Ionising Radiation Epidemiology of Childhood Leukaemia

Richard Wakeford

Visiting Professor in Epidemiology,

Dalton Nuclear Institute,

The University of Manchester, UK

(Richard.Wakeford@manchester.ac.uk)

MANCHESTER
1824

The University of Manchester
Dalton Nuclear Institute

Leukaemia among Radiologists

- In 1944, persuasive evidence was published for a raised risk of leukaemia among US radiologists.

  March HC. Leukemia in radiologists. *Radiology* 1944; **43**: 275-278

- An indication of a raised risk of myeloid leukaemia in French radiologists had been published in 1931.

  Aubertin C. Leukaemia in radiologists. *Gaz méd de France* 1931 pp. 333-335

MANCHESTER 1824

EU Scientific Seminar, "Childhood Leukaemia – Mechanisms and Causes", Luxembourg, Tuesday, 3 November 2009.

The University of Manchester
Dalton Nuclear Institute

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.

MANCHESTER
1824

The University of Manchester
Dalton Nuclear Institute

Leukaemia among Survivors

- In 1948, alert clinicians noted an increase of leukaemia among the A-bomb survivors.

- This observation contributed to the establishment in October 1950 of the Life Span Study (LSS) cohort of Japanese atomic bomb survivors.

MANCHESTER
1824

The University of Manchester
Dalton Nuclear Institute

Life Span Study (LSS)

- Follow-up of ~87 000 survivors, ~48 000 of whom were non-trivially exposed.

- Started in October 1950 and is still underway.

- General population of "healthy" individuals of both sexes and all ages.

- Mortality and cancer incidence investigated.

- Wide range of doses received with detailed organ dose estimates.

MANCHESTER 1824

The University of Manchester
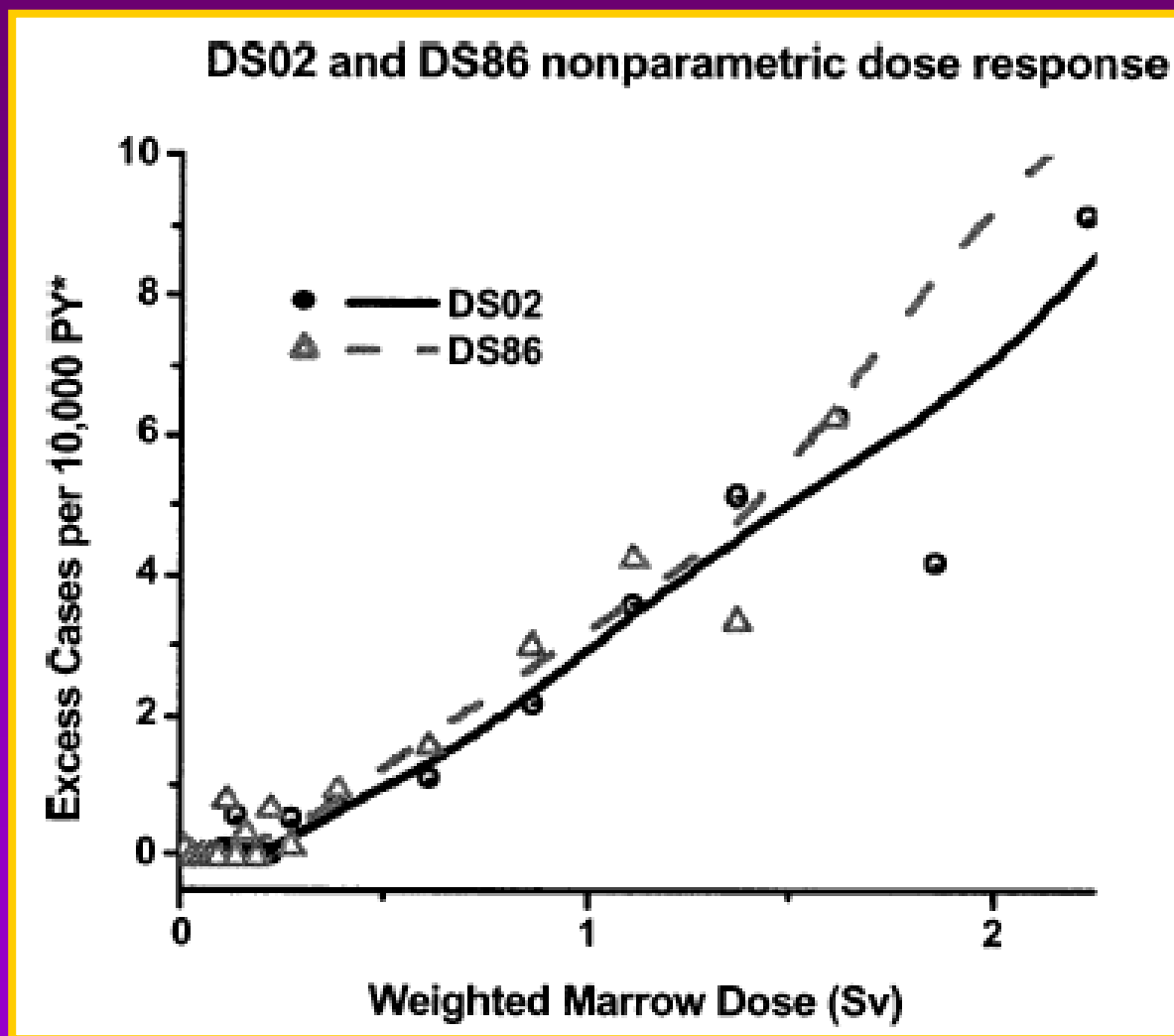Dalton Nuclear Institute

Leukaemia

- Clear and pronounced excess risk of leukaemia in the atomic bomb survivors.

