Benzene, Benzene Poisoning and Lymphohaemopoietic Malignancy

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This paper was presented at the Fifth National Workshop on the Assessment of Site Contamination

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Proceedings of the Fifth National Workshop on the Assessment of Site Contamination

Editors: Langley A, Gilbey M and Kennedy B

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Printed version ISBN 0-642-32355-0 Electronic (web) ISBN 0-642-32371-2

Benzene, Benzene Poisoning and Lymphohaemopoietic Malignancy

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1 INTRODUCTION

Benzene is a naturally occurring, hazardous volatile organic compound, first isolated in 1825 by Michael Faraday. It came into industrial use as a solvent in the printing and chemical industries.

The toxicity of benzene on blood formation have been recognised for over 100 years[1]. In 1897 Santessen[2] observed cases of aplastic anaemia in young women manufacturing bicycle tyres in Sweden. LeNoir and Claude[3] described haemorrhaging in a young man working in a dry cleaner.

The industrial uses of benzene rose dramatically after 1910 when it began to be widely used in the rubber industry and in the manufacture of toluene for explosives in World War 1. It found application in the artificial leather industry, rubber goods, adhesives, hat manufacture, printing inks, automobile manufacture, dry cleaning, coatings, automobile manufacture and in petroleum products.

There was a commensurate rise on the numbers of cases of benzene poisoning, associated with exposure in the 200 to 1000 ppm range. In 1926 Greenburg reported that one third of workers in 12 plants using benzene had low white cell counts (below 5000/cc). A high prevalence of abnormal white cell counts was seen at exposure levels above 90 ppm.

2 A REGULATORY HISTORY

In 1946 the American Conference of Government Hygienists recommended an occupational exposure limit of 100 ppm. Evidence for haematotoxicity prompted the lowering of this recommendation to 25 ppm in 1952, and to 10ppm in 1974. When the first results of the cohort studies on the Pliofilm rubber workers[4] showed a 5-10 fold increase in risk for an 8 hour Time Weighted Exposure (TWA_8) benzene exposure of 10 ppm, the Occupational Health and Safety Administration (OSHA) issued a 1 ppm atmospheric exposure limit. This standard was challenged by Petroleum Industry and in 1980 the US Supreme Court famously ruled that a determination of significant risk be based if possible on an analysis of the best available evidence through such means as quantitative risk assessment. This decision enshrined risk assessment as a requirement of chemical assessment prior to regulatory action. In 1987 a new occupational standard for benzene of 1ppm TWA_8 was promulgated by OSHA, subsequently revised in 1994 to 0.5 ppm.

The current Australian occupational exposure standard for benzene is 5 ppm TWA_8. The National Industrial Chemical Notification and Assessment Scheme (NICNAS) in 2001 completed a review of benzene toxicity as part of its Priority Existing Chemical Program.[5] They recommended a lowering of the occupational limit to 0.5 ppm – a decision based upon a low dose extrapolation of results from the Pliofilm cohort and achievability in an

Australian setting. The National Occupational Health and Safety Commission has responded by proposing an interim standard of 1ppm.

Australia has no current ambient air standard, although this is currently under development by NEPC. Average exposure to benzene in the urban environment has been estimated at 5.2 ppb.

2.1 HUMAN HEALTH EFFECTS

Short term and repeated dose toxicity in humans, with thresholds of effect where available are summarised in summarised in Table 1.

The blood forming organs show the greatest sensitivity to benzene. Of all cell lines present in bone marrow, lymphocytes seem to have the greatest sensitivity to benzene. Haematotoxicity has hitherto not been used as a critical effect in risk analyses of benzene.

In regulatory terms the critical effect which has been used as the basis for virtually all regulatory decision-making is the occurrence of leukaemia in benzene exposed workers. There is no suitable animal model for benzene leukaemogenesis.

The critical study which has informed standard setting is the Pliofilm cohort. Pliofilm is rubber hydrochloride sheeting used to provide water resistant coverings for food and supplies, particularly for the military. Rubber was dissolved in benzene and then moulded into sheets. Three plants produced this material between 1940 and 1970.

