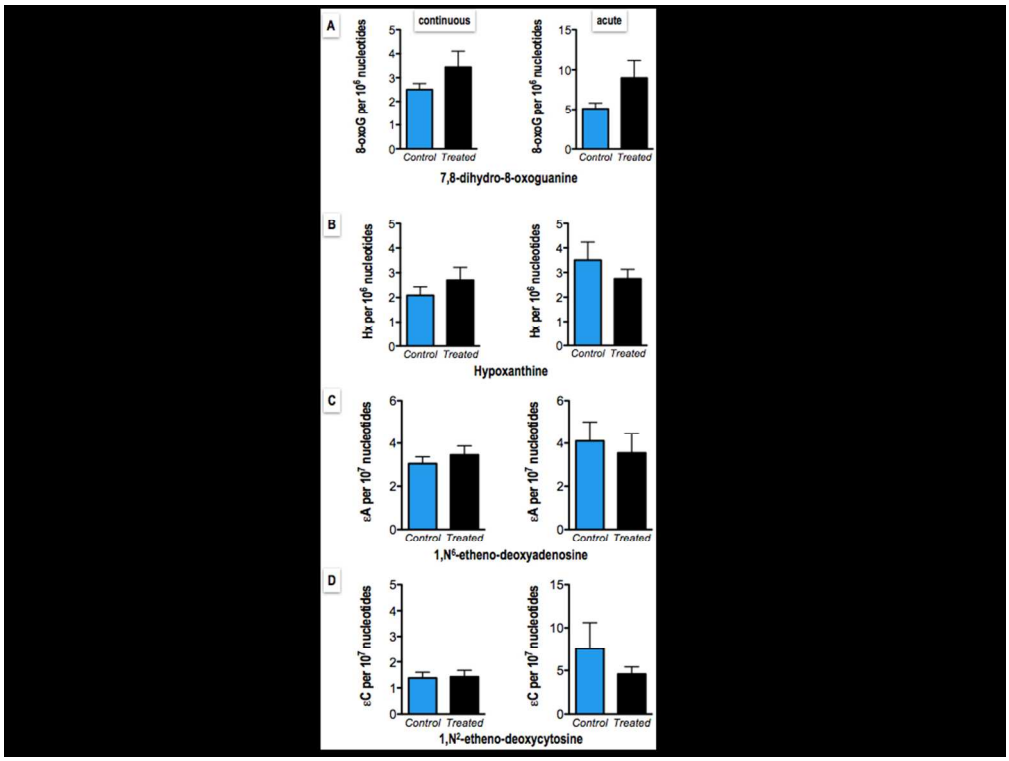
Figure Legends

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 Nm (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) (*$p < 0.05$).



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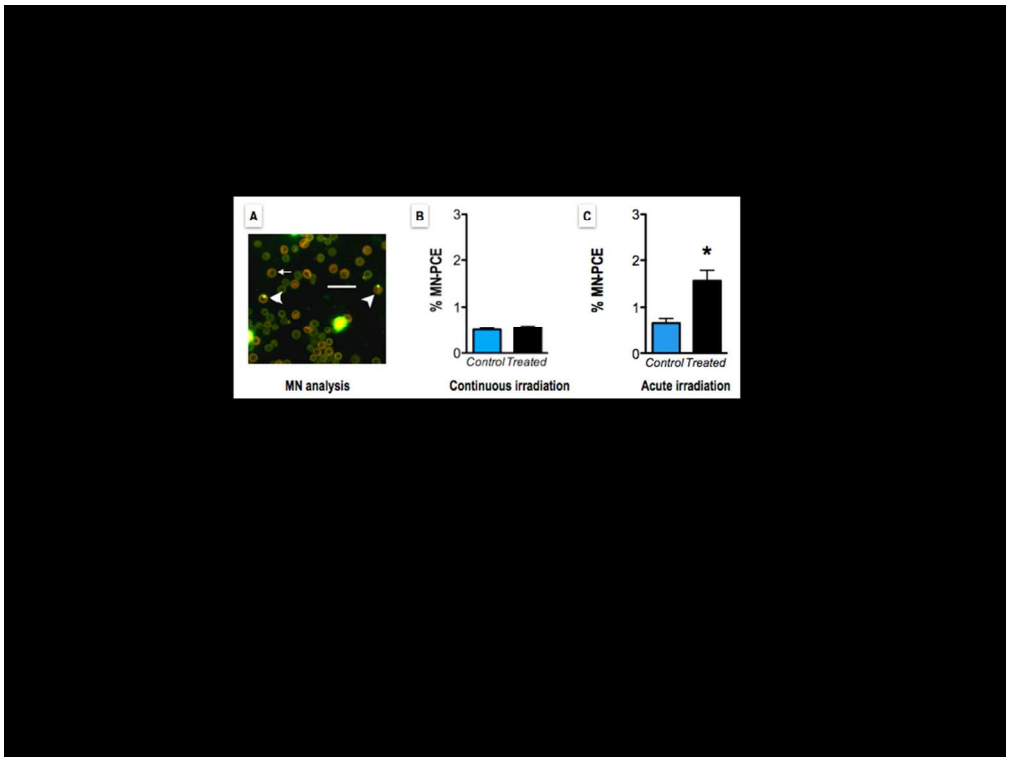

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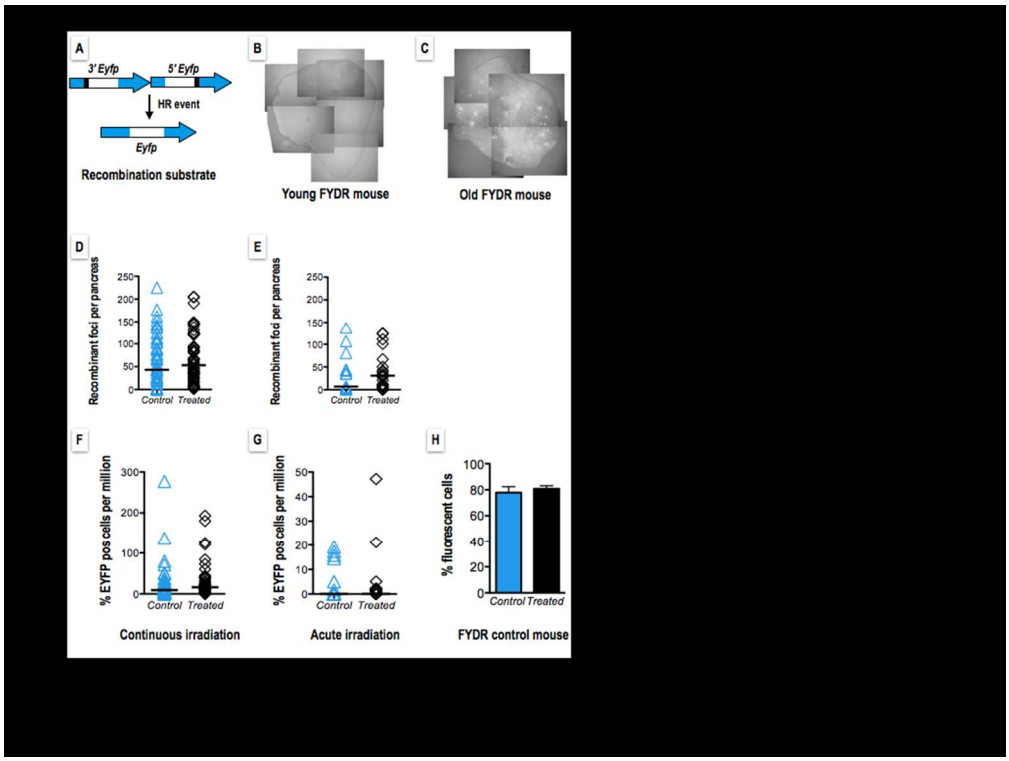

