Ionising radiation and childhood cancer – an overview

Richard Wakeford
Visiting Professor in Epidemiology,
Dalton Nuclear Institute,
The University of Manchester, UK
(Richard.Wakeford@manchester.ac.uk)

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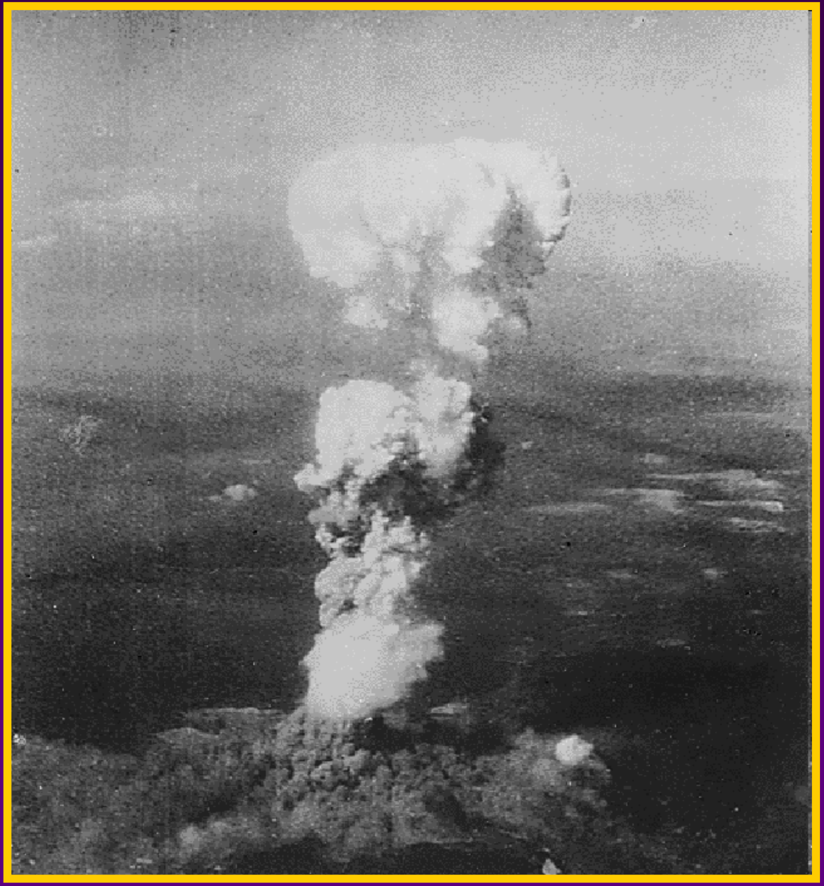
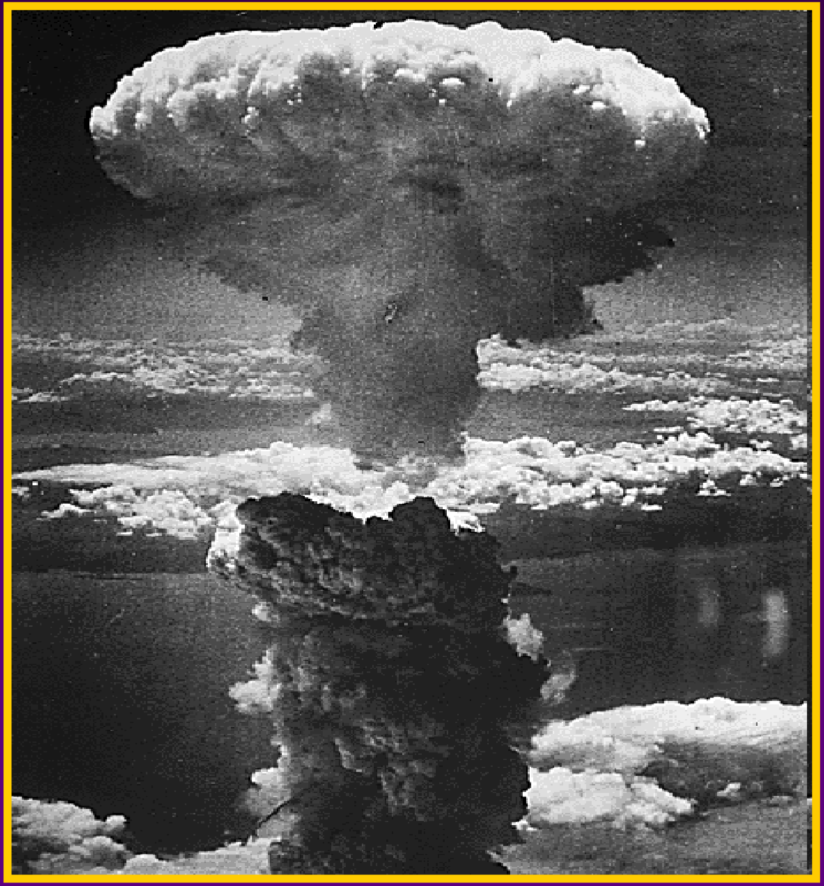
Radiation-induced Cancer

- It is established beyond reasonable doubt that exposure to moderate and high doses of ionising radiation can cause most types of cancer in humans, including some forms of cancer that are experienced in childhood.
- Ionising radiation is one of the few established causes of some childhood cancers.
- This presentation will review the evidence for ionising radiation being a cause of cancers in children.

