Childhood Leukaemia and Ionising Radiation

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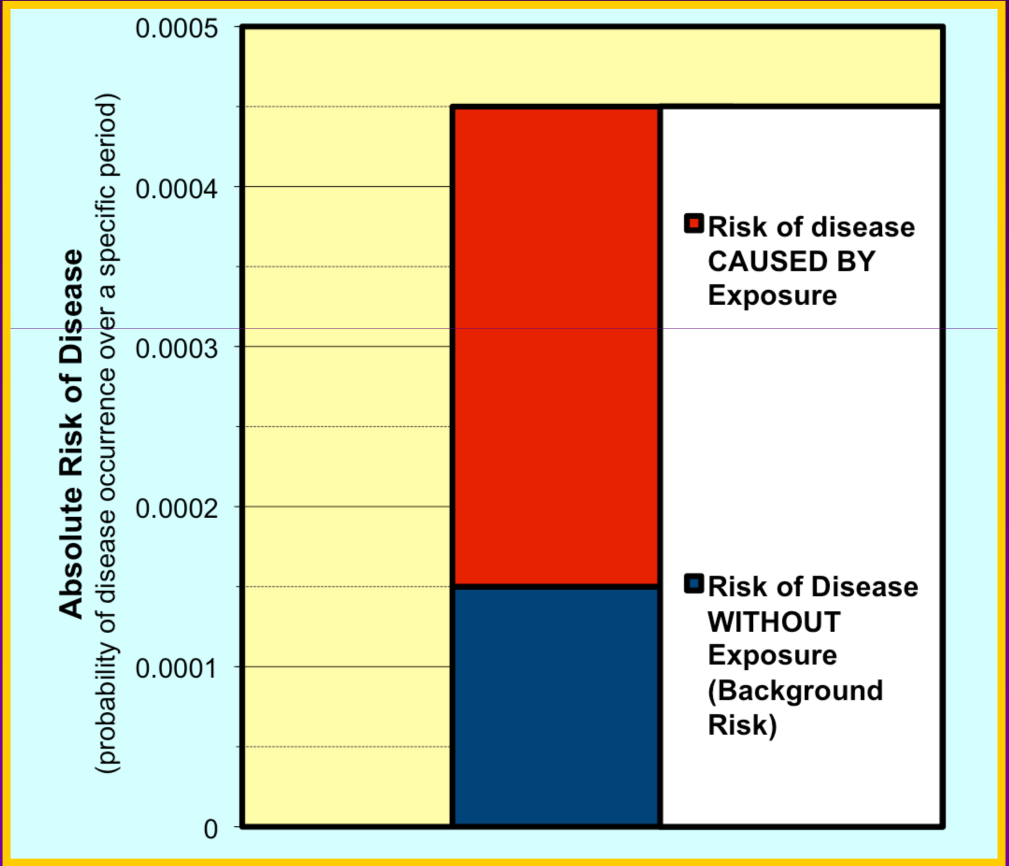
ERR and EAR

- Cancer risk models may be expressed as either the Excess Relative Risk (ERR) or the Excess Absolute Risk (EAR).
- The ERR is the proportional increase in risk over the background absolute risk (in the absence of exposure).
- The EAR is the additional risk above the background absolute risk.

Measures of Risk



- **ERR** = (0.00045 – 0.00015) / 0.00015

  = 2

- **EAR** = 0.00045 – 0.00015

  = 0.0003

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

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

Life Span Study (LSS)

- Follow-up of ~86 500 survivors, ~49 000 of whom were non-trivially exposed (>5 mSv).
- 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.

Leukaemia in LSS

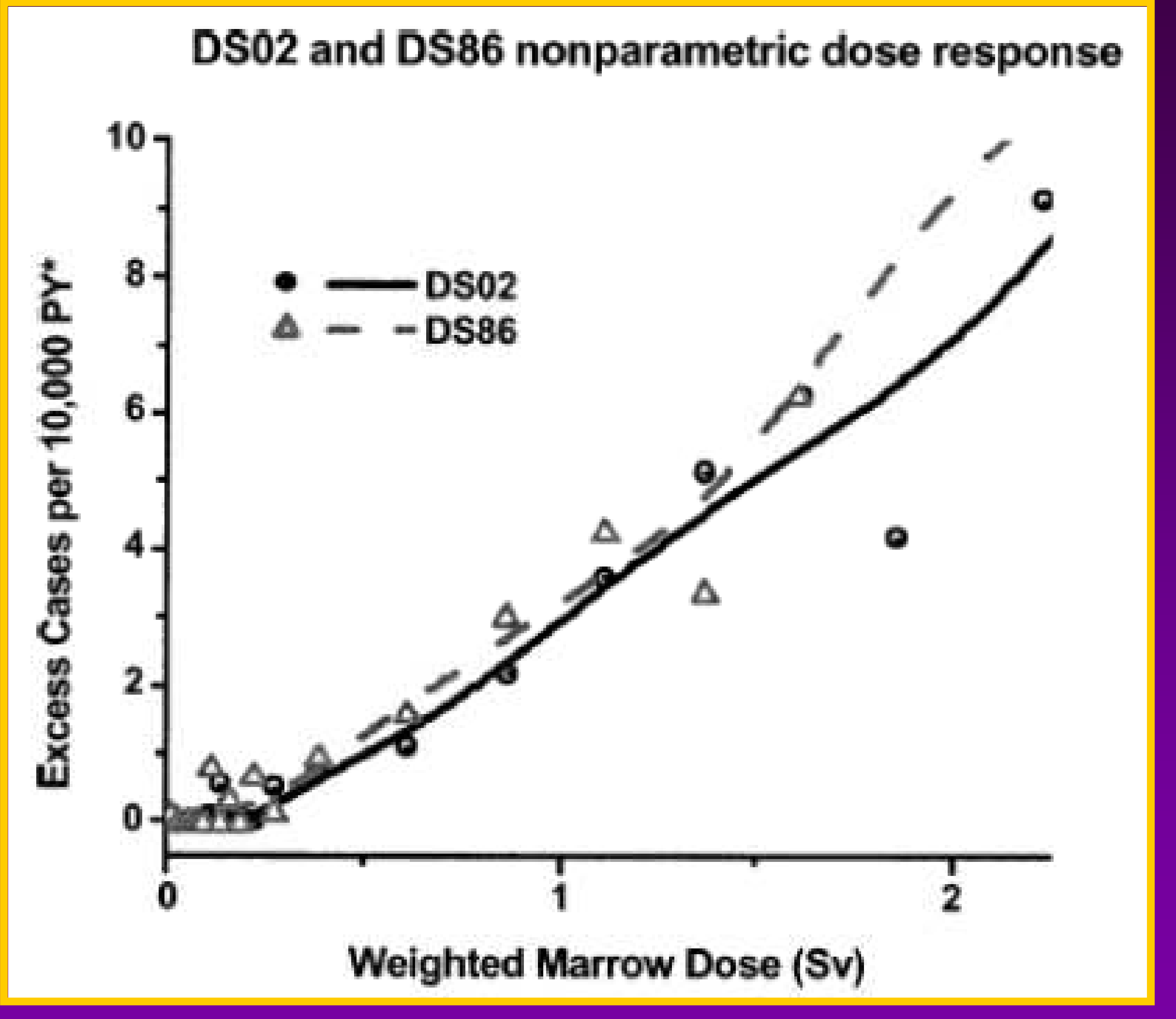
- Clear and pronounced excess risk of leukaemia in the atomic bomb survivors.

