IMPORTANT

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The Epidemiology of Leukaemia and other Cancers in Childhood after Exposure to Ionising Radiation

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Ionising Radiation and Cancer

- It is beyond rational dispute that exposure to moderate and high levels of ionising radiation increases the risk of most forms of cancer in the exposed individual.
- The epidemiological and experimental evidence for this is overwhelming.

Radiation-induced Cancer Risk

"No other environmental carcinogen, with the possible exception of tobacco, has been studied as extensively [as ionising radiation]; yet, there remains a public mystique about radiation that tends to exaggerate the actual hazard."

Harvard Report on Cancer Prevention, 1996.

Radiation-induced Cancer Risk

"While radiation is considered a universal carcinogen, it is a relatively weak one, in part because it is such an effective cell killer."

Harvard Report on Cancer Prevention, 1996.

Scientific Review

- Scientific evidence is reviewed internationally by (among others)
  - United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR)
  - International Commission on Radiological Protection (ICRP)
  - International Agency for Research on Cancer (IARC)

Scientific Review

- And nationally by (among others)
  - UK National Radiological Protection Board (NRPB)
  - US National Council on Radiation Protection and Measurements (NCRP)
  - Committee on Biological Effects of Ionizing Radiations (BEIR) of the US National Academy of Sciences

Radiation Epidemiology

"Studies of disease in human populations must adhere strictly to epidemiological principles in order to achieve valid quantitative results. These include sound case ascertainment, an appropriate comparison group, sufficient follow-up, an accounting for confounding factors and well-characterised dosimetry."

UNSCEAR 1994 Report

Leukaemia among Radiologists

- In 1944, persuasive evidence was published for a raised risk of leukaemia among US radiologists.
- An indication of a raised risk of myeloid leukaemia in French radiologists had been published in 1931.

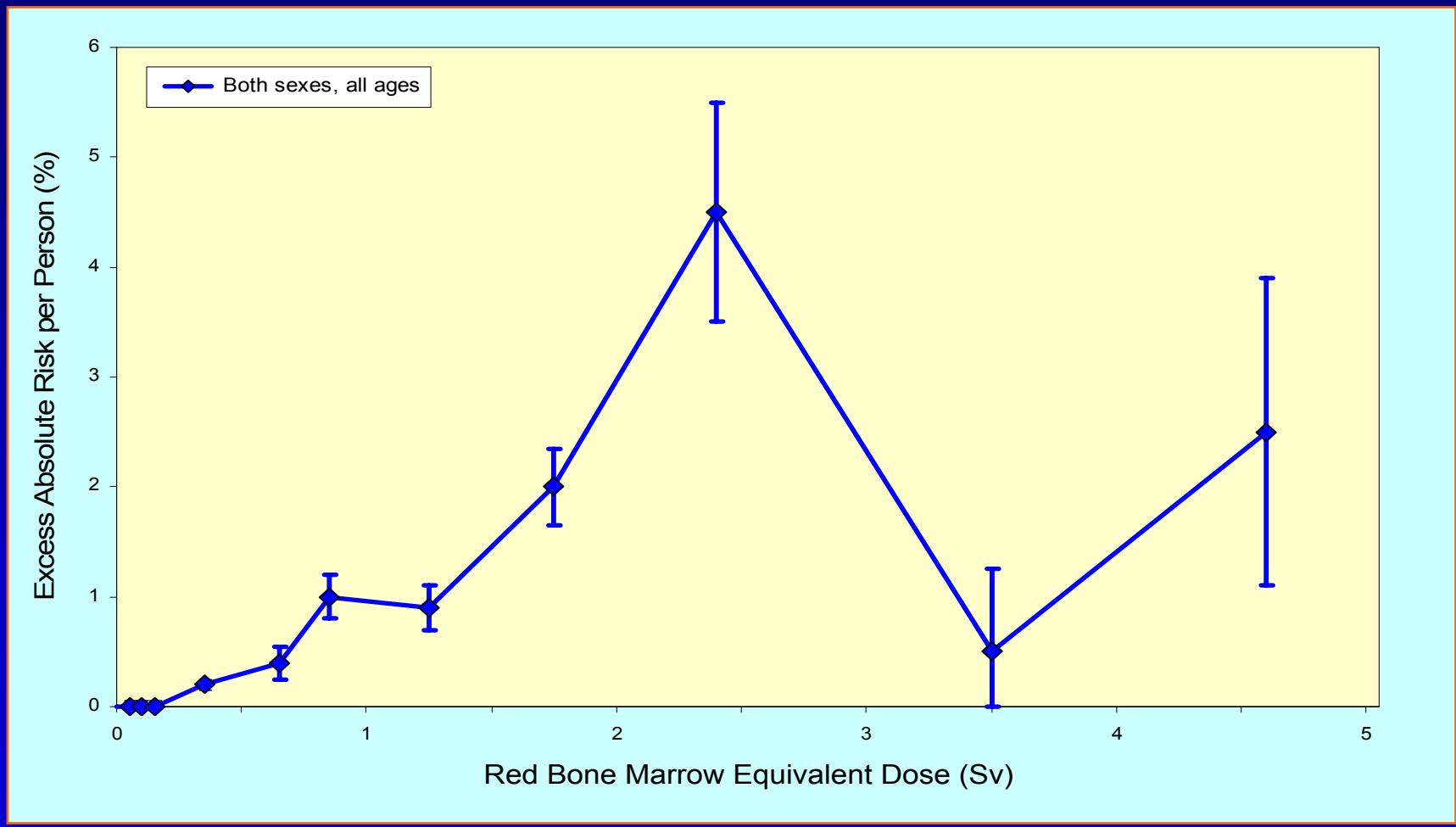
Hiroshima and Nagasaki

- The studies of the Japanese survivors of the atomic bombings of Hiroshima and Nagasaki in 1945 represent the epidemiological “gold standard” for radiation risk estimates.
- It is upon the experience of these Japanese survivors that the risk estimates underlying radiological protection are primarily (but not solely) based.

