

Statement on responses following publication of the 14th Report.

The COMARE's 14th report was published on the 6th May and presented to a press conference at the Science Media Centre attended by journalists from all the major news agencies.

The 14th report was entitled: "Further consideration of the incidence of childhood leukaemia around nuclear power plants in Great Britain". Its aim was to undertake a further review of the incidence of childhood leukaemia in the vicinity of nuclear power plants (NPPs), especially in Great Britain during 1969-2004, with particular reference to recent publications and studies from other countries and taking into account the conclusions in the tenth and eleventh COMARE reports (which consider the period 1969-1993). The main conclusion of the report was that the primary analysis of the latest British data revealed no significant evidence of an association between risk of childhood leukaemia (in under 5 year olds) and living in proximity to an NPP.

Following publication, a number of written responses and comments have been received by COMARE. These have all been considered carefully and this statement addresses the general points raised.

1. Relationships between the analyses in COMARE 14 and earlier studies

There appears to be confusion over the motivation for the study of British data in COMARE's 14th Report and its relationship to earlier studies. This study is the fourth in a series using the National Registry of Childhood Tumours (NRCT):

- 1) The first analysis was of all nuclear installations in England and Wales (Bithell et al, 1994). It covered all leukaemias plus non-Hodgkin lymphomas (NHL) among children aged 0-14 years who were registered in the years 1966-87. The analyses were geographical, using electoral wards or equivalent areas. Wards within circles of 25km radius around plants were analysed; the principal test of proximity was non-parametric and based on the sum of the reciprocals of the ranks of the distances of the cases. The numbers of cases near some sites were small and non-parametric tests were used since they were likely to give reliable tests in all circumstances. A similar analysis of sites in Scotland was published independently by Scottish workers (Sharp et al, 1996).
- 2) COMARE's 10th Report (COMARE, 2005) was the outcome of a request by the Department of Health to carry out the same analyses using data updated to 1993 and extended to include all childhood cancers around British plants. Because the leukaemia plus NHL dataset overlapped that of the previous studies, the results were similar.
- 3) The paper by Bithell et al (2008) was an initiative of workers at the Childhood Cancer Research Group, independently of the COMARE, in response to the KiKK study in Germany. Like the previous analyses it used wards as areas in a geographical analysis, but – in order to emulate the KiKK study as far as possible – it restricted the age of diagnosis to 0-4 years and focused on cases of acute leukaemia close to NPPs (some cases in the KiKK study would have

been further than 25km from an NPP, although this is not immediately apparent from the reports). The 2008 paper therefore considered a database of all cases within 50km of a plant and used a Poisson regression model on the reciprocal of distance as the natural equivalent of the conditional logistic regression used in the KiKK case-control study. This was specified as the principal test of proximity, though the paper also reported observed and expected numbers of cases within 5km distance bands. Again in order to emulate the KiKK study, no attempt was made to allow for confounding variables in this study. Following a letter in the journal querying some of the results (Körblein and Fairlie, 2010), a follow-up letter by the CCRG authors was published that reported the results of combining the effects in the few wards that were close to more than one plant (Bithell et al, 2010). This re-analysis also examined the effect of adjusting for population density – a variable suggested as important by Körblein and Fairlie (2010).

- 4) COMARE's 14th report resulted from a request by the Department of Health to review the latest evidence in the light of the KiKK study, and to consider how this might affect the conclusions of the 10th and 11th COMARE reports. The re-analysis of the NRCT data in Chapter 6 followed the lines of the 2008 paper by Bithell et al but, as in the 10th and 11th Reports, considered all leukaemias plus non-Hodgkin lymphoma (LNHL) as the principal disease grouping and included an adjustment for socio-economic status and other relevant variables. The details of the analysis were decided as described in paragraph 2 below. Originally it was hoped to update the data to 2005, but complete data after 2004 were unavailable from the cancer registries at the time of analysis, and it was judged that a delay was undesirable.

