Leukemia (1998) 12, 1319–1323

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MEETING REPORT

Ionising radiation and leukaemia potential risks: review based on the workshop held during the 10th Symposium on Molecular Biology of Hematopoiesis and Treatment of Leukemia and Lymphomas at Hamburg, Germany on 5 July 1997

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Unexplained clusters of childhood leukaemia have generated concern that they may be causally related to environmental exposure to ionising radiation. The workshop provides in-depth examination of the aetiology of childhood leukaemia, patterns of clustering exhibited by cases and the influence of exposure to ionising radiation. Special attention has been focussed on the EUROCLUS study of clustering of childhood leukaemia and monitoring of populations exposed to contamination following the Chernobyl accident. There is insufficient evidence to conclude that environmental ionising radiation exposure is a causative agent for small clusters such as that reported in the vicinity of the Krümmel nuclear facility
Keywords: childhood leukaemia; clusters; ionising radiation; common infections

Introduction

The workshop was conducted as an adjunct to a symposium on 'Molecular Biology of Hematopoiesis and Treatment of Leukaemias and Lymphomas' in Hamburg, 2–6 July 1997. A key motivational factor was the intense level of scientific, public health and community concerns regarding the 'Elbmarsch cluster' of childhood leukaemias.[1] Although the area concerned is geographically very close to a nuclear facility (the Krummel nuclear power plant) the workshop started from the premise that a broadly based scientific approach was appropriate and that this should consider other causes of leukaemias, other studies of clustering of childhood leukaemia, as well as other evidence of association between ionising radiation and leukaemia. This view was endorsed by Dr Fritz Vahrenholt, State Minister of the Environment who, in his welcome, stressed the need to consider the evidence for involvement of infectious agents in the aetiology of, specifically, childhood leukaemia and the relevance that this might have to the Elbmarsch cases.

Aetiology: current knowledge

Leukaemias constitute about 5% of all malignancies in most populations. There are four main subtypes of leukaemia (acute lymphoblastic leukaemia (ALL); acute myeloid leukaemia (AML); chronic lymphocytic leukaemia (CLL); and chronic myeloid leukaemia (CML)) that may not only differ in biological terms, but also in causal mechanisms. Incidence and mortality rates generally increase with age with the exception of acute lymphoblastic leukaemia which peaks in early childhood and then rises slowly with age from a trough in late adolescence. Rates have remained relatively stable in the recent past but show some population-specific variations. The distribution of subtypes differs markedly between adults and children, with ALL representing a small minority of adult cases but the majority of childhood cases. More subtle variations between adults and children occur within the four broad groups including ALL. Thus the aetiology of ALL in children and adults may differ.[2] Leukaemia aetiology was considered by Dr Alexander (speaking in place of Professor Greaves), Professor Gassman and Dr Zeeb.

Leukaemias can be induced experimentally in animals by ionising radiation, chemicals and viruses. In domesticated animals (cats, cattle, chickens) leukaemia/lymphoma can occur at a high rate due to interplay between retroviruses, social conditions and genetic background. In humans, the same group of causative factors are known to apply to particular subtypes of the disease. Experimental leukaemia/lymphoma can be induced indirectly in animals by proliferative stress in the immune system and at least one human lymphoid neoplasia (gastric lymphoma in adults) has a similar aetiology. At present no more than a small proportion of all cases (perhaps about 15%) can currently be attributed to known risk factors.

In a lecture focussing on adult leukaemias, Dr Zeeb reminded the workshop that the factor most commonly linked with leukaemia is ionising radiation. The elevated incidence compared to the baseline is much higher in leukaemias than in other cancers, as evident from the study of atomic bomb survivors. Studies involving persons exposed to low level ionising radiation suffer from a number of methodological problems. For workers in nuclear power plants, a slightly elevated risk for leukaemia has been reported. Studies among populations in proximity to nuclear power plants remain inconclusive. Studies of populations exposed to relatively high levels of ionising radiation have usually been interpreted as providing firm evidence that ionising radiation can cause all leukaemia cell-types apart from CLL; this view was, however, challenged by Dr Kellerer who, in a provocative lecture, questioned the strength of the evidence for ALL. In her talk on the aetiology of childhood leukaemia, Dr Alexander acknowledged an established causative role for exposure to ionising radiation (eg from exposure to the atomic bomb, *in utero* X-ray) but suggested that the proportion of cases explained in this way is likely to be small.