Leukaemia among Survivors

- In 1948, alert clinicians noted an increase of leukaemia among the atomic bomb survivors.
- This observation contributed to the establishment of the Life Span Study (LSS) cohort of ~94 000 Japanese survivors in October 1950.

Excess absolute risk (±1se) of leukaemia mortality for each Japanese atomic bomb survivor during 1950-1990 (Shimizu *et al.*, 1996)



Leukaemia Risk

- Dose-response is sub-linear (the slope increases as the dose increases) at moderate-to-high doses.
- Excess risk is greater at a younger age-at-exposure.
- Excess risk falls away with time-since-exposure.
- About one-third of ~300 leukaemia deaths among the bomb survivors are due to irradiation during the atomic bombings.

Childhood Leukaemia

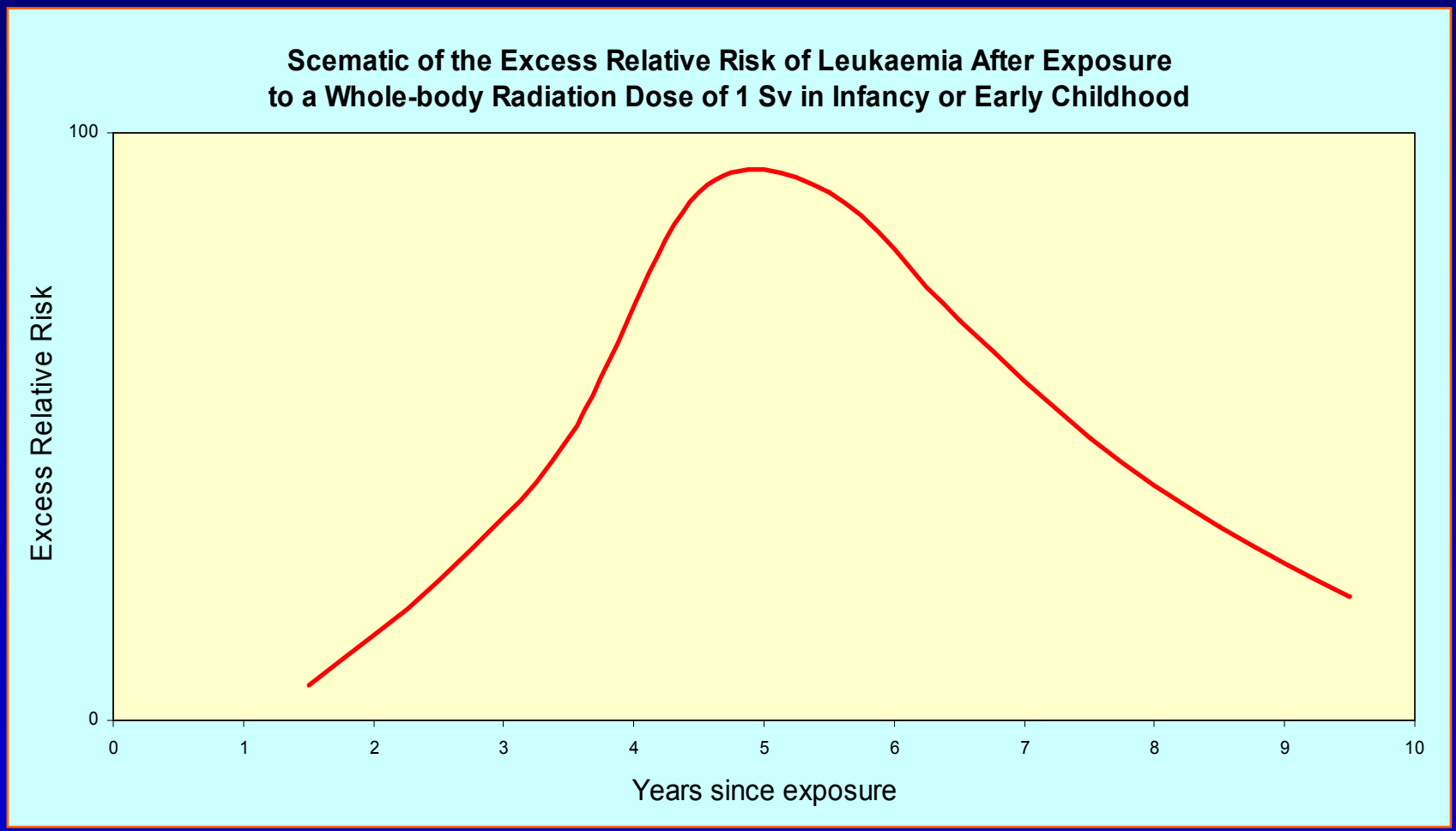
- After October 1950, 10 cases of leukaemia occurred among Japanese survivors under the age of 15 years.
- This compares with less than one case expected among these children.
- A clear excess risk of childhood leukaemia exists as a result of radiation exposure from the bombings.

