

Vedlegg 2

Fagfelleuttalelse fra Hermann Bolt

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Dr. Erik Dybing
Division Director and Professor
Division of Environmental Medicine
Norwegian Institute of Public Health
P.O. Box 4404 Nydalen
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Norway

*Re: Peer review of report from the Advisory Medical Expert Group – cancer cluster at NTNU;
Letter dated 22.11.2007 by the Royal Ministry of Education and Research, 200704030
KRA*

Dear Dr. Dybing,

In response to the above mentioned letter of the Royal Ministry of Education and Research, Oslo, I provide the following

Peer Review of the Report from the Advisory Medical Expert Group.

The review refers to the latest amended version of the Expert Group's report, received 19 Feb 2008, and background materials received later (11/19 Apr 2008)

The observation of a cluster of haematological malignancies among persons having worked earlier at the Rosenberg Laboratories of the Norwegian University of Science and Technology (NTNU) in Trondheim was the starting point of the present investigation, on which the report to be evaluated is based. Details of this cluster are also given on p. 25 in chapter 5.1.5.

After explaining the reasons of the investigation and the appointment of the Expert Group (chapters 2/3), chapter 4 presents important background information of the time-dependent incidences of cancer in total, and for leukaemia, non-Hodgkin lymphoma and Hodgkin's disease, as well as of skin cancer in Norway. An important point that is made here refers to the change in the pathological characterization and nomenclature of haematological malignancies, especially of non-Hodgkin lymphomas. This point has appropriately been taken into account in the present evaluation by the Expert Group.

Chapter 5 explains in detail the known / established risk factors for these diseases that might be relevant in teaching and research institutions, such as in those at NTNU. This chapter describes the present state-of-the-art knowledge of causative agents, with a focus on chemical and radiation exposure.

A very central point is the discussion how to view and to handle cluster observations. I explicitly agree with the fundamental statements made by the Expert Group. The methodology to assess the present case is up to the present scientific state.

The key results of the investigation are presented in chapter 6. Tables 6 and 7 give the overall data of the "initial" and "latest" analysis. Both analyses generally agree with each other. Relying of the expanded (latest) analysis of Tab. 7 (p. 47), it appears that PhD candidates and employees having worked at K2/K20 have an elevated risk for haematological neoplasias (SIR: 8.5 [2.3-21.6]). The epidemiological problem is that this high SIR is driven by the pre-existing cluster cases.

However, it is noteworthy that there is a slight (statistically not significant) rise in SIR also for students having worked at K2/K20. This is underlined in the text of the last paragraph on p.47. By contrast, an analysis of the haematological cancer risk for the total groups "Rosenborg 2" and "Rosenborg 1" has shown no difference between exposure times 1960-1979 (when occupational hygiene conditions were poor) vs. 1980-1995 (when the conditions had been much improved). This is a very important argument against a causal relationship.

As well established causes for haematological malignancies in humans, radiation and exposure to benzene are most important; these potential causes were discussed in-depth in by the Expert Group, and appropriate consideration to these factors has been given.

In principle, the observation of a cluster of malignancies (here: haematological malignancies) is an important starting point for further investigations, such as performed here. For occupational toxicology, cluster observations have been relevant in a number of classical cases. However, the basic difficulty is that that a cluster may well occur incidentally, and re-evaluations of the same situation will arrive at the same point. This problem has been classically addressed in the scientific literature. B.R. Friedlander (J. Occup. Med. 33: 1230-1232, 1991), in discussing the importance of "prior knowledge", noted that self-fulfilling prophecies are possible in epidemiological studies when one knows a potential excess prior to performing a study. K. Rothman (Am. J. Epidemiol. 132: S6-S13, 1990) refers to the same phenomenon as the "Texas sharpshooter procedure". The Texas sharpshooter first fires some shots and then draws the target where the shots hit the wall. This also illustrates the difficulty in the present case, which has well been taken into account by the Expert Group.

Although the amount of benzene used at the Rosenberg laboratories has been quite limited, there may be uncertainties with respect to the 1960s and 1970s. In any case, it will not be possible to rule out benzene exposure as a causative principle.

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.

The report is of high scientific quality, and its conclusions and recommendations appear well justified.

There have been some minor editorial matters which were appropriately considered in the response by the Expert Group.

A handwritten signature in black ink, reading "Hermann Bolt". The signature is written in a cursive style with a large initial 'H' and 'B'.

(Prof. Dr. Dr. Hermann M. Bolt)