- 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)

Leukaemia Mortality, 1950-2000

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



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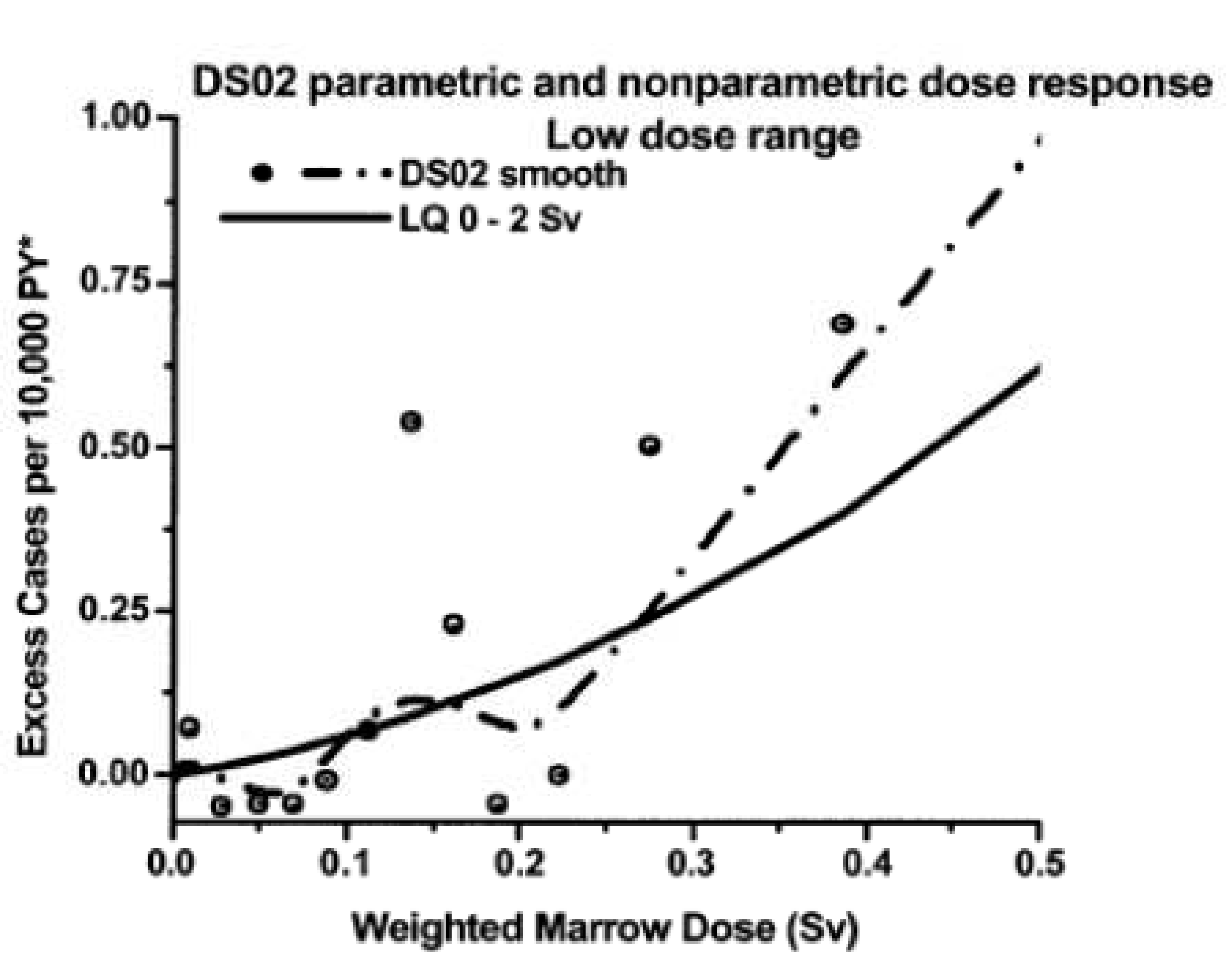
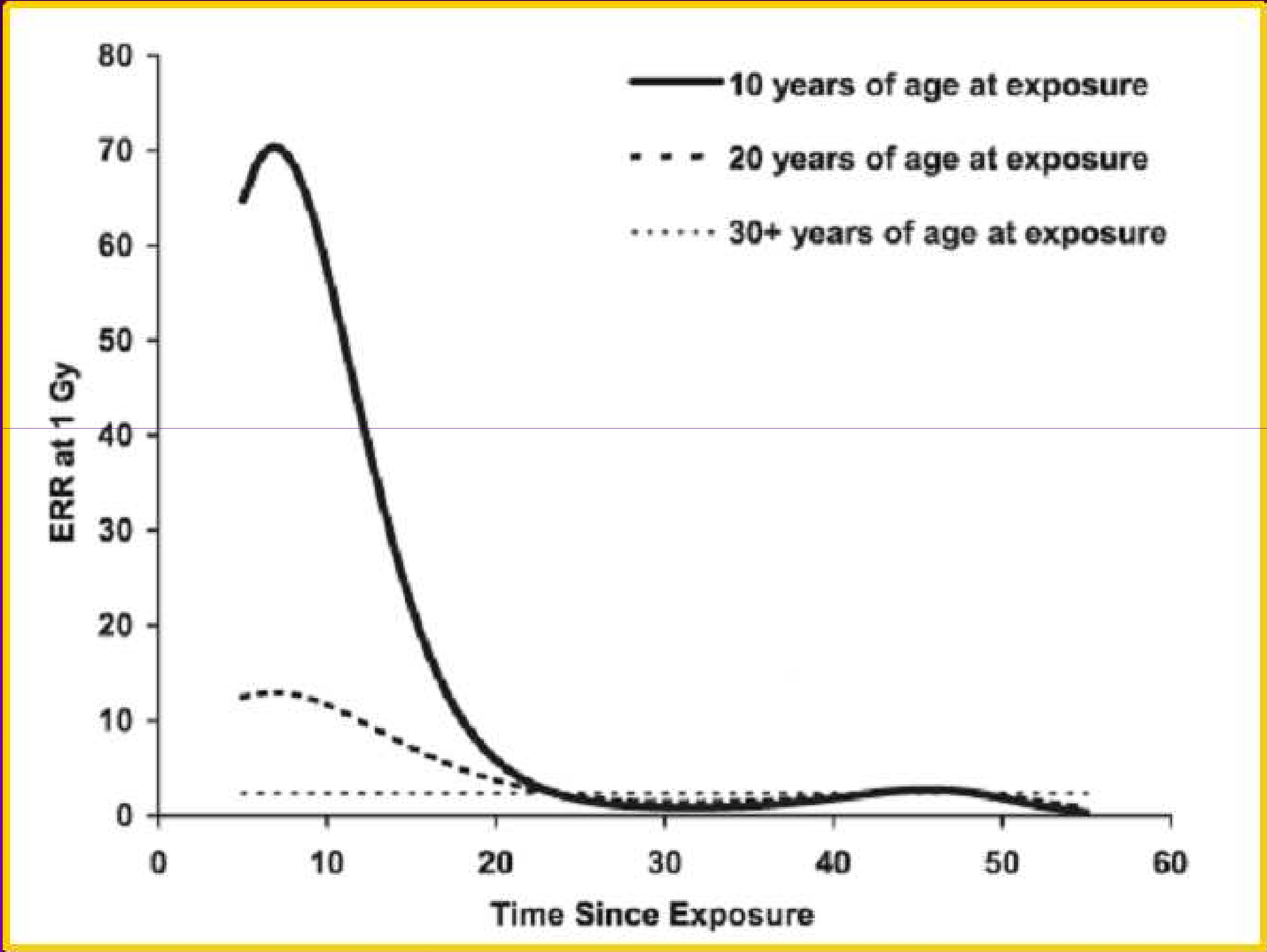
Leukaemia Mortality, 1950-2000

