

Vedlegg 4

Fagfelleuttalelse fra Paolo Vineis

Re: The cancer cluster at the Norwegian University of Sciences and Technology (NTNU)

Overall assessment

After examining (a) the whole report entitled "The cancer cluster at the Norwegian University of Sciences and Technology (NTNU)" that I have received from professor Dybing, (b) a response to the points I have previously raised, from the authors of the report, and (c) additional documents translated from Norwegian (STAMI/AMA/Cancer Registry reports), I have prepared the following overall assessment.

The cluster and the epidemiologic data

The Advisory Medical Expert Group has been appointed by the Norwegian Ministry of Education and Research to evaluate the case of an apparent cluster of hematolymphopoietic malignancies in former students, fellows and employees of NTNU. An epidemiological investigation set up by the Group led to the identification of a total of 25 malignancies, four of which occurred among 156 individuals who had been PhD candidates/employees in an area called K2/K20 (course in organic chemistry)(0.5 expected, relative risk 8.5, 95% confidence interval 2.3-21.6). Another 12 occurred in students in the same area (K2/K20, relative risk 1.6, 95% CI 0.8-2.8). The Advisory Expert Group also collected data on exposures of such individuals. Exposure to low levels of benzene occurred, mainly before 1992. No obvious relationship was detected with characteristics of exposure, although an association with duration of stay in K2/K20 was observed.

Main conclusions

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 cannot be excluded.
3. There is no reason to conduct any kind of medical investigation or screening in this population.

Limitations

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. **(This point has been noted in the most recent version of the report, page 49)**

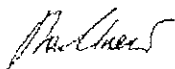
Criticisms

I have a few criticisms to raise.

1. There is a mistake on page 41: IARC bases its classification on groups 1, 2A, 2B, 3 and 4 (the latter are not mentioned) **(corrected in most recent version)**.
2. 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 levels of PCBs and non-Hodgkin's lymphomas (Engel et al, 2007). **(The response to this criticism says that "exposure to PCB is not relevant here". After re-examining the report I agree that exposure to PCB was either minimal or nonexistent.)**.
3. 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. **(now mentioned on page 59 of the report)**

Minor issues

1. Why do they refer to prevalence on page 6? It should be incidence. **(Corrected)**
2. I do not believe (page 38) that confounding by solar radiation can be invoked. **(In the response the authors say that solar radiation can be a confounder. I disagree, because there is no reason why laboratory personnel and students should be more exposed to sun than the rest of the population)**.
3. Italy is mentioned on page 40 but not on page 39. **(Corrected)**
4. 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. **(Now explained more clearly on page 54)**.
5. Have the Expert Group included Chronic Lymphocytic Leukemia into NHL as it should be? **(Now it has been explained that CLL was included in leukemias because the standard reference rates for Norway also included it among leukemias)**.



Paolo Vineis
23 April 2008

Dybing, Erik

Fra: Vineis, Paolo [p.vineis@imperial.ac.uk]**Sendt:** 5. mai 2008 17:37**Til:** Dybing, Erik**Kopi:** Jørgen H. Olsen; Staffan Skerfving; rej@uus.no; Tore Sanner; harri.vainio@ttl.fi; frank.hernes@kreftforeningen.no**Emne:** RE: Peer review of the report on the cancer cluster at NTNU, Trondheim, Norway

Dear Eric, thank you for this clarification. I think it answers the queries coming from Jenssen, Thangstad and Munro Jenssen and you can probably forward it to them.

Paolo

Professor Paolo Vineis, MD, MPH, FFPH
Chair in Environmental Epidemiology
Imperial College London
St Mary's Campus
Norfolk Place W2 1PG
London
tel 020 75943372
mobile 0044 7963975827
fax 020 75943196

From: Dybing, Erik [mailto:Erik.Dybing@fhi.no]**Sent:** Mon 05/05/2008 14:34**To:** Vineis, Paolo**Cc:** Jørgen H. Olsen; Staffan Skerfving; rej@uus.no; Tore Sanner; harri.vainio@ttl.fi; frank.hernes@kreftforeningen.no**Subject:** SV: Peer review of the report on the cancer cluster at NTNU, Trondheim, Norway

Dear Paolo,

I would have appreciated if you had contacted me before you responded to the letter from Jenssen, Thangstad and Munro Jenssen. The Expert Group received the same letter in late January and thanked the authors for their information and views. We told them that all their issues would be dealt with in the final report.

We have the following comments to your suggestions for additional reporting:

- 1) We have presented age-adjusted national incidence rates of leukaemia, non-Hodgkin lymphoma and Hodgkin's disease in Figures 2-4. The Norwegian Cancer Registry does not report information related to the various subtypes of leukaemia. Further, the diagnostic criteria of haematological diseases have changed over the years. Also, due to the extremely strict personal protection regulation in Norway, the Expert Group has not been given access to the specific diagnoses for the cluster individuals. Our information relating to diagnoses come from our interview with 7 individuals previously diseased/their relatives (of whom 6 belong to the cluster). Thus, we are not in a position to further present age-adjusted and age-specific incidence rates in the exposed population, overall and by subtype.
- 2) In Table 7 we presented the observed and expected risk for haematological cancer relative to 'job category' (i.e. students only, PhD-candidates/employees, which was the only information available). In Table 8 the year of birth and gender of the 7 (of the 8 in the cluster) interviewed individuals are presented. The Expert Group has not been given access by the Cancer Registry to formal analyses of cancer risk separately in each of the two genders. Also, we are in great doubt that it would really be informative and justified to perform analyses of

subgroups (e.g. gender among PhDs/employees), when there is no biological or other reason (e.g. exposure) to believe that there should be a gender-specific risk