Hiroshima and Nagasaki
6th and 9th August 1945



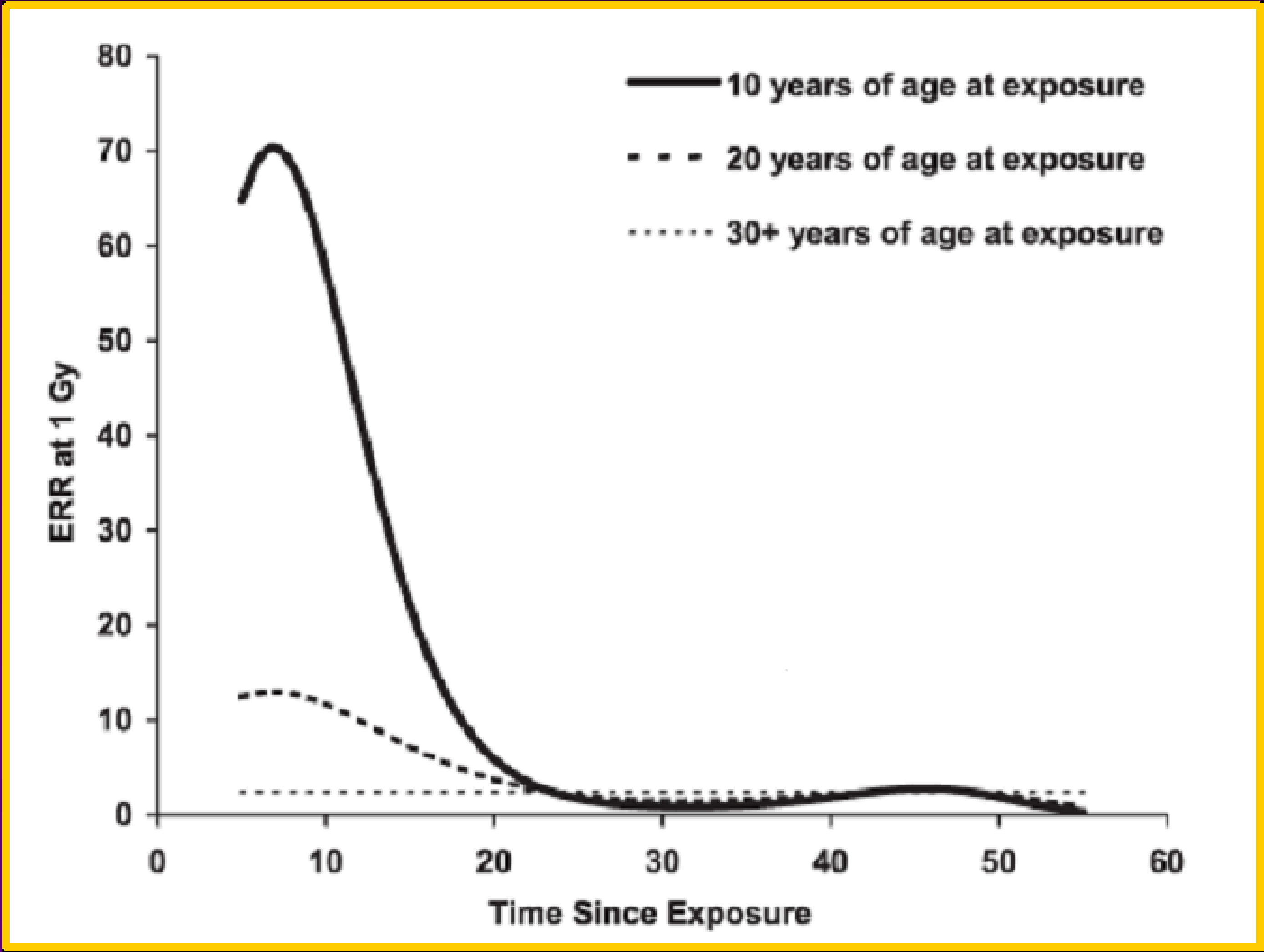


Leukaemia among Japanese Atomic-bomb Survivors

- 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 ~90 000 Japanese atomic-bomb survivors who were exposed after birth.
- Pronounced and highly significant radiation-related excess of leukaemia in the LSS.

Leukaemia Mortality, 1950-2000

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



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Childhood Leukaemia in the LSS

- After October 1950, 10 cases of leukaemia were incident among Japanese A-bomb survivors under the age of 15 years.
- This compares with ~1.6 cases expected among these children from contemporaneous Japanese national mortality rates.
- A clear excess risk of childhood leukaemia exists as a result of radiation exposure from the Japanese atomic-bombings.

Radiotherapy in Childhood

- The high relative risk of childhood leukaemia following irradiation of infants or young children during the atomic-bombings is largely (but not completely) confirmed by studies of those exposed therapeutically to treat a variety of malignant and benign medical conditions.
- Groups therapeutically exposed include: childhood cancers, enlarged thymus gland, ringworm of the scalp, and skin haemangioma.

Oxford Survey of Childhood Cancers (OSCC) – Diagnostic Exposure

- 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 an abdominal X-ray examination of the pregnant mother.

Antenatal Radiography

(Doll & Wakeford, *Br J Radiol* 1997; **70**: 130-139.
Wakeford & Little, *Int J Radiat Biol* 2003; **79**: 293-309.
Wakeford, *Radiat Prot Dosim* 2008; **132**: 166-174)

- The initial report of an association between the risk of childhood cancer and antenatal radiography was received with scepticism, but more refined analyses of the OSCC data (including those using records of maternal exposure) have confirmed the findings.
- The OSCC results have now been supported by the collective findings of many independent case-control studies from around the world.

Relative Risk of Childhood Cancer Associated with Antenatal Diagnostic Exposure to Radiation found by Case-control Studies

Case-control Study	Cases (Exposed/Total)	Statistical Information (Precision)	Relative Risk	95% Confidence Interval
All Childhood Cancers				
OSCC (singleton plus twin births)	2392/15437	872	**1.40**	**(1.31, 1.49)**
All Except OSCC (singleton plus twin births)	635/6815	376	**1.29**	**(1.17, 1.43)**
Childhood Leukaemia				
OSCC (singleton plus twin births)	620/4122	308	**1.51**	**(1.35, 1.69)**
All Except OSCC (singleton plus twin births)	811/11661	442	**1.27**	**(1.16, 1.40)**
All Childhood Cancers Except Leukaemia				
OSCC (singleton plus twin births)	672/4552	325	**1.46**	**(1.31, 1.62)**
All Except OSCC (singleton plus twin births)	292/3318	196	**1.26**	**(1.09, 1.45)**

Antenatal Radiography

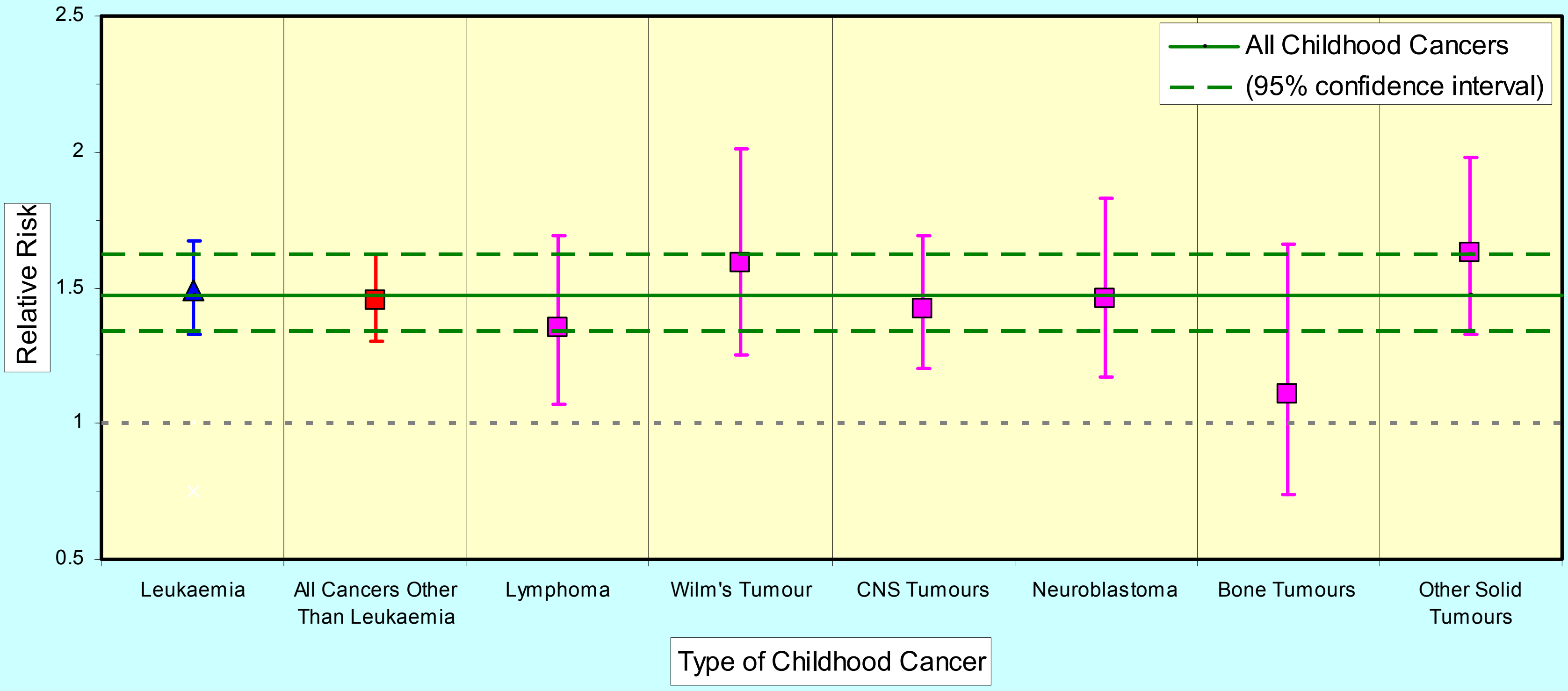
(Boice & Miller, *Teratology* 1999; **59**: 227-233)

- A causal interpretation of the statistical association between the risk of childhood cancer and antenatal radiography is not universally accepted.
- One of the main objections is the similarity between the relative risk of leukaemia and that of most of the other typical cancers of childhood.

