Epidemiologic Studies of Nuclear Workers

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Radiation Epidemiology Course
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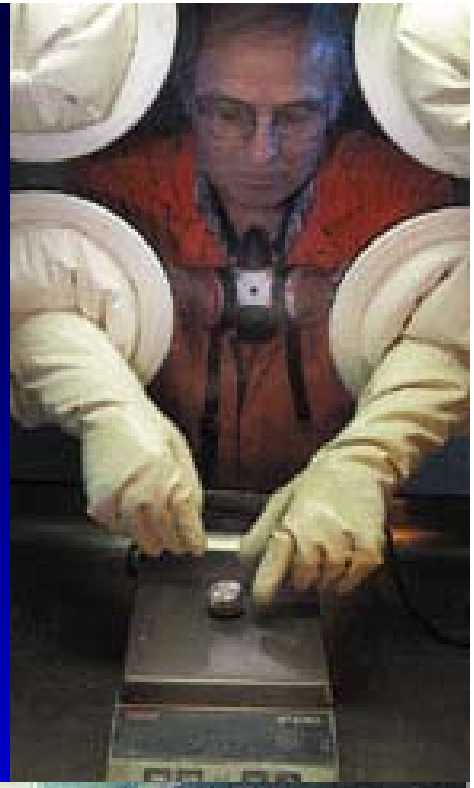
What is a Nuclear Worker?



What is a Nuclear Worker?

Involved in the

- **production of nuclear power**
- **manufacture of nuclear weapons**
- **enrichment and processing of nuclear fuel**
- **reactor or weapons research**

Does <u>not</u> include medical and dental workers or underground miners

Nuclear Worker Studies

- **Studies of workers exposed to low doses of external radiation**
- **Workers exposed to low doses from plutonium**
- **Mayak workers exposed at high doses (external and plutonium)**

Why study workers exposed to low doses of external radiation?

- Current risk estimates based on A-bomb survivors and others exposed at high dose rates
- For risk assessment, interest is primarily in low doses and dose rates
- Uncertainty in the extrapolation process

Why study workers?

- Exposures deliberately limited as a protection to the worker
- Dose estimates obtained from personal dosimeters worn by workers
- Provide a direct assessment of risks at low doses and dose rates
- Power limited, but worker studies can detect serious underestimation of risk

Magnitude of Doses

Current risk estimates:

Driven by doses of 0.5+ Gy

Worker-based estimates:

Driven by doses 0.1-0.5 Gy

Of interest for risk assessment:

0 - 0.1 Gy

Predicted relative risks* for adult male exposed at low dose rate

Dose	Solid cancers	Leukemia
1 Sv	1.1	2.8
0.5 Sv	1.05	1.9
0.2 Sv	1.02	1.4
0.1 Sv	1.01	1.2
0.01 Sv	1.001	1.02

*Linear estimates based on A-bomb survivors reduced by a factor (DDREF) of 2

History of Studies of Workers at Individual Facilities

Population	Country	Publication Date(s)
Hanford Site	US	1978, …, 1993
Oak Ridge Nat'l Lab.	US	1985, 1991
Atomic Energy Authority	UK	1985, 1993
Sellafield Plant	UK	1986, 1994, 1999
Rocky Flats Weapons Plant	US	1987
Atomic Energy of Canada	Canada	1987
Atomic Weapons Establish.	UK	1988
Savannah River Plant	US	1988, 1999
Mound Laboratory	US	1991
Los Alamos Nat'l Lab.	US	1994
Rocketdyne	US	1999
Mallinckrodt Chemical	US	2000

US Nuclear Worker Studies

Hanford

Los Alamos

Rocky Flats

National Studies

Population	Publication Dates
UK National Registry of Radiation Workers	1992, 1999
National Dose Registry of Canada	1998 (Mortality) 2001 (Incidence)
Nuclear industry workers in Japan	1997, 2003

Combined Analyses

- Obtain more precise estimates of risk
- Opportunity for understanding differences and similarities in studies
  - Comparable statistical methods
  - Results in comparable format
- Best overview or summary of studies

Combined Studies of Workers

Population	Country	Publication Dates
Hanford/Oak Ridge/Rocky Flats	US	1989, 1993
AEA/AWE/Sellafield	UK	1994
IARC 3-country	US/UK/Canada	1994, 1995
IARC 15-country	Results expected soon	

International Combined Analyses IARC 3-Country Study

- Conducted at the International Agency for Research on Cancer (IARC) in Lyon, France
- Includes data on published studies of workers in the US, UK, and Canada
- Comparability of dosimetry given considerable attention
- Best currently available summary of studies

IARC 3-Country Study

- **Main findings published in Lancet (1994)**
- **More detailed findings published in Radiation Research (Cardis et al. 1995)**

Studies Included in the IARC 3-Country Study

Population	No. of Workers	Total Person-Sv	No. of Deaths
United States:			
Hanford Site	32,595	877	6,445
Oak Ridge Nat'l Lab.	6,591	141	1,246
Rocky Flats	6,638	242	587
United Kingdom:			
AEA and AWE	20,000	959	4,629
Sellafield	9,494	1,310	2,027
Canada: Atomic Energy of Canada Limited	11,355	315	891
TOTAL:	**95,673**	**3,843**	**15,825**

