Vedlegg 5

The Cancer Cluster at NTNU

Reviewers' Comments

Comments	Response
Reviewer 1	
The reported is detailed and well-written and clearly shows the benefits of having an accurate population cancer registry in addressing cancer cluster concerns. However, I would have liked to have seen two things in the report:	OK
A more detailed description of the cases in the cancer cluster. I understand from p. 43 and elsewhere there were 8 cases in the original cluster, which were a mix of leukemias and lymphomas. Including all types of hematological malignancies as a cluster is problematic in my view, since it is known that these malignancies are etiologically and clinically quite disparate. For example, benzene and smoking are known causes of acute myeloid leukemia, but their relationship to chronic myelogenous leukemia is unclear. Similarly, smoking does not appear to be a strong risk factor for lymphoma. Hodgkin and non-Hodgkin lymphoma are usually considered separately (as in Table 2). I would therefore discuss the issue as to whether it is a cluster at all. What were the ages, occupational histories, diagnoses and cytogenetics of the cases? I think it important to show how diverse they are from a clinical viewpoint. Although as a group they are unlikely to have a single cause, could any of these cases be individually related to a specific exposure?	The Expert Group has had a possibility to interview seven of the eight cases in the original cluster, or their relatives (new table 8, page 48). The cases were six males and one female, with an average age at diagnosis of 40 (34-49) years. At the time of the interviews, three of the cases were deceased. There was one case of acute myeloid/-lymphatic leukaemia, three cases of chronic myeloid leukaemia and three cases of non-Hodgkin lymphoma. Hence, the original cluster turned out to be clinically fairly heterogenous. Six of the seven cases had participated in the K2/K20 course of organic chemistry. Four of them had a history of PhD studies and/or employment at Rosenborg, with an average of laboratory work for 5 (range 3-9) years. The interviews did not reveal information on exposure to benzene, ionizing radiation or other carcinogenic agents to an extent that raised immediate suspicion of a causal relationship between their work at Rosenborg (or elsewhere) and the diseases. The Expert Group decided not to collect further clinical information (including cytogenetics).
More prominence given to and expansion of the discussion on p. 22 regarding the high frequency of reported cancer clusters and the	We have given more prominence to the problems facing investigations on clusters, but have restricted the discussion to

problems faced in studying such clusters. Providing other examples of cluster investigations throughout the world in which causation could not be assigned would be useful. I would include discussion of the Long Island Breast Cancer study in NY where millions of dollars were invested to no valuable outcome. This may help discourage further investment of valuable resources.	leukaemia clusters. The following text is now included on page 22: 'In spite of the many obstacles to investigating cancer clusters in the community, some clusters may have common aetiological factors that have not yet been identified. For instance, numerous clusters of childhood leukaemia, and to a lesser extent lymphoma, are reported in the scientific literature. Leukaemia clusters have been recorded in Europe since the beginning of the 20th century (Boyle et al., 1996). The first extensive investigations of such clusters were conducted in Northumberland, United Kingdom (Knox 1964) and Niles, Illinois, USA (Heath and Hasterlik 1963) in the early 1960s. Other investigations of childhood leukaemia have generated scientific and media interest, such as the cluster near a nuclear power plant in Sellafield, United Kingdom (Openshaw et al., 1988; Law et al, 2003). An exceptionally large cluster of childhood leukaemia occurred in Churchill County, Nevada from 1997 to 2001. Eleven cases of leukaemia were identified over a five-year period among children in a community of 26,000 people. Four others who had previously lived in the area, but had moved away, were also diagnosed with leukaemia. Only one case every five years would be expected among the resident population of this age, based on the average incidence rates in Nevada (Nevada State Health Division, 2004). Extensive investigation failed to identify an underlying cause for the clustering. Although most statistical analyses suggest that clusters of childhood leukaemia occur somewhat more frequently than would be predicted by chance (Boyle et al., 1996; Knox and Gilman, 1996), such clustering explains only a small fraction of incident cases. Researchers have hypothesised that an as yet unidentified infectious exposure occurring at a particular stage in development may give rise to these clusters. '
Regarding benzene exposure, which is a particular area of my expertise, the discussion on the use of benzene on p 50 on and the estimation of the benzene exposure level on p.53 is somewhat misleading, as it	This has been addressed by a new paragraph on page 54: 'It should be noted that up until the mid 1980s, benzene was a common contaminant of many solvents, including toluene and hexane (Kopstein, 2006). Thus,