Types of Childhood Cancer

(Bithell & Stewart, *Br J Cancer* 1975; **31**: 271-287)

Relative Risk of Specific Types of Childhood Cancer Associated with an Antenatal Abdominal X-ray Examination.
OSCC Data for Deaths during 1953-1967 (Bithell and Stewart, 1975).
Error Bars and Band Show 95% Confidence Intervals.



Risk Coefficients

(Wakeford & Little, *Int J Radiat Biol* 2003; **79**: 293-309)

- A tentative estimate of the ERR/Gy may be obtained from the OSCC data and the assessed average fetal dose in 1958 made by the Adrian Committee (6.1 mGy):

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

  for all childhood cancers (including leukaemia).
- This is compatible with the ERR/Gy for childhood leukaemia derived from the LSS for exposure after birth.

Bomb Survivors Irradiated *In Utero*

(Wakeford & Little, *Int J Radiat Biol* 2003; **79**: 293-309)

- 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 hepatoblastoma and 1 Wilms' tumour) against, at most, 0.48 case expected from contemporaneous Japanese rates.

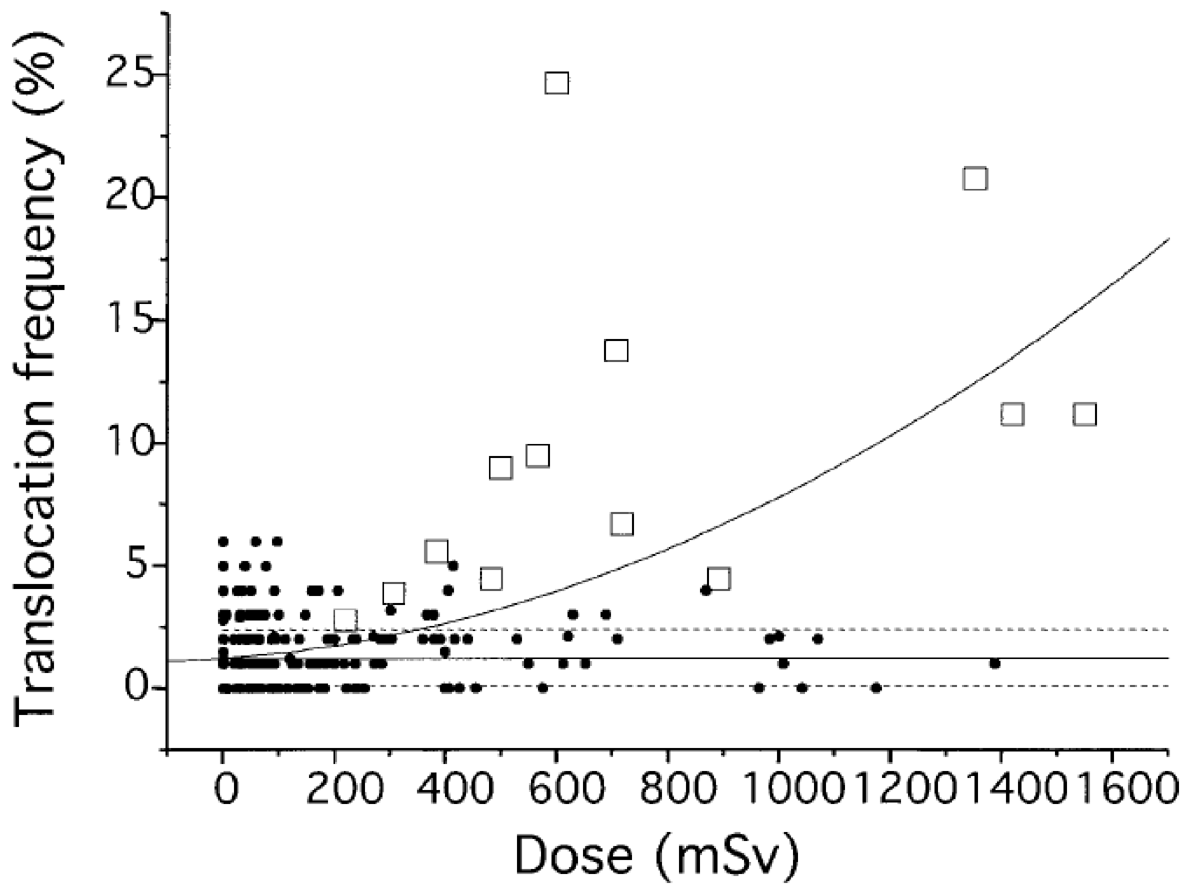
Bomb Survivors Irradiated *In Utero*

(Wakeford & Little, *Int J Radiat Biol* 2003; **79**: 293-309)

- 0 case of childhood leukaemia observed (O), but only 0.2 expected (E)
  - O/E has a 95% CI of (0,15).
- 2 cases of other childhood cancers observed, against 0.28 expected
  - O/E = 7.1 (95% CI: 1.2, 24).
- Possibility that some cases of childhood cancer (particularly childhood leukaemia) occurring among the survivors before October 1950 went unrecorded or undiagnosed.

Chromosome Translocation Frequencies in Peripheral Blood Lymphocytes Sampled from Atomic-bomb Survivors Exposed *in utero*(●), and from Some of their Mothers (□).

(Ohtaki *et al.*, *Radiat Res* 2004; **161**: 373-9)



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Other Childhood Cancers

Childhood Cancers Other Than Leukaemia

- The 2 cases among survivors irradiated *in utero* represent a significant excess
  - ERR/Gy compatible with the OSCC results.
- No case occurred among the Japanese atomic-bomb survivors irradiated after birth.
- Little evidence that these childhood cancers are sensitive to induction by radiation exposure after birth (with the exception of thyroid cancer, and the possible exception of some brain tumours).

Tentative Overview

Childhood Leukaemia

- Can be caused by exposure *in utero*
- Can be caused by exposure after birth

Other Common Cancers of Childhood

- Can be caused by exposure *in utero*
- Cannot, in general, be caused by exposure after birth

Antenatal Radiography

- Implication of OSCC findings is that intrauterine doses ~10 mGy of X-rays proportionally increase the risk of childhood cancer (both leukaemia and other cancers) by around 50%.
- A dose of 10 mGy of X-rays produces just a few electron traversals of a cell nucleus.
- Importance of this finding is that it implies that a *single* electron track can cause cancer, giving support to the linear no-threshold (LNT) dose-response model for radiation-induced cancer.

Paediatric CT Scans

- Estimates of childhood leukaemia risk using current models suggest that the effect of doses of several milligray of X-rays received during paediatric CT scans should be detectable in *large* case-control studies.
- Statistical power calculations are a prerequisite to ensure such studies are *large enough* to detect the predicted effect.
- Several large studies of CT scans are underway at the moment.