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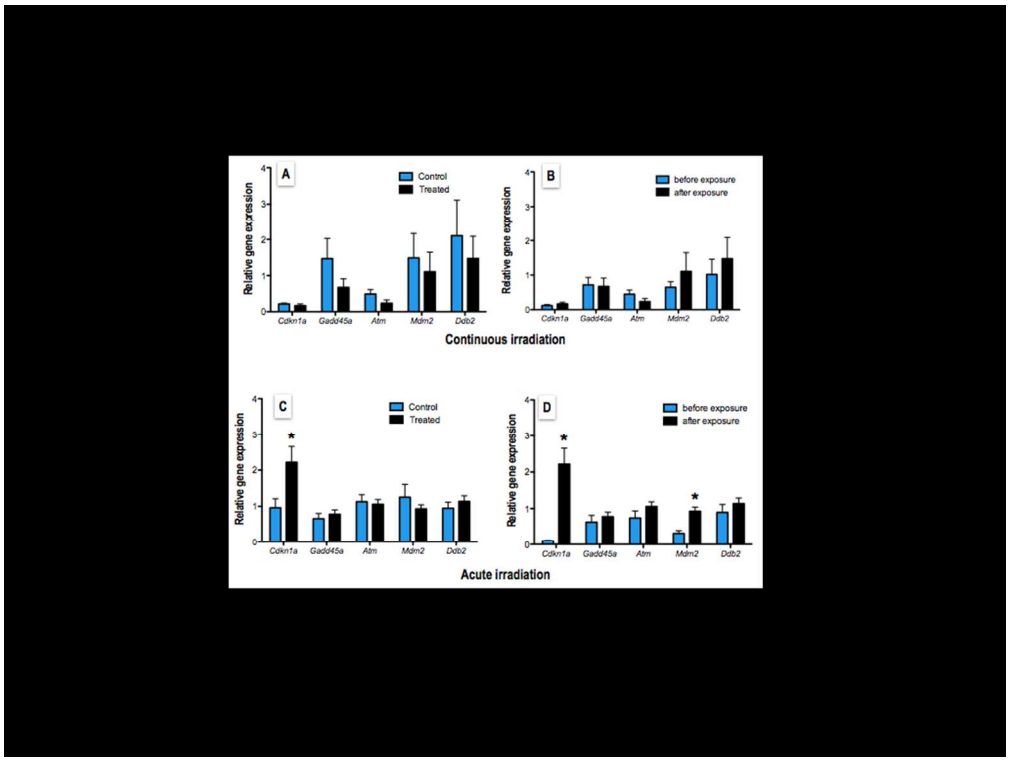

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Appendix 9

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Five-Hundred Life-Saving Interventions and Their Cost-Effectiveness

Tammy 0. Tengs,[1] Miriam E. Adams,[2] Joseph S. Pliskin,[3,6] Dana Gelb Safran,[4] Joanna E. Siegel,[5,7] Milton C. Weinstein,[6,7] and John D. Graham[6,7]

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We gathered information on the cost-effectiveness of life-saving interventions in the United States from publicly available economic analyses. "Life-saving interventions" were defined as any behavioral and/or technological strategy that reduces the probability of premature death among a specified target population. We defined cost-effectiveness as the net resource costs of an intervention per year of life saved. To improve the comparability of cost-effectiveness ratios arrived at with diverse methods. we established fixed definitional goals and revised published estimates, when necessary and feasible. to meet these goals. The 587 interventions identified ranged from those that save more resources than they cost. to those costing more than 10 billion dollars per year of life saved. Overall. the median intervention costs S-12.000 per life-year saved. The median medical intervention costs $19,000/life-year; injury reduction $48,000/life-year; and toxin control $2,800,000/life-year. Cost/life-year ratios and bibliographic references for more than 500 life-saving interventions are provided.

KEY WORDS: Cost-effectiveness; economic evaluation: life-saving; resource allocation.

1. INTRODUCTION

Risk analysts have long been interested in strategies that can reduce mortality risks at reasonable cost to the public. Based on anecdotal and selective comparisons. analysts have noted that the cost-effectiveness of risk-reduction opportunities varies enormously, often over several orders of magnitude.[1–5] This kind of variation is unnerving because economic efficiency in promoting survival requires that the marginal benefit per dollar spent be equal across investments.

Despite continuing interest in cost-effectiveness, we could find no comprehensive and accessible data set on the estimated costs and effectiveness of risk management options. Such a dataset could provide useful comparative information for risk analysts as well as practical information for decision makers who must allocate scarce resources. To this end, we report cost-effectiveness ratios for more than 500 life-saving interventions across all sectors of American society.

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2. METHODS

2.1. Literature Review

We performed a comprehensive search for publicly available economic analyses of life-saving interventions.

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"Life-saving interventions" were defined as any behavioral and/or technological strategy that reduces the probability of premature death among a specified target population. To identify analyses we used several on-line databases, examined the bibliographies of textbooks and review articles, and obtained full manuscripts of conference abstracts. Analyses retained for review met the following three criteria: (1) written in the English language, (2) contained information on interventions relevant to the United States, and (3) reported cost per year of life saved, or contained sufficient information to calculate this ratio. Most analyses were scientific journal articles or government regulatory impact analyses, but some were internal government memos, reports issued by research organizations, or unpublished manuscripts.

Two trained reviewers (from a total of 11 reviewers) read each document. Each reviewer recorded 52 items, including detailed descriptions of the nature of the life-saving intervention, the baseline intervention to which it was compared, the target population at risk, and cost per year of life saved. The two reviewers worked independently, then met and came to consensus on the content of the document.

Approximately 1200 documents were identified for retrieval. Of these 1200 documents, 229 met our selection criteria. The 229 documents contained sufficient information for reviewers to calculate cost/life-year saved for 587 interventions.

2.2. Definitional Goals

To increase the comparability of cost-effectiveness estimates drawn from different economic analyses, we established seven definitional goals. When an estimate failed to comply with a goal, reviewers attempted to revise the estimate to improve compliance.[8] In general, reviewers used only the irformation provided in the document to revise estimates. The seven definitional goals were:

I. Cost-effectiveness estimates should be in the form of "cost per year of life saved." Cost/life saved estimates should be transformed to cost/life-year by considering the average number of years of life saved when a premature death is averted.
2. Costs and effectiveness should be evaluated from the societal perspective.
3. Costs should be "direct." Indirect costs, such as foregone earnings, should be excluded.
4. Costs and effectiveness should be "net." Any resource savings or mortality risks induced by the intervention should be subtracted out.'
5. Future costs and life-years saved should all be discounted to their present value at a rate of 5%.
6. Cost-effectiveness ratios should be marginal or "incremental." Both costs and effectiveness should be evaluated with respect to a well-defined baseline alternative.
7. Costs should be expressed in 1993 dollars using the general consumer price index.

2.3. Categorization

Interventions were classified according to four-way typology. (1) Intervention Type (Fatal Injury Reduction, Medicine, or Toxin Control), (2) Sector of Society (Environmental, Health Care, Occupational, Residential, or Transportation), (3) Regulatory Agency (CPSC, EPA, FAA, NHTSA, OSHA, or None), and (4) Prevention Stage (Primary, Secondary, or Tertiary).

Interventions we classified as primary prevention are designed to completely avert the occurrence of disease or injury; those classified as secondary prevention are intended to slow, halt, or reverse the progression of disease or injury through early detection and intervention; and interventions classified as tertiary prevention include all medical or surgical treatments designed to limit disability after harm has occurred, and to promote the highest attainable level of functioning among individuals with irreversible or chronic disease.[6]

3. RESULTS

Cost-effectiveness estimates for more than 500 life-saving interventions appear in Appendix A. This table is separated into three sections according to the type of intervention: Fatal Injury Reduction, Toxin Control, and Medicine. The first column of Appendix A contains the reference number assigned to the document from which the cost-effectiveness estimate was drawn (references are in Appendix B.) The second column contains a very brief description of the life-saving intervention. The

[8] Appendices describing the cost-effectiveness formulas used operationalize these definitional goals, along with some examples of the calculations made by reviewers of the economic analyses, are available from Dr. Tengs.

[9] If savings exceed costs. the result could be negative, so that cost-effectiveness ratio might be ≤$0.

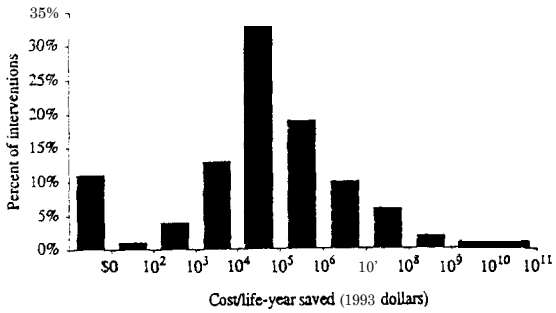

Fig. 1. Distribution of cost/life-year saved estimates (n = 587).

baseline intervention to which the life-saving intervention was compared appears parenthetically as "(vs. ——)" when the author described it. The last column of Appendix A contains the cost per year of life saved in 1993 dollars.

As shown in Fig. 1, these interventions range from those that save more resources than they consume, to those costing more than 10 billion dollars per year of life saved. Furthermore. variation over 11 orders of magnitude exists in almost every category.

In addition to the large variation within categories, variation in cost-effectiveness also exists between categories. As summarized in Table I, while the median intervention described in the literature costs $42,000 per life-year saved (n = 587), the median medical intervention costs $19,000/life-year (n = 310); the median injury reduction intervention costs $48,000/life-year (n = 133); and the median toxin control intervention costs $2,800,000/life-year (n = 144).