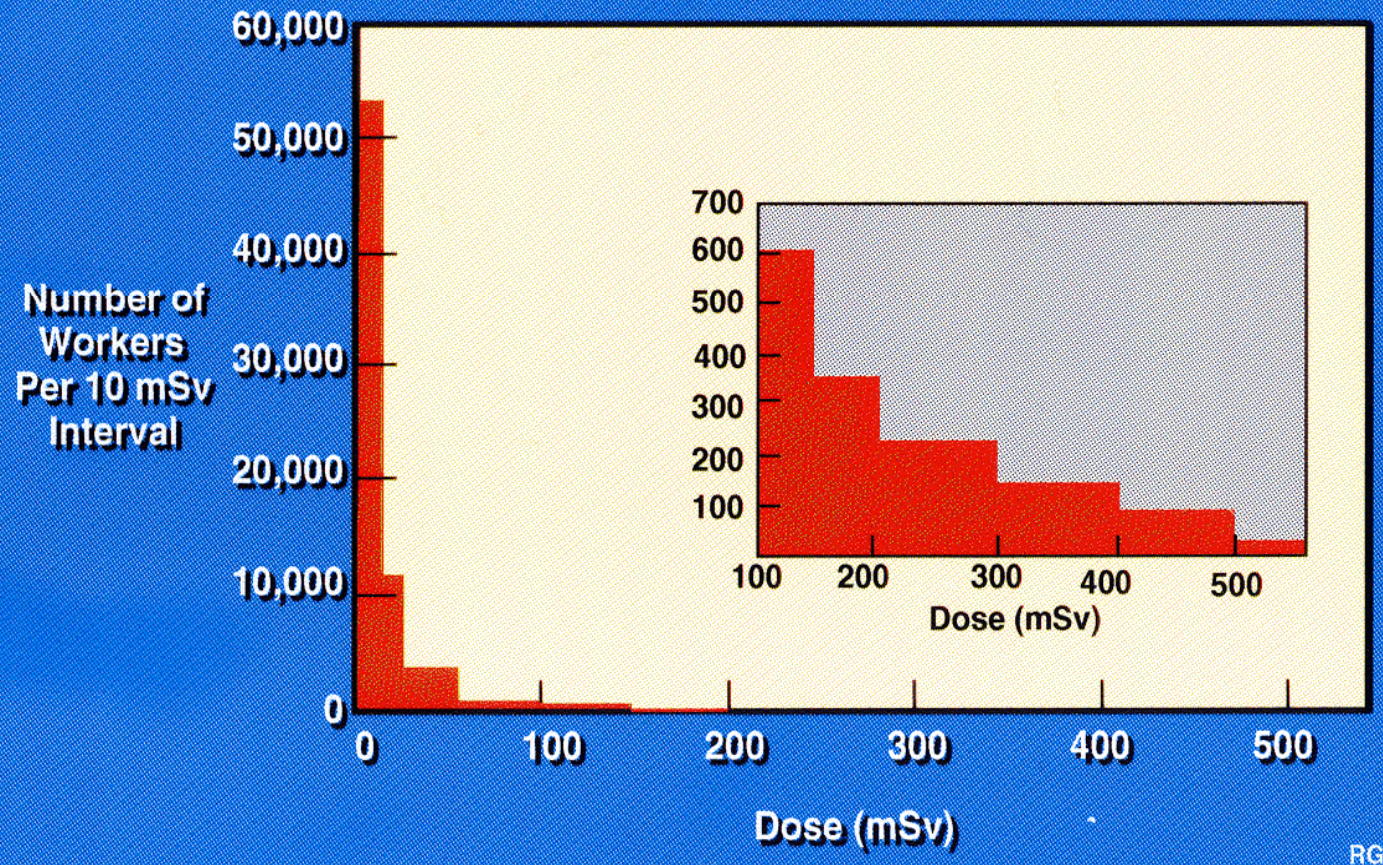
Characteristics of IARC 3-Country Study

	Males	Females (%)	Total
Number of workers	81,745	13,928 (15)	95,673
Collective dose (Sv)	3,758	85.8 (2.2)	3,843
Average dose (mSv)	46	6.2	40

IARC 3-Country Study: Cumulative Dose Distribution

Cumulative Dose (Sv)	No. of workers (%)
0-	53,896 (56)
0.01-	12,299 (13)
0.02-	12,608 (13)
0.05-	6,877 (7.2)
0.1-	4,848 (5.1)
0.2-	3,393 (3.6)
0.4+	1,752 (1.8)
Total	95,673 (100)

Distribution of Monitored Workers by Cumulative Dose (mSv)



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Approaches to Analyses

External Comparisons:

Compare cause-specific death rates with national rates (SMRs)

Internal comparisons:

Compare cause specific death rates by level of cumulative radiation dose

Standardized Mortality Ratios (Numbers of Deaths)

Population	All Causes	All Cancers
United States:		
Hanford Site	0.82 (9,452)	0.86 (2,195)
Oak Ridge	0.74 (1,524)	0.79 (346)
Rocky Flats	0.62 (409)	0.71 (95)
Mound	0.79 (309)	0.88 (66)
Los Alamos	0.63 (3,196)	0.64 (732)
Savannah River	0.78 (1,722)	0.82 (413)
Rocketdyne	0.68 (844)	0.79 (248)
Mallinckrodt	0.90 (1,013)	1.05 (283)

Standardized Mortality Ratios (Numbers of Deaths)

Population	All Causes	All Cancers
United Kingdom:		
Atomic Energy Authority	0.76 (3,021)	0.77 (796)
Atomic Weapons Estab.	0.73 (972)	0.79 (275)
Sellafield	0.96 (2,144)	0.96 (580)
Canada:		
Atomic Energy of Canada Limited	0.77 (878)	0.87 (227)

Approaches to Analyses

External Comparisons:

Compare cause-specific death rates with national rates (SMRs)

Internal comparisons:

Compare cause-specific death rates by level of cumulative radiation dose

Internal comparisons

- **Linear relative risk model:**

  RR = 1 + B dose, where B = ERR/Sv

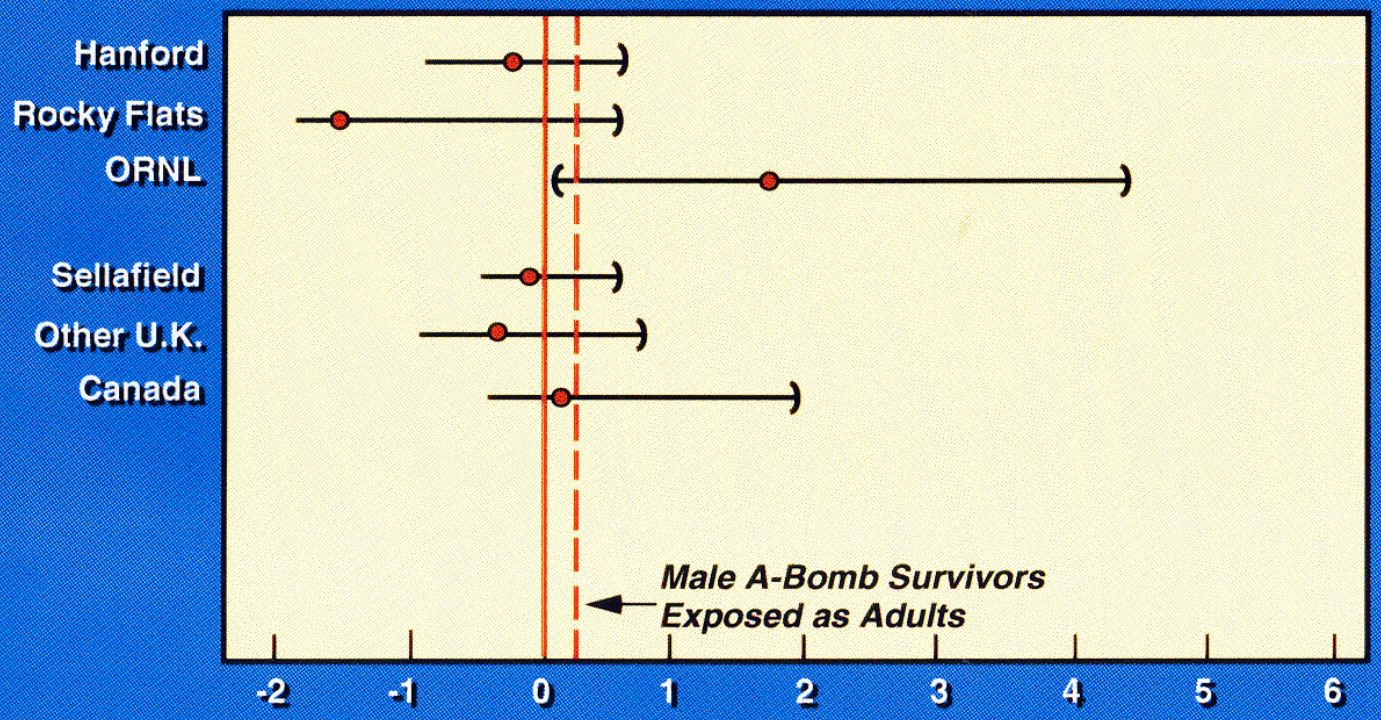
- **Choice of models driven by findings from A-bomb and other high dose studies**

- **Doses lagged by 2 years for leukemia,**

  10 years for other cancers

Excess Relative Risk Estimates (per Sv) with 90% Confidence Limits

(All Cancer Excluding Leukemia)



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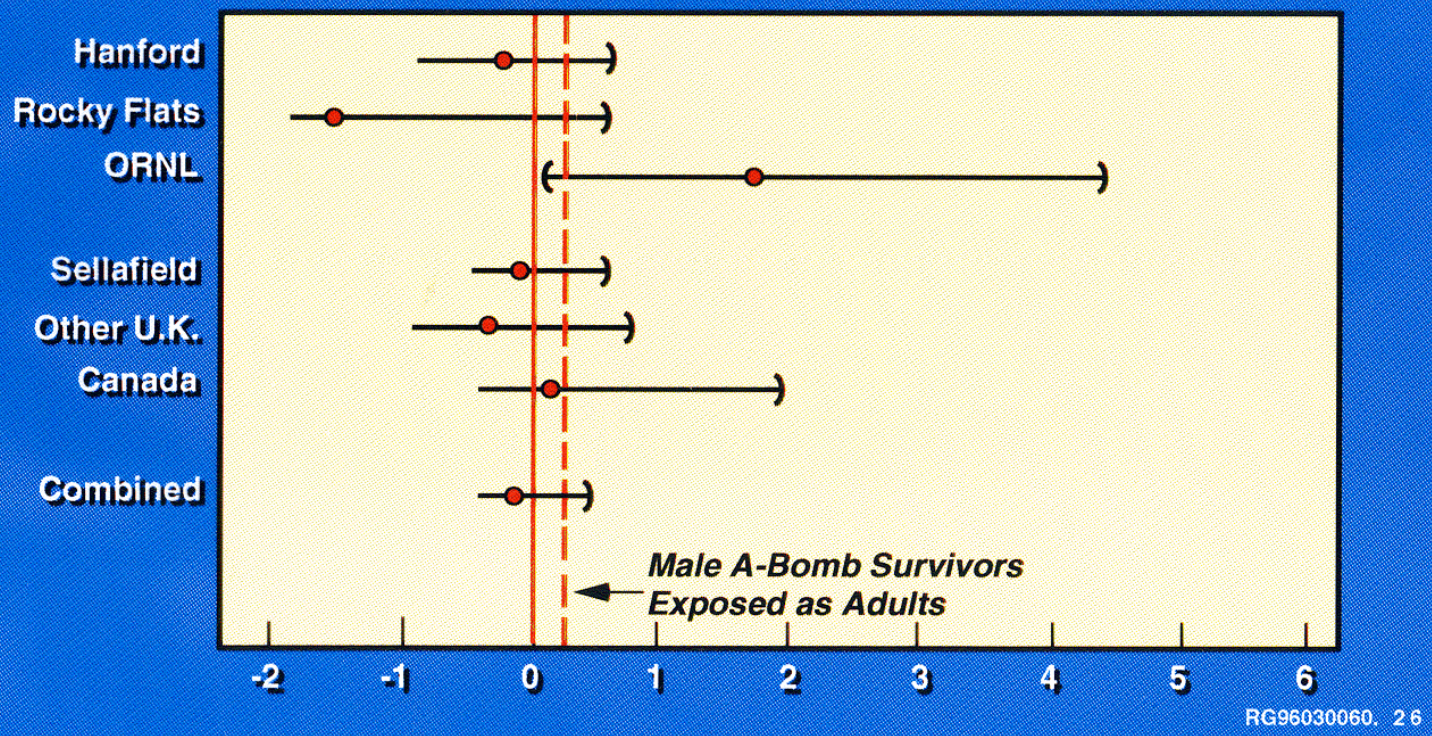
Excess Relative Risk Estimates (per Sv) with 90% Confidence Limits