assumes that the only pathway of exposure to benzene is through the use of pure benzene. Up until the mid 1980s, and in some countries up to the present day, benzene was a common contaminant in many solvents, including toluene and hexane (Kopstein M, J Occup Environ Hyg. 2006 Jan;3(1):1-8). Only rarely is benzene listed as an ingredient on MSDSs even though it often comprises more than 0.1% of petroleum solvents and, when its concentrations in petroleum-derived products are less than 0.1%, inhalation, exposures to benzene can be much higher that its OSHA PEL of one part per million (ppm) by volume (v/v). There is also the possibility of significant dermal exposure. Thus, focusing on the use of pure benzene as a solvent underestimates the true levels of exposure. However, it is unlikely that the use of organic solvents over time in the Chemistry course in question, or for the Rosenborg labs as a whole, differs significantly from that at many other institutions.	toluene might have contained up to 1 % and hexane up to 3.7 % benzene. However, these and other organic solvents that may have contained benzene, had limited use in the K2/K20 course and it seems unlikely that the evaporation of such compounds would have significantly increased the benzene inhalation exposure. Exposure to benzene via the skin could have occurred if benzene or benzene-containing solvents were used, since benzene is readily absorbed via the dermal route (Franz, 1984).'
Reviewer 2	
The report provides a comprehensive, balanced and evidence-based review of the main scientific issues concerning the evaluation of cancer clusters and summarizes adequately the main issues relevant to the assessment of the cluster at NTNU.	OK
Based on the information provided in the report, the conclusions and the recommendations of the Advisory Group appear to be well justified.	OK
A cluster of lympho-hematopoietic neoplasms has occurred in the group of 156 individuals (in the expanded study) who worked as PhD candidates or employees and were involved in the K2/K20 course (Table 7). It is regrettable that the report does not provide more specific information on the four cases which have occurred in this subgroup, including type of neoplasm, age at employment and period of employment. In addition to chance and exposure to benzene or other chemicals present in the laboratory (an hypothesis which is thoroughly discussed in the report and considered unlikely), transmission of an infectious agent is an	Due to confidentiality issues linked with the epidemiological study it has not been possible for the expert group to satisfactorily characterise the 4 individuals with lympho-haematopoietic neoplasms who belongs to the subgroup of 156 participants. However, the Expert Group had the opportunity to conduct interviews with 7 of the 8 individuals forming the cluster. Two of these (Nos. 1 and 4 in Table 8) were – for reasons indicated in the bottom paragraph of page 47 - not included in the epidemiological study. Of the remaining 5 cluster-cases, 4 belonged to the group of doctoral candidates/-employees and one to the student only group

