A new 'pooled' analysis of benzene effects on human health

A 'pooled' analysis of three human health studies sheds new light on low-level benzene exposure.

For many years, the effects of benzene on human health have been a concern of health experts and air quality regulators. Because of these concerns, regulatory limits and technological developments have resulted in progressive reductions in benzene concentrations in transport fuels and in ambient air. For example, the maximum amount of benzene in petrol was reduced to 1 wt% in 2000 while advanced vapour recovery systems at service stations were introduced to reduce exposure by employees and consumers to benzene emissions and other evaporative emissions[1]. Workplace limits on benzene and other priority pollutants in ambient air have also been reduced over the same time period resulting in significantly lower exposure to workers and the general public.

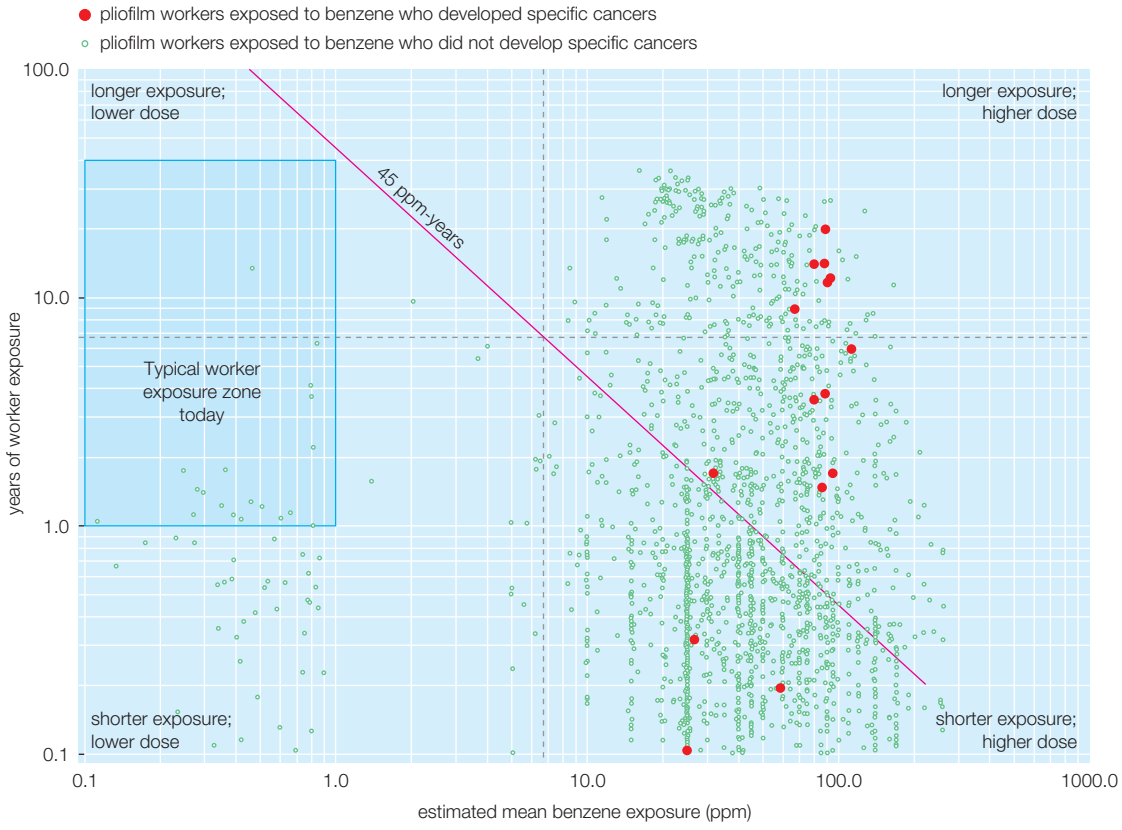
The basis for today's worker and environmental benzene regulations in Europe and in the USA were driven by an epidemiological study completed in the 1980s. This study, called the 'pliofilm study', evaluated benzene-induced leukaemia in workers exposed to benzene vapour through the manufacturing of pliofilm polymers, mainly in the 1950s and 1960s.

Most of the workers in this study were exposed to relatively high amounts of benzene, generally over only a few years. Figure 1 shows the average benzene exposure for workers evaluated in the pliofilm study compared to that typically experienced by workers today. The x-axis shows the mean benzene exposure concentration over a working career, while the y-axis shows the duration of benzene exposure in years. In this study, benzene-induced leukaemias were largely associated with higher benzene concentrations over longer exposure durations, which increased the health risk for these workers.

However, most workers in this pliofilm study were exposed to benzene concentrations that are much higher than they are today, typically much less than 10 ppm. Consequently, the pliofilm study has a number

[1] See CONCAWE *Review* Vol. 15, No. 2 (2006).