(All Cancer Excluding Leukemia)



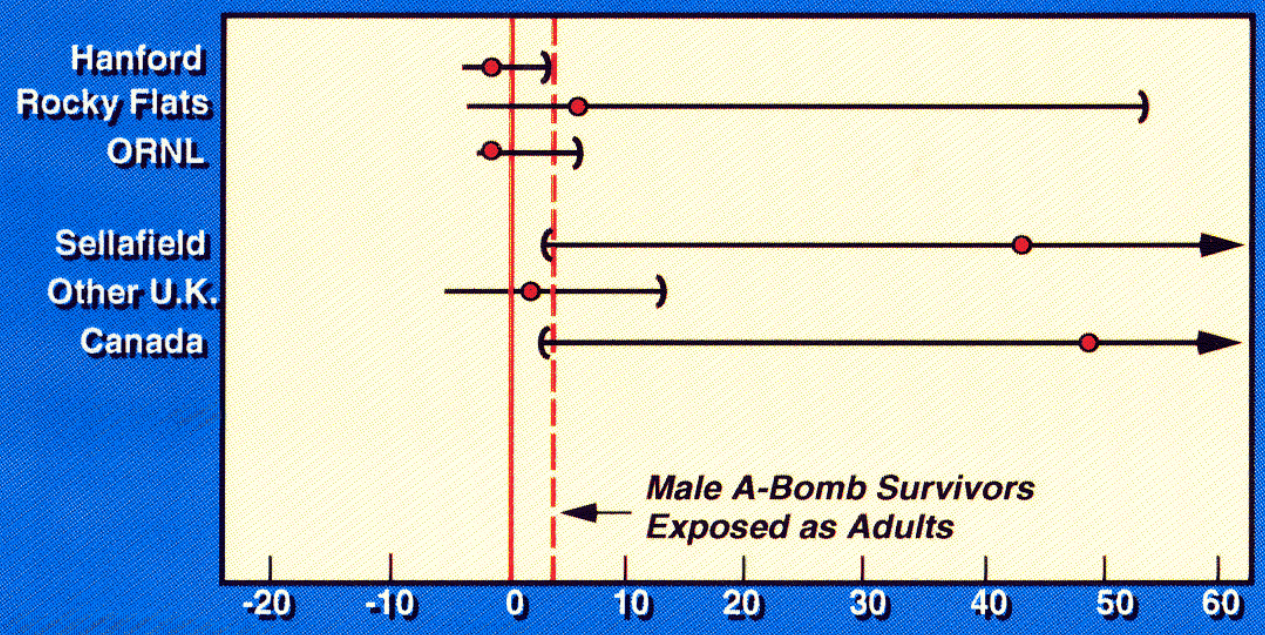
Risk Estimates for All Cancer Excluding Leukemia

	ERR/Sv (90% CI)	No. of Deaths
Hanford	-0.2 (<0, 0.6)	1452
Rocky Flats	-1.6 (<0, 0.5)	104
ORNL	1.7 (0.04, 4.8)	280
Sellafield	-0.03 (<0, 0.5)	533
Other UK	-0.4 (<0, 0.7)	1227
Canada	0.13 (<0, 2.1)	234
Combined	-0.07 (-0.4, 0.3)	3830

A-bomb 0.18 (0.05, 0.34)
(males exposed as adults)

Excess Relative Risk Estimates (per Sv) with 90% Confidence Limits

Leukemia Excluding CLL



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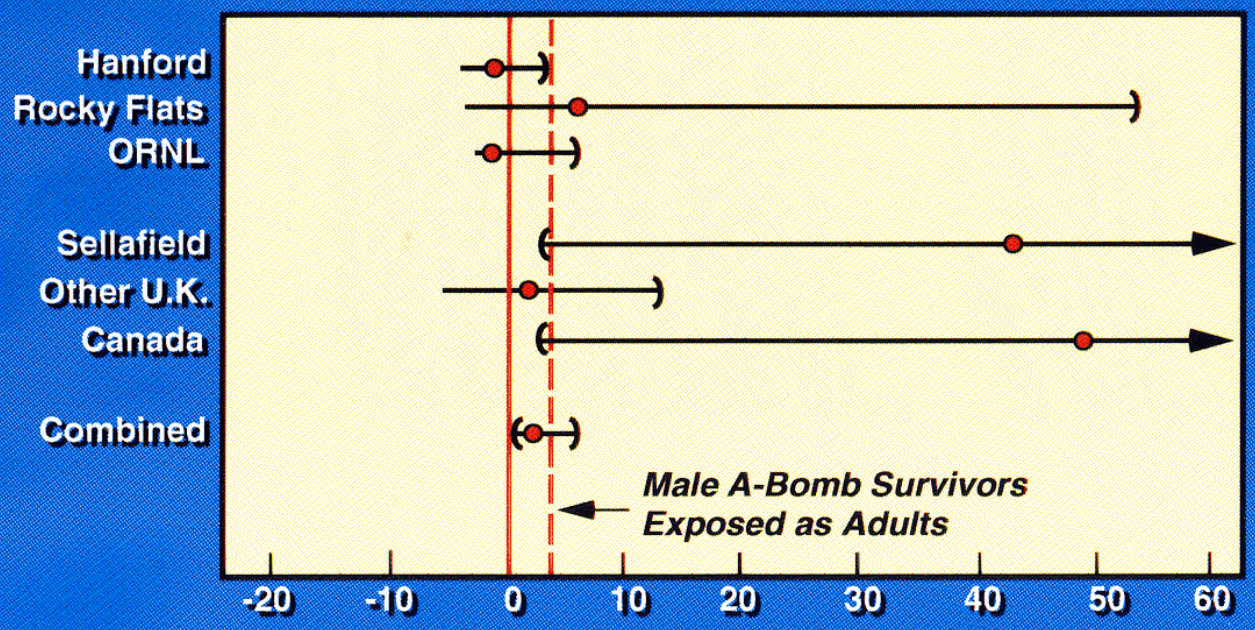
Excess Relative Risk Estimates (per Sv) with 90% Confidence Limits