additional explanation of the cluster (assuming leukemia is the predominant or only type of neoplasm in this subgroup). An infectious etiology has been strongly suggested for childhood leukemia, and it is a plausible hypothesis for leukemia in young adulthood. The report provides evidence against an excess of lympho-hematopoietic neoplasms outside the subgroup mentioned above.	(No. 6). We agree with the reviewer that it is regrettable that the report does not provide more specific information on the 4 cases in the 156-group. To partly address this limitation we have, with the permission of the patients and their relatives, inserted a new table 8, which gives key information from the interviews of the 7 persons from the cluster. The table is included on page 48 and is commented in the text at bottom of page 47 and top of page 48. The analysis of the epidemiological study showed that 3 of the 4 haematological cancer cases in the 156-group (K2/K20 exposed) belonged to the original cluster and that 1 of the 3 in the 384-group (never K2/K20 exposed) belonged to that group, indicating that 1 non-cluster haematological cancer is included in the 156-group of the epidemiological study. However, here we have an inconsistency between the registration of STAMI and the results of the interviews, as all 4 interviewed cases with prolonged contact with the Rosenborg labs informed us, that they had participated in the K2/K20 course. The Expert Group was not permitted access to any details (diagnostic or non-diagnostic) of index cases in the files of The Norwegian Cancer Registry and was not able to judge on the degree of similarity/dissimilarity of the cases included in the K2/K20 risk analyses.
I do not share the strong interest of the Advisory Group to explore the risk by gender (section 6.7, paragraph 5): assuming the distribution of expected cases in the subgroup of PhD candidates/employees involved in the K2/K20 course is 60% (men) vs. 40% (women), the corresponding SMR and 95% CI would be 13 (3.7, 34) and 0 (0-18), p-value of difference 0.10.	We agree with the reviewer that we could do a rough calculation of the SIRs associated with men and women, separately, on the assumption that the age distribution is approximately similar over time between the two sexes. This may, however, not be the case, as the sex-composition of the cohort (and the sub-cohorts) has likely changed quite a lot with women dominating the picture in recent times. A formal analysis would be preferred and should be easy to conduct.
I do not agree to include the two cases of lympho-hematopoietic neoplasms which did	The objection has been accepted. The cases have been removed from Table 7 in the

not quality for the epidemiological study in the calculation of the relative risk (paragraph 6.3, paragraph 6), since it would be necessary to include in the denominator all other potential cohort members who were not included in the study for similar reasons (e.g., emigration).	original version and commented in the revision in the seven last lines of page 47 and two first lines on page 48: 'These two cases have been ascertained among individuals who according to interview information given to the Expert Group (Table 8), have not been doctoral fellows or employed in the Rosenborg Laboratories, i.e. individuals who belong to the subgroup 'Students only, K2/K20'. According to the individuals themselves, for both cases they related to cancer of the chronic myeloid leukaemia type. It is formally not possible to calculate the risk with the inclusion of these cases, since no adequate comparison figures are available. However, it is reasonable to assume that the occurrence of these cases implies that the true risk for the group 'Students only, K2/K20' is somewhat higher than that which is presented in Table 7, but not markedly higher.'
6. The report is very consistent in presenting and discussing issues relevant to the possible excess of lympho-hematopoietic neoplasms, but the presentation of the background information and the results on melanoma risk is less consistent (e.g., melanoma is not mentioned in sections 2 and 3 but in section 4.3 the epidemiology of skin cancer is presented without a clear rationale for it). This reflects the fact that the initial cluster, and its implications in terms of public concern, concerned the former group of neoplasms. Efforts should be made to have a consistent presentation of the information regarding melanoma.	We believe that it is not logical to mention the melanoma issue in the Introduction section since the excess risk of melanoma appeared as an unexpected finding in first investigation conducted by STAMI/The Norwegian Cancer Registry/AMA ('Rosenborg 1'). We also find it difficult to include this problem in the section regarding appointment of the Expert Group. We have now included a small paragraph in the very beginning of Section 4.3 explaining why skin cancer came to be an issue in the Rosenborg case: 'In a preliminary analysis of cancer risks among subjects with contact to the Rosenborg Laboratories (the so-called 'Rosenborg 1' study, see also page 46) conducted by STAMI/The Norwegian Cancer Registry/AMA in early 2007, the investigators unexpectedly observed an increased risk of malignant melanoma of the skin as well as other cancers of the skin. This resulted in the skin appearing on the list of cancer sites of particular interest in the final follow-up study. Here we give some background information on skin cancer, including malignant melanomas'. Text on skin cancer is presented in the existing version of our report in the