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



Leukaemia Mortality, 1950-2000

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



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.

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.

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.

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.

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

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.

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)**

Risk Coefficients from OSCC

- Using an Excess Relative Risk (ERR) model obtained from the OSCC 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

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

  for all childhood cancers, which is taken to apply to childhood leukaemia.

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

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

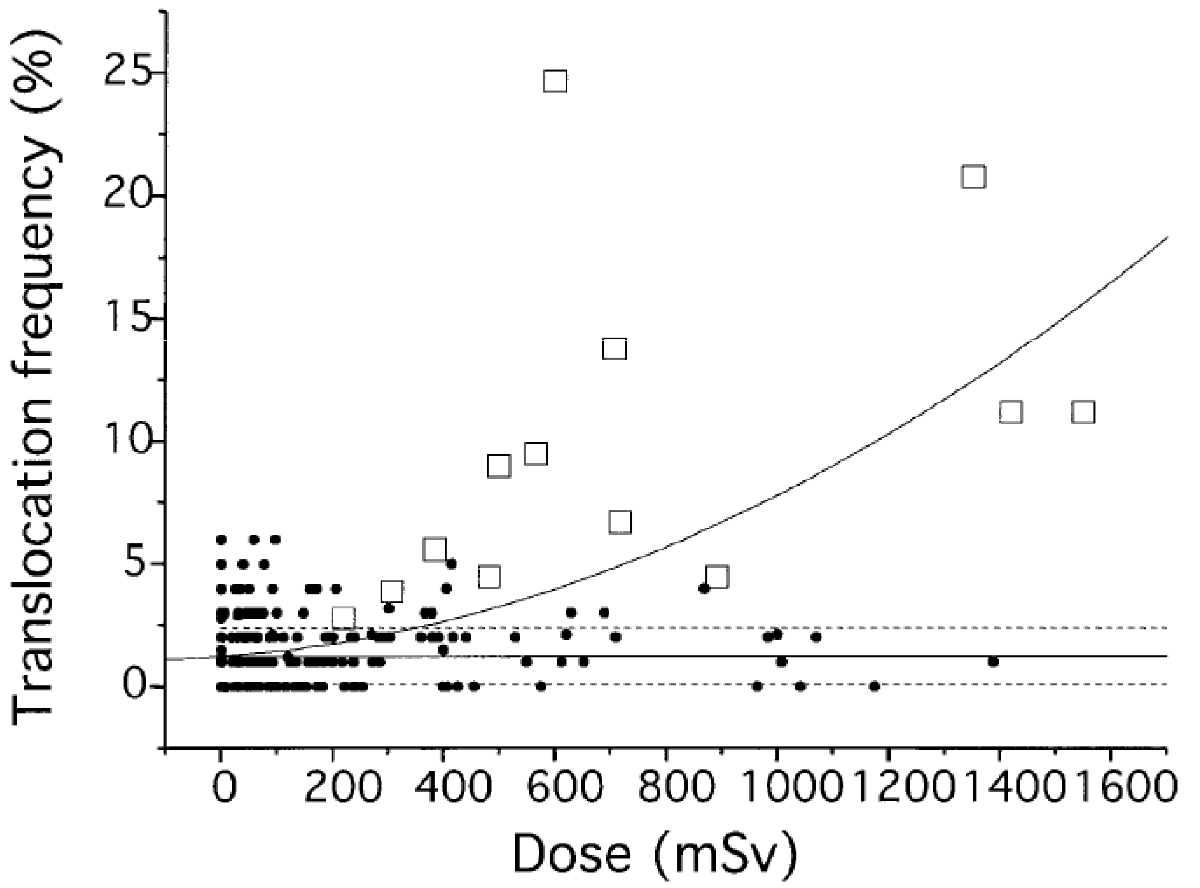
Bomb Survivors Irradiated *In Utero*

- 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 antenatal diagnostic radiography is compatible with that found among Japanese atomic bomb survivors irradiated postnatally.
- 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).

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)



Paediatric CT Scans

- Childhood leukaemia risk estimates suggest that the effect of doses ~10 mGy received during paediatric CT scans should be detectable in large case-control studies.
- Population prevalence rate of 5-10% is required for reasonable statistical power.
- Sufficiently high prevalence rates probably exist in the USA and Japan at the moment.

Natural Background Radiation

(Wakeford *et al., Leukemia* 2009; **23**: 770-6
Little *et al. J Radiol Prot* 2009; **29**: 467-82)

- Recent risk models for radiation-induced leukaemia suggest that ~15% 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
  - probably have insufficient statistical power

Natural Background Radiation

(Little *et al. Radiat Res* 2010; **174**: 387-402)

- Power calculations show that large studies are required to detect the predicted excess risk
  - to achieve 80% power, >8000 cases are needed in a case-control or geographical correlation study
- Greatest effect is from γ-rays, not radon.
- First results from a nationwide record-based case-control study of childhood cancer in Great Britain will be published soon.

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 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.

Danish Radon Study

(Raaschou-Nielsen *et al.*, *Epidemiology* 2008; **19**: 536-543)

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

Doses from Radon

- 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.

Childhood Leukaemia and Nuclear Installations

- Since the mid-1980s, attention (sometimes substantial) has been paid to reports of excess levels of childhood leukaemia in the vicinity of nuclear installations.
- Led to suggestions that radiation exposure as a consequence of operations at the installations was the cause.

Sellafield, Cumbria, UK

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At the End of the 1980s

- Evidence of excesses of childhood leukaemia near certain nuclear sites (Sellafield and Dounreay).
- No evidence that radiological assessments were seriously in error.