Medical Irradiation

- The high relative risk of childhood leukaemia following irradiation of infants or young children during the atomic bombings is confirmed by most (but not all) studies of those exposed therapeutically to treat a variety of malignant and benign medical conditions.

Temporal Expression of ERR

(Excess Relative Risk, ERR, is the proportional increase or decrease in risk when compared to the background risk.)



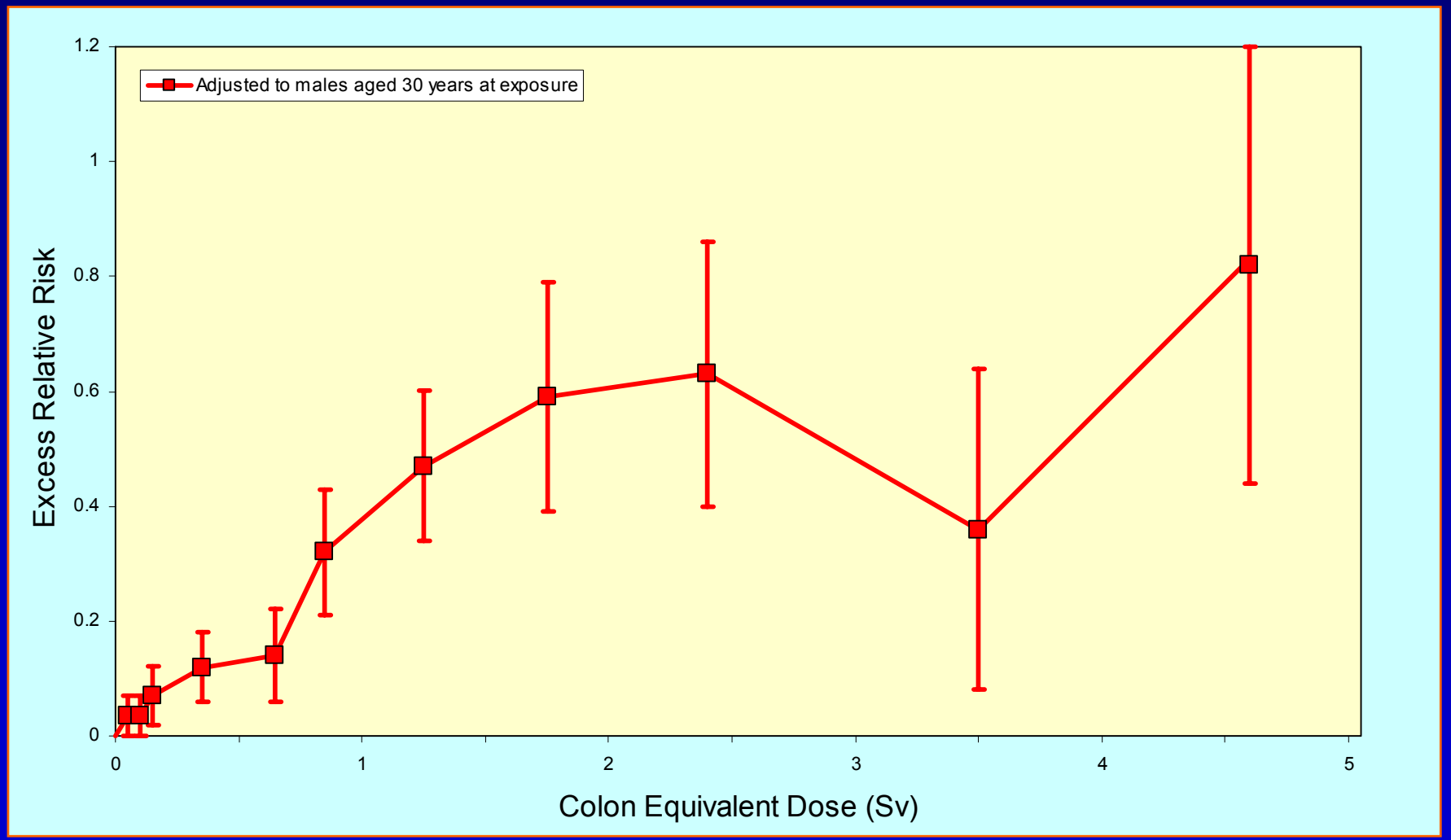
Natural Background Radiation

- Risk models for radiation-induced leukaemia suggest that about one-quarter of cases of childhood (<15 years of age) leukaemia in Great Britain may be caused by natural background radiation (red bone marrow dose ~1.3 mSv per annum).
- However, epidemiological studies have been unable to reliably demonstrate this source of risk.