Cost-effectiveness also varies as a function of the sector of society in which the intervention is found. For example, as shown in Table I, the median intervention in the transportation sector costs $56,000/life-year saved (n = 87), while the median intervention in the occupational sector costs $350,000/life-year (n = 36). Further dividing occupational interventions into those that avert fatal injuries and those that involve the control of toxins, reveals medians of $68,000/life-year (n = 16) and $1,400,000/life-year (n = 20), respectively.

As noted in Table II, the median cost-effectiveness estimate among those interventions classified as primary prevention is $79,000/life-year saved (n = 373), exceeding secondary prevention at $23,000/life-year (*n* = 111) and tertiary prevention at $22,000/life-year (n = 103). However, if medicine is considered in isolation, we find that primary prevention is more cost-effective that secondary or tertiary prevention at $5,000/life-year (*n* = 96).

Table I. Median of Cost/Life-Year Saved Estimates as a Function of Sector of Society and Type of Intervention

	Type of intervention			
Sector of society	Medicine	Fatal injury reduction	Toxin control	All
Health care	$ 19,000 (*n*=310)	N/A[a]	N/A	$ 19,000 (*n*=310)
Residential	N/A	$36,000 (*n*=30)	N/A	536.000 (*n*=30)
Transportation	N/A	956,000 (*n*=87)	NIA	$56,000 (*n*=87)
Occupational	N/A	568,000 (*n*= 16)	s1,400,000 (*n*=20)	$350,000 (*n*=36)
Environmental	N/A	NIA	$4,200,000 (*n*= 124)	$4,200,000 (*n*= 124)
All	s 19,000 (*n*=310)	$48,000 (*n*= 133)	$2,800,000 (*n*= 144)	$42,000 (*n*=587)

[a] Not applicable by definition.

Table II. Median of Cost/Life-Year Saved Estimates as a Function of Prevention Stage and Type of Intervention

	Type of intervetion			
Prevention stage	Medicine	Fatal injury reduction	Toxin *control*	All
Primary	$5,000 (*n*=96)	$48,000 (*n*=133)	$2,800,000 (*n*=144)	579,000 (*n*=373)
Secondary	$23,000 (*n*=111)	N/A	N/A	$23,000 (*n*=111)
Tertiary	$22,000 (*n*= 103)	N/A	N/A	522,000 (*n*=103)
All	$19,000 (*n*=310)	548,000 (*n*= 133)	$2,800,000 (*n*=144)	$42,000 (*n*=587)

The median cost-effectiveness of proposed government regulations for which we have data also varies considerably. Medians for each agency are as follows: Federal Aviation Administration, $23,000/life-year (n = 4); Consumer Product Safety Commission, $68,000/life-year (*n* = 11); National Highway Traffic Safety Administration, $78,000/life-year (n = 3 1); Occupational Safety and Health Administration, $88,000/life-year (*n* = 16); and Environmental Protection Agency, $7,600,000/life-year (*n* = 89).

4. LIMITATIONS

This compilation of existing data represents the most ambitious effort ever undertaken to amass cost-effectiveness information across all sectors of society. In

addition, our work to bring diverse estimates into compliance with a set of definitional goals has improved the comparability of cost-effectiveness estimates that were originally derived by different authors using a variety of methods. Nevertheless, several caveats are warranted to aid the reader in interpreting these results.

First. the accuracy of the results presented herein is limited by the accuracy of the data and assumptions upon which the original analyses were based. There remains considerable uncertainty and controversy about the cost consequences and survival benefits of some interventions. This is particularly true for toxin control interventions where authors often extrapolate from animal data. In addition, due to insufficient information in some economic analyses, reviewers were not always successful in bringing estimates into conformity with definitional goals. For example, if the original author did not report the monetary savings due to the reduction in nonfatal injuries requiring treatment, we were unable to "net out" savings, and so the costs used to calcula cost-effectiveness ratios remain gross. While some of these omissions are important, others are largely inconsequential given the relative size of cost and effectiveness estimates.

Second, the life-saving interventions described in this report include those that are fully implemented, those that are only partially implemented, and those that are not implemented at all. These interventions are best thought of as opportunities for investment. While they may offer insight into actual investments in life-saving, the cost-effectiveness of possible and actual investments are not equivalent. Work on the economic efficiency of actual expenditures is in progress.[9]

Third, this dataset may not represent a random sample of all life-saving interventions. so the generalizability of any descriptive statistics may be limited. This because interventions that have been subjected to economic analysis may not represent a random sample of all life-saving interventions due, for example, to publication bias. That is, those economic analyses that researchers have chosen to perform and journal editors have chosen to publish may be disproportionately expensive or inexpensive. However, the statistics presented herein are certainly applicable to the 587 life-saving interventions in our dataset which by themselves comprise a vast and varied set, worthy of interest even without generalization.

Finally, we recognize that many of these interventions have benefits other than survival, as well as adverse consequences other than costs. For example, interventions that reduce fatal injuries in some people may also reduce nonfatal injuries in others; interventions designed to control toxins in the environment may have short-term effects on survival, but also long-term cumulative effects on the ecosystem; medicine and surgery may increase quantity of life, while simultaneously increasing (or even decreasing) quality of life.

5. CONCLUSIONS

This compilation of available cost-effectiveness data reveals that there is enormous variation in the cost of saving one year of life and these differences exist both within and between categories. Such a result is important because efficiency in promoting survival requires that the marginal benefit per dollar spent be the same across programs. Where there are investment inequalities, more lives could be saved by shifting resources. It is our hope that this information will expand the perspective of risk analysts while aiding future resource allocation decisions.

APPENDIX A. FIVE-HUNDRED LIFE-SAVING INTERVENTIONS AND THEIR COST-EFFECTIVENESS

Ref no.[a]	Life-saving intervention[b]	Cost/life-year[c]
	Fatal injury reduction	
	Airplane safety	
174	Automatic fire extinguishers in airplane lavatory trash receptacles	516,000
173	Fiberglass fire-blocking airplane seat cushions	$17,000
174	Smoke detectors in airplane lavatories	$30,000
172	Emergency signs, floor lighting etc. (vs. upper lighting only) in airplanes	554,000
	Automobile design improvements	
190	Install windshields with adhesive bonding (vs. rubber gaskets) in cars	≤ $0
52	Dual master cylinder braking system in cars	$13,000
1128	Automobile dummy acceleration (vs. side door Strength) tests	$63,000
299	Collapsible (vs. traditional) steering columns in cars	567,000
189	Side Structure improvements in cars to reduce door intrusion upon crash	$110,000
52	Front disk (vs. drum) brakes in cars	5240,000
299	Dual master cylinder braking system in cars	$450,000
	Automobile occupant restraint systems	
1129	Driver automatic (vs. manual) belts in cars	≤ $0
59	Mandatory seat belt use law	$69
175	Mandatory seat belt use and child restraint law	$98
67	Driver and passenger automatic shoulder belt/knee pads (vs. manual belts) in cars	$1,300
59	Driver and passenger automatic shoulder/manual lap (vs. manual lap) belts in cars	$5,400
67	Airbag/manual lap belts (vs. manual lap belts only) in cars	$6,700
2	Airbag/lap belts (vs. lap/shoulder belts)	$ 17,000
56	Driver and passenger automatic (vs. manual) belts in cars	$32,000
1129	Driver airbag/manual lap belt (vs. manual lap/shoulder belt) in cars	$42,000
1129	Driver and passenger airbags/manual lap belts (vs. airbag for driver only and belts)	$61,000
59	Driver and passenger airbags/manual lap belts (vs. manual lap belts only) in cars	562,000
68	Child restraint systems in cars	573,000
1127	Rear outboard lap/shoulder belts in all (vs. 96%) cars	$74,000
56	Airbags (vs. manual lap belts) in cars	$120,000
1127	Rear outboard and center (vs. outboard only) lap/shoulder belts in all cars	5360,000
	Construction safety	
1137	Full (vs. partial) compliance with 1971 safety standard for concrete construction	≤ $0
1137	1988 (vs. 1971) safety standard for concrete construction	≤ $0
909	1989 (vs. no) safety standard for underground construction	$30,000
909	1989 (vs. 1972) safety standard for underground construction	$30,000
1132	1989 safety standard for underground gassy construction	$30,000
1132	Revised safety Standard for underground non-gassy construction	$46,000
106	Install canopies on underground equipment in coal mines	$ 170,000
910	Safety standard to prevent cave-ins during excavations at Construction sites	$ 190,000
1165	Full compliance with 1989 (vs. partial with 1971) safety standard for trenches	6350,000
1165	Full (vs. partial) compliance with 1971 safety standard for trenches	6400.000
	Fire, heat, and smoke detectors	
193	Federal law requiring smoke detectors in homes	≤ $0
13	Fire detectors in homes	≤ SO
306	Federal law requiring smoke detectors in homes	$920
19	Smoke and heat detectors in homes	$8,100
19	Smoke and heat detectors in bedroom area and basement stairwell	$150,000
303	Smoke detectors in homes	$2 10,000
	Fire prevention and protection, other	
122	Child-resistant cigarette lighters	$42,000
	Flammability standards	
292	Flammability standard for children's sleepwear size O-6X	≤ $0
306	Flammability standard for upholstered furniture	$300
292	Flammability standard for children's sleepwear size 7-14	$45,000

APPENDIX A. Continued.

