Scientific relevance and irrelevance of genetic susceptibility for standard setting in risk control.

Final summarising research report PS/17

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I INTRODUCTION

Since several years, the research team is trying to get a better understanding of the effects of low level of benzene exposure. It is well known that benzene exposure may lead to alterations in peripheral blood cell count, to severe alterations in the bone marrow called myelodysplastic syndrome and to cancers of the blood- and lymphatic system, the so-called haematolymphopoietic cancers (like leukaemia's or lymphomas).

According tot the Belgian regulations on workers protection, workers who are exposed to benzene must be controlled at regular intervals by the occupational health physician for possible adverse health effects. The most common biological test is a peripheral blood cell count (concentration of red and white blood cells and platelets). Abnormal tests results may lead to additional investigation of possible unexpected exposure, to adapting working conditions so that exposure can be avoided or restricted or to changing job (within the company if possible). The same test is used at pre-employment examination. While it is common and wise to consider alterations and especially numbers of cells outside of normal ranges in peripheral blood as possible effect indicators of benzene exposure, it is less sure what their meaning is for the person's health risk. This is especially troublesome when it comes to making decisions at pre-employment examination. Persons with low white blood cell count often will not be allowed to work under conditions that may lead to benzene exposure. This is part of a strategy which is underpinned by expert intuition, not by solid scientific data. Indeed, we are not sure what is the exact meaning for instance of a relatively low white blood cell count as to the possible risks issuing from exposure to low levels of benzene. Are these persons more at risk of having a myelodysplastic syndrome or a blood- or lymph cancer than persons with a number of white blood cells that is considered being within range of normality? And what about job candidates showing a white blood cell count which is higher than the upper level of 'normality'? Should they be considered as being at increased risk? These and many other questions remain unanswered. It is generally considered wise to handle in according with the precautionary principle (better take it the safe side, even if we are not completely sure) and therefore to exclude persons with blood cell counts considered as clearly outside the ranges of normality from benzene exposure. But we are lacking insight into the possible relationship of these numbers of blood cells with the risk for severe haematolymphopoietic disorders. This is why this research has been set up.

Investigating this problem is very complex. This project was a first attempt to try to see more clearly into the issue via a specific strategy. Basically this strategy is as follows: we know or may assume that genetic susceptibility may constitute part of the explanation why person's blood cell counts show different results following benzene

exposure. We should try to find out which type of genetic properties is correlated with particular types of effect on peripheral blood cell count. We identify for that purpose a series of so-called polymorphic genes. If certain types of certain genes are clearly more present in persons showing a particular effect that in the average population, there might be an association between that genetic property and that particular effect of benzene exposure. Next step in the strategy is to try to find if genetic variants associated with an increased risk of a particular effect of benzene exposure are also more present in persons suffering from myelodysplastic syndrome or blood and lymphatic cancers. In that case, we may indirectly create some hypothesis on the possibility that a particular type of peripheral blood cell count is predisposing to that particular type of severe haematolymphopoietic disorder. In other words, we might get a better insight into the meaning of particular blood cell count results as tot the risk of these severe disorders, and adopt a much more scientifically underpinned strategy for workers' protection.

Focusing on susceptibility in relation to standard setting for prevention of occupational cancer and other occupational diseases seemed to be in compliance with a growing societal interest and need to discuss and understand relevance and acceptability or non-acceptability of genetic susceptibility testing for employees exposed tot toxic agents.
One should know that the same research team has developed a theoretical framework to address the possible relevance or irrelevance of genetic testing as part of workers health protection strategies. One of the conclusions of the research team was that the more the number of polymorphic genes interfering with the risk, the less it is likely that relevant genetic susceptibility tests that may lead to correctly distinguish between person being more or less susceptible to disease will be found.

II METHOD

Benzene exposed workers

The database on benzene exposed workers included peripheral blood cell counts of 360 workers. The data were collected from the individual medical records archived by the occupational health physician of a petrochemical plant.

A particular procedure for selecting individuals from the population was developed based on two complementary approaches: a subjective interpretation of data by experts on the one hand (i), and a mathematical approach (ii) on the other.

The frequency of occurrence of the polymorphisms, alone and in combination, in the different 'effect' categories of benzene exposed workers, will be compared with their frequency in a population of persons suffering from myelodysplasia/leukaemia.