- Excess Relative Risk* (ERR) at 1 Sv of leukaemia mortality in both sexes and all ages during 1950-2000

  4.02 (90% CI: 3.02, 5.26)

* The Excess Relative Risk (ERR) is the proportional increase in risk above background, e.g. ERR = 1 represents a 100% increase above background, a doubling of the background risk.
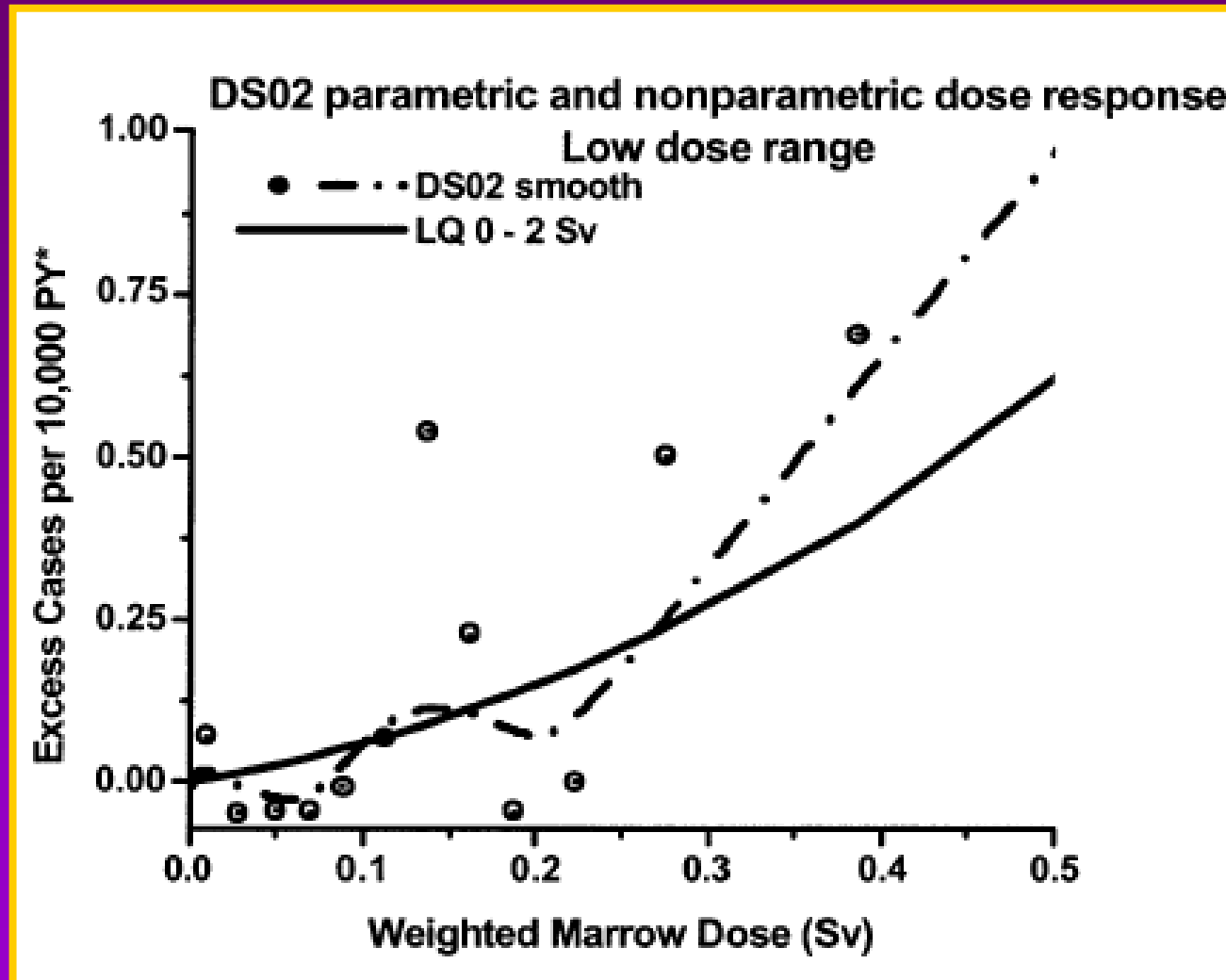
Leukaemia Mortality, 1950-2000

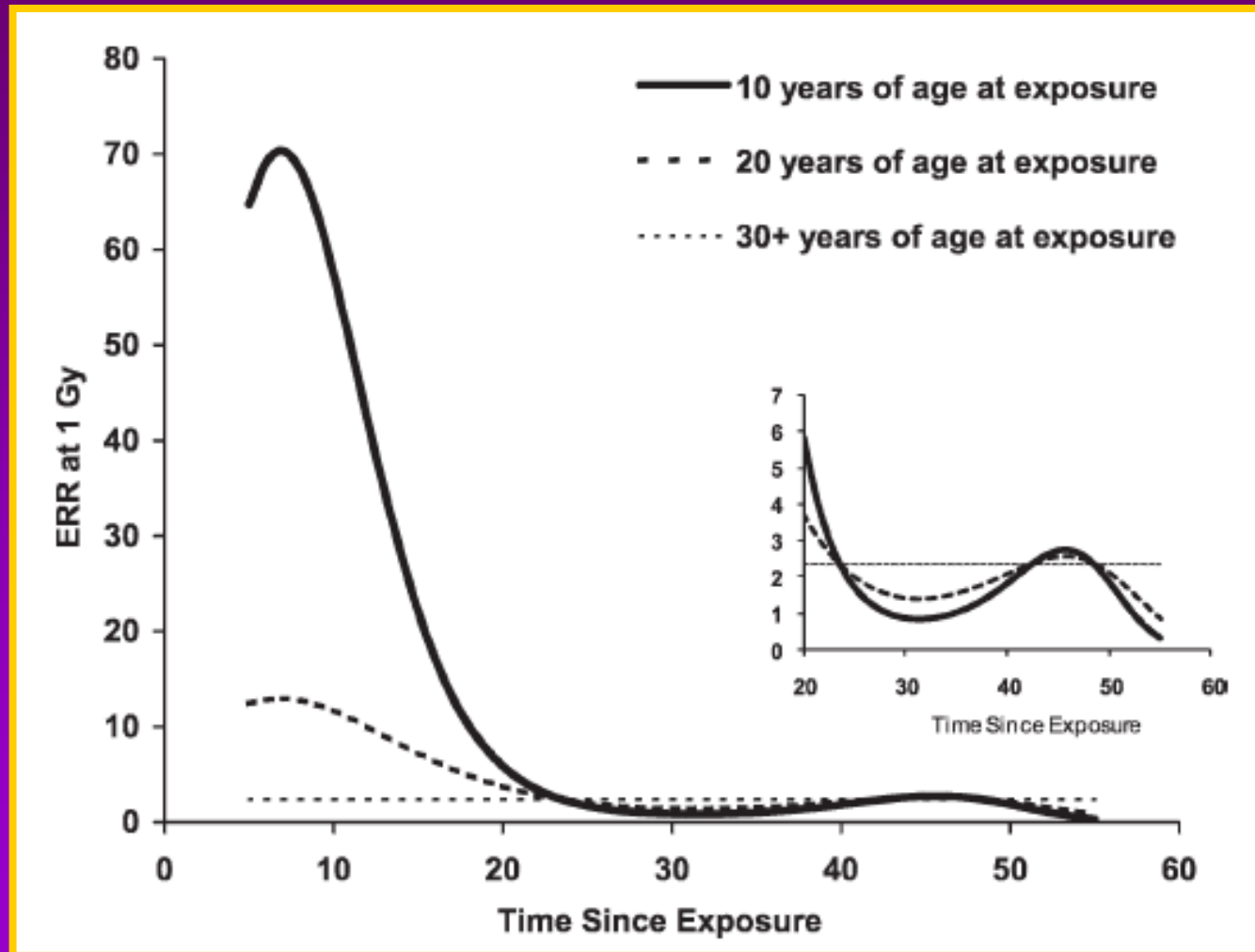(Preston *et al.*, *Radiat Res* 2004; **162**: 377-89)