A large number of studies have confirmed an increased risk of (adult) leukaemia, particularly AML, among workers exposed to benzene. Occupational exposure to a number of other solvents and other chemicals may also increase risk. There is limited evidence that similar exposures (eg to benzene via parental smoking) may influence childhood AML. Chemotherapy with alkylating agents for malignant tumours

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Received 14 April 1998, accepted 13 May 1998

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carries increased risk for AML as a second tumour, with the risk ratio elevated up to 300-fold. Chemotherapy appears to induce different subtypes of myeloid leukaemia, sometimes with short latent periods.

There is strong evidence for a viral causation of the adult T cell leukaemia/lymphoma (ATL). Infection with HTLV-1 early in childhood poses a 1–4% lifetime risk of ATL. Other viruses are currently being investigated with regard to their role in haematopoietic tumours. Dr Alexander described the current research focus on patterns of exposure and response to common infectious agents in childhood leukaemia. The work of Kinlen and colleagues[3–5] has repeatedly tested and confirmed the hypothesis that rates of total childhood leukaemia would be elevated in populations which, though once isolated, had experienced substantial population growth or mixing through other mechanisms. These demographic features would lead to dysregulation of herd immunity and contribute to micro-epidemics of common infectious agents. Several reported clusters of childhood leukaemia including four in the proximity of nuclear facilities can be interpreted in these terms.[3–6] The childhood peak of ALL has developed in diverse populations as they experience socio-economic development; this phenomenon is attributable to the common sub-type of ALL (cALL) and leads to a hypothesis that this specific subtype may arise as a result of patterns of exposure to common infections which are correlates of 'development'.[2] It is predicted that these patterns include absence of exposures during infancy followed, perhaps, by relatively late first exposure or high titre exposure. Epidemiology provides considerable indirect support for this hypothesis (reviewed in Ref. 7). The evidence includes both descriptive epidemiology and studies of individuals; an example of the latter is lower risk in children who are not first-born in their family and/or who attend early day-care.[8] Biological mechanisms could involve direct cellular transformation by viruses and almost certainly do for HTLV1, 2. Other indirect mechanisms may apply for childhood leukaemia, especially cALL. There is now evidence that inherited factors such as HLA haplotype may influence risk; this is supportive of a role for infectious agents.

From an epidemiological point of view, leukaemias pose an ongoing challenge, not least because currently established risk factors only explain to such a limited extent why these diseases occur.

Clustering of childhood leukaemia (The EUROCLUS study)

Clusters of childhood leukaemia are frequently reported but extremely difficult to evaluate. They have been tentatively linked to environmental hazards (eg polluted water supplies, ionizing radiation in the proximity of a nuclear facility). However, the possible role of chance should not be under-estimated. This can apply in several ways; firstly, random allocation of rare events will naturally contain a number of apparent clusters, secondly, cases caused by several different factors may happen to reside close together and thirdly, a genuine cluster, caused by shared exposure to another factor (eg an infectious agent) may, by chance, occur near to an obvious industrial or other factor which is readily suspected, though unrelated. No cause of a cluster has ever been identified with certainty. Two problems are ignorance of the causes of childhood leukaemia and of whether cases are likely to occur in clusters (ie more likely to do so than 'chance', or Poisson variability, would predict).

The EUROCLUS project was established with two objectives: firstly, to determine whether childhood leukaemia and/or specific subgroups show a general tendency to cluster within small areas of Europe, and secondly, to explain any clustering which is observed. The project involved the collection of leukaemia incidence data for 13 551 cases of childhood leukaemia (CL) diagnosed between 1980 and 1989 in defined geographical areas in 17 countries. The cases were geographically referenced to small census areas of which there were over 26 425 in the study regions. The Potthoff–Whittinghill method[9] was applied to test for evidence of generalised clustering within the small areas and to estimate the magnitude of clustering. Results indicate statistically significant evidence of generalised clustering of CL but this is of small magnitude.[10] It follows that intense clusters are unusual events and deserve serious attention. There is more evidence of clustering of ALL in the childhood peak ages than of other subgroups but this did not attain statistical significance. The clustering in the total data set was attributable both to proximity of these ALL cases and to proximity of cases of different cell-type and age group at diagnosis. It may, therefore, be influenced by some shared aetiological factor. Clustering is most evident in areas of intermediate population density (150–499 persons/km^2).

