

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A case-control study of occupational contact levels in the childhood leukaemia cluster at Seascale, Cumbria, UK.
AUTHORS	Kinlen, Leo

VERSION 1 - REVIEW

REVIEWER	Richard Wakeford Centre for Occupational and Environmental Health, The University of Manchester, UK I conduct research funded by the European Commission, the UK Department of Health and Children with Cancer UK. I also carry out some paid consultancy for industry, including the nuclear industry.
REVIEW RETURNED	29-May-2015

GENERAL COMMENTS	<p>This is a valuable additional study of the Seascale childhood leukaemia cluster, which is a marked case aggregation that has attracted a lot of scientific and media attention over the years. The finding of a link with levels of occupational contacts is an important one, particularly given the growing epidemiological evidence for an infective basis of childhood leukaemia.</p> <p>There are two main points:</p> <p>For those readers who do not have the benefit of a detailed knowledge of the "Seascale cluster", it would be useful if a summary table of the Seascale LNHL cases could be given in the paper, perhaps with the first paragraph of the Results section. The 13 LNHL cases were tabulated in the COMARE Seventh Report (Reference 7) (and most cases are also given in the COMARE Fourth Report, Reference 16) and the details given there (age at, and calendar year of, diagnosis, etc.), and possibly elsewhere, could be tabulated in this paper. I think this would improve understanding of what has been done in this study.</p> <p>There was a target of 20 controls per case, a total of 260 controls. In the tables it is apparent that only 183 controls were obtained. However, little is said about this attrition of controls (which the manuscript says was anticipated), apart from a remark made in the Methods that the number of controls per case ranged from 7 to 20. A paragraph is needed in the Results section (probably as a second paragraph) giving more information on the loss of controls, and why the number of controls per case varied quite so much.</p> <p>There are some minor points:</p> <p>Abstract, Objectives: should "as found" be "an association found"?</p> <p>Abstract, Primary outcome measures: "low or medium" might be better as "low/medium"</p> <p>Introduction, first paragraph: it would be worthwhile pointing out that the "official inquiry" was an independent official inquiry, which confirmed an (approximately tenfold) excess of childhood leukaemia</p>
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	<p>in Seascale. Also, the report of this inquiry recommended the establishment of COMARE, an independent expert committee advising the UK Government.</p> <p>Introduction, second paragraph: the West Cumbria case-control study was conducted as a result of a recommendation of the official inquiry.</p> <p>Discussion, first paragraph: the coverage of the literature on occupational contact studies might be helpfully expanded, particularly with respect to urban areas since these are mentioned later in the Discussion.</p> <p>Discussion, last paragraph: given the strength of the epidemiological evidence for an infective basis for childhood leukaemia, the lack of virus studies of the Seascale cluster (and apparently other clusters) is surprising. Perhaps more could be said about this seeming lack of interest in searches for candidate viruses?</p>
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REVIEWER	Laurier Dominique Institute for Radiological Protection and Nuclear Safety FRANCE
REVIEW RETURNED	05-Jun-2015

GENERAL COMMENTS	<p>The issue of childhood leukemia risk in the vicinity of nuclear installations is still highly controversial. Population mixing has been proposed as a major hypothesis to explain observed localized excess. This article investigates further this hypothesis of an infectious aetiology, presenting the results of a case-control study in the area of Seascale to evaluate the plausibility of an association between occupational contacts and childhood leukemia risk. It clearly provides an original contribution to this recurrent issue, and merits to be published.</p> <p>The article is well written. Additional elements could be added in the manuscript to improve the description of the data and to detail methodological aspects. Also, additional analyses may be worthwhile to better characterize the sensitivity of results to methodological choices.</p> <p>Specific comments</p> <p>Introduction, page 4, last paragraph: The “model of poliomyelitis” is presented in details in the discussion section on page 10, but it is not clear when it appears in the first instance of page 4.</p> <p>Methods, page 6, controls section: the number of controls per case varied from 7 to 20. Explanation for such large variation should be given here or in the discussion. What were the main criteria limiting the number of controls? Could this potentially induce bias in the analysis?</p> <p>Methods, page 7, occupational contacts categories section: as written on page 6 “There is clearly no objective method of measuring an individual’s level of contacts”. It is not obvious in the manuscript why workers in the construction industry are classified in the very high category (instead of high), or why workers based in active areas are classified in the high category (instead of low). Additional sensitivity analyses could be envisaged, similarly as what has been done for the workers at the R&D building. Also, the impact of</p>
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	<p>distributing controls with unknown occupations in another category than low/medium occupational contacts could be tested to verify the stability of the results.</p> <p>Methods, page 8, statistics section: the procedure to characterize and to adjust for social class should be better detailed.</p> <p>Methods, page 8: a statement about related ethical and data protection aspects should be added.</p> <p>Results, page 8: indeed, the list of cases has already been published elsewhere, but providing a table summarizing the main characteristics of the cases in the present paper would be very helpful (gender, year of birth, year and age at diagnostic, year of arrival in the area, type of occupation, category of occupational contacts...).</p> <p>Results, page 9: In the supplementary analysis with R&D and bar workers moved into the very high contact category, after social class adjustment, please provides the ORs for the 2 categories and not only for the highest category.</p> <p>Discussion, page 10: the recently published article “Lupatsch et al., EJE 2015” should be added in the discussion about the establishment of the PM hypothesis.</p> <p>Discussion, page 11: a discussion about classical limits of case-control studies should be added (potential biases linked to retrospective information, selection of controls, potential overmatching, low numbers of cases and statistical power ...). Also, the sensitivity of results to choices in the categories of occupational contacts would merit to be developed.</p> <p>Discussion, page 11: the recent article by Bunch et al suggested a diminution of the local childhood leukemia excess after 1990. The potential link between changes in occupational contacts and this observation would merit to be discussed.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Two main points:

- (1) A new table (table 1) has been added listing the 13 LNHL cases, as suggested.
- (2) The variation in the number of controls per case (actually ranging from 8 to 19; 7 to 20 was an error in the text and has been corrected) was mainly due to dropping of controls because the electoral rolls indicated that they had moved from Seascale by the date of diagnosis of the matched case. This has been added to the Results section.

Minor points:

- (a) The two changes suggested in the Abstract have been made.
- (b) The Introduction has been altered to indicate the recommendations of the (independent) official inquiry, and the approximate magnitude of the excess.

(c) The discussion of occupational contact studies has been extended (sited in paragraph 5 of the Discussion), together with the addition of two new references.

(d) It is difficult for an epidemiologist to say anything definite about work in another field, but a clause has been added stating that a viral search was not included among COMARE's recommendations.

Reviewer 2

(1) The wording of the reference to poliomyelitis as been amended in the Introduction. It is expanded in the Discussion section.

(2) The main reason for the ablation of controls was the individual moving out of Seascale in the interval before diagnosis of the matched case (owing to a slip 7 to 20 controls per case should read 8 to 19 in the text, and this has been corrected).

(3) Construction workers, particularly in rural PM situations, mix with many people on their work sites, there being much coming and going, and in rural areas many have to be drawn from outside the area. Their living conditions are often makeshift, in camps and caravans. The subject was dealt with in refs 13, 18, and 19.

Workers in 'active areas' were placed in the high (middle) category because of the regular congestion in or near the limited number of change rooms.

(4) The inclusion of workers of unknown occupation with the low/medium contact category was to be conservative (as they might have belonged to higher categories). This has been made clearer in the text.

(5) A new table (1) has been added, as suggested. Considerations of confidentiality influenced the omission of occupational details for the cases, and only details that have been published previously have been provided in the table.

(6) The details of the social class adjustment have been expanded at the end of Methods.

(7) A sentence on ethics has been added to the Methods.

(8) In Results, the omitted ORs have been added.

(9) The paper by Lupatsch et al was published after the manuscript was submitted to BMJ Open, but it did not refer to any extreme example of rural PM as studied by Kinlen et al. A response to this paper would be better addressed elsewhere as to deal with it here may divert attention from the subject of occupational contacts.

(10) The small number of cases is certainly true, making a case-control study virtually the only method of investigation of this notable cluster. The occupational contact categories are as used before, with the exception of the special occupations discussed in the manuscript, and a sensitivity analysis has been conducted for the R&D and bar workers because notice of their circumstances may have arisen from local knowledge.

(11) A sentence has been added to the end of the first paragraph of the Discussion on the decline of the excess (brought out by Bunch et al) in the early 1990s, when the numbers of construction workers suddenly declined, with the completion of THORP.

VERSION 2 – REVIEW

REVIEWER	Richard Wakeford Centre for Occupational and Environmental Health, The University of Manchester, Manchester, UK
REVIEW RETURNED	22-Jun-2015

GENERAL COMMENTS	<p>The revised manuscript has met my comments on the original manuscript. I have just a few remaining very minor comments:</p> <p>Page 4, Lines 12-13: Remove erroneous "I" at beginning of sentence.</p> <p>Page 9, Lines 8-9: I don't think Reference 15 actually tabulates the details of the Seascale cases, so this reference should be removed from the end of the sentence.</p> <p>Some formatting of the references seems to have gone awry: full stop after Reference 21, and References 36 and 37 have a different formatting from the rest of the references.</p>
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REVIEWER	LAURIER, Dominique IRSN, France
REVIEW RETURNED	05-Jul-2015

GENERAL COMMENTS	The author answered all my comments, and corrections made to the revised version improved the manuscript. I have no additional comments.
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