Sellafield, Cumbria, UK

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Leukaemia and Nuclear Sites

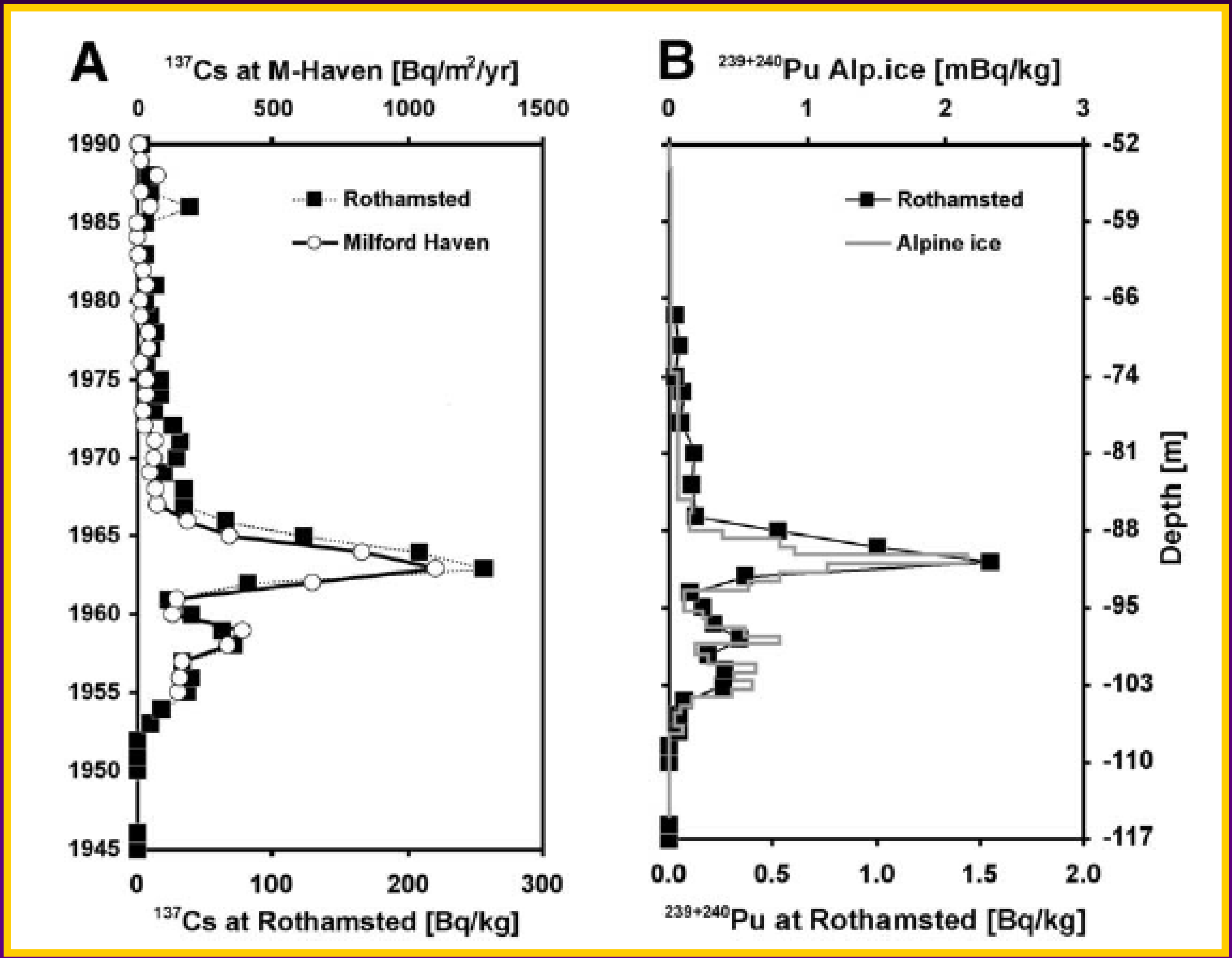
(Laurier *et al.*, *Radiat Prot Dosim* 2008; **132**: 182-90)