DS02 and DS86 nonparametric dose response

MANCHESTER 1824

The University of Manchester
Dalton Nuclear Institute

Leukaemia Mortality, 1950-2000

(Preston *et al.*, *Radiat Res* 2004; **162**: 377-89)

MANCHESTER
1824

The University of Manchester
Dalton Nuclear Institute

Leukaemia Mortality, 1950-2000

(Richardson *et al.*, *Radiat Res* 2009; **172**: 368-82)

MANCHESTER 1824

EU Scientific Seminar, "Childhood Leukaemia – Mechanisms and Causes", Luxembourg, Tuesday, 3 November 2009.

The University of Manchester
Dalton Nuclear Institute

Leukaemia Risk

- Dose-response is sub-linear (the slope increases as the dose increases) at moderate-to-high doses.

- Excess Relative Risk is greater at a younger age-at-exposure.

- Excess Relative Risk falls away with time-since-exposure.

- About ½ of ~200 leukaemia deaths among the exposed 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.

MANCHESTER
1824

The University of Manchester
Dalton Nuclear Institute

Childhood Leukaemia

- ERR coefficient for childhood leukaemia using incidence data from the LSS

$$34.4 \ (95\% \ CI: 7.1, \ 414) \ Sv^{-1}$$

- It is known that cases of leukaemia occurred before October 1950, but these cases are not included among those used to derive this ERR estimate.

MANCHESTER 1824

The University of Manchester
Dalton Nuclear Institute

Life Span Study (LSS)

- Acute, high dose-rate exposure.
- Malnourished Japanese population; low proportion of men of military age.
- Some (retrospective) dose estimates uncertain; predominantly external γ doses.
- "Healthy survivor effect".
- About half of the survivors still alive.
- Data prior to October 1950 missing.

MANCHESTER 1824

The University of Manchester
Dalton Nuclear Institute

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.

- Groups therapeutically exposed include: enlarged thymus gland, ringworm of the scalp, and skin haemangioma.

MANCHESTER 1824

EU Scientific Seminar, "Childhood Leukaemia – Mechanisms and Causes", Luxembourg, Tuesday, 3 November 2009.

The University of Manchester
Dalton Nuclear Institute

Medical Irradiation

- Although medically exposed groups offer a valuable complement to evidence derived from the Japanese atomic bomb survivors care in interpretation is required:
    - Exposure occurs because of known or suspected disease and this may affect the subsequent risk
    - Radiotherapy involves high and localised doses
    - Accurate dose estimates are often lacking

MANCHESTER
1824

The University of Manchester
Dalton Nuclear Institute

Oxford Survey of Childhood Cancers (OSCC)

- In the early-1950s a nationwide case-control study of mortality from leukaemia and other cancers among children in Great Britain was initiated by Dr Alice Stewart and her colleagues. This became the Oxford Survey of Childhood Cancers (OSCC).

- First results reported in *The Lancet* in 1956 showed a statistical association between childhood cancer and antenatal radiography.

MANCHESTER 1824

EU Scientific Seminar, "Childhood Leukaemia – Mechanisms and Causes", Luxembourg, Tuesday, 3 November 2009.

The University of Manchester
Dalton Nuclear Institute

Childhood Leukaemia

- The most recent result from the OSCC for childhood leukaemia as a separate category was reported by Bithell and Stewart (1975):

  Relative Risk (RR) = 1.49 (95% CI: 1.33, 1.67)

- Results have now been reported from many independent case-control studies from around the world:

Case-control Study	Study Details	Cases (Exposed/Total)	Information	RR (unadjusted)	95% CI
Bithell and Stewart (1975)	GB (**OSCC**); deaths, 1953-67	569/4052	297	1.49	(1.33, 1.67)
Monson and MacMahon (1984)	NE USA; deaths, 1947-60	94/704	76	1.48	(1.18, 1.85)
Robinette and Jablon (1976)	USA military hospitals; deaths, 1960-69	64/429	44	1.08	(0.80, 1.46)
Naumburg *et al.* (2001)	Sweden; incident cases, 1973-89	68/624	29	1.13	(0.78, 1.63)
Roman *et al.* (2005)	England & Wales (UKCCS); incident cases, 1992-96	37/1196	28	1.05	(0.73, 1.52)
Shu *et al.* (2002)	North America (CCG); ALL incident cases, 1989-93	55/1809	26	1.16	(0.79, 1.71)
Polhemus and Koch (1959)	Los Angeles; incident cases, 1950-57	66/251	23	1.23	(0.82, 1.85)
Infante-Rivard (2003)	Quebec; ALL incident cases, 1980-98	42/701	21	0.85	(0.56, 1.30)
Hopton *et al.* (1985)	N England; leukaemia and lymphoma incident cases, 1980-83	37/245	19	1.35	(0.86, 2.11)
Kaplan (1958)	California; acute leukaemia deaths, 1955-56	40/150	17	1.60	(1.00, 2.57)
Graham *et al.* (1966)	USA "tri-state"; incident cases, 1959-62	27/313	17	1.40	(0.87, 2.27)
van Steensel-Moll *et al.* (1985)	Netherlands; ALL incident cases, 1973-79	41/517	12	2.22	(1.27, 3.88)
Ford *et al.* (1959)	Louisiana; deaths, 1951-55	21/78	11	1.71	(0.96, 3.06)
Stewart (1973); Mole (1974)	GB (**OSCC**) twins; deaths, 1953-64	51/70	11	2.17	(1.19, 3.95)
Salonen (1976)	Finland; incident cases, 1959-68	15/300	10	1.01	(0.54, 1.90)
Ager *et al.* (1965)	Minnesota; deaths, 1953-57	20/107	10	1.27	(0.68, 2.37)
Roman *et al.* (1997)	S England; incident cases, 1962-92	16/143	10	0.72	(0.39, 1.34)
Golding *et al.* (1992)	SW England; incident cases, 1971-91	14/63	9	2.03	(1.06, 3.88)
Fajardo-Gutierréz *et al.* (1993)	Mexico City; incident cases	16/80	7	1.89	(0.91, 3.95)
Magnani *et al.* (1990)	N Italy; AL incident cases, 1981-84	10/164	6	1.09	(0.49, 2.44)
Rodvall *et al.* (1990)	Swedish **twins**; incident cases, 1952-83	10/27	5	1.83	(0.77, 4.31)
Gunz and Atkinson (1964)	New Zealand; incident cases, 1958-61	14/102	5	1.11	(0.47, 2.61)
Shu *et al.* (1988)	Shanghai; incident cases, 1974-86	8/309	4	1.86	(0.71, 4.87)
Roman *et al.* (1993)	S England; leukaemia plus NHL incident cases, 1972-89	5/37	4	1.12	(0.40, 3.15)
Shu *et al.* (1994)	North America (CCG); infant AL incident cases, 1983-88	7/291	4	1.10	(0.43, 2.83)
Harvey *et al.* (1985)	Connecticut **twins**; incident cases, 1935-81	5/13	3	1.81	(0.55, 5.99)
Wells and Steer (1961)	New York; incident cases	4/77	3	0.72	(0.22, 2.34)
Kjeldsberg (1957)	Norway; incident cases, 1946-56	5/55	3	0.59	(0.18, 1.93)
McKinney *et al.* (1999)	Scotland (UKCCS), incident cases, 1991-94	6/144	3	2.31	(0.69, 7.70)
van Duijn *et al.* (1994)	Netherlands; ANLL incident cases, 1973-79	6/80	3	2.35	(0.78, 6.99)
Murray *et al.* (1959)	New York; deaths, 1940-57	3/65	2	0.92	(0.25, 3.36)
Gardner *et al.* (1990)	NW England; incident cases, 1950-85	3/20	2	1.19	(0.31, 4.55)
Meinert *et al.* (1999)	Germany; incident cases, 1980-94	3/1184	2	0.93	(0.24, 3.60)
Shu *et al.* (1994)	Shanghai; AL incident cases, 1986-91	7/166	2	2.39	(0.61, 9.41)

Childhood Leukaemia
OSCC *vs.* The Rest
(Wakeford, *Radiat Prot Dosim* 2008; **132**: 166-174)

Case-control Study	Cases (Exposed/Total)	Statistical Information	Relative Risk	95% Confidence Interval
OSCC (singleton plus twin births)	620/4122	308	**1.51**	**(1.35, 1.69)**
All Except OSCC (singleton plus twin births)	769/10444	420	**1.28**	**(1.16, 1.40)**

MANCHESTER 1824

The University of Manchester
Dalton Nuclear Institute

Risk Coefficients from OSCC

- Using the Excess Relative Risk (ERR) model obtained from the OSCC birth cohort data, an ERR for a birth in 1959 may be obtained.

- Use the Adrian Committee average fetal dose estimate for 1958 of 6.1 mGy.

- Derive an ERR coefficient of

$$51 \ (95\% \ CI: 28, \ 76) \ Gy^{-1}$$

for all childhood cancers.

R. Wakeford and M. P. Little, *Int J Radiat Biol* 2003; **79**: 293-309

MANCHESTER 1824

The University of Manchester
Dalton Nuclear Institute

Bomb Survivors Irradiated *In Utero*

- 807 Japanese A-bomb survivors were irradiated *in utero* and received doses of at least 10 mGy (average dose 0.28 Gy).

- 2 incident cases of childhood (<15 years of age) cancer were observed among these survivors (1 liver tumour and 1 kidney tumour) against, at most, 0.48 case expected from contemporaneous Japanese rates.

R. Wakeford and M. P. Little, *Int J Radiat Biol* 2003; **79**: 293-309

MANCHESTER
1824

The University of Manchester
Dalton Nuclear Institute

Bomb Survivors Irradiated *In Utero*

- 0 case of childhood leukaemia observed, but only 0.2 expected
  - O/E has an upper 95% CL of 15.
- 2 cases of childhood solid tumours observed, against 0.28 expected
  - O/E = 7.14 (95% CI: 1.20, 23.60).
- Possibility that some cases of childhood cancer (particularly childhood leukaemia) occurring among the survivors before October 1950 went undetected.

Childhood Leukaemia
OSCC *vs.* Bomb Survivors

- The level of risk of childhood leukaemia associated with <u>antenatal</u> diagnostic radiography is compatible with that found among Japanese atomic bomb survivors irradiated <u>postnatally</u>.

- The absence of childhood leukaemia among A-bomb survivors irradiated *in utero* may be due to small numbers, missing cases or some other factor (e.g. cell killing).

MANCHESTER 1824

EU Scientific Seminar, "Childhood Leukaemia – Mechanisms and Causes", Luxembourg, Tuesday, 3 November 2009.

