INVITED EDITORIAL

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The latest (14th) Report of the UK Government’s expert advisory Committee on Medical Aspects of Radiation in the Environment (COMARE 2011), entitled ‘Further consideration of childhood leukaemia around nuclear power plants in Great Britain’, was published on 6 May 2011 (http://www.comare.org.uk/press_releases/documents/COMARE14report.pdf). The foreword explains that it was prompted by a request from the UK Department of Health following recent research findings, including the publication of the German Kinderkrebs in der Umgebung von Kernkraftwerken (KiKK) study. Here, researchers from the University of Mainz reported a statistically significant tendency for cases of childhood leukaemia (CL) at ages 0–4 years within 5 km of nuclear power plants (NPPs) in western Germany during 1980–2003 to occur closer to these plants than the matched control children relative to the area beyond 5 km (Kaatsch et al 2008a, Spix et al 2008). Though unmentioned in the COMARE Report, this study was associated with wide publicity and extravagant claims of its importance by the sponsoring body, the Federal Office for Radiation Protection (BfS 2007a, 2007b, 2009) in Germany, and these are likely to have played a part in attracting UK Government attention.

Epidemiology: study types

Chapter 2 of the COMARE Report summarises the types of epidemiological study that figure in later sections. Unfortunately, the treatment of case-control studies is misleading (paragraphs 2.8 to 2.11). With respect to population controls, only population registers are mentioned, and instead, hospital controls are recommended. In fact, population controls are always the ideal, hospital controls being subject to obvious bias. It is also confusing to be informed that ‘population registers are notoriously difficult to keep up to date’ (2.11), when the Report mentions only examples in Germany, where the legal requirements, referred to in paragraph 6.37, would imply reliability. No indication is given of how unusual it is to use a case-control study to determine whether a geographic excess exists, although in the case of a known excess, this method is commonly used to investigate its cause.

Geographical studies of incidence

The CL increase reported near German NPPs in the KiKK case-control study mentioned above is in marked contrast to the findings of national geographical incidence studies, which have found no significant increase in CL incidence near nuclear installations, including groups of NPPs, as indicated in the review forming chapter 3. Such an examination of geographical incidence of CL by the Mainz group found weak evidence of an excess at 0–4 years in small administrative units with centroids within 5 km of NPPs in western Germany, in the period 1980–2003: 34 observed (O), 24.09 expected (E); O/E 1.41 (95% confidence interval (CI) 0.98, 1.97) (Kaatsch et al 2008b). Because a significant excess near the Krümmel NPP in northern Germany has been known since 1992, an obvious question concerns CL incidence...
near NPPs after exclusion of Krümmel. After apparent reluctance by the original authors to report this data previously, COMARE usefully presents this for the first time, as received from Mainz. Exclusion of Krümmel removes the weak evidence of an excess mentioned above, O 26, E 21.54; O/E 1.21 (95% CI 0.79, 1.77), a finding that is close to a recent estimate made in the absence of exact data, O/E 1.20 (95% CI 0.78, 1.76) (Kinlen 2011).

The KiKK case-control study

The Mainz group insist, however, that an excess risk of CL among young children does exist close to NPPs other than Krümmel, based on the findings of a case-control study of childhood cancer, the KiKK study. The claim is the more unexpected since the two approaches both show the Krümmel excess, as well as similar numbers of CL cases in the <5 km zone around NPPs, whether determined by individual measurement (37) or belonging to communities with centroids in this zone (34). Careful consideration of the KiKK study methodology is therefore indicated. It covered 1592 cases of childhood cancer (of which 593 were CL) at 0–4 years in a wide area surrounding such plants in the period 1980–2003. For each case child, six age- and sex-matched controls with dates of birth closest to the case were selected from lists of candidate children supplied by the registration offices of communities randomly chosen from those in the same NPP area, weighted by the size of the population of the communities; a case within 5 km of an NPP could be matched with a control 70 km from the NPP, and vice versa. Measured distances from the plants to the homes of cancer cases were compared to the corresponding distances for their matched controls. For CL, a statistically significant association between risk and nearness to an NPP was found for a 5 km radius area (relative to the risk beyond 5 km): relative risk (RR) 2.11 (95% CI 1.38, 3.24) (table 4.3). A corresponding analysis of malignancies other than CL did not show this effect. For readers who wonder how much closer to an NPP CL cases in the <5 km zone lived than their controls, there is only the intriguing statement in paragraph 4.39 (taken from Spix et al 2008) concerning all cancers, that case children lived, not closer, but slightly further away from plants than did controls (3.2 versus 3.1 km).