Figure 1 Average benzene exposures for workers evaluated in the 1950–60s 'pliofilm study' compared to typical worker exposures today



of important limitations when considering today's exposure levels, notably the small number of exposed workers, the lack of actual benzene exposure measurements, and the relevance of these historically high exposure levels, which were 50 to 100 times higher than current workplace exposures. While the pliofilm study focused primarily on benzene-induced leukaemias, other scientific studies have reported a consistent picture between high benzene exposures and acute myeloid leukaemia (AML), but there is a much less clear relationship with other blood cancers such as non-Hodgkins lymphoma (NHL) and chronic lymphoid leukaemia (CLL).

To fill in some of the gaps from the pliofilm study, the petroleum industry sponsored three independent epidemiological studies in the 1990s on the health experiences of Australian, Canadian and British petroleum workers exposed to benzene. These studies did not find any relationship between benzene exposures and some types of leukaemia (e.g. chronic myeloid leukaemia (CML) and acute lymphatic leukaemia (ALL)) but a higher incidence of other forms of leukaemia, including AML and CLL, was observed in some of the studies. However, the findings were not consistent across the three studies and were therefore difficult to interpret. For example, in the Australian study, a higher incidence of AML in workers was observed at significantly lower concentrations of benzene (~1.0 ppm) than was found in the other two studies.

The 'pooled analysis'

In order to better understand these important studies, a 'pooled analysis' of the three epidemiology studies was initiated in 2006 to combine ('pool') and update the three previous worker populations. These populations were identified in an EU-funded study (ECNIS in 2006 and 2008) as likely to represent the highest quality epidemiological datasets upon which future benzene limits might be based. Pooling the existing studies in this way was also intended to clarify the significance of the previous inconsistent observations on AML and CLL. This recently-published pooled analysis is now the largest study of its type and its findings are expected to play a major role in future regulatory discussions on controlling workplace exposure to benzene.

By analysing together the results from many more workers, the design of the pooled study also allowed an examination of the relationships between benzene exposure and leukaemia types that may not have been apparent in the three independent studies. From a health sciences perspective, a larger number of exposed workers covering a broader range of benzene exposure concentrations provides more statistical certainty where more definitive conclusions can be reached. An add-on to the pooled study was to look at blood diseases that can be grouped according to the latest World Health Organization (WHO) classifications. This means that the association between benzene exposure and two new blood disease groups, myelodysplastic syndrome (MDS) and myeloproliferative disease (MPD), could be investigated in the new study.

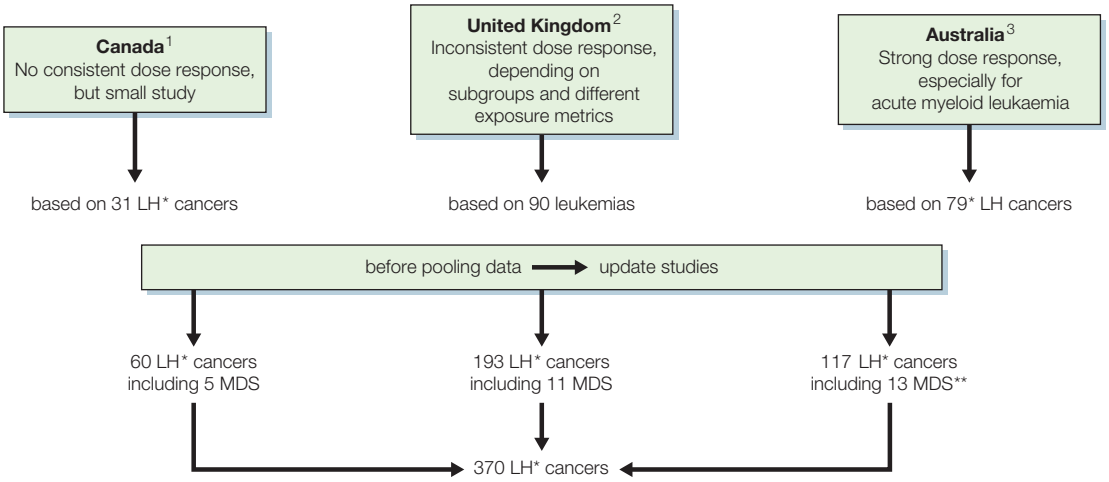
Methodology

The first step in conducting this benzene pooled analysis was to determine whether the three epidemiology studies could in fact be pooled, that is, whether the exposure conditions and measurements used in the studies were compatible. Clearly, this first step did indeed support a combined data analysis resulting in a study having much higher statistical power than any of the three individual studies.

This benzene pooled analysis is based on a case control design. This means that the exposure experiences of individuals who contracted leukaemia or other blood conditions ('cases') were compared to the exposure experiences of randomly selected workers of the same age who did not ('controls'). From a total combined study population in excess of 41,000 workers, the pooled population included 370 potential blood disorder cases and more than 1,500 suitable controls. This can be compared to only 15 blood disorder cases from a total of 1,700 exposed individuals in the pliofilm study.