Leukemia Excluding CLL



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Risk Estimates for Leukemia Excluding CLL

	ERR/Sv (90% CI)	No. of Deaths
Hanford	-0.9 (<0, 2.9)	47
Rocky Flats	4.1 (<0, 5)	4
ORNL	-1.1 (<0, 0.5)	18
Sellafield	44 (3, >100)	10
Other UK	1.5 (<0, 14)	35
Canada	48 (3, >100)	5
Combined	2.2 (0.1, 5.7)	119

A-bomb 3.7 (2.0, 6.5)
(males exposed as adults)

IARC 3-Country Study
Multiple Myeloma

- **Of 30 cancer types tested, multiple myeloma was the only specific cancer with a significant (p = .037) dose-response relationship (other than leukemia)**
- **Previously demonstrated in Hanford and Sellafield cohorts**
- **Could be chance finding given number of tests conducted**

IARC 3-Country Study Modifying Factors

- Little evidence from 3-country study that risks modified by
  - facility
  - sex
  - age at exposure
- Statistical power for detecting such modification limited

Studies Too Recent for 3-Country Analyses

- US: Savannah River, Mound, Los Alamos, Rocketdyne, Mallinckrodt
- National Registry of Radiation Workers (NRRW) in UK
- National Dose Registry (NDR) in Canada

National Registry of Radiation Workers (NRRW)

- 125,000 workers at several selected facilities in UK

- Most informative workers (38,500) included in IARC 3-country study (although with less complete follow-up)

- Latest publication on NRRW
  (Muirhead et al. J Radiol Prot 1999)

National Dose Registry of Canada

- 206,600 workers monitored for radiation in Canada in 24,000 organizations
- About half are medical and dental workers (not in other studies)
- Includes the 11,400 Canadian workers in the IARC 3-country analyses
- Both mortality and cancer incidence data

(Ashmore et al. AJE 1998; Sont et al. AJE 2000)

Characteristics of Large Worker Studies

	Number of workers	Total person-Sv	Av. Dose (mSv)	Number of cancers
IARC 3-country	95,673	3,843	40	3,976
NRRW (UK)	124,743	3,810	31	3,598
NDR (Canada)				
Mortality	206,620	1,293	6.3	1,632
Incidence	191,333	1,267	6.6	3,737

ERR/Sv From Large Worker Studies

	All cancer excluding leukemia	Leukemia excluding CLL
IARC 3-country	-0.07 (-0.4, 0.3)	2.2 (0.1, 5.7)
NRRW (UK)	0.09 (-0.3, 0.5)	2.6 (-.03,7.2)
NDR (Canada)		
Mortality	3.0 (1.1, 4.8)	0.4 (<0, 5.7)
Incidence	2.3 (1.1, 3.9)	2.7 (<0, 19)
A-bomb survivors	0.18 (0.05, 0.34)	3.7 (2.0, 6.5)

National Dose Registry of Canada: Results from Mortality Study (Males)

External comparisons:

All cause SMR:	**0.59 (4,210 deaths)**
All cancer SMR:	**0.68 (1,136 deaths)**

Ashmore et al. 1997

National Dose Registry of Canada: Results from Mortality Study (Males)

Dose-response analyses: (ERR/Sv)

All cancers:	3.0 (1.1 - 4.9)
All causes:	2.5 (1.5 - 3.5)
Circulatory disease:	2.3 (0.9 - 3.7)
Accidents:	8.8 (2.7 - 15.0)

Ashmore et al. 1997

Limitations in Low Dose Worker Studies

- Low statistical power and imprecisely estimated risks
- Strong potential for confounding
- Uncertainties in dose estimates

Predicted relative risks* for adult male exposed at low dose rate Solid cancers

Dose	A-bomb estimate	10 x A-bomb estimate
0.2 Sv	1.02	1.2
0.1 Sv	1.01	1.1
0.01 Sv	1.001	1.01

*Linear estimates based on A-bomb survivors reduced by a factor (DDREF) of 2

Predicted relative risks* for adult male exposed at low dose rate Leukemia

Dose	A-bomb estimate	10 x A-bomb estimate
0.2 Sv	1.4	5.0
0.1 Sv	1.2	3.0
0.01 Sv	1.02	1.2

*Linear estimates based on A-bomb survivors reduced by a factor (DDREF) of 2

Limitations in Low Dose Worker Studies

- Low statistical power and imprecisely estimated risks
- Strong potential for confounding
- Uncertainties in dose estimates

Sources of Error in Dose Estimates for Nuclear Workers

- Laboratory measurement error in reading dosimeters
- Biases resulting from recording practices
- Bias resulting because doses from neutrons and internal emitters could not be reliably measured.
- Recorded doses are not unbiased estimates of dose to bone marrow and other organs

IARC 15-Country Study

- Includes workers in 15 countries
- Planning began in 1988
- Study group with representatives from each country met several times
  - Epidemiology subcommittee
  - Dosimetry subcommittee
- Results should be published soon

IARC 15-Country Study

Australia
Belgium
Canada
Finland
France
Hungary
Japan
Korea
Lithuania
Slovakia
Spain
Sweden
Switzerland
UK
US

Dosimetry for 15-Country Study

- Dosimetry subcommittee
- Extensive dosimetry questionnaires
  - Dosimetry practices
  - Radiation environments
- Special studies of representative
  - Nuclear power plant (Switzerland)
  - Mixed activities (France -- Saclay site)
- Testing of several representative dosimeters

Dosimetry for 15-Country Study

Objectives

- **Develop factors for converting recorded doses to organ doses (bone marrow, lung, etc.)**
- **Evaluate uncertainties in these factors**
- **Take account of this uncertainty in dose-response analyses**

What is the Role of Low-Dose Nuclear Worker Studies?