For the second objective, up to 25 small areas were selected in each of the 17 regions as the most 'clustered'; these were matched to 'control' areas of similar size but without evidence of excess CL. The clustered areas were examined for evidence of temporal overlap of cases at times of predicted susceptibility to exposure (eg for the childhood peak of ALL, the 18 months preceding diagnosis). Clustered and control areas were compared for two sets of factors: demographic and environmental. Data for these comparisons were extracted from routine sources or by observers blind to area status. The temporal patterns in the clustered areas confirmed predictions based on the aetiological hypothesis of shared exposures at critical times and these results were highly statistically significant.[11] When clustered areas were compared with control areas, the clustered areas showed statistically significant evidence of demographic features indicative of initial isolation and subsequent population mixing; this was evident using both objective criteria (population density) and more subjective criteria (eg housing influx, construction camps and others used by Kinlen and colleagues). Very few clustered areas had identifiable environmental factors such as have been noted for single reported clusters (eg proximity to nuclear facilities, which applied to just four of the 240 clustered areas) and no comparisons of clustered/control areas were statistically significant.

These results from EUROCLUS (see Table 1) strongly suggest that clustering of cases of CL occurs and is related to the aetiology and biology of the disease but involves distribution of infectious agents rather than environmental hazards.

The Elbmarsch childhood leukaemia cluster near the nuclear power plant of Krümmel

In the early 1990s, a childhood leukaemia cluster was recognised in the 1500 children of a small community, Samtegemeinde Elbmarsch, south of the nuclear power plant of Krümmel near Hamburg.[1] This phenomenon prompted a retrospective incidence study encompassing the years 1984–1993. Leukaemias and related disorders were ascertained in 4 800 000 inhabitants (up to age 65 years) of three counties surrounding the nuclear plant (Lüneburgh, Hersogtum Lauen-

Table 1 EUROCLUS key points

1	Childhood leukaemia (CL) does not display strong spatial clustering in small areas in Europe over a 10 year period. • Intense clusters should be taken seriously.
2	CL shows evidence of spatial clustering in small areas of Europe which is statistically significant but of small magnitude (2% addition to Poisson variation).
3	Clustering of CL is focussed in areas of intermediate population density (150–500 persons/km^2) where addition to Poisson variation is 5%. • For areas with density 250–500 persons/km^2, this is 15% • For areas with density 500–750 persons/km^2 incidence is (uniformly) elevated • For more densely populated areas, incidence is reduced and clustering is generally absent
4	Cluster areas compared with control areas have demographic characteristics indicating • isolation (initially) • population mixing Their (final) population density is likely to be moderately dense (500–750 persons/km^2) rather than sparse or very dense. Their separation from towns is most likely to be moderate (ie journey times $\frac{1}{2}$–1 h).
5	Cluster areas compared with control areas fail to demonstrate any unequivocal association with environmental hazards.
6	Within cluster areas, cases show statistically significant evidence of temporal overlap involving putative critical times identified in advance: • The childhood peak of ALL, during 18 months preceding diagnosis • CL diagnosed later (5–14 years), during 2 years around birth • Infant cases during *in utero* period
7	Aetiology: these results support hypotheses involving association of CL with micro-epidemics of as yet unknown infectious agent(s). Populations of density 250–500/km^2 and 500–750/km^2 are most likely to support epidemics. For the childhood peak of ALL, delayed first exposure may increase the risk but the agent may be causal for some other cases, including some infants.

From Alexander *et al*.[23]

burg, Hamburg-Harburg). The investigators[12] calculated the leukaemia incidence rate by distance to the nuclear power plant discriminating the following areas: <5 km, 5–10 km, 10–15 km, 15–20 km, >20 km and reported an increased risk of leukaemia for adults living in the 5-km circle surrounding the nuclear plant (78% increase of total leukaemias).

A critique of the interpretation of these results was provided to the workshop by Professor Gassmann. The most important point he raised was the geographic distinction between the areas where incidence was elevated in children (south of the nuclear plant in the community Samtegemeinde Elbmarsch), and in adults (north of the plant); these areas were at opposite sides of the river Elbe. In the 3000 children of the northern half of the 5-km area (city of Geesthacht) just one more case of leukaemia could be found in 1984 (1.55 had been expected). In the adults of the Samtegemeinde Elbmarsch (7900 inhabitants), the leukaemia rate observed was that expected. This is true, too, for the first 5-year period, as well as for the years 1989–1993 (five cases observed, 4.3 cases expected). In the adults of the northern area of the 5-km area (city of Geesthacht) (24 000 inhabitants), surrounding the nuclear power plant, an increased number of leukaemias was found in the 10-year period. Excesses were evident for CLL (19 cases observed, 13.7 expected) and CML (eight cases observed, 4.2 expected) but not for acute (lymphoid/myeloid) leukaemias for which observed numbers were less than expected. It should be remembered that CLL is known not to be caused by exposure to ionising radiation.