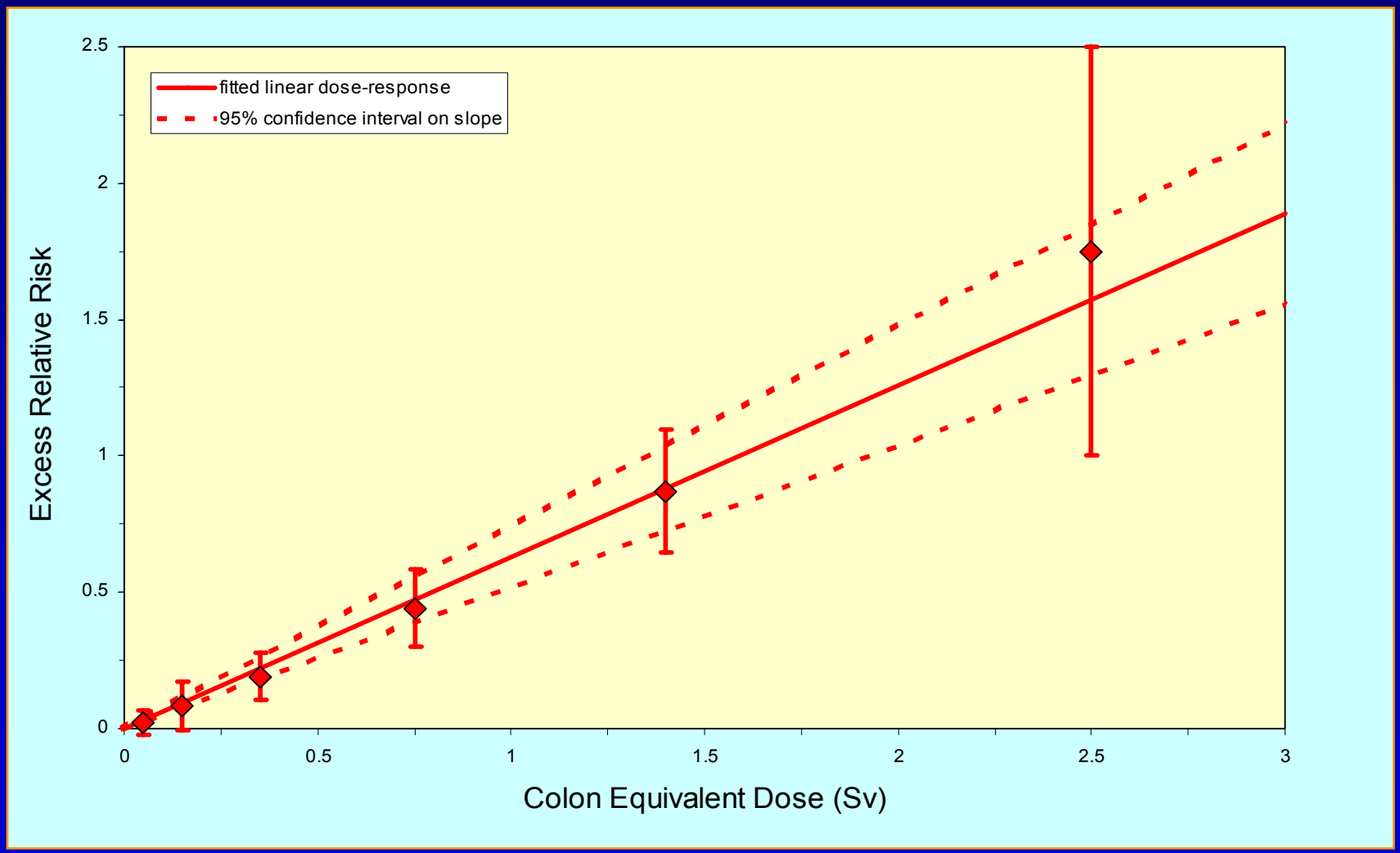
Solid Tumours

- An excess risk of solid tumours among the Japanese atomic bomb survivors appeared later than that for leukaemia.
- Excess risk follows background risk.
- Excess risk still apparent 50 years after exposure – there was an approximately 6% (~740) excess of cases during 1958-1994.
- Thyroid, breast and lung cancers are particularly radiosensitive.

Excess relative risk (±1se) of solid tumour mortality among the Japanese atomic bomb survivors during 1950-1990 (Shimizu *et al.*, 1996)