Ref no.[a]	Life-saving intervention[b]	Cost/life-year[c]
372	Flammability standard for upholstered furniture	$68,000
12	Flammability standard for children's sleepwear size 7-14	$160,000
292	Flammability standard for children's clothing size 0–6X	$220,000
292	Flammability standard for children's clothing size 7-14	$15,000,000
	Helmet promotion	
31	Mandatory motorcycle helmet laws	≤ $0
186	Federal mandatory motorcycle helmet laws (vs. state determined policies)	$2,000
175	Mandatory motorcycle helmet laws	$2,000
1006	Promote voluntary helmet use while riding All-Terram Vehicles	$44,000
	Highway improvement	
747	Grooved pavement on highways	$29,000
1105	Decrease utility pole density to 20 (vs 40) poles per mile on rural roads	$31,000
747	Channelized turning lanes at highway intersections	$39,000
747	Flashing lights at rail-highway crossings	$42,000
747	Flashing lights and gates at rail-highway crossings	$45,000
747	Widen existmg bridges on highways	$82.000
1107	Widen shoulders on rural two-lane roads to 5 (vs. 2) feet	$120,000
1105	Breakaway (vs. existing) utility poles on rural highways	$150,000
1107	Widen lanes on rural roads to 11 (vs. 9) feet	$150,000
1105	Relocate utility poles to 15 (vs. 8) feet from edge of highway	$420,000
	Light truck design improvements	
1091	Ceilings of 0–6000 lb light trucks withstand forces of 1.5 X vehicle's weight	$13,000
1091	Ceilings of O-10.000 lb light trucks withstand forces of 1.5 X vehicle's weight	$14,000
1091	Ceilings of O-8500 lb light trucks withstand forces of 1.5 X vehicle's weight	$78,000
1091	Ceilings of 0–10,000 lb light trucks withstand 5000 lb of force	$170,000
1126	Side door strength standard in light trucks to minimize front seat intrusion	$190,000
1091	Ceilings of O-6000 lb light trucks withstand 5000 lb of force	$1,100,000
1126	Side door strength standard in light trucks to minimize back seat intrusion	$1o,ooo,ooo
	Light truck occupant restraint systems	
1089	Driver and passenger nonmotorized automatic (vs. manual) belts in light trucks	$14,000
834	Push-button release and emergency locking retractors on truck and bus seat belts	$14,000
1089	Driver and passenger motorized automatic (vs. manual) belts in light trucks	$50,000
1089	Driver airbag (vs. manual lap/shoulder belt) in light trucks	$56,000
1089	Driver and passenger airbags (vs. manual lap/shoulder belts) in light trucks	$67,000
	Natural disaster preparedness	
1221	Soils testing and improved site-grading in landslide-prone areas	≤ $0
1221	Ban residential growth in tsunami-prone areas	≤ $0
710	Strengthen unreinforced masonry San Francisco bldgs to LA standards	$21,000
710	Strengthen unreinforced masonry San Francisco bldgs to beyond LA standards	$1,000,000
1221	Triple the wind resistance capabilities of new buildings	$2,600,000
1221	Construct sea walls to protect against 100-year storm surge heights	$5,500,000
1221	Strengthen buildings in earthquake-prone areas	$18,000,000
	School bus safety	
1124	Seat back height of 24" (vs. 20") in school buses	$150,000
1124	Crossing control arms for school buses	$410,000
1124	Signal arms on school buses	$430,000
1124	External loud speakers on school buses	$590,000
1124	Mechanical sensors for school buses	$1,200,000
1124	Electronic sensors for school buses	$1,500,000
1124	Seat belts for passengers in school buses	$2,800,000
1124	Staff school buses with adult monitors	$4,900,000
	Speed limit	
9	National (vs. state and local) 55 mph speed limit on highways and interstates	$6,600
175	Full (vs. 50%) enforcement of national 55 mph speed limit	$16,000

APPENDIX A. Continued.

Ref no.*	Life-saving intervention†	Cost/life-year‡
353	National (vs. state and local) 55 mph speed limit on highways and interstates	330,000
185	National (vs. state and local) 55 mph speed limit on highways	659.000
2	National (vs. state and local) 55 mph speed limit	889,000
185	National (vs. state and local) 55 mph speed limit on rural interstates	$5 10,000
	Traffic safety education	
175	Driver improvement schools suspending/revoking license) for bad drivers	≤ $0
175	Media campaign increase voluntary use of seat belts	5310
175	Public pedestrian safety information campaign	$500
175	Improve traffic safety information for children grades K-12	$710
175	Motorcycle rider education program	$5,700
175	Improve motorcycle testing and licensing system	88,700
157	Improve basic driver training	$20,000
175	Alcohol safety programs for drunk drivers	$21,000
175	Multimedia retraining courses for injury-prone drivers	$23,000
175	Improve educational curriculum for beginning drivers	$84,000
175	First aid training for drivers	$180,000
1124	Improve pedestrian education programs for school bus passengers grades K-6	$280,000
175	Warning letters sent to problem drivers	$720,000
	Vehicle inspection	
864	Random motor vehicle inspection	$1,500
1172	Compulsory annual motor vehicle inspection	$20,000
864	Periodic motor vehicle inspection	$21,000
64	Periodic motor vehicle inspection	$57,000
175	Periodic inspection of motor vehicle sample focusing on critical components	5390.000
175	Periodic motor vehicle inspection	$1,300,000
	Injury reduction interventions. miscellaneous	
192	Terminate sale of three-wh All-Terrain Vehicles	≤ $0
175	Require front and rear lights to be on when motorcycle is in motion	$1,100
175	Selective traffic enforcement programs at high-risk times and locations	$5,200
217	Insulate omnidirectional CB antennae to avert electrocution	38,500
311	Oxygen depletion sensor systems for gas space heaters	$13,000
863	Require employers to ensure employees' motor vehicle safety	$25,000
372	"American" oxygen depletion sensor system for gas space heaters	$51,000
1160	Workplace practice standard for electric power generation operation	$59,000
175	Pedestrian and bicycle visibility enhancement programs	$73,000
315	Lock out or tag out of machinery in repair	599,000
372	"French" oxygen depletion sensor system for gas space heaters	$130,000
1005	Redesign chain saws to reduce rotational kickback injuries	8230,000
101	Ground fault circuit interrupters	$1,100,000
468	Ejection system for Air Force B-58 bomber	$1,200,000
1161	Equipment. work practices, and training standard for hazardous waste cleanup	$2,000,000

Toxin control

	Arsenic control	
497	Arsenic emission standard (vs. capture and control) at high-emit copper smelters	$36,000
1216	Arsenic emission control at high-emitting copper smelters	$74,000
497	Arsenic emission standard (vs. capture and control) at glass plants	$2,300,000
1183	Arsenic emission control at low-er ASARCO/El Paso copper smelter	$2,600,000
1216	Arsenic emission control at glass plants	$2,900,000
497	Arsenic emission standard (vs. capture and control) at low-emit copper smelters	$3,900,000
881	Arsenic emission control at secondary lead plants	$7,600,000
1216	Arsenic emission control at low-emitting copper smelters	$16,000,000
1183	Arsenic emission control at low-emitting copper smelters	$29,000,000
881	Arsenic emission control at primary copper smelters	$30,000,000
881	Arsenic emission control at glass manufacturing plants	$5 1,000,000

APPENDIX A. Continued.