COMARE was fortunate in obtaining additional unpublished data from the Mainz workers in order to explore differences between the findings of the KiKK and the geographical incidence studies. Importantly, the Report shows the influence of the Krümmel excess in the case-control data for 1991–2003, as in the incidence data. It also demonstrates that the main disparity between the two studies is in the early period, 1980–90: for CL in the 5 km radius inner zone, the geographical incidence study gives an unremarkable RR of 1.29 (95% CI 0.68, 2.26) whereas the case-control study gives a RR of 2.86 (95% CI 1.32, 6.17), each involving 13 cases (table 4.3).

Cancer registration

Certain other statements are likely to cause confusion. Paragraph 4.84 states that an under-registration of cases during the early years of the German Childhood Cancer Registry (GCCR) might contribute to the relative excess of CL in 1980–90 near NPPs. For many readers, an understanding of this point requires additional details that are not provided. In the early years of operating, it has been the general experience of cancer registries around the world that ascertainment of cases falls short of completeness. This is particularly likely here, since the network of paediatric oncologists, who represent the only source of ascertainment, did not have clinical care of all CL cases throughout West Germany when the registry was founded (in 1980). Because concerns there over radiation have been particularly intense, CL cases near
NPPs were more likely to be notified to the GCCR during its early operating years than the more distant cases. Although chapter 7 of the Report stresses the high quality of the National Registry of Childhood Tumours (NRCT) in Britain, the reader is not informed that this largely rests upon the use of multiple sources of case ascertainment. The different position in the GCCR, with cases notified only by paediatric oncologists, is not highlighted: the claim by the Mainz registry of almost complete ascertainment for CL from 1980 (paragraph 7.39) lacks reality, having no independent support. A relative lack of familiarity with wider standards of cancer registration may be relevant here, since most forms of cancer registration are prohibited in Germany.

Control selection problems in the KiKK study

The KiKK workers have referred to the design of their study as being exceptionally painstaking. Its execution, however, cannot be so described, since an important aspect of the selection of controls was performed beyond the scrutiny of the research workers, by community registrars, for whom this was not normal work. Indeed in the study overall (i.e. of all cancers), some 10% of registrars declined to cooperate, the proportion being higher within the 5 km zone (16%); some registrars did not follow instructions, selecting potential control children for an inappropriate calendar year (i.e. not the year of diagnosis of the case), as in 15% of the 45% of controls that could be checked. The longer interval before control selection (from 2003) for cases diagnosed in the earliest period (1980–90) allowed greatest ‘scope’ for residential moves by potential controls, and therefore for such errors. But this is the same period which COMARE highlighted as when the disparity with the incidence data occurred. However, this significant point is not brought out in the Report, which simply states that ‘some problem’ with control selection in this period was a possibility (paragraphs 4.84 and 4.92); while in the conclusions, there is no hint that there were grounds for considering selection to be any more problematic in the inner zone in the early period (9.7). It is relevant that data on the extent of non-cooperation or of defective control selection have not been presented for CL (or for cancer other than CL) separately, let alone by sub-period and proximity zone. As a result, their extent in 1980–90 for CL within 5 km of NPPs is masked in the wider data for the controls for all cancers in all distance zones and all periods combined. These issues could well bias the KiKK study findings towards greater risk of CL in the early period near NPPs. In failing to bring out the above points, COMARE’s conclusions (chapter 9) are correspondingly weakened.

Though not mentioned in the Report, the finding, after checking, that a control address received earlier was correct in the diagnosis year, is not equivalent to checking on the correctness of the selection process. Some children chosen as controls from the register for an incorrect year of diagnosis would be found to have the same address in the diagnosis year, simply because they had not moved house in the interval, but this does not mean that they would have been selected if the process had been rigorously carried out. This requires that the pool of potential controls be restricted to the year of diagnosis of the relevant case, and no indication is given that this was done in each checking. The above concerns apply also to the (supportive) re-examination carried out by Darby and Read (in SSK 2009), conducted as part of the review of the KiKK study by the German Commission on Radiological Protection (SSK 2008), which was based on the same raw data as received and collated by the Mainz workers; in neither instance were differences from the geographic incidence data explored. The investigators’ assurances that their errors were ‘not serious’ do not relate specifically to CL in the inner zone in the early period, and in any case do not address other concerns raised above. Thus, neither the control selection, nor the presentation of the most important findings, can be described as transparent.
Promotion of the KiKK study

The hyperbole surrounding the KiKK study may distract attention from shortcomings both in the raw data provided by community registrars, and in the presentation of study findings by zone, time period and malignancy sub-type. Even one of the principal papers (Kaatsch et al 2008b) states: ‘The KiKK study has repeatedly been described as “the most painstakingly designed and most exhaustive survey worldwide”’ (e.g. press release of the Federal Office for Radiation Protection (BfS), 10 December 2007) (see BfS 2009). The president of the BfS (politically appointed, and not a scientist) welcomed the findings with acclaim, stating that ‘the question of the connection between vicinity of the home to a reactor and risk of contracting cancer has thus been clearly answered for Germany’ (BfS 2007a). Perhaps unexpectedly, the KiKK investigators do not attribute their finding of an elevated CL risk near NPPs to radiation. An external BfS panel of experts (the list headed by Greiser; see below) was also laudatory, but stated their conviction in the probable role of radiation (BfS 2007b). This is in marked conflict with the estimated excess radiation exposures of individuals living near German NPPs given by the KiKK study authors as likely to be at least 1 000 times lower than background radiation exposure (Kaatsch et al 2008b).