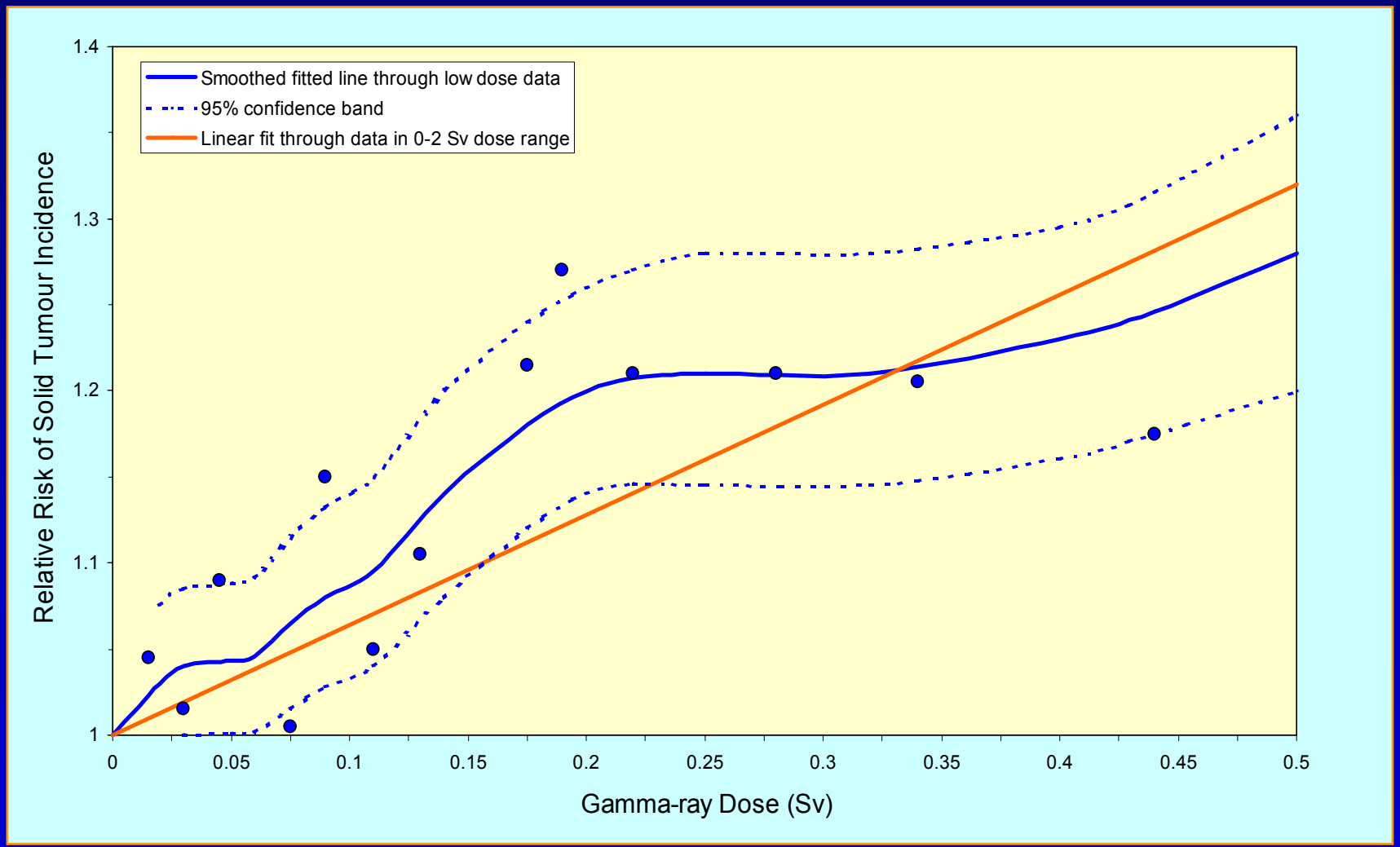


Excess relative risk (and 95% CI) of solid tumour incidence among the Japanese atomic bomb survivors during 1958-1987 (UNSCEAR, 1994)



Relative Risk of Solid Tumour Incidence among the Japanese Atomic Bomb Survivors during 1958-1994

(Pierce and Preston, 2000)



Childhood Solid Tumours

- No case of a solid tumour was observed among the Japanese atomic bomb survivors before the age of 15 years (less than one case expected).
- The absence of a notable excess risk of the typical solid tumours of childhood is largely confirmed by studies of medical irradiation.
- Contrasts with the notable excess of childhood leukaemia.

Relative Risk of Childhood Cancer Mortality Associated with a Radiographic Examination of the Pregnant Mother

(Stewart *et al.*, 1956)

Deaths from Childhood Cancer during 1953-1955						
Maternal irradiation during relevant pregnancy	Leukaemia*			Other Cancers*		
	Cases	Controls	Relative Risk (95% confidence interval)	Cases	Controls	Relative Risk (95% confidence interval)
Abdomen	42	24	1.92 (1.12, 3.28)	43	21	2.28 (1.31, 3.97)
Other	25	23	1.19 (0.65, 2.16)	33	32	1.15 (0.68, 1.94)
None	202	222	1 (reference)	202	225	1 (reference)

* Death under 10 years of age

Relative Risk of Cancer in Childhood Associated with an Obstetric X-ray Examination

(Doll and Wakeford, 1997)

Results of Studies of Cancer in Childhood and Radiation Exposure *In Utero*			
Study	**Amount of Evidence[1]**	**Relative Risk (unadjusted)**	**95% Confidence Interval**
OSCC	852.4	1.39	(1.30,1.49)
NE United States	114.7	1.47	(1.22, 1.77)
Inter-regional Study, UK	39.0	1.23	(0.90, 1.68)
Los Angeles	23.9	1.34[2]	(0.90, 2.00)
Louisiana	18.3	1.70	(1.08, 2.69)
Helsinki	17.9	1.18	(0.74, 1.87)
California	17.8	1.68[2]	(1.06, 2.67)
Tri-state (US)	16.6	1.40[2]	(0.87, 2.27)
Swedish Twins	11.6	1.38	(0.78, 2.46)
Minnesota	10.2	1.28[2]	(0.69, 2.37)
All Other[3]	42.4	1.13	(0.84, 1.53)
All Except OSCC	312.4	1.37	(1.22, 1.53)
All	1164.8	1.38	(1.31, 1.47)

[1] Measure of statistical information contained in a study
[2] Leukaemia only
[3] Includes cohort studies other than the Japanese atomic bomb survivor cohort

Antenatal Radiography

- Intrauterine doses ~10 mSv increase the risk of childhood cancer.
- Relative risk of childhood solid tumours raised to about the same level as that of childhood leukaemia – in contrast with postnatal irradiation studies.
- Cells from which the common solid tumours of childhood arise are radiosensitive principally *in utero*?

Bomb Survivors Irradiated *In Utero*

- ~800 Japanese survivors were exposed *in utero* (average dose ~0.25 Gy).
- 0 case of childhood leukaemia observed, but only 0.2 expected.
- 2 cases of childhood solid tumours observed, against 0.28 expected – a marginally significant ($p < 0.05$) excess.
- ERR coefficient (excess relative risk per unit dose) compatible with that derived from the antenatal radiography studies.

Seascale Childhood Leukaemia

- In November 1983, a television documentary reported an approximately tenfold excess of childhood leukaemia in the coastal village of Seascale.
- The excess was based upon 10 cases of childhood leukaemia and non-Hodgkin's lymphoma (NHL) over a thirty-year period.