J W Stather *et al.*, *The Risk of Childhood Leukaemia Near Nuclear Establishments. Report NRPB-R215.* National Radiological Protection Board, Chilton, 1988.

T E Wheldon, The assessment of risk of radiation-induced childhood leukaemia in the vicinity of nuclear installations. *J R Statist Soc* A 1989; **152**: 327-39.

- Alternative explanations sought.

Paternal Preconceptional Irradiation (PPI)

(Gardner *et al.*, *BMJ* 1990; **300**: 423-9)

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

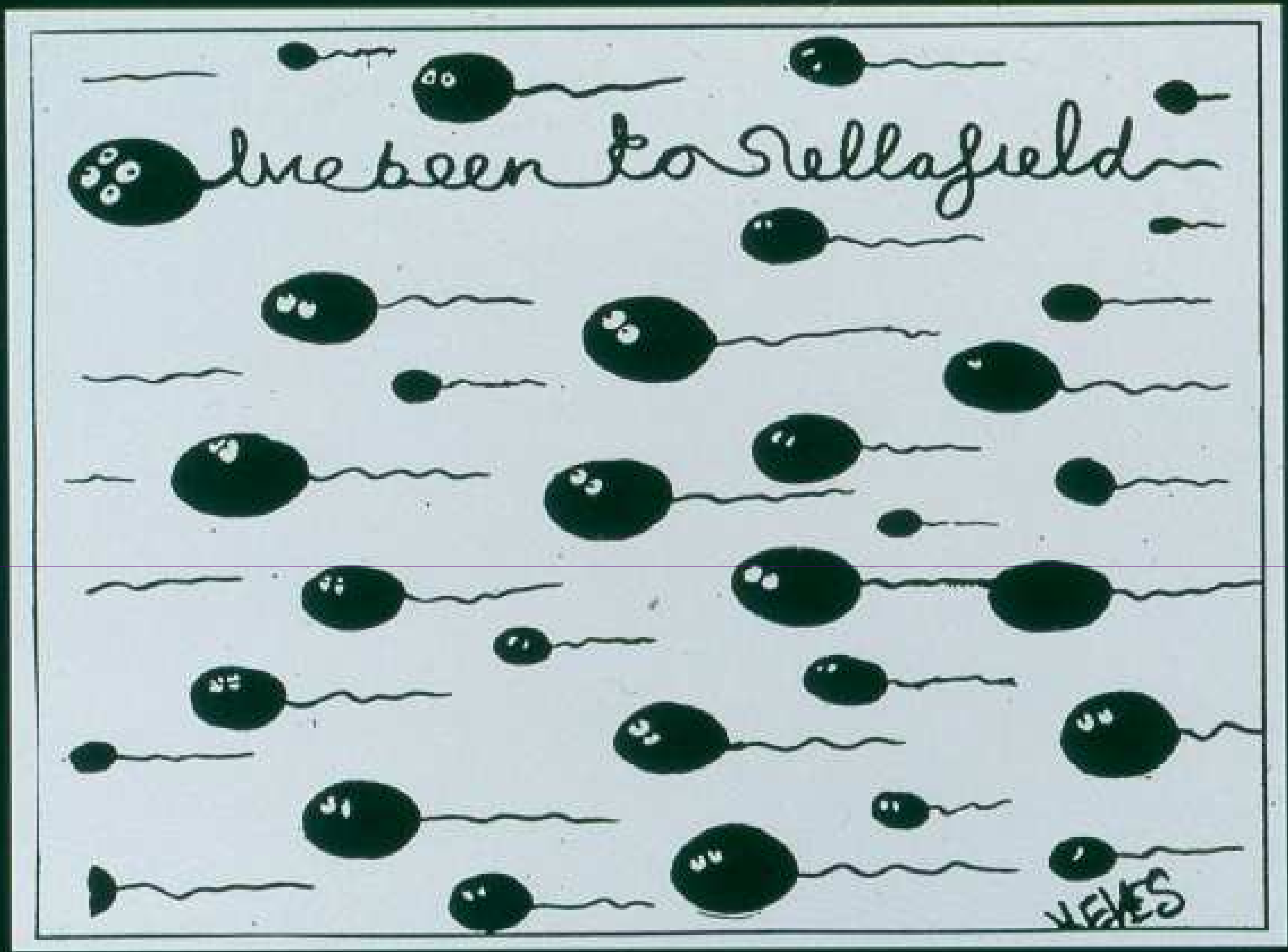
* "local" controls

THE INDEPENDENT

16 February 1990

Sellafield Fathers in Child Cancer Link

A definite link between exposure to radiation at Sellafield and leukaemia in the children of men working at the nuclear reprocessing plant has been established for the first time, scientists said yesterday.



The Guardian, 23 October 1993

Studies of PPI and Childhood Leukaemia/NHL

(Wakeford, *J Radiol Prot* 2002; **22**: 191-194)

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

COMARE Seventh Report

"We find no convincing evidence to suggest that ionising radiation alone at the doses to which male radiation workers have been exposed results in an increased incidence of childhood cancer."

Committee on Medical Aspects of Radiation in the Environment, 2002

KiKK Study in Germany

(Spix *et al.*, *Eur J Cancer* 2008; **44**: 275-84
Kaatsch *et al.*, *Int J Cancer* 2008; **1220**: 721-6)

- KiKK Study was a population-based case-control study of cancer in young children (<5 years of age) living near 16 nuclear power stations in Germany.
- Suggested that cases of leukaemia resident within 5 km of a station tended to live closer to the station than unaffected matched control children.

KiKK Study in Germany

(COMARE Fourteenth Report, 2011)

- The interpretation of the KiKK Study results is not straightforward
  - significant association driven by data from 1980-90, when data least reliable
  - significant association not confirmed by comparable geographical study
- German SSK concludes that radiation doses from station emissions are too small by >1000 to explain the KiKK Study findings.