Professor Gassmann concluded that the two separate phenomena (high rate of childhood leukaemia south of the power plant *vs* high leukaemia rate for adults in the northern region with normal rates for the complementary populations) must, if real, have separate causes.

There are, however, also clear indications of better case ascertainment in the 5-km area compared to the other areas: 42% of the cases in the 5-km area were reported by three or more institutions compared to 20% in the 5–10 km area and 29%, 25% and 31% in distant regions.

The health impact of environmental pollution in Belarus after the Chernobyl disaster

The question of health effects from the severest nuclear accident in history has been a matter of considerable controversy and debate. Reports to the workshop were made by Professor AM Kellerer, Professor E Konoplya and Dr R Hille. In the wake of the catastrophic breakdown of the reactor in Chernobyl, there was limited information from the former Soviet Union for at least 2 years after the accident. Professor Kellerer argued that this 'second disaster' enhanced the prevailing uncertainties and led to a lasting loss of credibility and that resulting confusion and fears have made it extremely difficult to establish a reliable picture of the health effects among the population in the contaminated zones.

The initial exposures due to the short-lived radioiodine have led to a dramatic increase in thyroid tumours, especially in the young.[13–16] This has created a grave health problem that requires increased efforts for early diagnoses of thyroid diseases and for effective treatment. The continued radiation exposure due to the long-lived radioactivity is a different and difficult problem. It has involved decisions on the evacuation or resettlement of certain regions and the imposition of various constraints that affect the living conditions of the population. It is the long-term health impact of this exposure pattern that is subject to the greatest uncertainty and controversy. As leukaemia, especially in children, is the first and most sensitive indicator of late effects due to whole body radiation exposures, a major effort has been made to document any alteration in childhood leukaemia rates in regions most affected by the disaster. In an earlier project within the framework of the European Commission's Program on Radiation Research, cooperation with the Institute of Radiation Medicine, Kiev, has led to the publication of cancer trends in the highly contaminated regions of the Ukraine.[17] No increase in leukaemia or cancers (excluding thyroid) were found. This result is in line with the magnitude of exposure of the popu-

lation, but it differs greatly from the almost universal public perception.

The highest contaminations have occurred in Belarus. Childhood leukaemia rates have been assessed in the seven major regions of Belarus for the period 1982 to 1994.[19] This is the first detailed documentation of the childhood leukaemia rates in Belarus before and after the accident. There is no increase in childhood leukaemia rates in any one of the six regions of Belarus. These findings are, however, based on small numbers, and are consistent with increased risk of up to 20% in individual regions. Further careful monitoring of trends in leukaemia and cancer incidence are therefore set to continue with the support of the German and French Ministers of the Environment.

The Chernobyl accident also provides a unique opportunity to confirm or refute risk estimates derived from the atomic bomb exposure in Japan. However, this requires reliable dosimetric measurements of exposure. For this purpose, measurements have been carried out in the highly contaminated areas of Belarus by Belarussian and German scientists. The German measurements in the years 1992 and 1993 involved contaminated food and environmental samples and 42 000 measurements of individuals. Averaged incorporated radioactivity of the population was significantly higher than in control areas, but only 2% of exposed cases showed body activities of more than 25 kBq per person. This low level represents only a slightly enhanced cancer risk, but justifies careful monitoring as with radiation workers in the nuclear industry. The individuals with the higher body burdens were mostly elderly persons consuming contaminated food, including milk or forest products, and the fact they are older reduces their life-time cancer risk.

The average accumulated dose for the most highly contaminated settlements was below 100 mSv in 10 years. This dose is high (10 × average background) though similar natural or background levels do exist as in the Kerala region of south west India. No significant health impact has been recorded there.