Ref no.[a]	Life-saving intervention[b]	Cost/life-year[c]
1183	Arsenic emission control at low-emttting Copper Range/White Pine copper smelter	$890,000,000
Asbestos control		
881	Ban asbestos in brake blocks	$29.000
819	Asbestos exposure standard of I .0 (vs. 2.0) fibers/cc in asbestos cement industry	$55,000
881	Ban asbestos in pipeline wrap	$65.000
881	Ban asbestos in specialty paper	$80,000
651	Ban products containing asbestos (vs. 0.2 fibers/cc standard)	$220.000
651	Phase in ban of products containing asbestos (vs. 0.2 fibers/cc standard)	$240,000
819	Asbestos exposure standard of 1 .0 (vs. 2.0) fibers/cc in textile industry	$400,000
387	Asbestos exposure standard of 0.2 (vs. 2.0) fibers/cc in ship repair industry	$410.000
881	Ban asbestos in rooting felt	$550,000
881	Ban asbestos in friction materials	$580,000
881	Ban asbestos in non-roofing coatings	$790,000
881	Ban asbestos in millboard	$920,000
819	Asbestos exposure standard of 0.2 (vs. 0.5) fibers/cc in friction products industry	$1,200,000
819	Asbestos exposure standard of 0.2 (vs. 0.5) fibers/cc in cement industry	$1,900.000
881	Ban asbestos in beater-add gaskets	$2,000,000
881	Ban asbestos in clutch facings	$2,700,000
881	Ban asbestos in roof coatings	f5.200.000
881	Ban asbestos in sheet gaskets	$5,700,000
881	Ban asbestos in packing	$5,700,000
819	Ban products containing asbestos (vs. 0.5 fibers/cc) in textile industry	$6,800,000
881	Ban asbestos in reinforced plastics	$8,200.000
881	Ban asbestos in high grade electrical paper	$15,000,000
387	Asbestos exposure standard of 0.2 (vs. 2.0) fibers/cc in construction industry	$29,000.000
881	Ban asbestos in thread, yam. etc.	$34,000,000
819	Asbestos exposure standard of 1 .0 (vs. 2.0) fibers/cc in friction products industry	$41 ,000.000
881	Ban asbestos in sealant tape	$49,000,000
881	Ban asbestos in automatic transmission components	$66,000.000
881	Ban asbestos in acetylene cylinders	$350,000,000
881	Ban asbestos in missile liner	$420,000,000
881	Ban asbestos in diaphragms	$1,400,0000,000
Benzene control		
1139	Benzene exposure standard of 1 (vs. 10) ppm in rubber and tire industry	$76.000
881	Control of new benzene fugative emissions	$230.000
881	Control of existing benzene fugative emissions	$240,000
721	Benzene exposure standard of 1 (vs. 10) ppm	$240.000
881	Benzene emission control at pharmaceutical manufacturing plants	$460,000
881	Benzene emission control at coke by-product recovery plants	$1,400,000
1139	Benzene exposure standard of 1 (vs. 10) ppm in coke and coal chemicals industry	$3,000.000
881	Benzene emission control during transfer operations	$4,100.000
881	Control of benzene storage vessels	$14,000,000
881	Benzene emission control at ethylbenzene/styrene process vents	$14,000,000
881	Benzene emission control during waste operations	$19,000,000
881	Benzene emission control at maleic anhydride plants	$20,000,000
881	Benzene emission control at service stations storage vessels	$91,000,000
881	Control of benzene equipment leaks	$98,000,000
881	Benzene emission control at chemical manufacturing process vents	$180,000,000
881	Benzene emission control at bulk gasoline plants	$230,000,000
881	Benzene emission control at chemical manufacturing process vents	$530,000,000
881	Benzene emission control at rubber tire manufacturing plants	$20,000,000,000
Chlorination		
42	Chlorination of drinking water	$3.100
42	Chlorination, filtration and sedimentation of drinking water	$4,200
Coal and coke oven emissions control		
38	Coal-fired power plants emission control through high stacks etc.	≤ $0

APPENDIX A. Continued.

Ref no.[a]	Life-saving intervention[b]	Cost/life-year[c]
38	Coal-fired power plants emission control through coal beneficiation etc.	$37,000
745	Coke oven emission standard for iron- or steel-producing plants	$130,000
745	Acrylonitrile emission control via best available technology	$9,000,000
	Formaldehyde control	
716	Ban urea-formaldehyde foam insulation in homes	$11,000
311	Ban urea-formaldehyde foam insulation in homes	$220,000
1164	Formaldehyde exposure standard of 1 (vs. 3) ppm in wood industry	$6,700,000
	Lead control	
1217	Reduced lead content of gasoline from 1.1 to 0.1 grams per leaded gallon	≤SO
	1,3 Butadiene control	
1138	1.3 Butadiene exposure standard of 10 (vs. 1000) ppm PEL in polymer plants	$340,000
1138	1,3 Butadiene exposure standard of 2 (vs. 1000) ppm PEL in polymer plants	$770,000
	Pesticide control	
713	Ban chlorobenzilate pesticide on noncitrus	≤SO
403	Ban amitraz pesticide on apples	≤SO
403	Ban amitraz pesticide on pears	$350,000
713	Ban chlorobenzilate pesticide on citrus	s1,200,000
	Pollution control at paper mills	
844	Chloroform emission standard at 17 low cost pulp mills	≤ $0
844	Chloroform private well emission standard at 7 papergrade sulfite mills	$25,000
844	Chloroform private well emission standard at 7 pulp mills	$620,000
844	Chloroform reduction by replacing hypochlorite with chlorine dioxide at 1 mill	3990,000
844	Dioxin emission standard of 5 lbs/air dried ton at pulp mills	$4,500,000
844	Dioxin emission standard of 3 (vs. 5) lbs/air dried ton at pulp mills	$7,500,000
844	Chloroform emission standard of 0.001 (vs. 0.01) risk level at pulp mills	$7,700,000
844	Chloroform reduction by replace hypochlorite with chlorine dioxide at 70 mills	$8,700,000
844	Chloroform reduction at 70 (vs. 33 worst) pulp and paper mills	s15,000,000
844	Chloroform reduction at 33 worst pulp and paper mills	$57,000,000
844	Chloroform private well emission standard at 48 pulp mills	$99,000,000,000
	Radiation control	
468	Automatic collimators on X-ray equipment to reduce radiation exposure	$23,000
881	Radionuclide emission control at underground uranium mines	$79,000
881	Radionuclide emission control at Department of Energy facilities	$730,000
1216	Radionuclide control via best available technology in uranium mines	5850,000
44	Radiation standard "as low as reasonably achievable" for nuclear power plants	$1,100,000
468	Radiation levels of 0.3 [vs. 1.0) WL at uranium mines	$1,600,000
1215	Radiation standard "as low as reasonably achievable" for nuclear power plants	$2,500,000
881	Radionuclide emission control at surface uranium mines	$3,900,000
881	Radionuclide emission control at elemental phosphorous plants	$9,200,000
881	Radionuclide emission control at operating uranium mill tailings	S 11 ,000,000
1216	Radionuclide control via best available technology in phosphorous mines	S16,000,000
881	Radionuclide emission control at phosphogypsum stacks	$29,000,000
881	Radionuclide emission control during disposal of uranium mill tailings piles	$40,000,000
1216	Rdiation emission standard for nuclear power plants	$100,000,000
468	Radiation emission standard for nuclear power plants	s 1 80,000,000
926	Thin, flexible, protective leaded gloves for radiologists	S190,000,000
881	Radionuclide emission control at coal-fired industrial boilers	$260,000,000
881	Radionuclide emission control at coal-fired utility boilers	$2,400,000,000
881	Radionucfide emission control at NRC-licensed and non-DOE facilities	$2,600,000,000
881	Radionuclide emission control at uranium fuel cycle facilities	$34,000,000,000

APPENDIX A. Continued.

Ref no.[a]	Life-saving intervention[b]	Cost/life-year[c]
	Radon control	
1266	Radon remediation in homes with ≥12 vs. 6 pCi/L	$6,100
1267	Radon remediation in homes with ≥8 vs. 4 pCi/L	$35,000
1030	Radon limit after disposal of uranium mill tailings of 2 pCi/m2s (vs. 60)	$49,000
1265	Radon remediation in homes with ≥4 pCi/L	$140,000
1030	Radon limit after disposal of uranium mill tailings of 20 pCi/m2s (vs. 60)	$260,000
881	Radon emission control at Department of Energy facilities	$5,100,000
	SO2 control	
923	SO2 controls by installation of capacity to desulphurize residual fuel oil	≤ $0
	Trichloroethylene control	
1215	Trichloroethylene standard of 2.11 micrograms/L in drinking water	$34,000,000
	Vinyl chloride control	
881	Vinyl chloride emission control at EDCNC and PVC plants	$1,600,000
718	Vinyl chloride emission standard	$1,700,000
	VOC control	
1122	South Coast of California ozone control program	$610,000
	Toxin control, miscellaneous	
725	Process safety standard for management of hazardous chemicals	$77,000
	Medicine	
	Alpha antinypsin replacement therapy	
1004	Alpha antitrypsin replacement (vs. med) therapy for smoking men age 70	$31,000
1004	Alpha antitrypsin replacement (vs. med) therapy for smoking women age 40	$36,000
1004	Alpha antitrypsin replacement (vs. med) therapy for nonsmoking women age 30	$56,000
1004	Alpha antitrypsin replacement (vs. med) therapy for nonsmoking men age 60	$80,000
	Beta-blocker treatment following myocardial infarction	
952	Beta blockers for myocardial infarction survivors with no angina or hypertension	$360
952	Beta-blockers for myocardial infarction survivors	$850
176	Beta-blockers for high-risk myocardial infarction survivors	$3,000
176	Beta-blockers for low-risk myocardial infarction survivors	$17,000
	Breast cancer screening	
142	Mammography for women age 50	$810
283	Mammography every 3 years for women age 50–65	$2,700
658	Annual mammography and breast exam for women age 35-49	$10,000
658	Annual physical breast cancer exam for women age 35-49	$12,000
611	Annual mammography and breast exam (vs. just exam) for women age 40-64	$17,000
1230	Annual mammography and breast exam for women age 40–49	$62,000
1230	Annual mammography and breast exam (vs. just exam) for women age 40–49	$95,000
86	Annual mammography for women age 55-64	$110,000
1230	Annual mammography (vs. current screening practices) for women age 40–49	$190,000
	Breast cancer treatment	
1238	Postsurgical chemotherapy for premenopausal women with breast cancer	$18,000
1238	Postsurgical chemotherapy for women with breast cancer age 60	$22,000
1269	Bone marrow transplant and high (vs. standard) chemotherapy for breast cancer	$130,000
	Cervical cancer screening	
1316	Cervical cancer screening every 3 years for women age 65+	≤ $0
120	Cervical cancer screening every 10 years for women age 30-39	$410
618	One time mass screening for cervical cancer for women age 38	$1,200
1316	Cervical cancer screening every 5 years for women age 65+	$1,900
1316	One time cervical cancer screening for women age 65+	52,100