	evaluation section (Section 6.7) and in the summary section.
The effort made by the Advisory Group to reconstruct past exposure level of benzene (section 6.4) is particularly commendable.	OK.
A minor comment concerns the so-called Norwegian-IARC cohort. IARC is mentioned in section 5.3, paragraph 5 as owner of the cohort. This is not the case: as for all other international studies coordinated by IARC, the ownership of the data rests exclusively with the national investigator, in this case the University of Oslo.	This has been corrected.
Reviewer 3	
I concur with the main conclusions of the Expert Group: 1. Like most clusters of (rare) cancers it is difficult to conclude whether this is the expression of a really causal phenomenon related to some local exposure, or it is a chance finding. 2. Overall the evidence is rather weak, but a causal association between a cluster of hematolymphopoietic cancers and low-level exposure to benzene and other carcinogens (including PCBs, see below) cannot be excluded. 3. There is no reason to conduct any kind of medical investigation or screening in this population.	OK. However, we do not believe that exposure to PCB is relevant here, at least not from sources inside the Rosenborg Laboratories, see below).
There are several limitations in the work that has been done, not necessarily attributable to the Expert Group. The main one is lack of data on gender-specific relative risks. As the Expert Group points out, all 4 cases of the cluster occurred in men, who were only 60% of the population of 156. This suggests that the true relative risk in men may be much higher. However, the reasons for sex-specificity are unclear.	We are in agreement with this comment and have modified the original text with the following (now appearing at the end of the first paragraph on page 49): 'Although the reasons for the apparent preponderance of risk in males are unclear, the expert group regrets that it has not been given access to formal analyses of cancer risk separately in each of the two genders.'
There is a mistake on page 41: IARC bases its classification on groups 1, 2A, 2B, 3 and 4 (the latter are not mentioned).	This has been corrected.
A serious mistake is on page 55, where it is stated that there is no evidence that PCBs can cause hematolymphopoietic malignancies. In fact recent prospective studies with biochemical measurements clearly show a dose-response relationship between serum	Sorry for missing this. Reference to the Engel et al.-study is now presented on page 56, paragraph 1, lines 3-5. However, we do not agree that exposure to PCBs is a major concern for this population, in as much as no specific PCB source has been identified in

levels of PCBs and non-Hodgkin's lymphomas (Engel et al, 2007). Exposure to PCBs is a subject for major concern in this population.	the Rosenborg Laboratories (see same pragraph lines 5-8).
On page 59 I have the impression that the quotations on the life-time risk of cancer related to benzene exposure are not updated. The recent work done by the US NCI in China should be considered.	The dose-response information still relies on the comprehensive study performed by the NCI and the Chinese Academy of Preventive Medicine which was reported by Hayes et al. in 1997. This is now mentioned on page 59.
Why do they refer to prevalence on page 6? It should be incidence.	This has been corrected.
I do not believe (page 38) that confounding by solar radiation can be invoked.	We are here discussing the evidence for laboratory work being causally related to melanoma induction. We believe that these studies cannot exclude solar radiation as a confounder.
Italy is mentioned on page 40 but not on page 39.	This has been corrected.
On page 54, whereas I understand the basis for the calculation of 48 ppm as the concentration of benzene in the air, I do not understand the basis for the calculation of 0.3 ppm.	The calculation has been explained more clearly on page 54.
Have the Expert Group included Chronic Lymphocytic Leukemia into NHL as it should be?	In the epidemiological runs on the risk of cancer among cohort members 1960-2005, CLL was included in the group of leukaemias. This was done because the standard reference rates for cancer incidence in Norway during this period included CLL in the group of leukaemias. The Expert Group does acknowledge, however, that CLL by many researchers is regarded as a disease belonging to the lymphoma family.
Reviewer 4	
In essence, *I fully concur with the report presented by the Expert Group*, including its recommendations. The report appears well balanced and is based on the present state-of-the-art knowledge.	OK
Minor remark: The citations "Creech and Johnson 1974" and "Bender et al. 1989" (p.22, chapter 5.1.4, 2nd para) are missing from the attached list of references.	These references have been included in the list of references.