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

Nuclear Weapons Testing

Cs-137 and Pu in Fallout

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



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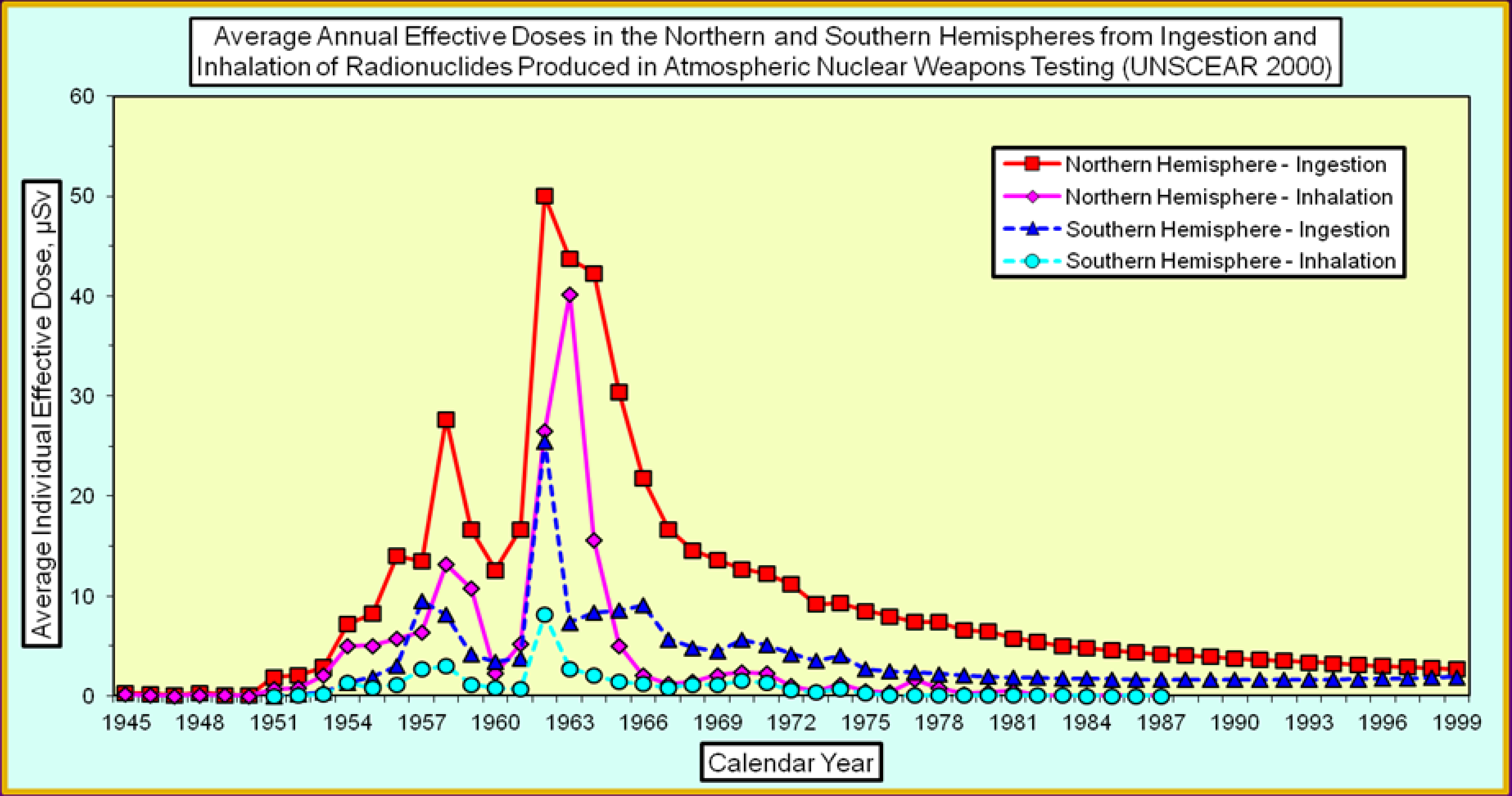
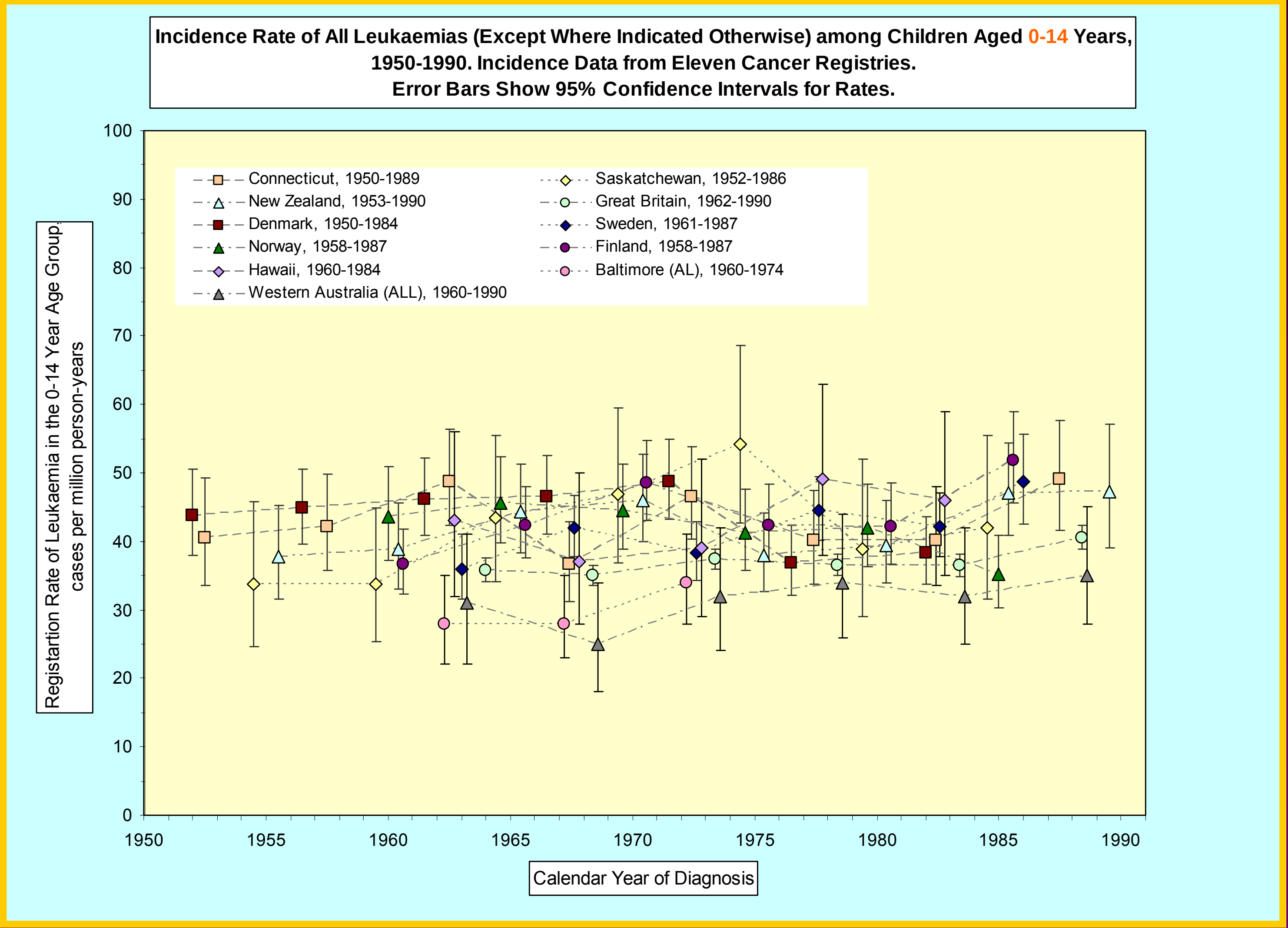
Weapons Testing Fallout



Childhood Leukaemia Incidence

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



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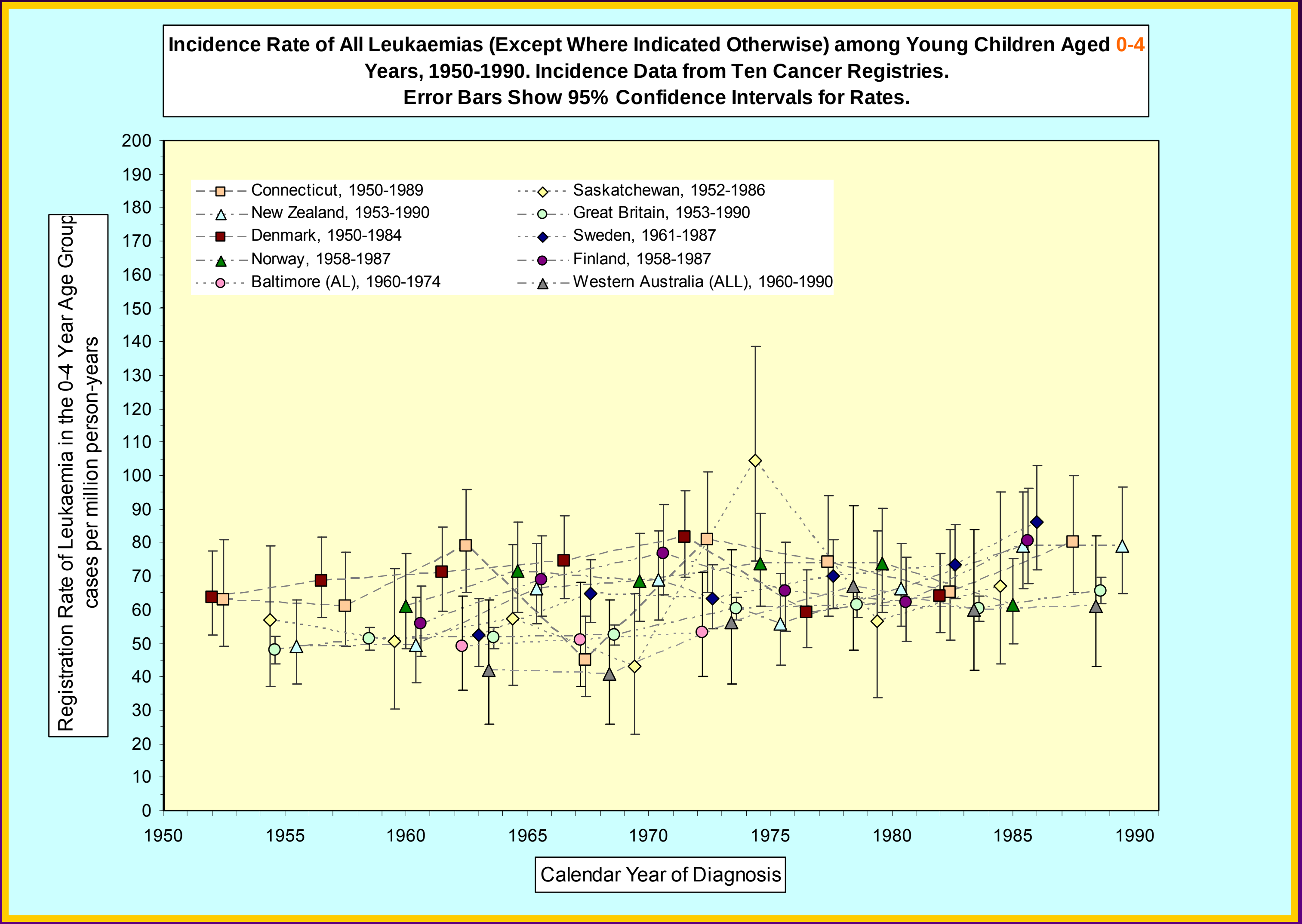


Radon and Childhood Leukaemia

- Several studies have examined the potential link between exposure to naturally-occurring inhaled radon and childhood leukaemia.
- The most persuasive of these studies is the nationwide Danish case-control study of Raaschou-Nielsen *et al.* (2008)

(*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 exposure and childhood ALL, and inferred that 9% of cases in Denmark could be attributable to radon.
- However, statistical power is *low* (860 ALL cases), and the lower 95% CL for the attributable proportion is 1%, which is compatible with conventional models.
- Accuracy of model-predictions of radon concentrations needs further investigation.