In addition to the greater statistical confidence that the analysis of a larger exposure population provided, the pooled analysis used a standardized approach to characterize historic benzene exposures across all three studies. This was combined with a rigorous evaluation of how blood diseases, including cancers have been assessed and classified. Importantly, the pooled study assessed diseases using the recently revised WHO def-

Figure 2 Pooled data from three previous studies



*LH: lymphohematopoietic **MDS: myelodysplastic syndrome

1. Schnatter *et al*., 1996. Lymphohaematopoietic malignancies and quantitative estimates of exposure to benzene in Canadian petroleum distribution workers. *Occupational and Environmental Medicine* (*OEM*); 53: 773-781

2. Rushton *et al*., 1997. A case-control study to investigate the risk of leukaemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom. *OEM*; 54:152-166

3. Glass *et al*., 2003. Leukemia risk associated with low-level benzene exposure. *Epidemiology* 14: 569-577

initions of tumours of the blood and lymph systems, and the clinical diagnoses of individuals in the pooled study were reviewed and confirmed by independent medical professionals.

Results

There were three major findings from the pooled analysis of the three separate benzene studies.

Firstly, no consistent relationship was identified between benzene exposure and AML. Because AML was the type of leukaemia that had previously been associated with exposure to higher benzene concentrations, this finding may indicate that benzene exposures higher than those experienced in the pooled study populations may be necessary for a significant risk of AML to occur.

Secondly, for today's more typical benzene exposure levels (i.e. those less than about 1 ppm on average) no relationship was identified with other blood-forming tumour sub-types, e.g. CML, CLL and MPD. These sub-types have been hypothesized as being associated with higher benzene exposure levels, which would be consistent with the finding from the pooled study.

Thirdly, MDS, a blood condition that can develop into leukaemia and which has previously been associated with exposure to benzene, was found to be related to benzene exposure but at lower benzene levels than had previously been reported. In this study, a regular peak exposure was defined as a short-term (15–60 minutes) exposure to more than 3 ppm benzene at least once per week for at least one year. Workers who experienced this regular peak exposure seemed to be most closely associated with the MDS blood condition. A number of other exposure metrics were also associated with MDS, but with lower levels of statistical significance. MDS was not identified in the earlier studies of petroleum workers, largely because it was not a reported condition until the 2001 WHO publication on the classification of blood and lymphatic tumours specified clearer criteria for MDS diagnosis.

Conclusions

Importantly, the pooled study did not find a clear relationship between various blood leukaemias and today's typical benzene exposure levels. This is an important finding because the incidence of leukaemia has been used as the basis for current benzene workplace and environmental regulatory standards for many years. This conclusion suggests that existing regulatory standards for benzene, such as occupational exposure limits, are already sufficient to protect worker health for benzene-related leukaemias. The new finding concerning MDS-type blood conditions requires more research to determine whether this is a robust finding and whether there are implications for today's benzene exposure control strategies.

This benzene pooled study has now been published in a peer-reviewed journal (Schnatter *et al.*, 2012)[2]. With these new and important results in hand, CONCAWE is now fulfilling its REACH obligations by updating the petroleum substance registration dossiers with this new epidemiology information.

[2] Schnatter, R.A., Glass, D.C., Tang, G., Irons, R.D., Rushton, L., 2012. Myelodysplastic Syndrome and Benzene Exposure Among Petroleum Workers: An International Pooled Analysis. *Journal of the National Cancer Institute*: DOI 10.1093/jnci/djs411. Available at: jnci.oxfordjournals.org/content/104/22/1724.full.pdf+html (Accessed 3 December 2012)

Epidemiology

Epidemiology is the study of the complex patterns and determining factors that have an impact on human health in defined populations. There are three important components to a well-designed epidemiology study: the test protocol, the selection and collection of data, and the statistical analysis of the results. Each component plays an important role in providing a well-reasoned blueprint for collecting, analysing and interpreting the data. A properly conducted study can provide health professionals with the information needed to assess a worker's risk of experiencing a specific health impact from exposure to petroleum products in the workplace.

Due to major advances in health science over the past two decades, there has been a dramatic shift in how different blood diseases are classified. Today, the origin of the blood disease is used instead of the anatomy of the cancer cells and provides a much better link to the cause of the health effect:

- Traditional approach based on the anatomy of the cancer cells:
  - Leukaemias (cancer in peripheral blood)
  - Lymphomas (cancer in lymph system)
- New approach based on the origin of the cancer cells:
  - Myeloid tumours, such as:
    - Myeloproliferative disease (MPD)
    - Myelodysplastic syndrome (MDS)
    - Acute myeloid leukaemias (AML)
  - Lymphoid tumours, such as:
    - B-cells and T-cells (leukaemias and lymphomas)

Several blood-related diseases are now examined closely for potential links between human health and exposure of workers to substances like benzene. These diseases can include:

- Acute myeloid leukaemia (AML)
- Chronic myeloid leukaemia (CML)
- Chronic lymphoid leukaemia (CLL)
- Myelodysplastic syndrome (MDS)
- Myeloproliferative disease (MPD)