APPENDIX A. Continued.

Ref no.*	Life-saving intervention†	Cost/life-year‡
120	Cervical cancer screening every 2 (vs. 3) years for women age 30-39	$2,300
1316	Cervical cancer screening every 3 years for women 65+	52,800
120	Annual (vs. every 2 years) cervical cancer screening for women age 30-39	$4,100
783	One time cervical cancer screening for never-screened poor women age 65	$5,000
707	Annual cervical cancer screening for women beginning at age 60	$11,000
81	Cervical cancer screening every 4 years (vs. never) for women age 20	$12,000
88	One time mass screening for cervical cancer	$13,000
258	Cervical cancer screening every 5 years for women 35+ with 3+ kids	$32,000
1316	Cervical cancer screening every 3 years for regularly-screened women 65+	$41,000
1316	Annual (vs. every 3 years) cervical cancer screening for women 65+	$49,000
707	Annual cervical cancer screening for women beginning at 20	550.000
603	Annual cervical cancer screening for women beginning at age 20	$82,000
81	Cervical cancer screening every 3 (vs. 4) years for women age 20	$220,000
456	Annual cervical cancer screening for women beginning at age 20	5220,000
81	Cervical cancer screening every 2 (vs. 3) years for women age 20	$3 10,000
81	Annual (vs. every 2 years) cervical cancer screening for women age 20	$1,500,000
	Childhood immunization	
65	Immunization for all infants and pre-school children (vs. scattered efforts)	≤ $0
143	Pertussis, diphtheria. and tetanus (vs. just diphtheria and tetanus) immunization	≤ $0
349	Measles, mumps, and rubella immunization for children	≤ $0
8 12	Polio immunization for children age O-4	≤ $0
812	Rubella vaccination for children age 2	≤ $0
1178	National measles eradication program for children	≤ $0
	Cholesterol screening	
605	Cholesterol screening for boys age 10 and their first-degree relatives	$4,600
605	Cholesterol screening for boys age 10	$6,500
	Cholesterol treatment	
1071	Lovastatin for men age 35-54 with heart disease and ≥ 250 mg/dL	≤ $0
785	Low-cholesterol diet for men age 60 and 1 mg/dL	$12,000
2	Low-cholesterol diet for men age 30	$19.000
1071	Lovastatin for men age 55–64 with heart disease and ≤ 250 mg/dL	$20,000
791	Oat bran cholesterol reduction for men age 48 and ≥ 265 mg/dL	$24,000
785	Lovastatin/low cholesterol diet (vs. diet) for men age 60 and 3 mg/dL	$26,000
785	Cholestyramine/low cholesterol diet (vs. diet) for men age 60 and 3 mg/dL	$3 1,000
1071	Lovastatin for men age 45-54 with no heart disease and ≥ 300 mg/dL	$34,000
768	Cholestyramine/low cholesterol diet (vs. diet) for age 35-39 and 2 mg/dL	$100,000
768	Cholestyramine/low cholesterol diet (vs. diet) for men age 50-54 and 2 mg/dL	$150,000
791	Cholestyramine for men age 48 and ≥ 265 mg/dL	$160,000
768	Cholestyramine/low cholesterol diet (vs. cholestyramine) age 35-39 2 mg/dL	$200,000
1191	Cholestyramine for men with cholesterol levels above the 95th percentile	$230,000
785	Low-cholesterol diet for men age 20 and 1 mg/dL	$360,000
1071	Lovastatin 40 (vs. 20) mg for women age 35-44 with heart disease and ≥ 360 mg/dL	$360,000
768	Cholestyramine/low cholesterol diet (vs. diet) for men age 65-69 and 2 mg/dL	$920,000
1071	Lovastatin for women age 35–44 with no heart disease and ≥ 300 mg/dL	$1,200,000
785	Cholestyramine/low cholesterol diet (vs. diet) for men age 20 and 2 mg/dL	$1,300,000
785	Cholestyramine/low cholesterol diet (vs. diet) for men age 20 and 2 mg/dL	$1,800,000
	Clinical trials	
1134	Women's Health Trial to evaluate low-fat diet in reducing breast cancer	$18,000
1004	Clinical trial to evaluate alpha antitrypsin replacement therapy	$53,000
	Colorectal screening	
86	Annual stool guaiac colon cancer screening for people 55+	≤ SO
96	One stool guaiac colon cancer screening for people age 40+	$660
528	One hemoccult screening for colorectal cancer for asymptomatic people age 55	$1,300
1135	Colorectal cancer screening for people age 40+	$4,500
1135	Colonoscopy for colorectal cancer screening for people age 40+	$90,000
96	Six (vs. five) stool guaiacs colon cancer screening for people 40+	$26,000,000

APPENDIX A. Continued.

Ref no.[a]	Life-saving intervention[b]	Cost/life-year[c]
	Coronary artery bypass graft surgery (CABG)	
358	Left main coronary artery bypass graft surgery (vs. medical management)	$2,300
99	Left main coronary artery bypass graft surgery (vs. medical management)	$5,600
99	3-vessel coronary artery bypass graft surgery (vs. medical management)	$12,000
1200	3-vessel coronary artery bypass graft surgery (vs. PTCA) for severe angina	$23,000
358	2-vessel coronary artery bypass graft surgery (vs. medical management)	$28,000
99	2-vessel coronary artery bypass graft surgery (vs. medical management)	575,000
1200	3-vessel coronary artery bypass graft surgery (vs. PTCA) for mild angina	$ 100,000
1200	2-vessel coronary artery bypass graft surgery (vs. PTCA) for severe angina	$430,000
	Drug and alcohol treatment	
86	Occupational assistance programs for working problem-drinkers	≤ $0
650	Detoxification for heroin addicts	≤ $0
650	Methadone maintenance for heroin addicts	≤ $0
650	Narcotic antagonists for heroin addicts	≤ $0
	Emergency vehicle response	
987	Defibrillators in emergency vehicles for resuscitation after cardiac arrest	$39
987	Defibrillators in emergency vehicles staffed with paramedics (vs. EMTs)	$390
986	Defibrillators in ambulances for resuscitation after cardiac arrest	$460
987	Emergency vehicle response for cardiac arrest	$820
2	Advanced life support paramedical equipped vehicle	$5,400
237	Advanced resuscitative care (vs. basic emergency services) for cardiac arrest	$27,000
175	Combined emergency medical services for coordinated rapid response	$120,000
	Gastrointestinal screening and treatment	
578	Sclerotherapy (vs. medical therapy) for esophageal bleeding in alcoholics	≤ $0
148	Truss (vs. elective inguinal hemiorrhaphy) for inguinal hernia in elderly patients	≤ $0
352	Expectant management of silent gallstones in men age 30	≤ $0
797	Home (vs. hospital) parenteral nutrition for patients with acute loss of bowels	≤ $0
797	Home parenteral nutrition for patients with acute loss of bowels	≤ $0
584	Pre-operative total parenteral nutrition in gastrointestinal cancer patients	≤ $0
235	Ulcer therapy (vs. surgery) for duodenal ulcers	$6,600
577	Medical or surgical treatment for advanced esophageal cancer	$12,000
587	Surgery for liver cirrhosis patients with acute variceal bleeding	$17,000
1046	Ulcer (vs. symptomatic) therapy for episodic upper abdomen discomfort	$41.000
1067	Misoprostol to prevent drug-induced gastrointestinal bleed in at-risk patients	$47,000
587	Medical management for liver cirrhosis patients with acute variceal bleeding	$61,000
1067	Misoprostol to prevent drug-induced gastrointestinal bleed	$210,000
1046	Upper gastrointestinal X-ray and endoscopy (vs. ulcer therapy) for gastric cancer	$300,000
1046	Upper gastrointetinal X-ray and endoscopy (vs. antacids) for gastric cancer	$420,000
	Heart disease screening and treatment, miscellaneous	
518	Exercise stress test for asymptomatic men age 60	$40
358	Pacemaker implant (vs. medical management) for atrioventricular heart block	$1,600
251	Reconstruct mitral valve for symptomatic mitral valve disease	$6,700
350	Exercise stress test for age 60 with mild pain and no left ventricular dysfunction	$13,000
990	Implantable cardioverter-defibrillator(vs. medical therapy) for cardiac arrest	$23.000
1066	Coronary angiogaphy (vs. medical therapy) in men age 45-64 with angina	$28,000
346	Regular leisure time physical activity, such as jogging, in men age 35	$38,000
25 1	Replace (vs. reconstruct) mitral valve for symptomatic mitral valve disease	$150,000
	Heart transplantation	
544	Heart transplantation for patients age 55 or younger and favorable prognosis	$3,600
835	Heart transplantation for patients age 50 with terminal heart disease	$100,000
	HIV/AIDS screening and prevention	
6	Voluntary (vs. limited) screening for HIV in female drug users and sex partners	≤ $0
1097	Screen blood donors for HIV	$14,000
1100	Screen donated blood for HIV with an additional FDA-licensed test	$880,000