2. Choice of details in the primary NRCT data analysis in Chapter 6

A large number of analyses could be carried out in studies like those reported in Chapter 6, varying the diagnostic groups included, the ages, the distance from the nearest plant, the choice of confounding variables and the statistical methodology. It would be highly misleading and unethical to carry out analyses and choose results that appeared to support a particular standpoint. COMARE is well aware of the danger of “cherry-picking” or “boundary tightening” (as the practice has been described). To avoid any question of doing so – even inadvertently – the working group charged with preparing the 14th Report convened a special meeting. The characteristics of the analysis to be performed were systematically considered without any knowledge of how particular choices would affect the results. The member of the group involved in the analyses drew up the list of characteristics but gave no intimation of what might have been known from handling the data and did not take part in any decision. Some of the reasons for selecting particular characteristics are given in COMARE's 14th report (paragraphs 6.6, 6.7 and Annex 6A).

3. Choice of Cancer Group to include in analysis

In particular, mention has been made of the inclusion of non-Hodgkin lymphoma (NHL). This was consistent with a recommendation made in the 2nd COMARE report, and also with the cancer grouping adopted in the 10th and 11th COMARE reports. The grouping was considered in detail by the subgroup (one of whose members was a paediatric oncologist) with additional input from two experienced academic epidemiologists. It was not known before the analyses were carried out how many additional cases would be included by using the grouping of all leukaemias and NHL rather than just acute leukaemias, as used by Bithell et al (2008). In any event, the small number of additional cases involved necessitates caution when interpreting the results. COMARE refutes the regrettable accusations of selection of the evidence.

4. Interpretation of results that do not reach statistical significance

Interpretation of “statistical significance” is controversial and full of pitfalls. A significance test computes the probability that a result at least as deviant from that expected as the one actually observed would occur by chance in the absence of any genuine underlying reason. The selection of significance levels, such as 5% or 10%, is a balance between producing “false negative” results (by using a significance level that is too stringent) and “false positive” results (by using a significance level that is too lax). A significance level of 5% is commonly used, but the selection of a level to determine “statistical significance” is essentially arbitrary. Nothing in the COMARE report was intended to represent a firm black and white conclusion; at the same time a threshold for giving more consideration to a given result is required, and this was the approach used in the report.

In addition to ‘p-values’, the report quoted confidence intervals where appropriate. These are more informative than the p-value alone as they illustrate the likely range of the true value of the risk given the estimate actually observed in a study.

The Committee had already considered (paragraphs 6.31-36) in general terms and in relation to the British study the reasons why a study might fail to detect a small true risk; these were deemed unlikely to have affected the conclusions.

5. The importance of small risks

COMARE’s 14th Report has been criticised for regarding any apparent risk as small, but relative and absolute risks are different. A doubled risk (i.e. a relative risk of 2) is a matter of concern (the degree of concern will depend on the size of the absolute background risk which is doubled), but smaller relative risks, of 1.3 for example should be treated with caution especially where small numbers are used. Some authorities have suggested that anything less than a doubled relative risk should be disregarded since biases and confounding factors could easily cause such relative differences, especially when dealing with small numbers, and it is in this light that a relative risk of 1.22 should be regarded. The impact of a small or moderate relative risk on a small background absolute risk – such as that for childhood cancer and leukaemia – produces a small excess absolute risk (i.e. the risk that an individual is affected as a result of exposure to the risk factor). The impact in public health terms is also small.

6. Relationship of observed risk to distance

For the primary analysis, COMARE chose a regression analysis for the 0-25 km circle. If the effect is concentrated close to a plant this would be less powerful than restricting analyses to a smaller circle, but there is no reason to suggest that an elevated risk should cease at, say, the 10 km boundary and smaller areas are inevitably affected by smaller numbers. The strongest comparison within the KiKK study was between the 0-5 km circle and the 5-10 km annulus, for which there would seem to be little prior justification; the result was heavily influenced by a deficit of cases in the annulus, as compared with the rest of the region. COMARE considered that this was due to chance and should not be given particular weight, although relevant results were given in COMARE 14. A similar pattern was shown by the British analysis, but could easily be due to chance. The recent Swiss study also found no evidence of a dose response over distance categories (Spycher et al 2011).