Sellafield and Seascale

Seascale Childhood Leukaemia

- A detailed radiological assessment conducted by the NRPB for the Black Advisory Group found that doses in Seascale from Sellafield discharges were generally less than natural background doses, and too small by a factor of >100 to explain the cluster.
- A gross underestimation of the risk?

Seascale Childhood Leukaemia

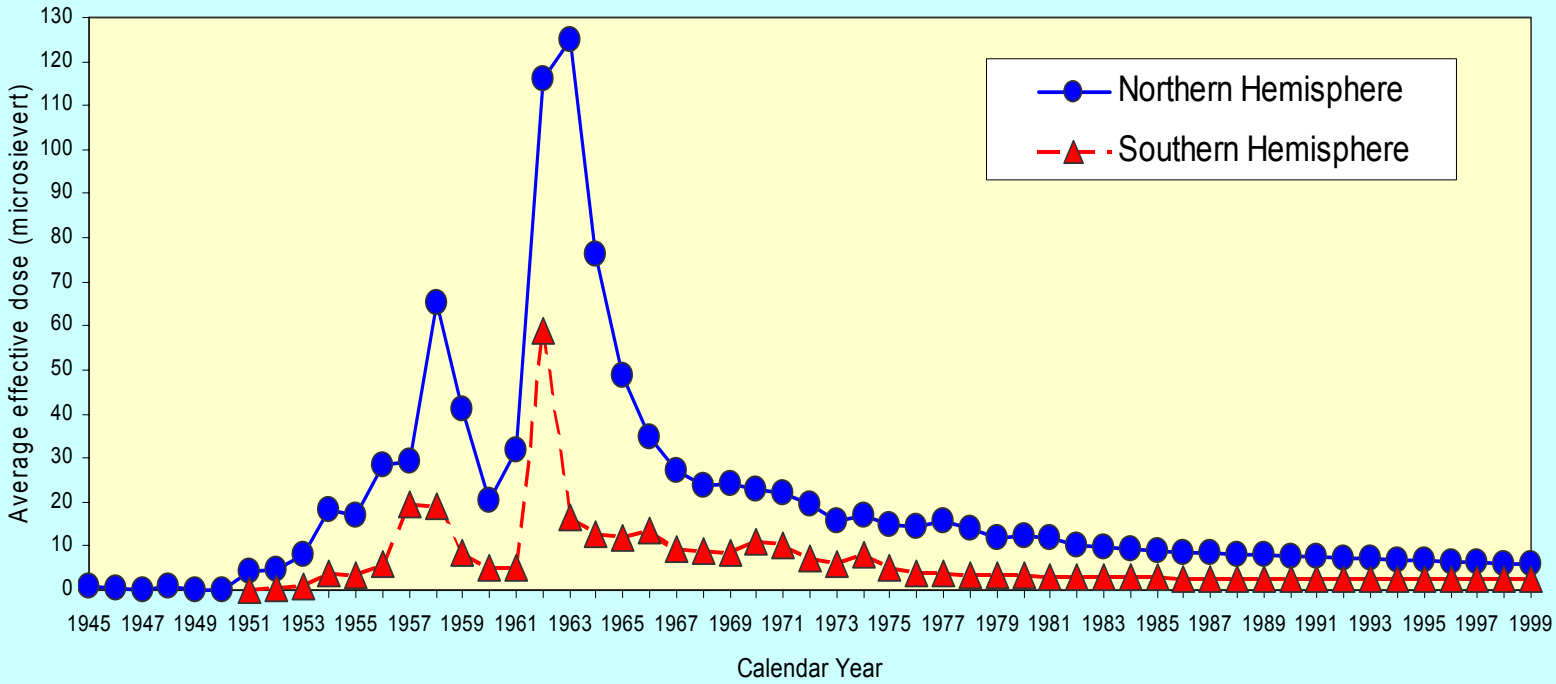
- Prime suspects
  - intake of radioactive material much higher than predicted
  - relevant radiation exposures (e.g. from plutonium) and/or associated childhood leukaemia risk much higher than predicted.
- Concern increased by the observation of an excess of childhood leukaemia around Dounreay (particularly in Thurso).