The University of Manchester Dalton Nuclear Institute

Chromosome Translocation Frequencies in Atomic Bomb Survivors Exposed *in utero* (●), and in some of their Mothers (□). (Ohtaki *et al.*, *Radiat Res* 2004; **161**: 373-9)

MANCHESTER 1824

The University of Manchester
Dalton Nuclear Institute
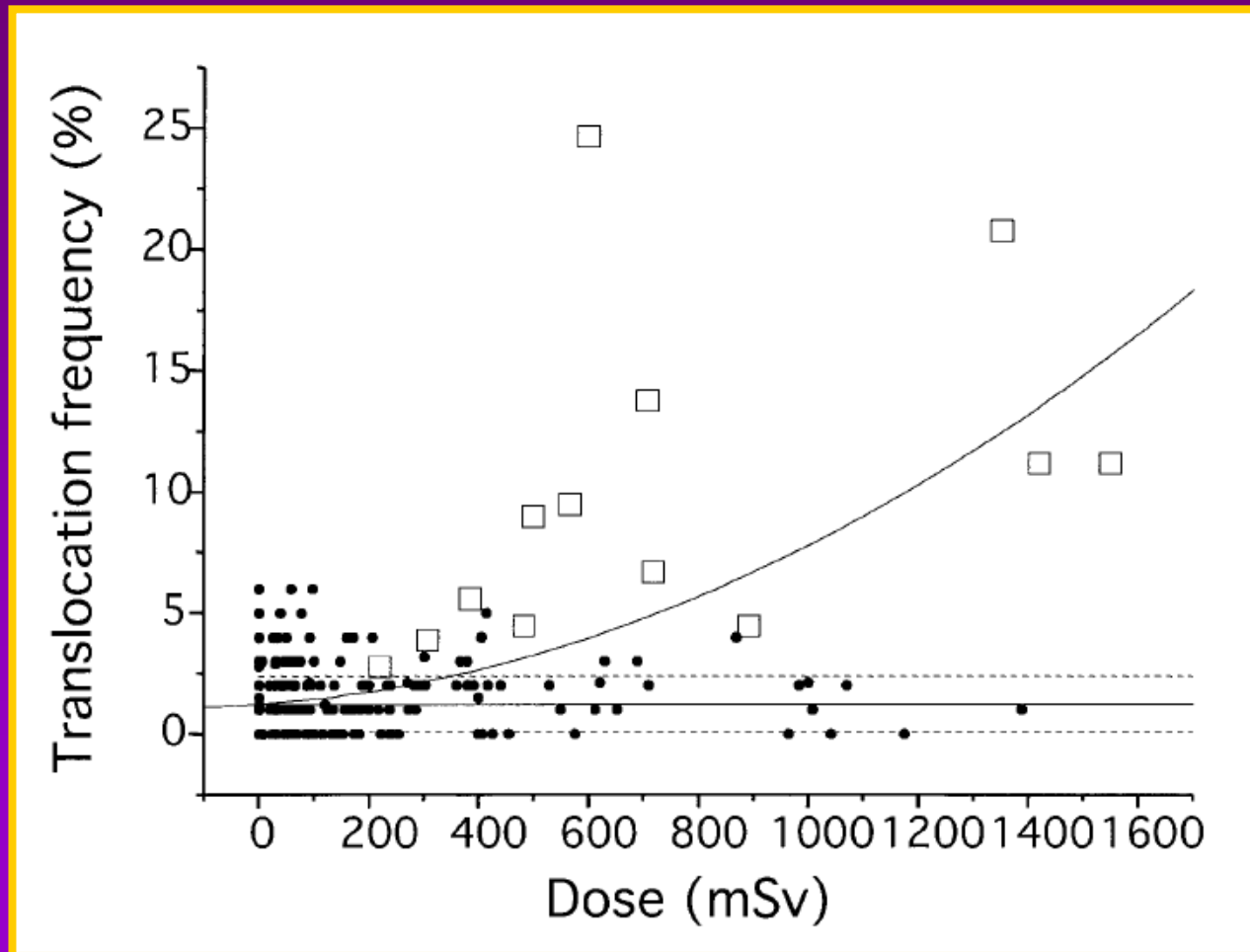
Natural Background Radiation

- Risk models for radiation-induced leukaemia suggest that 15-20% 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

- Epidemiological studies have been unable to reliably demonstrate this source of risk

  – variation in dose is not sufficiently great?

MANCHESTER 1824

The University of Manchester
Dalton Nuclear Institute

Radon and Childhood Leukaemia

- Several studies have examined the potential link between exposure to radon and childhood leukaemia.

- The most persuasive of these studies is the recent nationwide Danish case-control study of Raaschou-Nielsen *et al.* (*Epidemiology* 2008; **19**: 536-543).

- This study used model-predicted radon concentrations, which avoids participation bias but introduces exposure uncertainty.

MANCHESTER
1824

The University of Manchester
Dalton Nuclear Institute

Danish Radon Study

- Found a statistically significant association between radon and childhood ALL, and concluded that 9% of cases in Denmark were attributable to radon.

- However, the lower 95% CL for the attributable proportion is 1%, which is compatible with conventional risk models.

- Accuracy of model-predictions of radon concentrations needs further investigation.