Natural Background Radiation

(Wakeford *et al.*, *Leukemia* 2009; **23**: 770-6.
Little *et al. J Radiol Prot* 2009; **29**: 467-82.
Kendall *et al.*, *Leuk Res* 2011; **35**: 1039-43.)

- 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 <u>insufficient statistical power</u>

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 covering the whole of Great Britain.
- Greatest effect is from γ-rays, <u>not</u> radon.
- The extensive data from the National Registry of Childhood Tumours (Childhood Cancer Research Group) make such a study feasible.

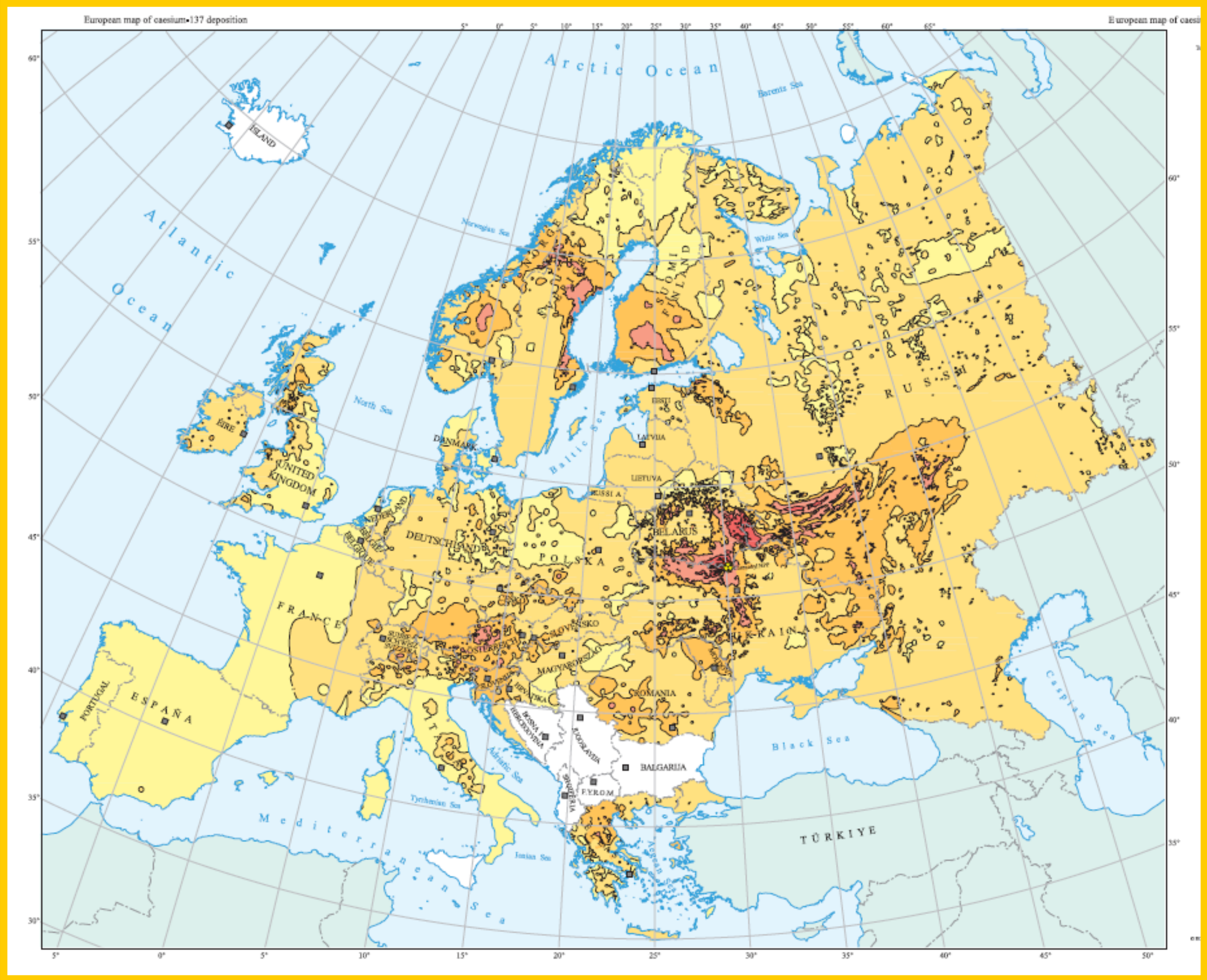
Natural Background Radiation

(Kendall *et al.*, submitted)

- First results from a large nationwide record-based case-control study of childhood cancer in Great Britain will be published soon.
- What would be expected from *prior evidence*?
  - Childhood leukaemia
    - A detectable positive effect of γ-radiation
    - No detectable effect of radon
  - Childhood cancers other than leukaemia
    - No detectable effect of either γ-radiation or radon

