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Letter to the Editor

Comment on: Implications of latency period between benzene exposure and development of leukemia—A synopsis of literature

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It has been argued that the risk of lung cancer decreases with increasing duration of abstinence after smoking cessation [1]. Similarly, a recent paper in this journal has argued that the risk of leukaemia is small or even absent 10–15 years after exposure to benzene has stopped, with higher risks only occurring after recent exposure [2]. This was suggested to be due to a short biological half-life of benzene and effective repair pathways including apoptosis.

If genuine, the time-dependence of the risk of leukaemia after benzene exposure should impact on claims for compensation for leukaemia as an occupational disease, especially if the disease occurs long after the exposure. However, we are not convinced that repair mechanisms are likely to reverse the relevant benzene-induced damage in the years after exposure and that the individual risk for benzene related occupational disease really decreases with time.

First, the argument that the risk of leukaemia decreases with time after cessation of exposure, as it is proposed in the above-mentioned paper [2], is based on small numbers of cases with malignancy and not all of the studies presented in favour of this argument even fully support the case. For example, based on data from a large study from Australia [3] – discussed in [2] – we think that the risk decrease with increased lag time is only convincing for cumulative exposures below 10 ppm-years.

Second, it must be kept in mind that the proposed time-dependence does not apply to all haematological malignancies: Hayes et al. [4] – also a study discussed in [2] – found that, while the risk for acute nonlymphocytic leukaemia and myelodysplastic syndromes appeared increased with recent benzene exposure more so than with distant exposure, the development of non-Hodgkin lymphoma was linked most strongly to distant exposure (occurring at least 10 years before diagnosis).

Third, even if the decrease in the incidence of some haematological malignancies with time after exposure to benzene is genuine, this does not necessarily mean a decrease in the individual risk of developing the disease. We would like to offer an alternative explanation. We propose that there are inter-individual differences in the susceptibility to benzene-induced leukaemia. Genetic differences in the susceptibility to benzene poisoning (a risk factor for haematological malignancy) and benzene-induced haematotoxicity are well documented [5,6]. Furthermore, there is good evidence for genetically determined individual differences in the susceptibility to leukaemia in general, implicating a number of genes including the one coding for NAD(P)H:quinone oxidoreductase 1 (NQO1), an enzyme involved in the detoxification of the benzene metabolite benzoquinone [7–12], though more work is needed to clarify the precise relationships.

If there were individuals of different susceptibility to benzene-related disease in an exposed cohort, with time more and more of the susceptible individuals would become diseased (with leukaemia or perhaps with another benzene-related disease) and may die, so that the remaining members of the exposed cohort (now depleted of 'susceptible' individuals) would have – apparently – less and less of an increased risk of contracting leukaemia when compared with a control group. This would be an *apparent* lowering of the risk only because if individuals of the *same inherent susceptibility to benzene-induced disease* in the exposed and control groups were compared, there would likely still be an elevated risk. The findings of Hayes et al. [4] of a decrease in the risk for nonlymphocytic leukaemia and myelodysplastic syndromes after long *continuous* exposure to benzene vs. shorter exposure would be more consistent with depletion of susceptible individuals in the exposed group rather than with a limitation of benzene's effects because of a short biological half-life and effective repair mechanisms; these could only be expected to exert an effect after cessation of exposure.

Fourth, the proposal that the carcinogenic effects of benzene are reversible challenges a central tenet in toxicology: the *dose–time relationship for chemical carcinogens*. This states, based on work by Druckrey et al. in 1963 [13], that the product of time and dose of a carcinogen is constant. The findings of Druckrey et al. were later confirmed in large animal studies [14] and the dose–time relationship for chemical carcinogens has been generally accepted as dogma, provided that genotoxic mechanisms are involved. Both classical and recent epidemiological evidence supports that this notion is not restricted to experimental animals: Pott showed in 1775 that chimney sweepers did not get scrotal cancer until after puberty [15]. Smokers have an elevated, though apparently decreasing, lung cancer risk even many years after they have stopped smoking [1,16]. The genotoxic effect of benzene was repeatedly shown in vitro [17,18], in experimental animals, and in humans [19–22]. It is now commonly believed that carcinogenic effects of genotoxic carcinogens are irreversible.

Of course DNA repair does occur by a variety of mechanisms. However, these mechanisms have two major aspects in common: DNA repair occurs very early after exposure and miss-repair leads to irreversible manifestation of DNA damage. In addition, certain damage to genetic material – including chromosome deletions and translocations – as far as we know cannot be repaired. Such lesions are often found in leukaemia and were even shown to be of key importance in the causation of leukaemia in case of the Philadelphia chromosome.

What do the above arguments mean with regard to compensation for leukaemia as an occupational disease, especially if the

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disease occurs long after benzene exposure? The irreversibility of certain mutations associated with leukaemia and alternative explanations of the apparent decrease in risk over time lead us to the conclusion that – based on current evidence – a long latency between exposure and disease should not necessarily rule out compensation. An individual with a low inherent susceptibility for leukaemia may develop the disease as a result of a multi-step process of accumulating relevant mutations over decades, with early benzene-induced mutations being contributory. Only a comparison with non-exposed low susceptibility individuals would be comparing like with like and establish the true individual risk increase, not a comparison with an 'unselected' group of controls. Such a selected comparison is impossible at present because we do not know how to reliably identify low susceptibility individuals; this remains a task for future research.

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Sebastian Straube*
Götz A. Westphal
Ernst Hallier
Department of Occupational and Social Medicine, University of Göttingen, Waldweg 37 B, D-37073 Göttingen, Germany

* Corresponding author. Tel.: +49 551 39 8044; fax: +49 551 39 6184.
E-mail addresses:
sebastian.straube@googlemail.com (S. Straube),
westphal@ipa-dguv.de (G.A. Westphal),
ehallie@gwdg.de (E. Hallier)

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