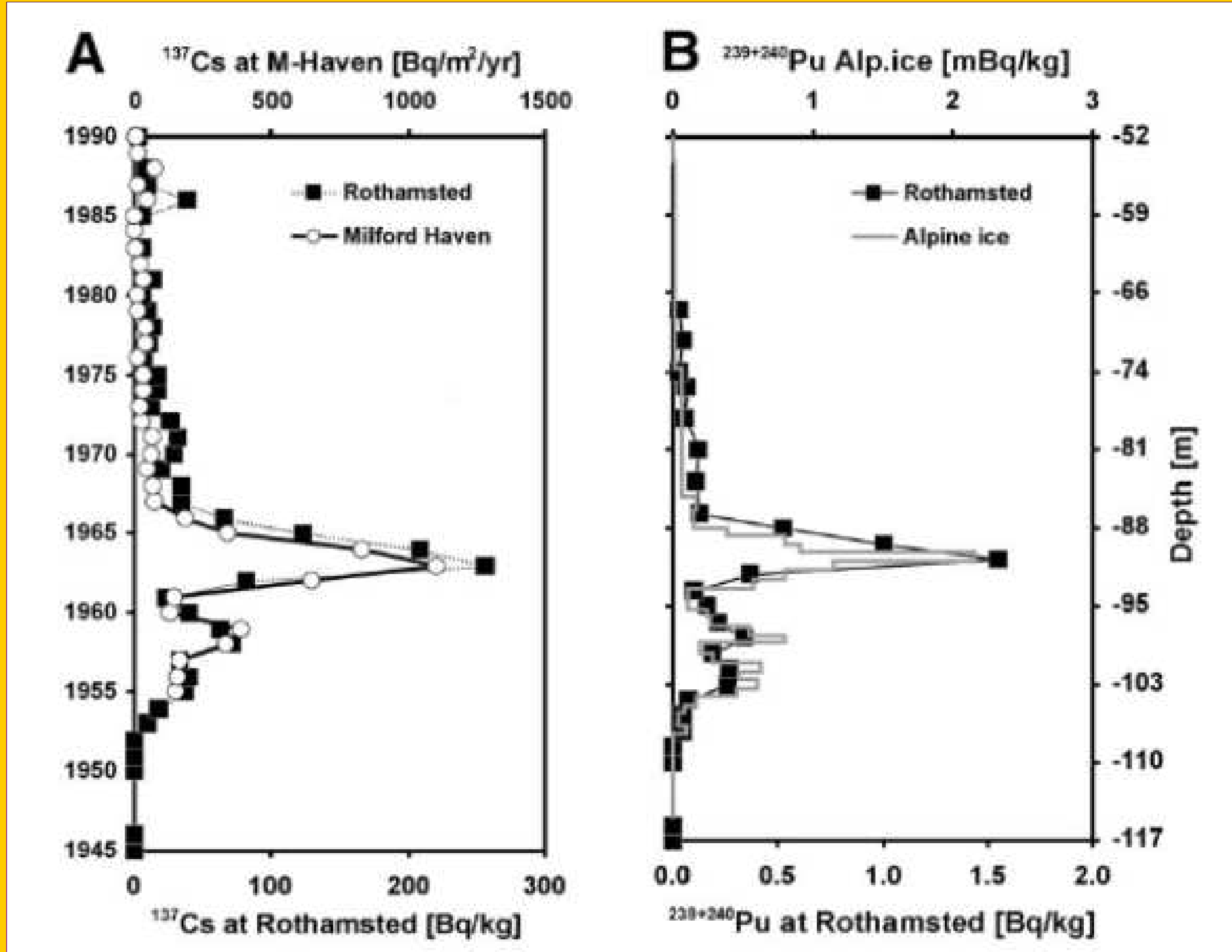
Leukaemia and Nuclear Sites

(Laurier *et al.*, *Radiat Prot Dosim* 2008; **132**: 182-90)

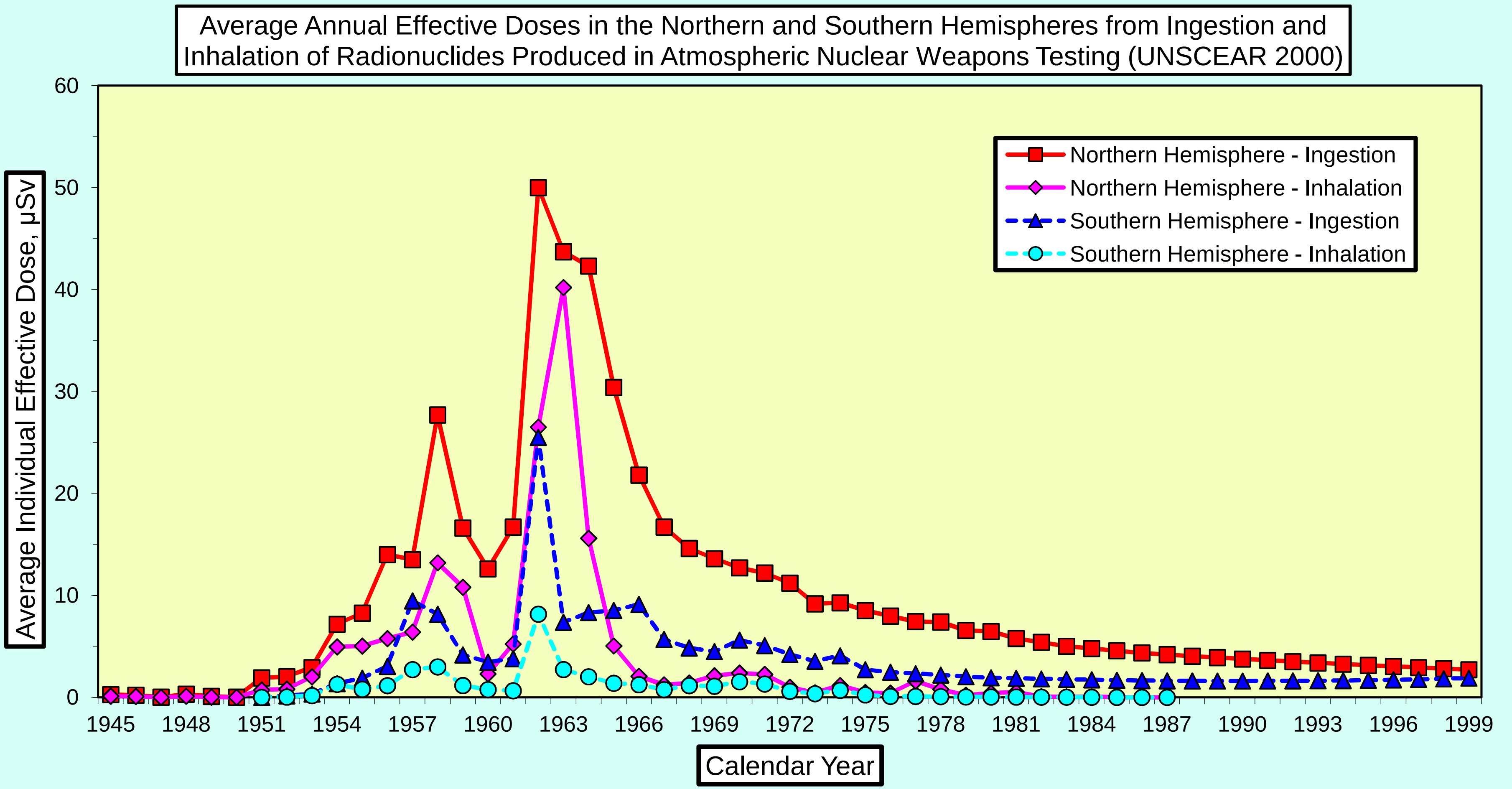
- Clear evidence of excesses of childhood leukaemia incidence near Sellafield, Dounreay and Krümmel.
- Perhaps the risk of childhood leukaemia from the intake of radioactive materials has been *grossly* underestimated?
- Suggestion not confirmed by the UK Committee Examining Radiation Risks of Internal Emitters (CERRIE).