Chernobyl – 26 April 1986

Chernobyl Contamination



Chernobyl Contamination

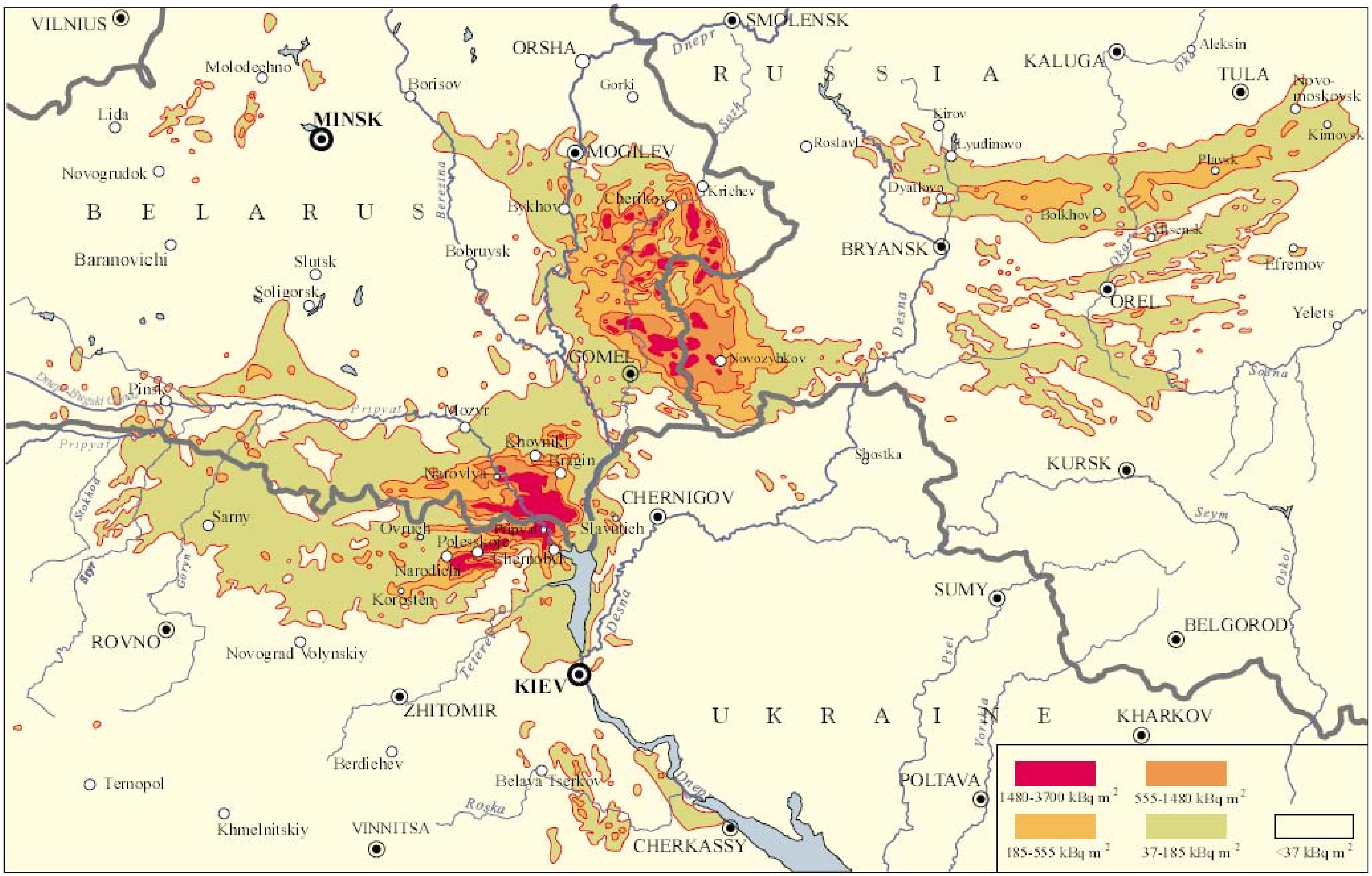
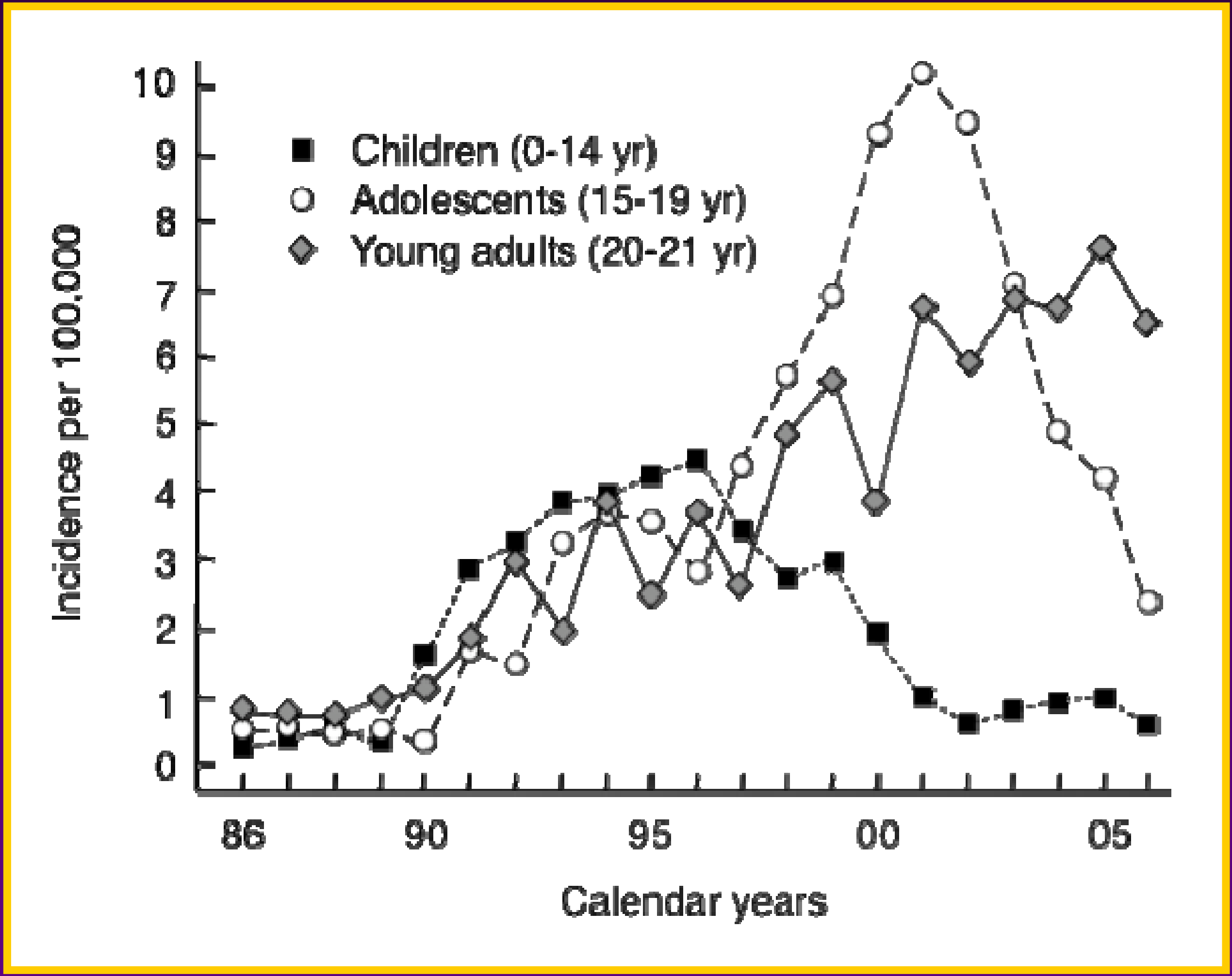


Figure VI. Surface ground deposition of caesium-137 released in the Chernobyl accident [I1, I3].

Chernobyl – Thyroid Cancer

(Demidchik *et al.*, *Arq Bras Endocrinol Metab* 2007; **51**: 748-62)