From these studies, the speakers concluded that no significant increase of long-term health effects other than thyroid cancer are to be expected in Belarus. However, the scientists involved emphasize that this prediction does not exclude individual radiation-related problems and for this reason, humanitarian aid and medical support for the people in the highly contaminated areas is still necessary and fully justified. Recent studies[18] indicating that children from Gomel, including those born after the Chernobyl accident, may have higher incidence of non-random chromosome translocations compared with a control series of Italian children suggest that continued monitoring of cancer rates is warranted.

In April 1997, the Korma project 'Children and Future of Korma' was initiated to make a more detailed evaluation of the radiological and health situation for two special settlements in the highly contaminated region. The aim was to evaluate the interdependence between the soil and food contamination, the radiation exposure and the social status and health consequences for individuals. The two villages involved in the project, Voronovka and Vassokaja, are situated in the Korma region with an average ground contamination of about 15 Ci/km^2 Cs-137. Soil and food samples have been taken and evaluated in the Institute of Radiobiology at Minsk. A measuring vehicle equipped with body counters and a dosimetric and medical laboratory has been placed at Voronovka. Blood samples have been taken and analysed in the nearby Korma district hospital. Dosimetric monitors are also distributed to the population and gathered after 2–3 weeks for the evaluation.

Preliminary results show that internal exposure of the population varies considerably with a mean value of about 100 Bq. In two cases there was an association between contaminated food and high internal doses. The study is continuing.

Alongside the scientific studies reported above it should be noted that the ECLIS study[20,21] and others have monitored childhood leukaemia and cancer in areas contaminated to lesser extents by the Chernobyl disaster. No evidence of increases have been reported except for thyroid cancer and infant leukaemia[22] but the causal nature of the latter association is unclear.

Concluding remarks

The workshop succeeded, as hoped, in considering the issues in a very broad context. Presently known risk factors for leukaemias certainly include exposure to ionising radiation but explain only a minority of cases. Amongst risk factors under investigation, especially for childhood leukaemia, patterns of exposure to common infectious agents are likely to be important. EUROCLUS, the largest study ever to have been conducted of clustering of childhood leukaemia points to limited generalised clustering of which further scrutiny points to explanations in terms of demographic factors suggestive of a role for infectious agents. Examination of the Elbmarsch area and of other noteworthy clusters fails to link them firmly to environmental exposure to ionising radiation. Most are, however, capable of explanation in terms of population demography. The intense monitoring that has been in progress since the Chernobyl disaster has found little evidence of excess leukaemia in populations having 'environmental level' exposures. In summary, there is at present insufficient evidence on which to base the conclusion that radiation exposure is causative agent for the Elbmarsch childhood leukaemia cluster.

Acknowledgements

The Editor wishes to thank Professor Rolf Neth for his incredible commitment to dissemination of information on the leukaemias now, as well as in the past, in organizing the first brain storming sessions in the barn of Wilsede, in the Lüneburger Heide in Northern Germany. Professor MF Greaves and Dr FE Alexander are acknowledged for their input in making available to us their thoughts and clear thinking on this intricate, at times emotional and often controversial topic. Supported by Walter Gastreich-Stiftung im Stifterverband für die Deutsche Wissenschaft.

References

1 Hoffman W, Dieckmann H, Schmitz Feuerhake I. A cluster of childhood leukemia near a nuclear reactor in northern Germany. *Arch Environ Health* 1997; **52**: 275–280.
2 Greaves MF. Aetiology of acute leukaemia. *Lancet* 1997; **349**; 344–349.
3 Kinlen LJ. Evidence for an infective cause of childhood leukaemia: comparison of a Scottish new town with nuclear reprocessing sites in Britain. *Lancet* 1988; **2**: 1323–1327.
4 Kinlen LJ, O'Brien F, Clarke K, Balkwill A, Matthews F. Rural population mixing and childhood leukemia – effects of the North