APPENDIX A. Continued.

Ref no.*	Life-saving intervention°	Cost/life-year<
1102	Universal (vs. category-specific) precautions to prevent HIV transmission	$890,000
	HIV/AIDS treatment	
1199	Zidovudine for asymptomatic HIV+ people	≤SO
1121	Oral dapsone for prophylaxis of PCP in HIV+ people	516,000
1121	Aerosolized pentamidine for prophylaxis of PCP in HIV+ people	520,000
1096	AZT for people with AIDS	826,000
1264	Prophylactic AZT following needlestick injury in health care workers	$41,000
1117	Zidovudine for asymptomatic HIV+ people	$45,000
	Hormone replacement therapy	
227	Estrogen for menopausal women age SO	≤ $0
748	Estrogen-progesrin for symptomatic monopausal women age 50	$15,000
748	Estrogen for symptomatic menopausal women age 50	$26,000
748	Estrogen-progestin for 15 years in asymptomatic menopausal women age SO	$30,000
748	Estrogen-progestm for 5 years in asymptomatic menopausal women age SO	532,000
90	Estrogen for post-menopausal women age 55-70	$36,000
227	Estrogen for menopausal women age 50	$42,000
90	Estrogen for asymptomatic post-menopausal women age SO-65	877,000
90	Estrogen for symptomatic post-menopausal women age 50–65	$81,000
748	Estrogen for asymptomatic menopausal women age 50	589,000
244	Hormone replacement for asymptomatic perimenopausal white women age SO	$120,000
227	Estrogen-progestin for post-menopausal women age 60	5130,000
90	Estrogen for asymptomatic post-menopausal women age 55–70	$250,000
	Hypertension drugs	
225	Antihypertensive drugs for men age 25+ and 125 mmHg	$3,800
225	Antihypertensive drugs for men age 25+ and 85 mmHg	$4,700
1068	Beta-blockers for hypertensive patients age 35–64 no heart disease and ≥ 95 mmHg	$14,000
91	Antihypertensive drugs for patients age 40 and ≥ 105 mmHg	816,000
91	Antihypertensive drugs for patients age 40 and 95–104 mmHg	632,000
1068	Captopril for people age 35–64 with no heart disease and ≥ 95 mmHg	$93,000
	Hypertension screening	
111	Hypertension screening for Black men age 55–64 and ≥ 90 mmHg	$5,000
761	Hypertension screening for men age 45-54	$5,200
111	Hypertension screening for White men age 45-54 and ≥ 90 mmHg	$6,500
111	Hypertension screening for Black women age 45–54 and ≥ 90 mmHg	$8,400
1202	Hypertension screening for asymptomatic men age 60	311,000
1202	Hypertension screening for asymptomatic women age 60	$17,000
1202	Hypertension screening for asymptomatic men age 40	$23,000
761	Hypertension screening every 5 years for men age 55-64	$31,000
1202	Hypertension screening for asymptomatic women age 40	$36,000
111	Hypertension screening for White women age 18-24 and ≥ 90 mmHg	537,000
1202	Hypertension screening for asymptomatic men age 20	$48,000
1202	Hypertension screening for asymptomatic women age 20	587,000
	Hysterectomy to prevent *uterine cancer*	
750	Hysterectomy without oopherectomy for asymptomatic women age 35	≤ $0
750	Hysterectomy with oopherectomy for asymptomatic women age 40	$51,000
758	Hysterectomy for asymptomatic women age 35	$230,000
	Influenza vaccination	
455	Influenza vaccination for all citizens	$140
156	Influenza vaccination for high risk people	$570
156	Influenza vaccination for people age 5+	$1.300
	Intensive care	
422	Coronary care unit for patients under age 65 with cardiac arrest	$390
125	Intensive care for young patients with barbiturate overdose	$490
1208	Intensive care and mechanical ventilation for acute respiratory distress syndrome	53,100

APPENDIX A. Continued.

Ref no.[a]	Life-saving intervention	Cost/life-year[c]
125	Intensive care for young patients with polyradiculitis	$3,600
1208	Intensive care and mechanical ventilation for acute respiratory failure	$4,700
854	Intensive care for unstable patients with unpredictable clinical course	$21,000
1208	Intensive care for patients with heart disease and respiratory failure	$21,000
125	Intensive care for patients with multiple trauma	$26,000
89	Coronary care unit for emergency patients with acute chest pain	$250,000
602	Intensive care for very ill patients undergoing major vascular surgery	$300,000
602	Intensive care for very ill patients with operative complications	$390,000
602	Intensive care for seriously ill patients with multiple trauma	$460,000
602	Intensive care for very ill patients undergoing neurosurgery for head trauma	$490,000
125	Intensive care for men with advanced cirrhosis, kidney and liver failure	$530,000
602	Intensive care for very ill patients with emergency abdominal catastrophes	$660,000
602	Intensive care for very ill patients undergoing neoplastic disease operations	$820,000
602	Intensive care for very ill patients undergoing major vascular operations	5850,000
602	Intensive care for very ill patients with gastrointestinal bleeding, cirhosis etc.	$950,000
Leukemia treatment and infection control		
1095	Bone marrow transplant (vs. chemotherapy) for acute nonlymphocytic leukemia	512,000
1095	Bone marrow transplant for acute nonlymphocytic leukemia in adults	$20,000
1095	Chemotherapy for acute nonlymphocytic leukemia in adults	527,000
672	Therapeutic leukocyte transfusion to prevent infection during chemotherapy	$36,000
672	Prophylactic (vs. therapeutic) leukocyte transfusion to prevent infection	$210,000
1239	Intravenous immune globulin to prevent infections in leukemia patients	$7,100,000
Neonatal intensive care		
335	Neonatal intensive care for infants weighing 1000-1499 grams	$5,700
83	Neonatal intensive care for infants weighing 751-1000 grams	$5,800
335	Neonatal intensive care for infants weighing 500-999 grams	$18,000
1249	Neonatal intensive care for low birth weight infants	$270,000
Newborn screening		
1195	PKU genetic disorder screening in newborns	≤ $0
1196	Congenital hypothyroidism screening in newborns	≤ SO
1141	Sickle cell screening for Black newborns	$240
1141	Sickle cell screening for non-Black high risk newborns	5110,000~'
1141	Sickle cell screening for newborns	$65,000,000
1141	Sickle cell screening for non-Black low risk newborns	$34,000,000,000
Organized health services		
1249	Special supplemental food program for women, infants, and children	$3,400
653	Comprehensive (vs. fragmented) health care services	$5,700
653	Comprehensive (vs. fragmented) health care services for mothers and children	$11,000
1249	Organized family planning services for teenagers	$16,000
1191	No cost-sharing (vs. cost sharing) for health care services	$74,000
1249	Community health care services for women and infants	$100,000
Osteoporosis screening		
244	Bone mass screening and treat if < 0.9 g/(cm)² for perimenopausal women age 50	$13,000
244	Bone mass screening and treat if < 1.0 g/(cm)² for perimenopausal women age 50	$18,000
244	Bone mass screening and treat if < 1.1 g/(cm)² for perimenopausal women age 50	$41,000
Percutaneous transluminal coronary angioplasty (PTCA)		
358	PTCA (vs. medical management) for men age 55 with severe angina	$5,300
1200	PTCA (vs. medical management) for men age 55 with severe angina	$7,400
358	PTCA (vs. medical management) for men age 55 with mild angina	$24,000
1200	PTCA (vs. medical management) for men age 55 with mild angina	$110,000
Pneumonia vaccination		
8 12	Pneumonia vaccination for people age 65 +	$1,800
782	Pneumonia vaccination for people age 65+	$2,000
347	Pneumonia vaccination for people age 65+	$2,200

APPENDIX A. Continued.