The suggestion of a dose-response with proximity in the COMARE analysis is likewise very weak. It has been noted that this relationship *within* the 5km circle is negative, the main contrast being between the inner circle and the adjacent annulus, although there was no a priori reason to expect this.

The difficulties of interpretation of “positive” results are illustrated by the finding of a significant increase in the incidence of LNHL near one of seven ‘potential’ (or ‘control’) sites examined. These were sites in Britain where NPPs had been planned but not built. The increase observed was actually higher than that for the operational sites as a whole.

7. Case-control and geographical studies

Some criticisms of COMARE’s 14th report concern the methodology of the British study, and it has been suggested that the same case-control methodology as was used in the KiKK study should have been used by COMARE. This shows a lack of understanding of the available data, for the KiKK study used population registers for the selection of controls, which are unavailable in the UK, there being no requirement (as there is in Germany) to declare officially the place of residence. These differences and limitations were discussed in paragraphs 6.37-38.

The main limitation of the British analyses concerns the distance of residence from the plant, which is approximated in the British analyses by the population centroid of the ward of residence. Population density varies enormously, however, and most people live close to their population centre so that the inaccuracy induced by this limitation is less than is sometimes supposed.

On the other hand, case-control studies, while capable of capturing information at the individual level, are subject to potential biases between the cases and the controls. This is particularly true when the basis of data collection is different for the two groups. In the KiKK study, details of the cases were ascertained from records obtained from the cancer registry. In contrast, the controls were obtained by a complex method of sampling from population registers and it is known that inaccuracies exist in this selection process. These considerations necessitate caution in the interpretation of the KiKK case-control study, as well as the geographical studies.

8. Exclusion of Sellafield

The aim of the 14th COMARE report was to investigate nuclear power plants, and the Sellafield site was excluded from the analysis for a number of reasons, which were presented in detail in the report (paragraphs 6.12-6.15). The COMARE's 10th report considered all nuclear installations individually, so that it is perfectly possible to identify the well-known excess of cases near the plant. The COMARE is committed to a review of the incidence of childhood cancers around both Sellafield and Dounreay, which is currently underway.

It should be noted also that a continuing nuclear power programme would be possible without a UK reprocessing facility.

9. Potential causes of leukaemia excess

In the COMARE 11th report, a non-uniform distribution of childhood leukaemia risk throughout Great Britain was demonstrated, which must be taken into account when interpreting the findings of studies confined to particular sites (such as NPPs).

The excess of childhood leukaemia around potential NPP sites is likely to be due to chance, but the result could point to some feature of the sites chosen for NPPs that increases the risk of childhood leukaemia. This possibility was first noted by Cook-Mozaffari et al (1989b) (see paragraph 3.6 of the 14th report), but the nature of such a feature has yet to be identified. Similar findings were reported from earlier German geographical studies and also in the recent study carried out in Switzerland (Spycher et al 2011).

These results add to the evidence that patterns of infection, such as those caused by unusual population mixing, might play a role in childhood leukaemia. Further, a study in the US has recently suggested infection as the cause of a pronounced childhood leukaemia cluster in Fallon, Nevada, which is the most marked cluster ever reported and is far from any nuclear installation (Francis et al, 2011).

Recommendation 2 of the 14th report addressed this issue.

10. Conclusion

In considering the comments and responses received following the publication of its 14th report, COMARE has reviewed its conclusions and recommendations, and the evidence used to come to these. The Committee has concluded that these comments and responses do not affect the conclusions or recommendations. It reaffirms the advice provided in the report, namely that there is no significant evidence of an increased risk of childhood leukaemia in the vicinity of British nuclear power plants due to radiation exposure.

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