Other sections of the Report

Chapter 5 deals with meta-analyses of CL studies around NPPs. Major problems were found in each of these (including COMARE’s), but particularly that by Greiser (2009), which omitted certain studies that found no effect. A new geographic study, commissioned by COMARE, of CL incidence at ages 0–4 years near NPPs in Britain in the period 1969–2004 is the subject of chapter 6, differing from that carried out by Bithell et al (2008, 2010) in covering NHL and CL, instead of only acute CL. No significant association was found within 5 km of NPPs: O 20, E 16.35; O/E 1.22 (95% CI 0.75, 1.89). As in the previous study, an excess in this zone was found in relation to potential NPPs (i.e. planned but not built). Chapter 8 covers radioactive discharges from NPPs, and radiation doses to the public.

Infection underlying CL

Chapter 7 is concerned with cancer registration and CL aetiology. Since only exceptionally is any individual case of CL attributable to radiation—or indeed to any specific cause—paragraph 7.17 is unnecessarily cautious in stating that ‘there is much evidence to suggest that factors other than radiation are likely to be important in many cases’ [reviewer’s italics]. If COMARE is tentative both here and over control selection in the KiKK study, there is no such reticence in relation to infection underlying CL. Paragraph 7.13 contains the strongest statement in the whole Report: ‘it must be emphasised that at this point no specific agent has been identified in CL’, failing to indicate that no proper viral search has yet been made, as stressed in a recent review (Kinlen 2011) with which COMARE is familiar. This lack of balance towards the subject of infection and CL has apparently persisted since the Fourth Report (COMARE 1996), which included major errors in this connection (Kinlen et al 1997). Indeed, it is notable that in its many years of providing advice to government, COMARE has made no recommendation to stimulate viral studies in CL, which might well have influenced decisions on research funding priorities. This failure is the more noticeable given the convincing evidence of infectivity in CL, pointing to a (unidentified) specific microbe, and further supported by recent investigation (Francis et al 2011) of the striking Fallon cluster in the US (Kinlen and Doll 2004).
That CL is a rare response to a common (but unidentified) infection has been extensively tested by epidemiological studies of situations of unusual population mixing in rural areas, where the lower population density is conducive to a higher prevalence of individuals susceptible to the postulated infection. Such mixing would promote mini-epidemics of the mainly subclinical infection, and if on sufficient scale, to excess CL cases; the evidence has recently been reviewed (Kinlen 2011). Among the many examples of such rural population mixing are rural construction projects, military camps and the areas around the remote Sellafield and Dounreay nuclear fuel reprocessing plants in Britain. But Krümmel is the only NPP (as opposed to other nuclear installations) to be associated with a notable CL excess. However, in contrast to the intense efforts to investigate whether radiation was the cause of the Krümmel excess—with negative results (paragraph 4.22)—no detailed investigation of the potential role of infection has been made. This is the case, despite the excess being most pronounced in the rural parts of the area (where population mixing has its main effects)—a notable gulf in research priorities between infection and newsworthy radiation.

Conclusion

Although there are indications that the 14th COMARE Report was finalised without being carefully checked for errors, omissions and overall balance, the Report makes useful contributions to the evidence of CL and NPPs in the wake of the highly publicised KiKK study in Germany. It shows that there is no evidence of a significant increase of CL in the vicinity of NPPs in Britain. It also does a useful service in presenting previously unpublished data from Germany, which show that differences between the KiKK and the geographic incidence studies come mainly from the zone closest to the plants in the early period 1980–90. However, it does not highlight sufficiently that it was here that control selection problems were most likely, and also where radiation concerns would promote more complete notification of CL cases near NPPs in the early period of the Mainz registry. In consequence, there are grounds for scepticism over the KiKK study results. Readers may speculate whether concern for German sensibilities played a part in COMARE’s failure to reach a firmer conclusion about the claimed excess risk of CL near NPPs in Germany.

References


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1 As for example in chapter 2 (see above), and in table 3.1, where the period studied by Bithell et al (2008, 2010) is given incorrectly as 1969–1993, instead of 1969–2004, a period that is mentioned only once (and unobtrusively) in paragraph 3.18. Other errors include the statements in paragraphs 1.8 and 9.2 that COMARE’s study of British NPPs covered 35 years (instead of 36 years, 1969–2004), and that the KiKK study covered 23 years (instead of 24 years, 1980–2003). Annex 6A lacks mention of the age group under discussion, both in the table and the text.


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