In Vivo Measurements

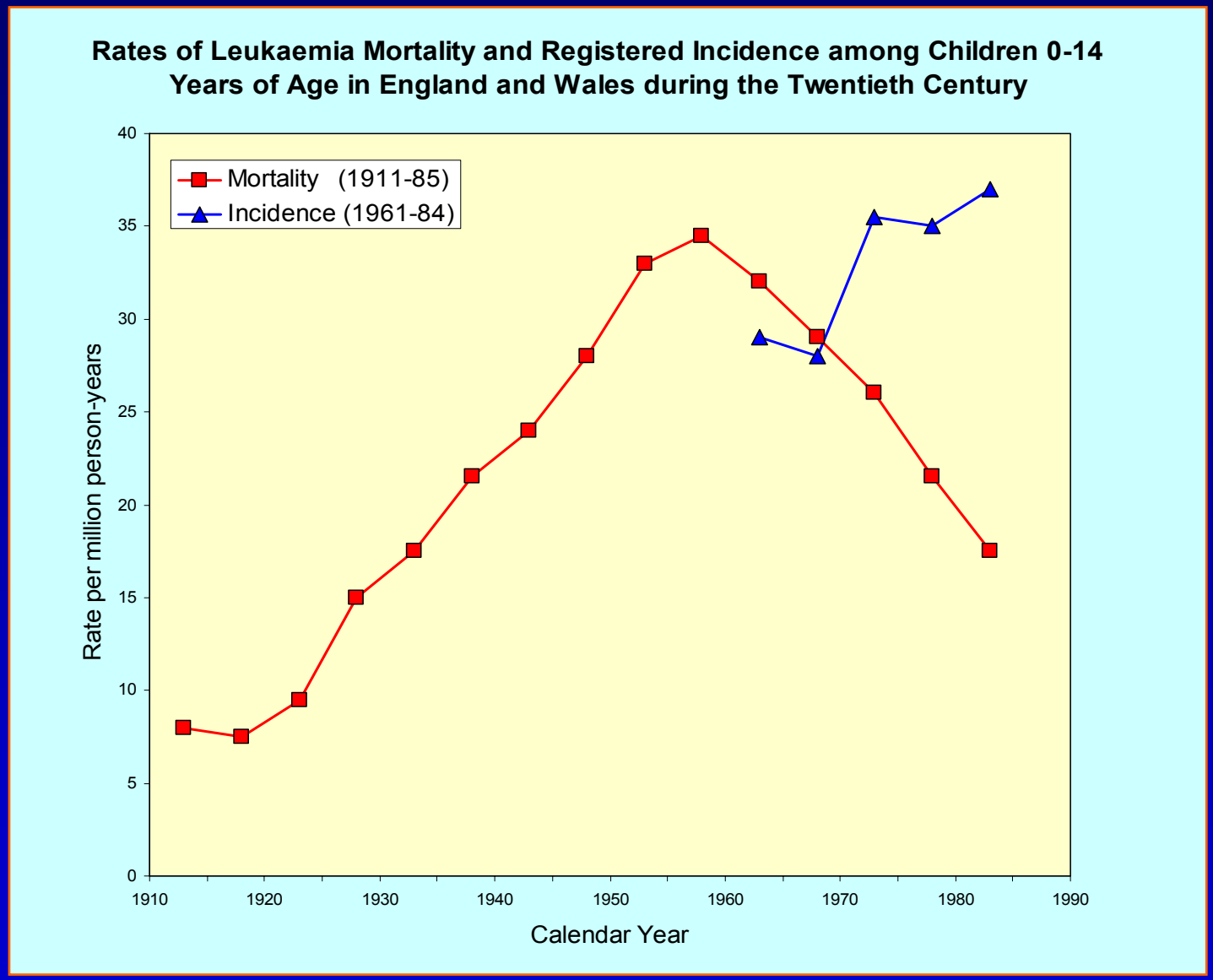
- Measurements made of radioactive material present in people, e.g. whole-body monitoring, radionuclides in urine, and radionuclides in tissues sampled at autopsy.
- These *in vivo* measurements did not indicate that intakes of radioactive materials have been grossly underestimated.

Weapons Testing Fallout

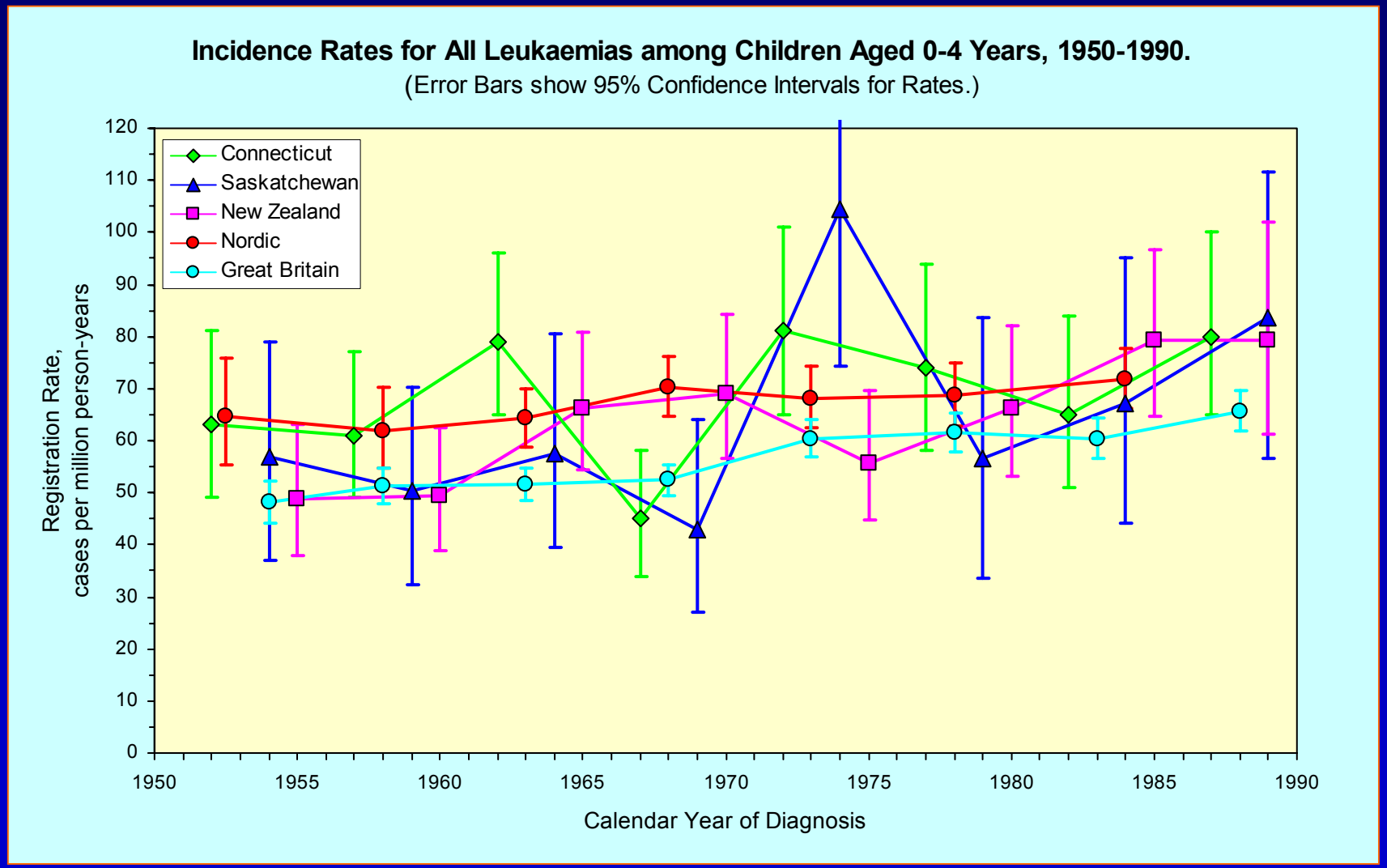
Average annual effective dose in the Northern and Southern Hemispheres from radionuclides produced in atmospheric nuclear weapons testing (UNSCEAR, 2000)