Ref no.[a]	Life-saving intervention[b]	Cost/life-year
693	Pneumoma vaccination for people age 65+	52,200
812	Pneumonia vaccination for high risk immunodeficient people age 65+	46,500
812	Pneumonia vaccination for people age 45-64	$ 10.000
782	Pneumonia vaccination for high risk people age 25–44	$14.000
812	Pneumonia vaccination for high nsk immunodeficient people age 45-64	$28.000
782	Pneumonia vaccination for low risk people age 25-W	$66.000
782	Pneumonia vaccination for children age 2–4	S 160,000
347	Pneumoma vaccination for children age 2-l	$170,000
693	Pneumonia vaccination for children age 23	5170,000
Prenatal care		
1253	Term guard uterine activity monitor (vs. self-palpation) to detect contractions	≤ $0
924	Financial incentive of $100 to seek prenatal care for low risk women	≤ $0
1250	Universal (vs. existing) prenatal care for women with < 12 years of education	≤ $0
1250	Universal (vs. existing) prenatal care for women with > 12 years of education	≤ $0
1250	Universal (vs. existing) prenatal care for women with 12 years of education	≤ $0
1251	Prenatal screening for hepatitis B in high risk women	≤ $0
1220	Brady method screening for group B streptococci colonization during labor	≤ $0
1256	Prenatal care for pregnant women	≤ $0
340	Antepartum Anti-D treatment for Rh-negative primiparae pregnancies	$1,100
1249	Prenatal care for pregnant women	52,100
340	Antepartum Anti-D treatment for Rh-negative multiparae pregnancies	$2,900
1220	Isada method screening for group B streptococci colonization during labor	55,000
Renal dialysis		
801	Home dialysis for chronic end-stage renal disease	520,000
1049	Home dialysis for end-stage renal disease	$22,000
157	Home dialysis for end-stage renal disease	$23,000
139	Home dialysis for people age 45 with chronic renal disease	$24.000
419	Home dialysis for people age 64 or younger with chronic renal disease	$25,000
1049	Hospital dialysis for end-stage renal disease	s3 1,000
418	Home dialysis for people age 55–60 with acute renal failure	532,000
357	Dialysis for people age 3.5 with end-stage renal disease	938,000
419	Hospital dialysis for people age 55-64 with chronic renal failure	$42,000
689	Home dialysis for end-stage renal disease	$46,000
418	Hospital dialysis for people age 55–60 with acute renal failure	$47,000
342	Dialysis for end-stage renal disease	$51,000
1049	Center dialysis for end-stage renal disease	955,000
1050	Center dialysis for end-stage renal disease	$63,000
157	Center dialysis for end-stage renal disease	$64,000
139	Center dialysis for people age 45 with chronic renal disease	$67,000
801	Center dialysis for end-stage renal disease	$68,000
689	Center dialysis for end-stage renal disease	$71,000
342	Hospital dialysis for end-stage renal disease	$74,000
689	Home dialysis (vs. transplantation) for end-stage renal disease	579,000
Renal dialysis and transplantation		
689	Home dialysis then transplant for end-stage renal disease	$40,000
689	Hospital dialysis then transplant for end-stage renal disease	$46,000
Renal transplantation and infection control		
1065	Cytomegalovirus immune globulin to prevent infection after renal transplant	$3,500
1065	Cytomegalovirus immune globulin to prevent infection after renal transplant	$14,000
157	Kidney transplant for end-stage renal disease	517,000
419	Kidney transplant and dialysis for people age 15–34 with chronic renal failure	$17,000
139	Kidney transplant for people age 45 with chronic renal disease	4 19,000
1050	Kidney transplant from live-related donor for end-stage renal disease	$19,000
357	Kidney transplant from cadaver with cyclosporine (vs. azatbioprine)	$27,000
357	Kidney transplant from cadaver with cyclospotine	$29,000
357	Kidney transplant from cadaver with azathioprine	$29,000

APPENDIX A. Continued.

Ref no.[a]	Life-saving intervention[b]	Cost/life-year[c]
1065	Cytomegalovirus immune globulin to prevent infection after renal transplant	$200,000
Smoking cessation advice		
1185	Smoking cessation advice for pregnant women who smoke	≤ $0
952	Smoking cessation among patients hospitalized with myocardial infarction	≤ $0
773	Smoking cessation advice for men age 50-54	$990
773	Smoking cessation advice for men age 45-49	$1,100
773	Smoking cessation advice for men age 35-39	$1,400
773	Smoking cessation advice for women age 50-54	$1,700
773	Smoking cessation advice for women age 45-49	41.900
773	Smoking cessation advice for women age 35-39	$2,900
771	Nicotine gum (vs. no gum) and smokmg cessation advice for men age 45-49	$5,800
119	Nicotine gum (vs. no gum) and smoking cessation advice for men age 35-69	$7,500
771	Nicotine gum (vs. no gum) and smoking cessation advice for men age 65–69	$9,100
771	Nicotine gum (vs. no gum) and smoking cessation advice for women *age* 50-54	$9,700
86	Smoking cessation advice for people who smoke more than one pack per day	$9,800
119	Nicotine *gum (vs.* no gum) and smoking cessation advice for women age 35-69	$11,000
771	Nicotine gum (vs. no gum) and smoking cessation advice for women age 65-69	$13,000
Tuberculosis treatment		
784	Isoniazid chemotherapy for high risk White male tuberculin reactors age 20	≤ $0
784	Isoniazid chemotherapy for low risk White male tuberculin reactors age 55	$17,000
Venous thromboembolism prevention		
230	Heparin (vs. anticoagulants) to prevent venous thromboembolism	≤ $0
769	Compression stockings to prevent venous thromboembolism	≤ $0
770	Compression stockings to prevent venous thmmboembolism	≤ $0
170	Heparin to prevent venous thromboembolism	≤ $0
770	Hepatin and dihydroergotamine to prevent venous thromboembolism	≤ $0
770	Intermittent pneumatic compression to prevent venous thromboembolism	≤ $0
770	Heparin and stockings to prevent venous thromboembolism	≤ $0
770	Warfarin sodium to prevent *venous* thromboembolism	≤ $0
769	Intermittent pneumatic compression and stockings to prevent thromboembolism	$400
230	Dextran (vs. anticoagulants) to prevent venous thromboembolism	$640
769	Heparin to prevent venous thromboembolism	$960
769	Heparin and stockings to prevent venous thromboembolism	$1,000
769	Heparin and dihydroergotamine to prevent venous thromboembolism	$1,700
769	Intermittent pneumatic compression to prevent venous thromboembolism	$2,400
787	Heparin, 1 day, for women with prosthetic heart valves undergoing surgery	$5,100
769	Hepatin'dihydroergotamine (vs. stockings) to prevent venous thromboembolism	$42,000
787	Heparin, 3 days, for women with prosthetic heart valves undergoing surgery	$4,300,000
Medicine miscellaneous		
443	Broad-spectrum chemotherapy for cancer of unknown primary origin	≤ $0
728	Cefoxitinigentamicin (vs. ceftizoxime) for intra-abdominal infection	$880
728	Mezlocillinfgentamicin (vs. ceftizoxime) for hospital acquired pneumonia	$1,400
646	Computed tomography in patients with severe headache	$4,800
709	Continuous (vs. nocturnal) oxygen for hypoxemic obstructive lung disease	$7,000
906	Preoperative chest X-rav to detect abnormalities in children	$360,000

[a] Reference numbers correspond to records in the database and to the references listed in Appendix B.

[b] Due to space limitations, life-saving interventions are described only briefly. When the original author compared the intervention to a baseline of "the status quo" or "do nothing" the baseline intervention is omitted here. Other baseline interventions appear as "(vs.).'' Cost-effectiveness estimates are based on the particular life-saving intervention, base case intervention, target population, data, and methods as detailed by the original author(s). It is suggested the reader review the original document to gain a full appreciation of the origination of the estimates.

[c] All costs are in 1993 U.S. dollars and were updated with the general consumer price index. To emphasize the approximate nature of estimates. they are rounded to two significant figures.

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[a] Reference numbers correspond to records in the database and to interventions described in Appendix A. Missing numbers reflect documents that were retrieved but did not contain suitable cost-effectiveness data.

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