The possible relationship between particular types of changes in peripheral blood cell count and the risk of severe haematolymphopoietic disorders may be assessed subsequently.

Since no information is available in this database about genetic polymorphisms, results of tests for genetic polymorphisms had to be collected from selected members of the study population willing to participate. All this was done in full agreement and cooperation with the occupational health physician, and after approval by the companies direction to which we are grateful for their openness and respect for this impartial research, and of the legal Committee for Prevention and Protection, in which representatives of employees must meet every month. They were fully informed about the study, its aims and methods and possible outcomes, as well as its possible consequences. Also all privacy considerations were openly discussed, including the informed consent procedure. The Committee has unanimously approved the participation in the project.

The following series of genotypes were tested for: GSTM1, GSTM3, GSTT1, GSTP1, CYP2E1, CYP2A6, CYP1A1, NQO1, NAT2, XRCC1, XRCC3, XPD.
The analysis of the samples was done at the Finnish Institute of Occupational Health (laboratory of Dr. A. Hirvonen).

For those selected employees who were still employed, samples were taken by the occupational health physician during the periodical medical examination which is done in accordance with legal requirements. The OHP asked to every selected employee at that occasion an additional written informed consent (in top of the previous agreement given by the elected workers health and safety committee).

A certain number of the selected employees were already retired at the time of the investigation. They were contacted via the association of company retirees, and invited to attend a meeting in which the researchers explained as clear and complete as possible what the research is about, why their population was selected, how the research is conducted, how their privacy will be protected. All volunteers gave a blood sample following written informed consent. It should be stressed that all of the invited persons who were physically able tot attend the meeting were present, and that each one of them contributed with a sample, and were happy to do so.

Patients suffering from myelodysplasia / leukaemia

The study base consists of all adult patients suffering from myelodysplasia or a type of possibly benzene-related leukaemia which were – during a precise period - diagnosed and/or treated in the haematology service of one of the hospitals which are part of the network of a previous study. These patients are invited to participate. Those who accept are the study population.

III. RESULTS

Connecting the individual results with the effect categories revealed already at the first tentative analysis, that no associations of a particular genetic make-up with a particular benzene-exposure effect on peripheral blood cell counts would come out.

IV. CONCLUSIONS

With the number of subjects at hand in each effect category, it would only have been possible to demonstrate such an association, if this were a strong one. The genetic tests showed a huge variability in outcomes. Already at first sight, it was clear that no association could be detected between a particular effect category and a particular genetic property or combination of genetic properties. Given the limited number of persons within each effect-category, any further statistical analysis is highly unlikely to show any association between a particular effect category and a particular genetic property or combination of properties.
As a consequence, a further comparison of the genetic properties of effect categories with the genetic properties of myelodysplastic syndrome patients could not show any relevant result. The efforts to prepare this part of the research were therefore discontinued.

The outcome of this study may be illustrative of the fact that genetic susceptibility is a very complex phenomenon, and that in many cases, it cannot easily be demonstrated. As a consequence, it is highly unlikely that within the near future, human epidemiological studies might give the answer to the question to what extent particular benzene induced effects (or the lack of it following benzene exposure) on the peripheral blood cell count might reveal an increased susceptibility to myelodysplastic syndrome or haematolymphopoietic cancers following benzene exposure.

For the very same reason, genetic tests do not (yet) constitute an added value in combination with peripheral blood cell counts to identify persons who are considerably more at risk of showing MDS or a haematolymphopoietic cancer following benzene exposure.

This was publicly funded research. Public funding is a tool for promoting impartial research. Research organised and financed by the industry itself can be impartial as well, but it is the presence of a well-developed and strong research, based on public resources that will stimulate the impartiality of any research, including research financed by other sources. Public funding in the field of occupational health should in the long run contribute to social protection.

The crucial question as to social protection is in which direction we are going on the axis between - on the one hand - adapting humans to labour, i.e. selecting people, and adapting labour to humans on the other hand. The scientific research that is necessary for underpinning a strategy of social protection will only be generated if governments specifically support such research by starting up research programmes.

This study allowed to further developing both accurate and pragmatic approaches to complying with ethical requirements.

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