- **Most informative of studies of persons exposed at low doses and dose rates**
- **Statistical uncertainties and high potential confounding impose important limitations**

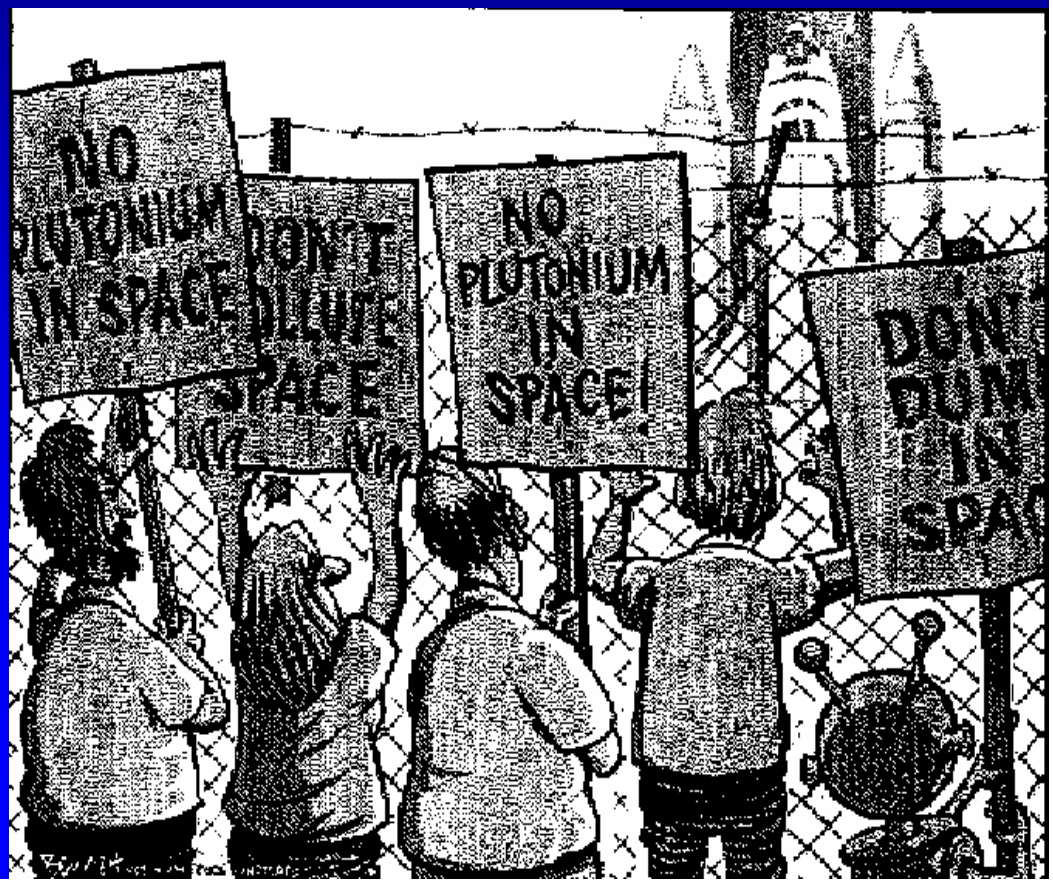
What has been Learned from Studying Workers Exposed to Low Doses of External Radiation?

- Indicate that extrapolation from high dose studies has not seriously underestimated risks
- Provide some evidence of association of leukemia and exposure at low doses and dose rates
- Leave open the possibility that risks may be overestimated