Cs-137 and Pu in Fallout

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



Weapons Testing Fallout



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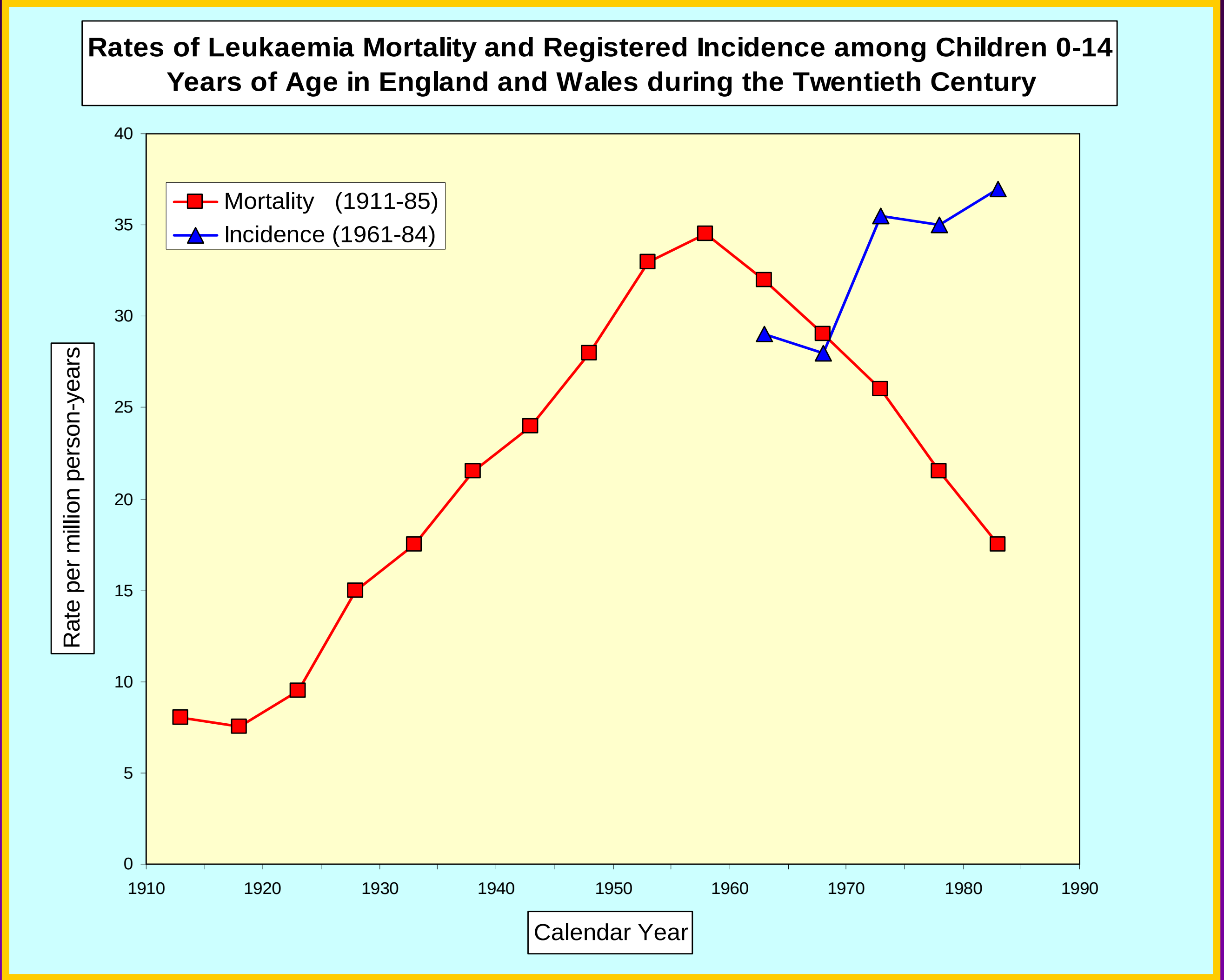
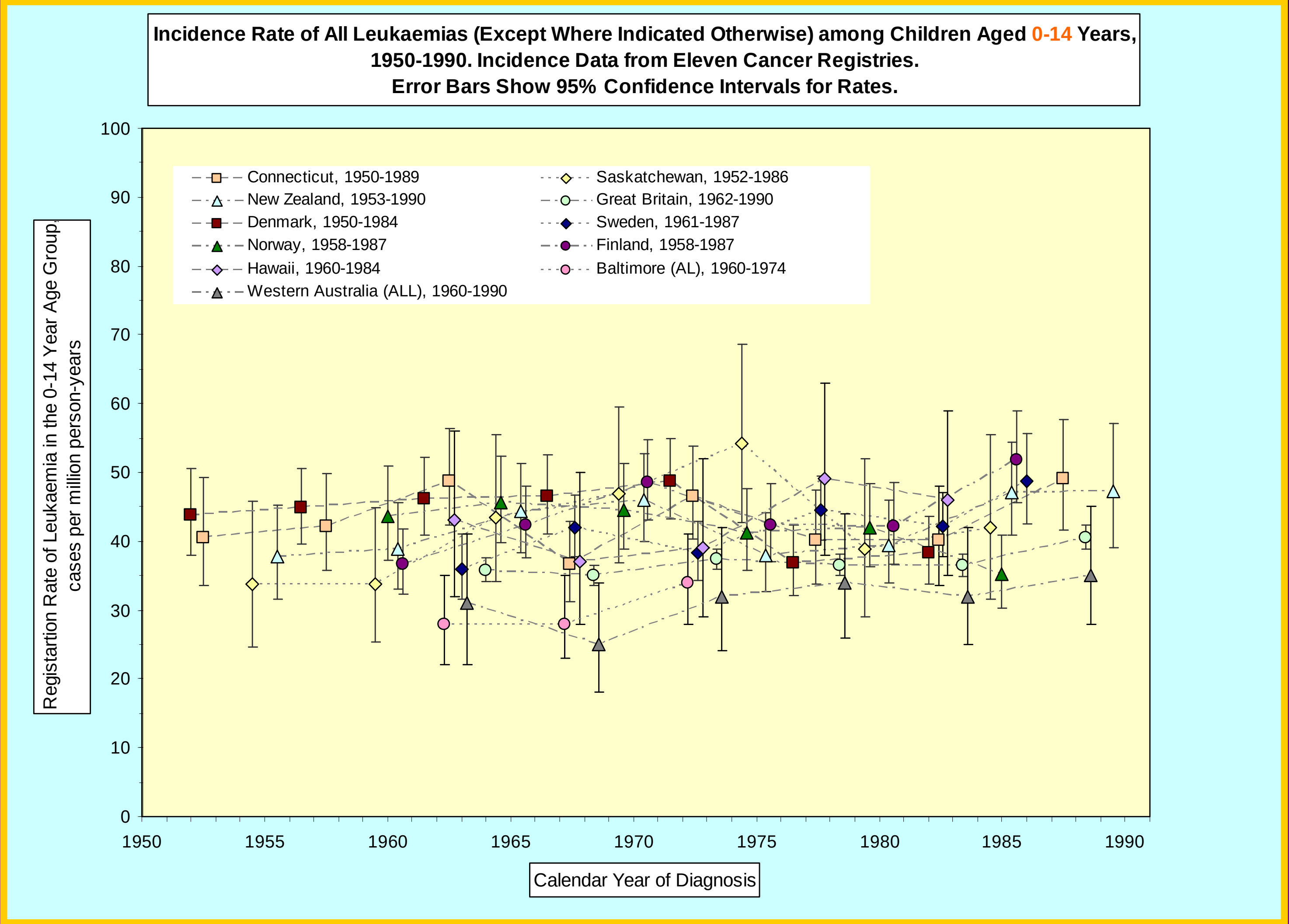
Childhood Leukaemia Trends