Childhood Leukaemia Trends



Childhood Leukaemia Incidence



Paternal Preconceptional Irradiation (PPI)

(Gardner *et al.*, 1990)

Leukaemia in West Cumbria, 1950-1985				
Cumulative Preconceptional Dose (mSv)	**Leukaemia Cases‡**	**Controls***	**Relative Risk**	**95% Confidence Interval**
0	38	236	1.0	Reference
1-49	3	26	0.77	(0.20, 3.00)
50-99	1	11	0.78	(0.08. 7.73)
100+	4	3	8.38	(1.35, 51.99)

‡ diagnosed while under 25 years of age

* “local” controls

Studies of PPI and Childhood Leukaemia/NHL

Study Group	Dose-response Model	Relative Risk (100 mSv vs. 0 mSv)	95% Confidence Interval
Sellafield	Exponential	1.6	(1.0, 2.2)
Inside Seascale	Exponential	2.0	(1.0, 3.1)
Outside Seascale	Exponential	1.5	(0.7, 2.3)
Other British workers	Exponential*	0.96	(0.31, 2.93)
Ontario workers‡	Exponential	0.75	(0.07, 3.31)
	Linear	0.63	(<0.27, 3.40)
US workers	Linear	0.75	(<0.75, 3.5)
Danish Thorotrast patients	Exponential	<0.11	(<0.11, 1.11)
	Linear	<0.97	(<0.97, 1.56)
Japanese atomic bomb survivors‡, †	Exponential	0.76	(<0.31, 1.03)
	Linear	<0.98	(<0.98, 1.10)

* Adjusted for radiation worker status
‡ Leukaemia only
† Paternal dose only

Mayak Workforce

- Intense pressure in the former USSR during the late 1940s and 1950s to produce materials for nuclear weapons.
- Led to high exposures to external radiation and plutonium among the workers at the Mayak facility in the Southern Urals.

Leukaemia at Mayak

(Shilnikova *et al.*, 2003)

Leukaemia[α] Mortality in the Mayak Workers		
Time Since Exposure (years)	**Excess Relative Risk per gray[β] (90% confidence interval)**	
3-5	7.6 (3.2, 17)	6.9 (2.9, 15)
5-10	0.3 (<-0.1, 2.7)	0.45 (0.1, 1.1)
10-20	0.8	
20+	0.4	

[α] All types of leukaemia except chronic lymphoid leukaemia (CLL)

[β] Cumulative dose of radiation from external sources

Plutonium Exposure at Mayak

- Clear excesses of bone, liver and lung cancers associated with plutonium exposure, i.e. at those sites where plutonium is expected to accumulate.
- **No** excess of leukaemia associated with plutonium exposure, despite the clear excess of leukaemia associated with exposure to external radiation.

Childhood Thyroid Cancer

- Atomic bomb survivors and therapeutically irradiated patients demonstrate that the thyroid glands of children are very sensitive to radiation-induced cancer.
- Ron *et al.* (1995) conducted a pooled analysis of seven externally irradiated groups. For those exposed before the age of 15 years the ERR coefficient was 7.7 Sv^{-1} (95% CI: 2.1, 28.7).

Chernobyl

- Substantial numbers of children in some areas of the former USSR received high thyroid doses (up to 1 Sv or more) as a result of the release of radioiodine during the Chernobyl reactor accident.
- 2,000 excess thyroid cancers to date with the possibility of five times this number eventually.

Chernobyl

- Little evidence for excesses of other childhood cancers (including childhood leukaemia) or adult cancers (including thyroid cancer) being associated with Chernobyl contamination.
- Suggestive evidence for a raised underlying risk of infant (<1 year of age) leukaemia, but further data are required before a reliable conclusion can be reached.

Conclusions

- Childhood leukaemia is particularly sensitive to induction by ionising radiation.
- Childhood thyroid cancer also has a high ERR coefficient.
- The typical solid cancers of childhood are not readily induced by exposure after birth, but may be produced by irradiation *in utero*.

REMINDER

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