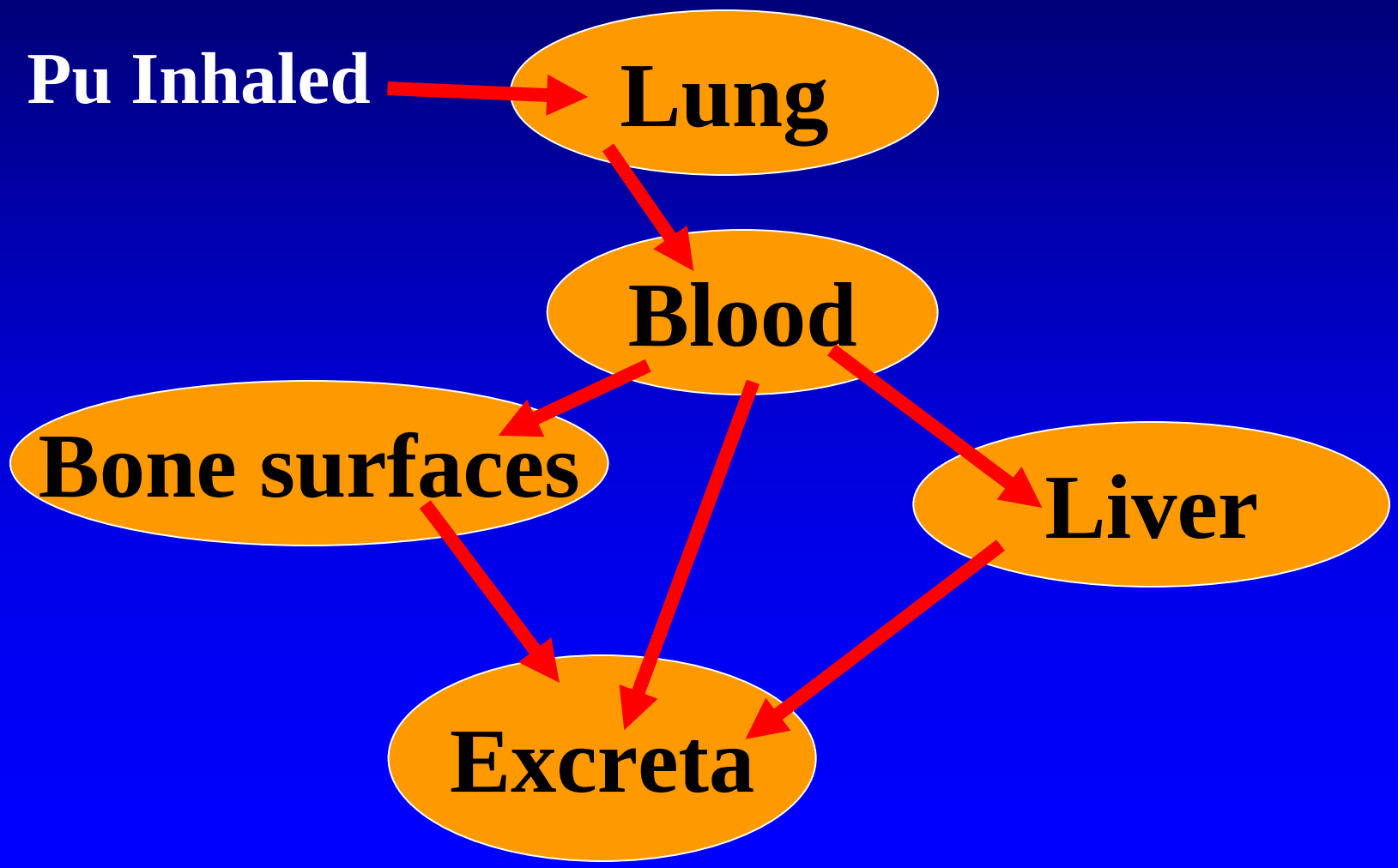
Nuclear Worker Studies

- Studies of workers exposed to low doses of external radiation
- Workers exposed to low doses from plutonium
- Mayak workers exposed at high doses (external and plutonium

Plutonium: “The most hazardous substance known to man?”



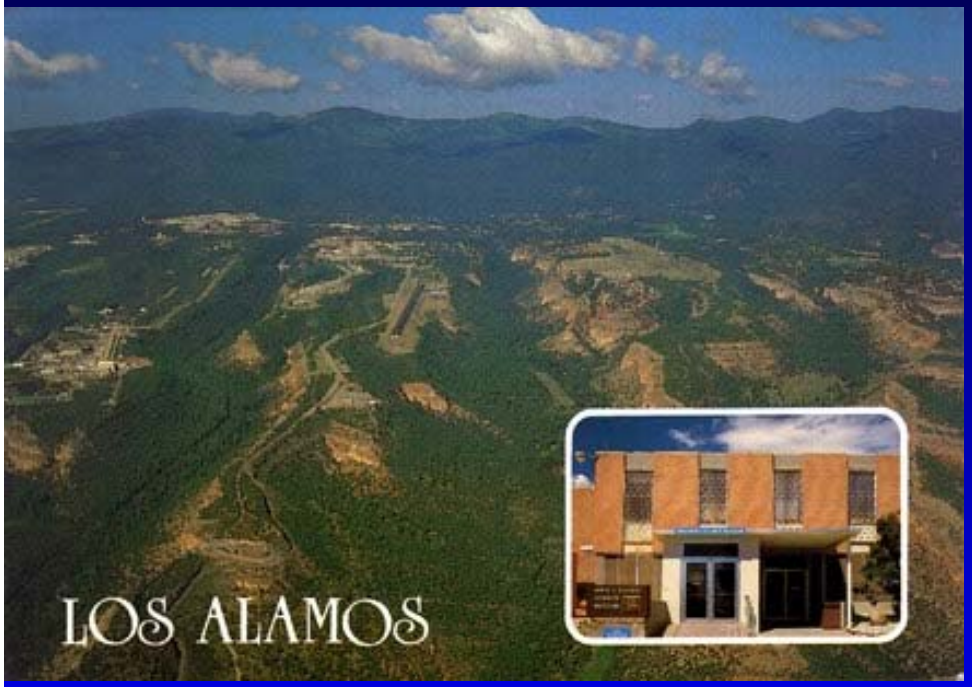
An Overly Simple View of Inhaled Plutonium Dynamics



Studies of Workers Exposed to Low Doses from Plutonium

- US: Los Alamos, Rocky Flats, Mound, Hanford
- UK: Sellafield

26 Manhattan Project Workers



- Worked at Los Alamos during World War II
- Most highly exposed plutonium workers in US

•Body burdens ranged from 0.05 to 3.2 kBq

•One worker died of bone cancer (0.6 kBq)

Voelz et al. Health Physics, 1997

Sellafield (UK) Plutonium Workers

4609 workers with plutonium doses assessed

Mean doses (mGy)

Lung	9.7
Liver	4.6
Bone surfaces	35.6

Rate Ratios for Plutonium Workers[1] (Numbers of Deaths)

Population	All Causes	All Cancers
Los Alamos[2] (303)	0.89 (75)	1.07 (22)
Los Alamos[3] (26)	0.77 (7)	1.5 (3)
Rocky Flats[2] (1451)	1.14 (84)	1.01 (17)
Sellafield (4609)	NA	1.05 (384)
Hanford (3065)	0.93 (585)	0.87 (170)

[1]Compared to other workers

[2]Workers with body burdens > 0.074 kBq (2 nCi)

[3]Manhatten project workers (subgroup)

Rate Ratios for Plutonium Workers[1] (Numbers of Deaths)

Population	Cancer of the		
	Lung	Liver	Bone
Los Alamos[2]	1.8 (8)	0.0 (0)	-- (1)[4]
Los Alamos[3]	3.3 (1)	0.0 (0)	-- (1)[4]
Rocky Flats[2]	0.7 (4)	0.8 (1)	0.0 (0)
Sellafield	1.1 (133)	0.9 (1)	0.0 (0)
Hanford	0.8 (59)	NA	NA