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



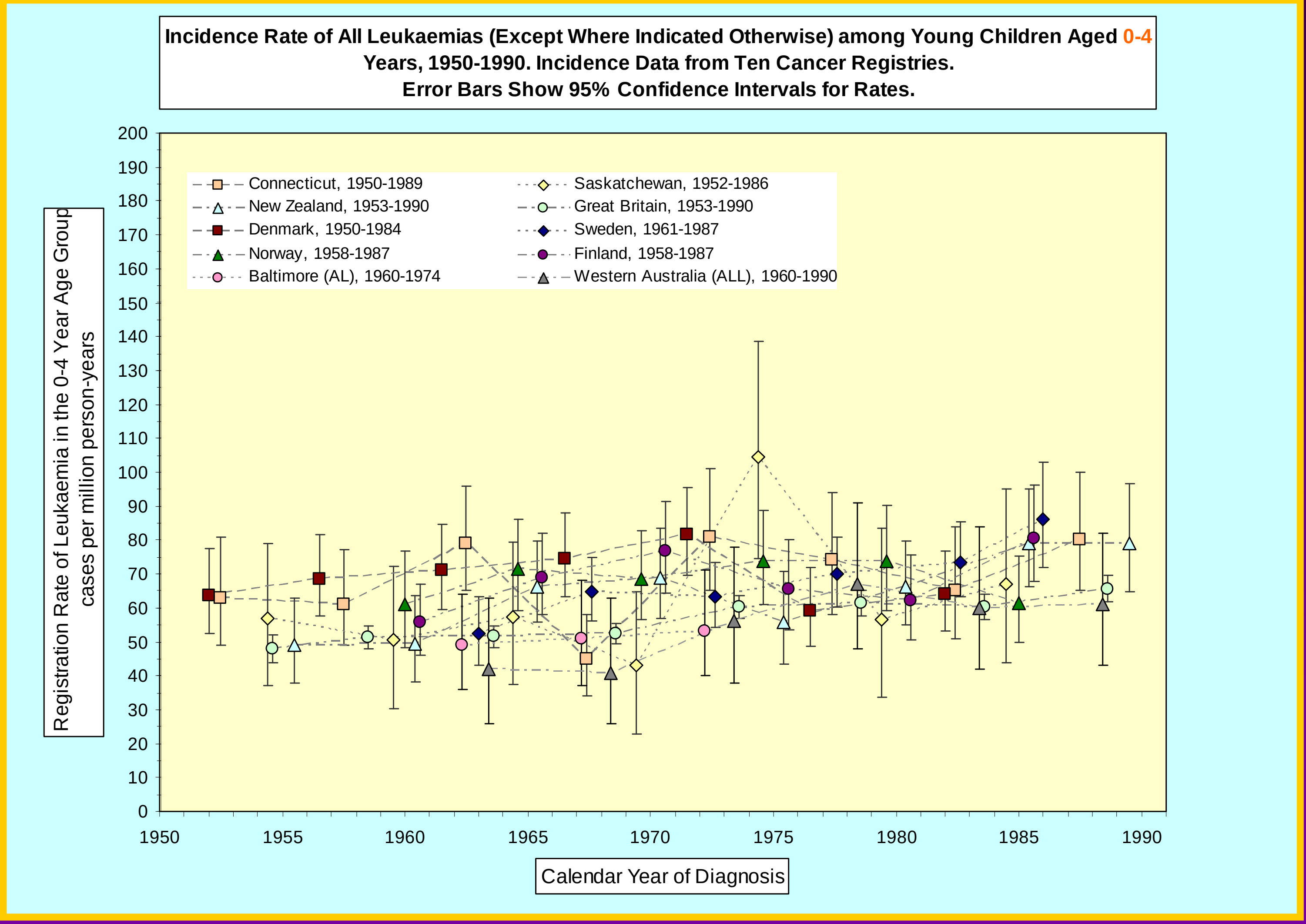
Childhood Leukaemia Incidence

(Wakeford *et al.*, *Radiat Environ Biophys* 2010; **49**: 213-27)



Childhood Leukaemia Incidence

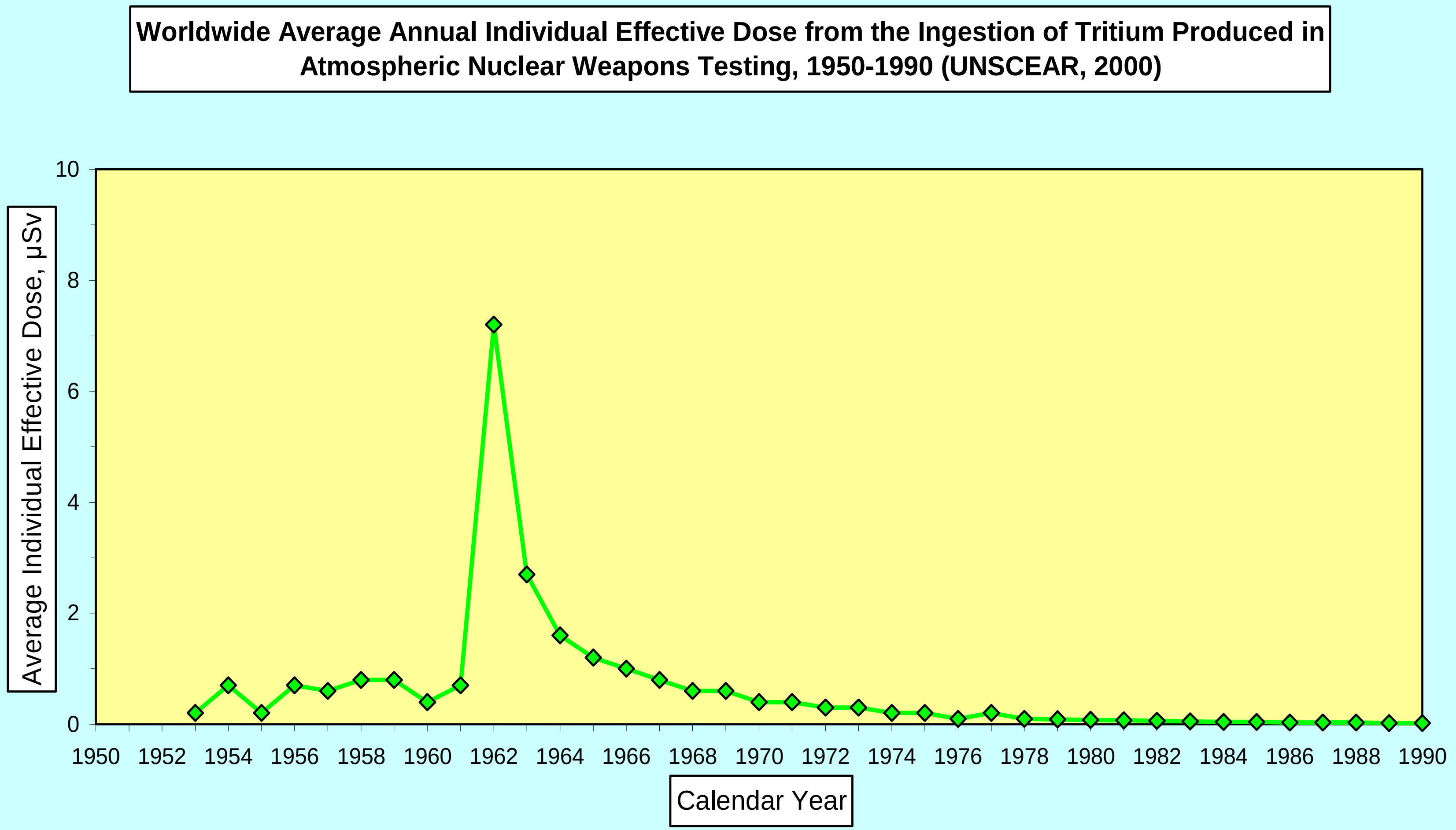
(Wakeford *et al.*, *Radiat Environ Biophys* 2010; **49**: 213-27)