MANCHESTER 1824
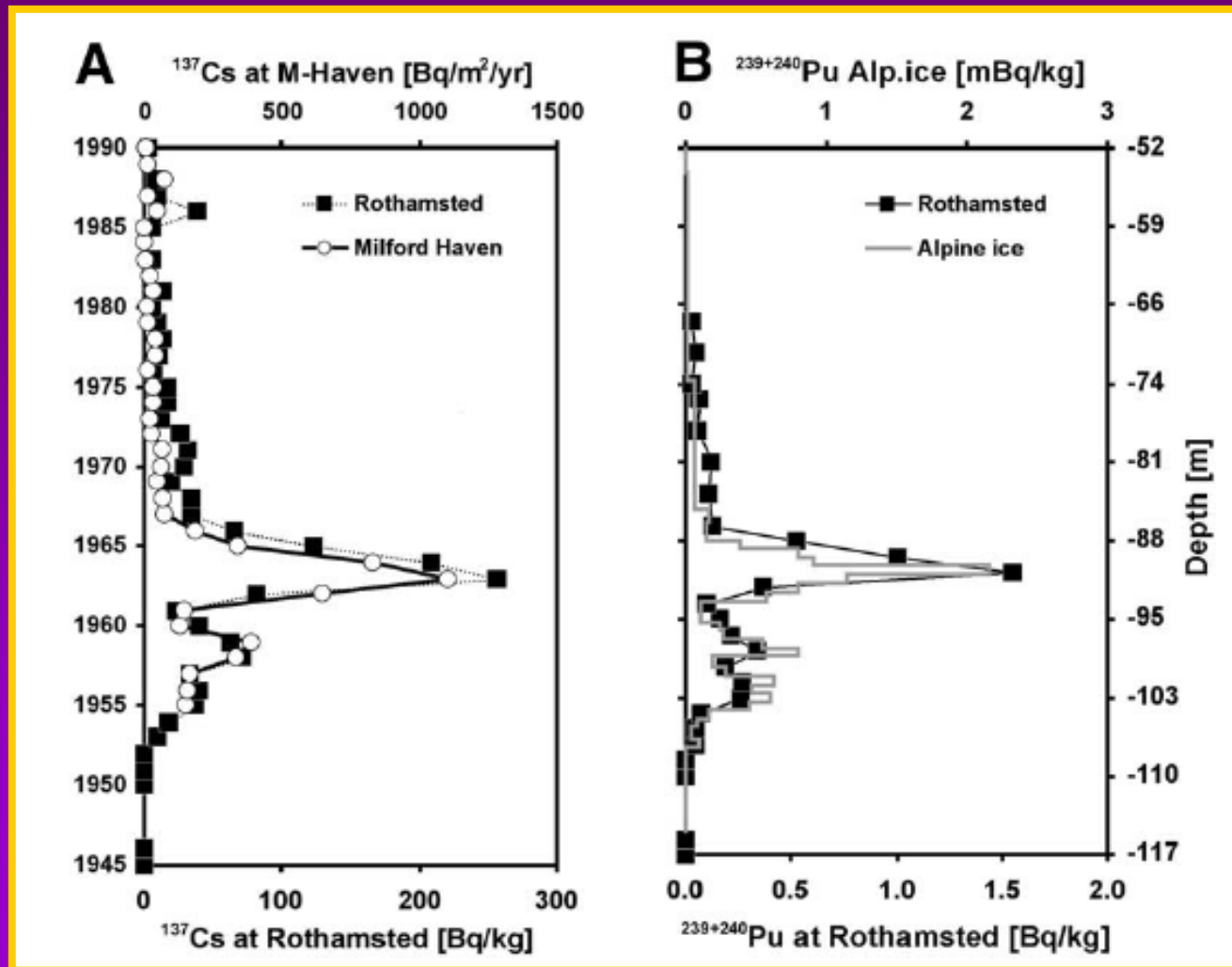
The University of Manchester
Dalton Nuclear Institute

Doses from Radon

- Recently, Harley and Robbins *(Health Phys* 2009; **97**: 343-347) have suggested that doses from radon to circulating lymphocytes in the bronchial epithelium could be high.

- However, lymphocytes remain for only a short time in the bronchial epithelium and the dose from radon to circulating lymphocytes needs further examination.

MANCHESTER
1824

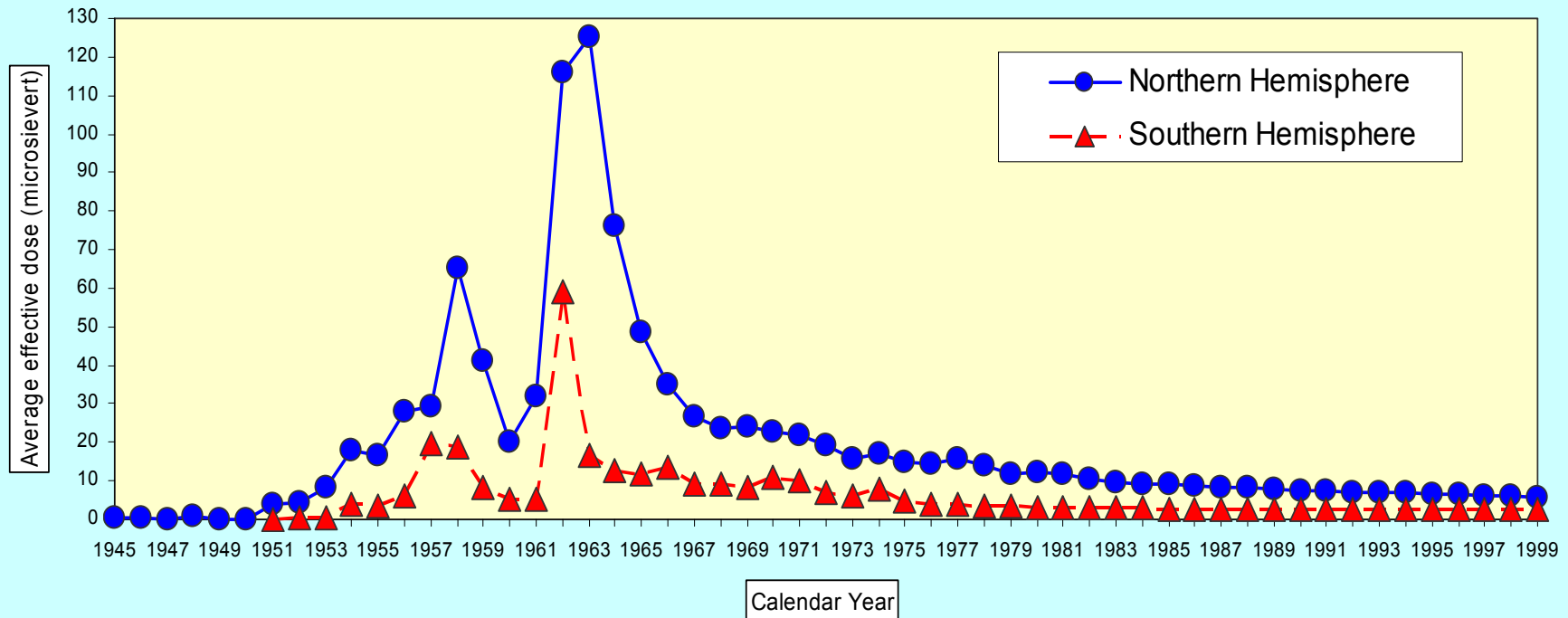The University of Manchester
Dalton Nuclear Institute

Sellafield, Cumbria, UK

Cs-137 and Pu in Fallout

(Warneke *et al.*, *Earth Planet Sci Lett* 2002; **203**: 1047-57)