Sea oil industry in Scotland, including the area near Dounreay nuclear site. *Br Med J* 1993; **306**: 743–748.
5 Kinlen LJ, Hudson C, Stiller LA. Contacts between adults as evidence for an infectious origin of childhood leukaemia: an explanation for the excess near nuclear establishments in West Berkshire? *Br J Cancer* 1991; **64**: 549–554.
6 Viel J-F, Pobel D. Incidence of leukaemia in young people around La Hague nuclear waste re-processing plant: a sensitivity analysis. *Statist Med* 1995; **14**: 2459–2472.
7 Greaves MF, Alexander FE. An infectious etiology for common acute lymphoblastic leukemia in childhood. *Leukemia* 1993; **7**: 349–360.
8 Petridou E, Kassimos D, Kalmanti M, Kosmidis H, Haidas S, Flytzani V, Tong D, Trichopoulos D. Age of exposure to infections and risk of childhood leukaemia. *Br Med J* 1993; **307**: 774.
9 Muirhead CR, Butland K. The Potthoff–Whittinghill method. In: Alexander FE, Boyle P (eds). *Statistical Methods of Investigating Localised Clustering of Disease*. IARC: Lyon, 1996, pp 28–39.
10 Alexander FE, Boyle P, Carli PM, Coebergh JW, Draper GJ, Ekbom A, Levi F, McKinney PA, McWhirter W, Michaelis J, Peris-Bonet R, Petridou E, Pompe-Kirn V, Plesko I, Pukkala E, Rahu M, Storm H, Vatten L, Wray N on behalf of the EUROCLUS project. Spatial clustering of childhood leukaemia: summary results from the EUROCLUS project. *Br J Cancer* 1998; **77**: 818–824.
11 Alexander FE, Boyle P, Carli PM, Coebergh JW, Draper GJ, Ekbom A, Levi F, McKinney PA, McWhirter W, Michaelis J, Peris-Bonet R, Petridou E, Pompe-Kirn V, Plesko I, Pukkala E, Rahu M, Storm H, Vatten L, Wray N on behalf of the EUROCLUS project. Spatial temporal patterns in childhood leukaemia: further evidence for an infectious origin. *Br J Cancer* 1998; **77**: 812–817.
12 Hoffman W, Greiser E. Increased incidence of leukaemias in the vicinity of the Kümmel nuclear power plant in northern Germany. In: Frenzel-Beyne R, Ackermann-Liebrich U, Bertazzi PA *et al* (eds). *Environmental Epidemiology in Europe*. Proc Int Symp, Bremen, Germany: European Commission Directorate General V, 1996, pp 185–206.
13 Becker DV, Robbins J, Beene GW, Bouville AC, Wachholz BW. Childhood thyroid cancer following the Chernobyl accident – a status report. *Endoc Meta Clin N Am* 1996; **25**: 197–211.
14 Sobolev B, Heidenreich WF, Kaior I, Jacob KP, Goulko G, Likhtarev I. Thyroid cancer incidence in the Ukraine after the Chernobyl accident comparison with spontaneous incidences. *Radiat Environ Biophys* 1997; **36**: 195–199.
15 Danese D, Gardini A, Farsetti A, Sciacchitano S, Andreoli M, Pontecorvi A. Thyroid carcinoma in children and adolescents. *Eur J Pediatr* 1997; **15**: 190–194.
16 Henshaw DL. Chernobyl 10 years on – thyroid cancer may be the only measurable health effect. *Br Med J* 1996; **312**: 1052–1053.
17 Prisyazhniuk A, Gristchenko V, Zakordonets V, Fouzik N, Slipeniuk Y, Ryzhak I. The time trends of cancer incidence in the most contaminated regions of the Ukraine before and after the Chernobyl accident. *Radiat Environ Biophys* 1995; **34**: 3–6.
18 Scarpato R, Lori A, Panasiuk G, Barale R. FISH analysis of translocations in lymphocytes of children exposed to the Chernobyl fallout: preferential involvement of chromosome 10. *Cytogenet Cell Genet* 1997; **79**: 153–156.
19 Ivanov EP, Tolchoko GV, Shuvaeva LP, Becker S, Nekolla E, Kellerer AM. Childhood leukaemia in Belarus before and after the Chernobyl accident. *Radiat Environ Biophys* 1996; **35**: 75–80.
20 Parkin DM, Cardi SE, Masuyer E *et al*. Childhood leukemia following the Chernobyl accident – the European Childhood Leukemia Lymphoma Incidence Study (ECLIS). *Eur J Cancer* 1993; **29A**: 87–95.
21 Parkin DM, Clayton D, Black RJ *et al*. Childhood leukemia in Europe after Chernobyl – 5-year follow-up. *Br J Cancer* 1996; **73**: 1006–1012.
22 Petridou E, Trichopoulos D, Dessypris N, Flytzani V, Haidas S, Kalmanti M, Koliouskas D, Kosmidis H, Piperopoulou F, Tzortzantau F. Infant leukaemia after *in utero* exposure to radiation from Chernobyl. *Nature* 1996; **382**: 352–353.

Appendix 1

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