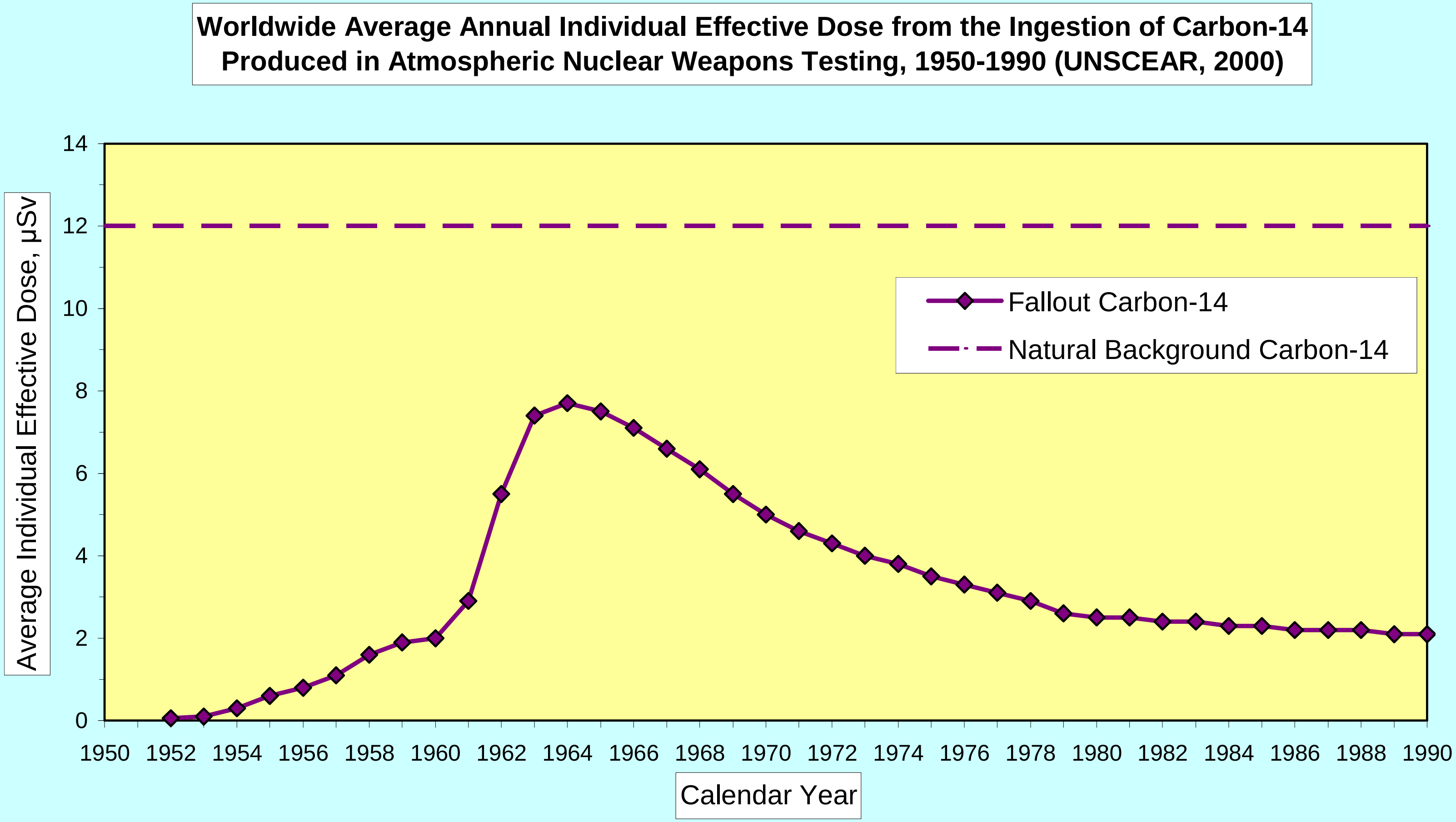
H-3 and C-14

- Suggestions have been made that the KiKK Study findings might be explained in terms of tritium and carbon-14 releases from nuclear reactors.
- Again, this is inconsistent with the absence of a large impact of fallout upon childhood leukaemia incidence.

Tritium from Fallout



Carbon-14 from Fallout



Pieces of the Jigsaw?

- Perhaps the excesses of childhood leukaemia reported near nuclear sites are just a few pieces of the jigsaw describing its geographical distribution?
- COMARE Eleventh Report finds a significantly non-uniform geographical distribution of childhood leukaemia throughout Great Britain.

Infection

- Compelling epidemiological evidence now exists for an infectious basis for most cases of childhood leukaemia.
- Raised levels of childhood leukaemia have been found following a wide variety of population mixing conditions.
- It would be remarkable if relevant areas around nuclear facilities were not similarly affected in this way.

Conclusions

- There is a broad consistency of results from the epidemiological study of childhood leukaemia and exposure to ionising radiation.
- 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.
- Potentially important additional evidence (e.g. from studies of CT scans and natural background radiation) could be available soon.

Conclusions

- Studies of childhood leukaemia near nuclear installations can only be properly understood in the context of the major causes of childhood leukaemia.
- Studies should be directed towards these major causes, and the role of infections is of primary importance in these investigations.

Fin