- 3) The belief of the authors that the amount of benzene used was larger than reported officially is hearsay and speculation. The documented evidence of benzene use and exposure is described on pages 53-55 in the enclosed version of the report. The only information related to benzene exposure of the cases (6 of the 8) is whether they were students only or continued on as PhD-candidates/employees (as described in Table 8 and on page 48).

Thus, we do not think that we can follow up on your proposal to write a separate document with the suggested content, due to the limitations in the material presented above.

Best regards,

Erik

Fra: Vineis, Paolo [mailto:p.vineis@imperial.ac.uk]

Sendt: 1. mai 2008 16:02

Til:

Kopi: DYBING, ERIK

Emne: R: Peer review of the report on the cancer cluster at NTNU, Trondheim, Norway

Dear Dr Jenssen, thank you for your document, which is certainly a useful addition to the material I had already received. You raise the following issues:

1. you believe that the amount of benzene used was larger than reported officially
2. collective codes for hematolymphopoietic malignancies have been used, but the excess might be concentrated in some sub-type
3. the age distribution is atypical for some of these malignancies, as well as the gender distribution
4. you would like to see data on chromosome translocations
5. you claim that 2 CML cases were not included among the observed cases
6. you point out that 8 out of 27 cases are CML and they have an unusual age distribution.

I think that an answer to your queries should come from the Experts Group. I recommend that a short document be written by the Experts Group, which not only answers these queries, but also reports clearly:

- age-standardized and age-specific incidence rates in the exposed population, overall and by subtype
- observed and expected figures overall, by department/job category, by age groups and gender, and by histologic subtype
- a descriptive table with each of the cases, a summary job history and exposure assessment based on best evidence, particularly for benzene exposure.

Thanks
Paolo

Professor Paolo Vineis, MD, MPH, FFPH
Chair in Environmental Epidemiology
Imperial College London
St Mary's Campus
Norfolk Place W2 1PG
London
tel 020 75943372
mobile 0044 7963975827
fax 020 75943196

Da: |

Inviato: mer 30/04/2008 18:54

A: Vineis, Paolo

Oggetto: Re: Peer review of the report on the cancer cluster at NTNU, Trondheim, Norway

Thank you ,
I sent the comments as an attachment to the mail I sent yesterday, I am attaching it again. I hope you can open it since sometimes there is a problem because my computer is a Mac.

Best wishes
Einar Jenssen

Dear Drs Jensen, Thangstad and Jenssen,
thank you for this message. I have received, I believe, all the relevant information from professor Dybing but I am happy to answer any question you have. So, if you want to forward me these questions I will try to answer.

Paolo

http://eu.wiley.com/WileyCDA/WileyTitle/productCd-0470027436.html?cid=RSS_WILEY2_LIFEMED

Professor Paolo Vineis, MD, MPH, FFPH
Chair in Environmental Epidemiology
Imperial College London
St Mary's Campus
Norfolk Place W2 1PG
London
tel 020 75943372
mobile 0044 7963975827
fax 020 75943196

From: [redacted]
Sent: Tue 29/04/2008 09:31
To: Vineis, Paolo
Subject: Peer review of the report on the cancer cluster at NTNU,Trondheim, Norway

Dear

Professor Paolo Vineis
CHAIR IN ENVIRONMENTAL EPIDEMIOLOGY
Division of Epidemiology, Public Health and Primary Care
Imperial College London, South Kensington Campus, London SW7 2AZ
UK

PEER REVIEW OF THE REPORT ON THE ROSENBERG CANCER CLUSTER

In September 2007 a group of students and employees who were part of the Rosenberg cancer cluster were invited to a meeting by the Norwegian University of Science and Technology, NTNU. In this meeting it was proposed that before being made public, Ekspertutvalgets final report would be translated into English for peer review by two institutions or experts in the field.

The academic process of peer review would normally involve the editor of a scientific journal selecting two or more of the author's peers for this task. In the communication following this meeting between Kunnskapsdepartementet (Ministry of Education and Research) and those affected, some disagreement regarding the review process of Ekspertutvalgets scientific report became apparent.

- Our intention was to make sure that all parties with an interest (medical and legal) in this case, including the scientific community involved, would find the review process acceptable. We have agreed a way forward with the Minister of Education, Tora Aasland, and now have full confidence in the review process.
- In December 2007, based on recommendations from colleagues in the scientific community, we suggested that the Ministry of Education should appoint two additional peer-reviewers, one being you.
- We also have several questions regarding this case that we would like you to consider. We sent these to Dr. Dybing who after conferring with the Ministry of Education suggested that we send the questions directly to you, the peer reviewers.

Sincerely yours,
On behalf of those affected .
Einar D. Jenssen, Ole Petter Thangstad, Bjørn Munro Jenssen