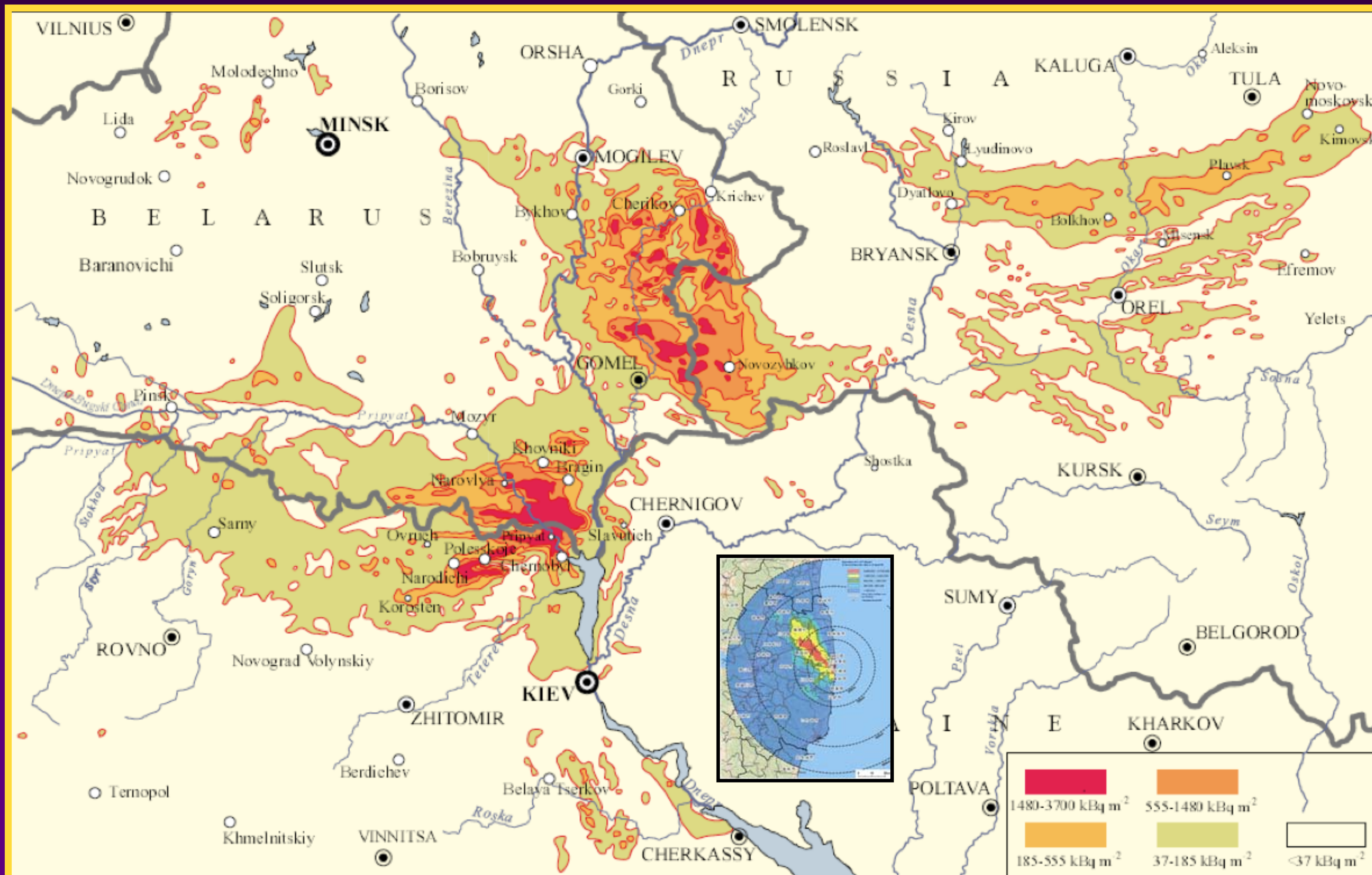
Thyroid Cancer
(<15 years of age at exposure)

Exposure	Study	ERR/Gy (95% CI)
External	Pooled Analysis Ron *et al.*, *Radiat Res* 1995; **141**: 259-277	**7.7 (2.1, 29)**
Chernobyl	Case-control (Belarus & Russia) Cardis *et al.*, *J Natl Cancer Inst* 2005; **97**: 724-32	**4.5 (1.2, 7.8)**
Chernobyl	Cohort* (Ukraine) Tronko *et al.*, *J Natl Cancer Inst* 2006; **98**: 897-903 * <18 years of age at exposure	**5.2 (1.7, 27)**
Chernobyl	Cohort* (Belarus) Zablotska *et al.*, *Br J Cancer* 2011; **104**: 181-187 * <18 years of age at exposure	**2.2 (0.8, 5.5)**
Chernobyl	Cohort* (Ukraine) Brenner *et al.*, *Environ Health Perspect* 2011; **119**: 933-939 * <18 years of age at exposure	**1.9 (0.4, 6.3)**

Comparison of ^{137}Cs Contamination around Chernobyl with that around Fukushima (inset)

The two areas shown are approximately to the same scale.

The orange/red areas around Chernobyl correspond approximately to the green/yellow/red areas around Fukushima in level of contamination.



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Conclusions

- There is a broad consistency of results from the epidemiological study of childhood leukaemia and exposure to ionising radiation after birth.
- Childhood leukaemia risk from OSCC appears compatible with the predictions of leukaemia risk models based upon the experience of the Japanese atomic-bomb survivors in the LSS.
- The fetal haematopoietic system may be hypersensitive to cell-killing by radiation.
- Important additional evidence (e.g. from studies of CT scans and natural background radiation) should be available soon.

Conclusions

- The common cancers of childhood other than leukaemia appear to be capable of induction by irradiation *in utero*, but **not** (or only rarely) after birth.
- The typical cancers of childhood (both leukaemia and other cancers) seem to be capable of induction by low doses (~10 mGy of X-rays) received *in utero*.
- Thyroid cancer (rare in childhood) is particularly susceptible to induction by radiation at a young age.

Fin

The relative risk (RR), and 95% confidence interval (CI), of leukaemia and non-Hodgkin's lymphoma combined (LNHL) at 100 mSv cumulative recorded paternal preconceptional dose from external sources of radiation received while working at the Sellafield nuclear complex, as reported by Dickinson and Parker (2002) from their cohort study of live births in Cumbria during 1950-1991. Results for the offspring of Sellafield workers are given for births in the village of Seascale and in Cumbria outside Seascale. The Sellafield findings are compared with the results of five studies that have used independent data. (Table after Wakeford (2002).)

Study	Dose-response model[a]	RR (95% CI) at 100 mSv
All Sellafield radiation workers[b,c]	Exponential[d]	1.6 (1.0, 2.2)
Seascale subgroup	Exponential[d]	2.0 (1.0, 3.1)
Outside Seascale subgroup	Exponential[d]	1.5 (0.7, 2.3)
Japanese atomic bomb survivors (paternal dose only used in analysis)[e,g,h]	Linear Exponential	<0.98 (<0.98,1.10) 0.76 (<0.31, 1.03)
Ontario radiation workers[f,g,h]	Linear Exponential	0.63 (<0.27, 3.40) 0.75 (0.07, 3.31)
Danish Thorotrast patients[b,g]	Linear Exponential	<0.97 (<0.97, 1.56) <0.11 (<0.11, 1.11)
British radiation workers (RLS)[f,i,j]	Exponential[k]	0.92 (0.28, 2.98)
US 'Three Site' radiation workers[f,l]	Linear	0.75 (<0.75, 3.5)

[a] Linear or exponential dose-response model fitted to the data.

Age at diagnosis: [b] 0–24, [e] 0–19, [f] 0–14 years.

[c] The original study of Gardner *et al.* (1990) reported a RR of 8.30 (95% CI: 1.36, 50.56) for the cumulative paternal preconceptional dose category ≥100 mSv and using "local controls", based on 4 cases and 3 controls; 3 of the cases were born to mothers resident in Seascale. The reasons for the difference in RR from the case-control study of Gardner *et al.* (1990) and that from the cohort study of Dickinson and Parker (2002) are set out by Dickinson *et al.* (2003).

[d] Exponential dose-response model assumed to have been used by the authors.

[g] Based on the results of Little *et al.* (1996).

[h] Leukaemia only.

[i] RLS: Record Linkage Study (Draper *et al.*, 1997).

[j] Overlap with Dickinson and Parker (2002) of one case (born in Cumbria outside Seascale and diagnosed after the end of the period studied by Gardner *et al.* (1990); paternal preconceptional dose <50 mSv).

[k] Adjusted by the authors for radiation worker status.

[l] Hanford, Idaho Falls, Oak Ridge workers; Sever *et al.* (1997) (see Wakeford, 2000).