Childhood Leukaemia Trends
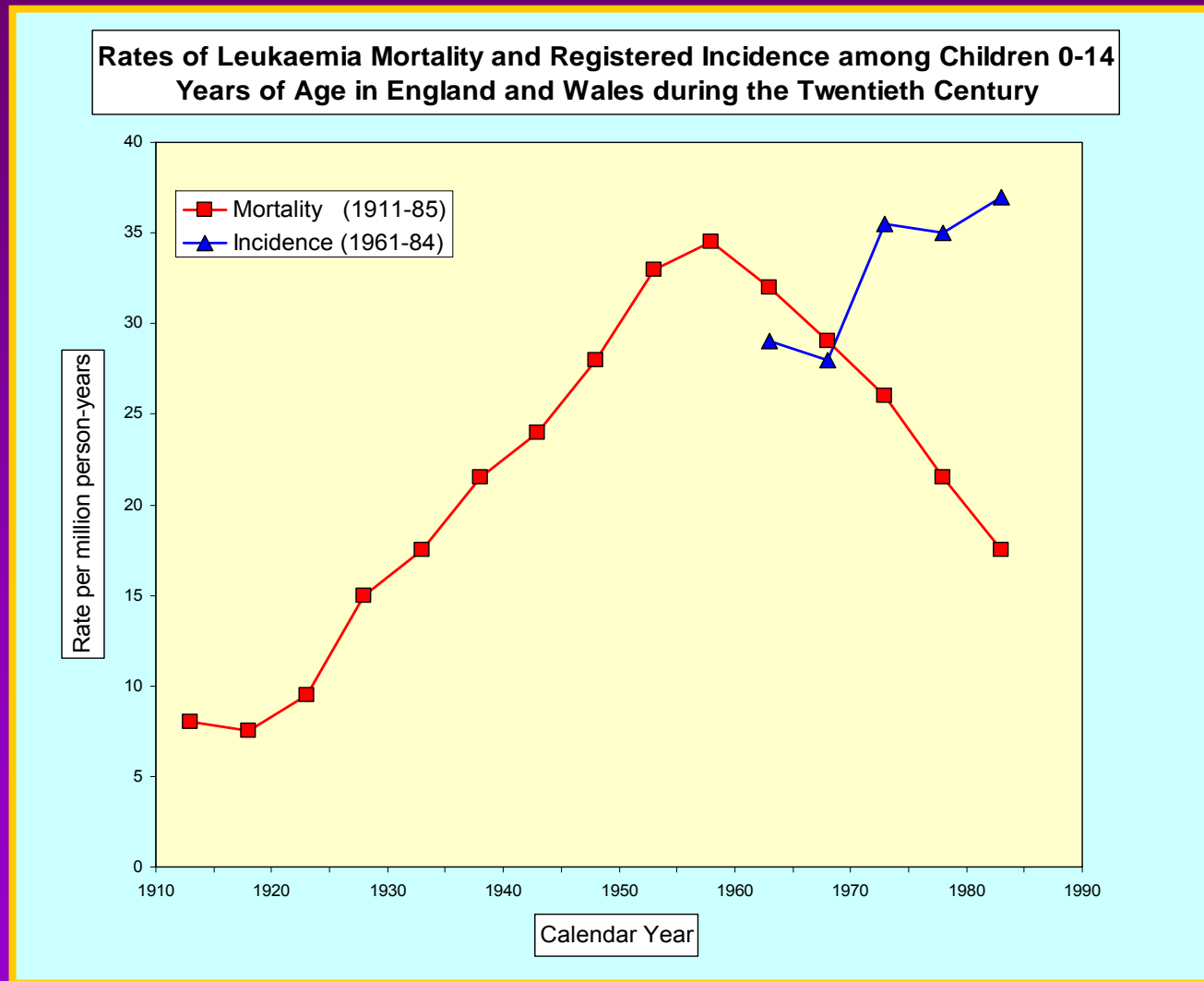
(Doll, *J R Statist Soc* A 1989; **152**: 341-351)

Rates of Leukaemia Mortality and Registered Incidence among Children 0-14 Years of Age in England and Wales during the Twentieth Century

MANCHESTER 1824

The University of Manchester
Dalton Nuclear Institute

Childhood Leukaemia Incidence

Incidence Rate of All Leukaemias (Except Where Indicated Otherwise) among Children Aged 0-14 Years, 1950-1990. Incidence Data from Eleven Cancer Registries. Error Bars Show 95% Confidence Intervals for Rates.
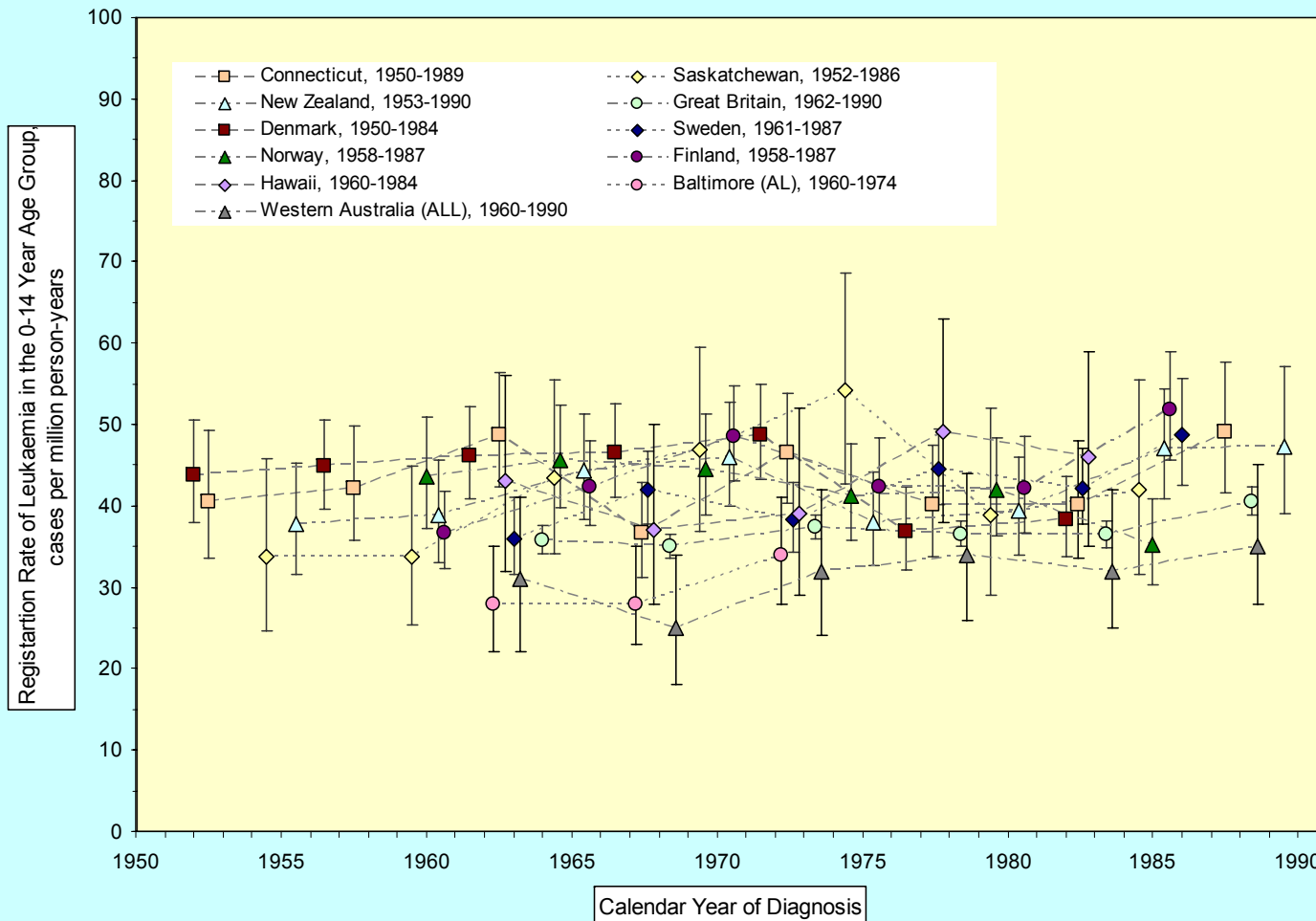
MANCHESTER 1824