[1]Compared to other workers

[2]Workers with body burdens > 0.074 kBq (2 nCi)

[3]Manhatten project workers (subgroup)

[4]No bone cancers in controls

Studies of Workers Exposed to Low Doses from Plutonium: Summary

- **Strong "healthy worker effect" (US)**
- **Little evidence of adverse effects**
- **Sample sizes and exposures small**

Nuclear Worker Studies

- **Studies of workers exposed to low doses of external radiation**
- **Workers exposed to low doses from plutonium**
- **Mayak workers exposed at high doses (external and plutonium)**

Mayak Nuclear Facility

- Located in the town of Ozyorsk (formerly Chelyabinsk-65) in the Chelyabinsk region of the Russian Federation
- Began operations in 1948
- Mission was to produce plutonium for USSR nuclear weapons program
- Large exposures to both workers and general public, mostly in the 1940's and 1950's

Acknowledgement

Work funded by the US National Cancer Institute (NCI) and US Department of Energy (DOE)

Collaborators in Mayak Worker Study

Southern Urals Biophysics Institute:

Principal investigator: Nina Koshurnikova

Other investigators: Natalia Shilnikova
Mikhail Sokolnikov

Radiation Effects Research Foundation: Dale Preston

National Cancer Institute: Elaine Ron

Mayak nuclear facility

Unique Features of Mayak Cohort

- Large protracted external doses
- Both male and female workers exposed
- Substantial exposure from internally deposited plutonim

Mayak Nuclear Facility

- 21,800 workers hired 1948-72
- 24% female

Plant	Workers	Exposure
Reactor	4400	External
Radiochemical	7900	External + Plutonium
Plutonium	6500	External + Plutonium
Auxiliary	2700	Little potential

Mayak Worker Registry

- Demographic data
- Occupational histories
- Annual external doses
- Plutonium exposure
  - Body burden
  - Annual doses to lung, liver, and bone surfaces
- Mortality data through 2000
  - Vital status known for 90% of cohort

Mayak Dosimetry

External exposure

- **Monitored for external exposure with individual film badges**

Plutonium exposure

- **Body burden and dose estimates based on urine monitoring data**

- **Work underway to improve both external and internal dose estimates**

Plutonium Doses in Mayak and Sellafield Workers

	Mayak	Sellafield
Number monitored for plutonium	5,738	4,609
Mean dose (Gy) to		
Lung	0.26	0.010
Liver	0.29	0.005
Bone surfaces	1.81	0.036

Mayak Worker Plutonium Exposures

- Highest burden among US workers: 3.2 kBq
- Mayak workers

Exposure	Number of workers
1.5 – 3.7 kBq	598
3.7 – 7.4 kBq	215
7.4 – 18.5 kBq	152
18.5 – 173 kBq	109
1.5+ kBq	1,074

Estimating Risks from Plutonium

- Lung cancer risks evaluated by
  - Tokarskaya et al. (1997)
  - Koshurnikova et al. (1998)
  - Kreisheimer et al. (2000, 2003)
  - Gilbert et al. (submitted)
- Bone and liver cancer risks evaluated
  - Koshurnikova et al. (2000)
  - Gilbert et al. (2000)
  - No published dose-response analyses

Uncertainties in Plutonium Dosimetry

- Imprecision in urine measurements
- Uncertainties in when plutonium exposure occurred and form of plutonium
- Uncertainties in biokinetic models and parameter values used to estimate deposition and clearance in organs of the body
- Models can only approximate behavior of plutonium in a given individual

Mayak workers: Plutonium

- Clear that plutonium exposure increases risks of lung, bone, and liver cancers
- Further dosimetry work needed to quantify risk and to compare risk of dose from plutonium (alpha) with that from external exposure

Mayak Workers: Mean External Dose (Gy)

All workers	0.81
Males	0.80
Females	0.82
Hired 1948-58	1.14
Hired 1959-72	0.17
IARC 3-country study (US, UK, Canada)	0.04

Results: External Dose

Reference:

- **Shilnikova et al. Cancer mortality risk among workers at the Mayak nuclear complex (Radiat. Res. 2003)**

Results: External Exposure

- All solid cancer
  - Lung, liver and bone cancers
  - Remainder
- Leukemia excluding CLL
- Analyses adjusted for plutonium exposure

Shilnikova et al. 2003

Solid Cancer and External Dose

- Statistically significant increase in solid cancer risk with dose ($p < .001$)
- Remained statistically significant when lung, liver, and bone cancers were excluded
- ERR per Gy for lung, liver and bone cancers more than twice that for remaining solid cancers

Shilnikova et al. 2003

Solid Cancer and External Dose

- ERR per Gy for women very similar to that for men
- Decrease in risk with increasing age at hire
- Risks reasonably constant over time following exposure

Shilnikova et al. 2003

Leukemia and External Dose

- Statistically significant increase in leukemia risk with dose ($p < .001$)
- No evidence of modification by sex or age at hire
- Strong evidence ($p < .001$) of dependence on time since exposure with larger risks for more recent doses

Shilnikova et al. 2003

Leukemia and External Dose

Years since dose received	ERR* per Gy
3 - 5 years	7.6 (3.2, 17)
5 + years	0.45 (0.1, 1.1)
5 - 10	0.3
10 - 20	0.8
20+	0.4

*Excess relative risk

Shilnikova et al. 2003

Results: External Dose

For both solid cancer and leukemia

- **Evidence of non-linearity in dose-response**
  - **Might be because the largest doses are overestimated**
- **Conclusions about magnitude of effect and shape of dose-response must await dosimetry improvements**

Shilnikova et al. 2003

Summary Comments

Mayak worker cohort

- **Unique resource for evaluating**
  - **Risk from protracted external exposure**
  - **Risk from exposure to plutonium**

- **Important to continue**
  - **Follow-up of cohort**
  - **Efforts to improve both external and internal dose estimate**