The University of Manchester
Dalton Nuclear Institute

Childhood Leukaemia Incidence

Incidence Rate of All Leukaemias (Except Where Indicated Otherwise) among Young Children Aged 0-4 Years, 1950-1990. Incidence Data from Ten Cancer Registries. Error Bars Show 95% Confidence Intervals for Rates.
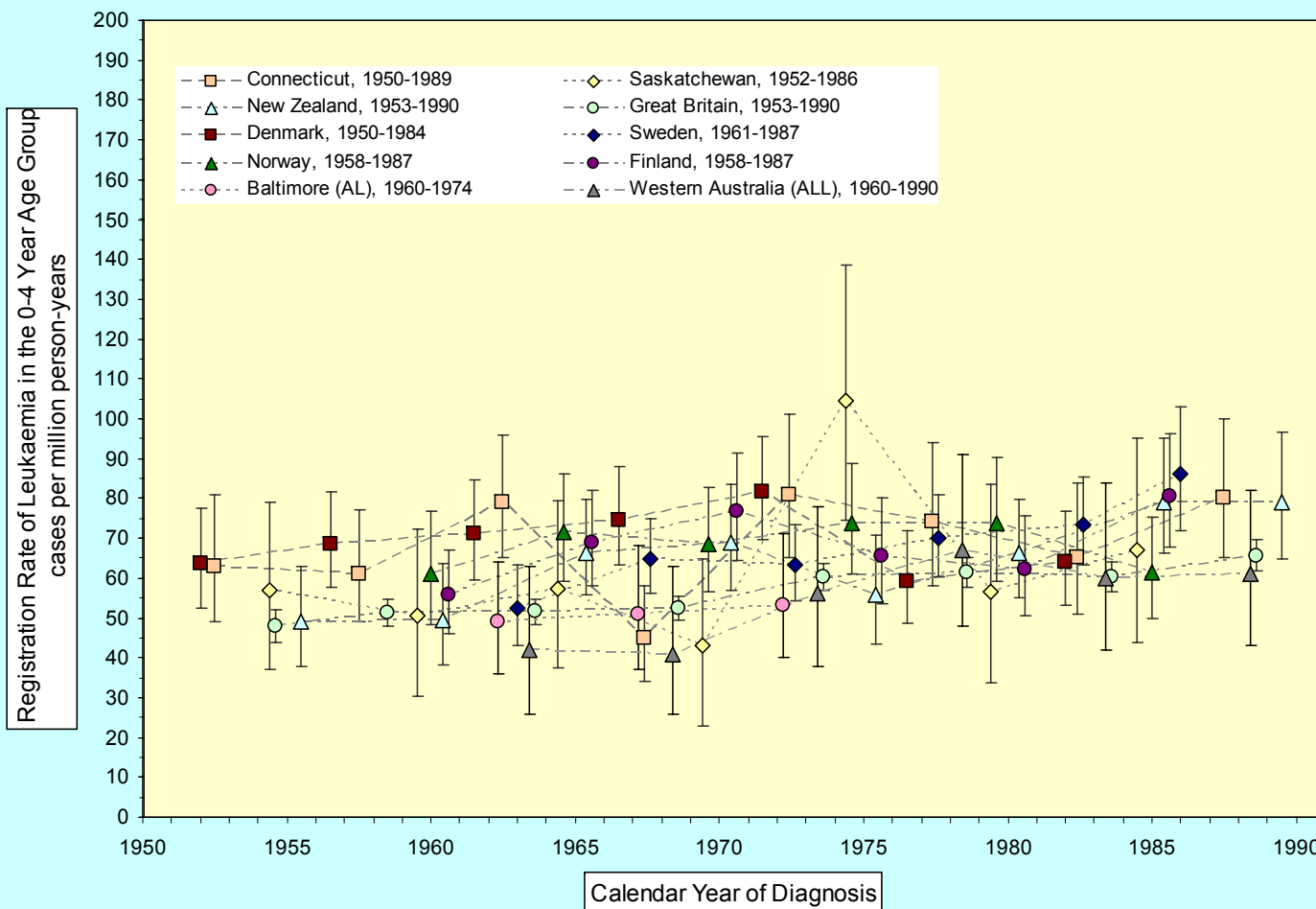
Conclusion

There is a broad consistency of results from the epidemiological study of childhood leukaemia and exposure to ionising radiation, and low dose/dose-rate risks appear to be compatible with the predictions of leukaemia risk models based upon the experience of the Japanese atomic bomb survivors, although, of course, certain aspects (e.g. radon) require further investigation.

MANCHESTER 1824

The University of Manchester
Dalton Nuclear Institute