The data emerging from a very large cohort of nearly 80,000 benzene workers in China, supported by the US National Cancer Institute[6], is providing challenging new data on the carcinogenic risks of benzene. There are a number of key points:

- Firstly, these data are more informative in the cumulative dose range below 400 ppm years.
- Secondly, it is clear that myeloid or non-lymphocytic leukaemia has a stronger association with benzene exposure than other types of leukaemia.
- Thirdly, this study has convincingly demonstrated a strong relationship between a prior history of benzene poisoning and subsequent development of leukaemia. In a sub group of 11,700 of these workers, a history of benzene poisoning, defined as a white cell count of less than 4000 cells/cc conferred a large increase in risk of myeloid leukaemia, although the number of cases were small (Table 2). These risks did not seem to be dependent of benzene exposure occurring after the episode of benzene poisoning, suggesting a threshold effect. These results are summarised in Table 3. Benzene poisoning thus defined was uncommon in this cohort, but was observed at very low levels of exposure. This may be genetically mediated.
- In a separate analysis of the temporal relationship of exposure to disease, the investigators have found that more recent, rather than distant exposure was more indicative of leukaemia occurrence[7]. A model of carcinogenesis emerging from the work of the National Cancer Institute of short latency and a wave like increase then a decrease is analogous to the patterns of leukaemia occurrence after the atomic bombings in Hiroshima and Nagasaki, and after some chemotherapeutic treatments.

These epidemiological observations are generally coherent with data from human and animal studies which show a shift towards the more genotoxic metabolites as benzene exposure increases, a state which has been shown to be exacerbated in some common

genetic polymorphisms, such as the *NQO1* $^{609}C \rightarrow T$. Links have been demonstrated between haematotoxicity and chromosomal aberrations[11] such as mitotic recombination, which probably play an important part in leukaemogenesis[8].

2.2 DOSE AND RESPONSE ASSESSMENT

Dosemeci[9] has described a dose response relationship for benzene poisoning in workers observed over an 18-month period. The prevalence of benzene poisoning increased with cumulative exposure over this period. A LOAEL for benzene poisoning in humans, defined as a white cell count below 4000 cells/ml, has been determined at 7.6 ppm[10,11]. This is similar to the LOAEL for haematotoxicity in mice. There is no convincing evidence of a NOAEL in humans or in animals.

For benzene related leukaemia, the reanalysis by Paxton[12] of data from the Pliofilm cohort used three available estimates of exposure by Rinsky[13,14], Crump[15] and Paustenbach[16]. The main differences between these exposure estimates was that Rinsky did not account for likely increases in exposure associated with wartime production, and that Paustenbach was the only study to include dermal exposure. Paxton used a proportional hazards methodology to evaluate leukaemia risk. This method permits incorporation of quantitative estimates of individual benzene exposure accumulated in the course of employment. Using the exposure estimates of Crump and Paustenbach she estimated from the slope of the leukaemogenic dose response 0.3-0.5 additional deaths per 1000 workers with 45 ppm lifetime cumulative benzene exposure. This assessment underpins the recommendations of NICNAS for both occupational and non-occupational exposure. Table 3 is drawn from the NICNAS report and presents a summary of the extrapolation of risks of lifetime exposure environmental benzene exposure at 1 ppb, using estimates obtained from the Pliofilm cohort. Lifetime exposure is assumed to be 24 hours per day, 365 days per year for 78 years.

Hayes has argued that the Pliofilm cohort is essentially uninformative below a cumulative dose of 200 ppm years. Dose response information from the Chinese cohort has recently been updated, and the investigators have also challenged some of the criticisms that have been made of the exposure assessment in this group. This study shows a doubling of risk of ANLL at average exposure levels of 10 ppm[17]. (Figure 1)

3 CONCLUSION

Although the current occupational and putative environmental exposure limits for benzene exposure are not haematotoxic, close attention should be paid to the absolute lymphocyte count in monitoring workers and others exposed to benzene because of the large increase in leukaemia risk after benzene poisoning.

There is good evidence of a doubling of myeloid leukaemia risk in the 0-10 ppm average range. The adoption of results from NCI/Shanghai cohort as the critical study in benzene risk assessment would seem to be justified.

Table 1 Acute and Repeated Dose Effects of Benzene

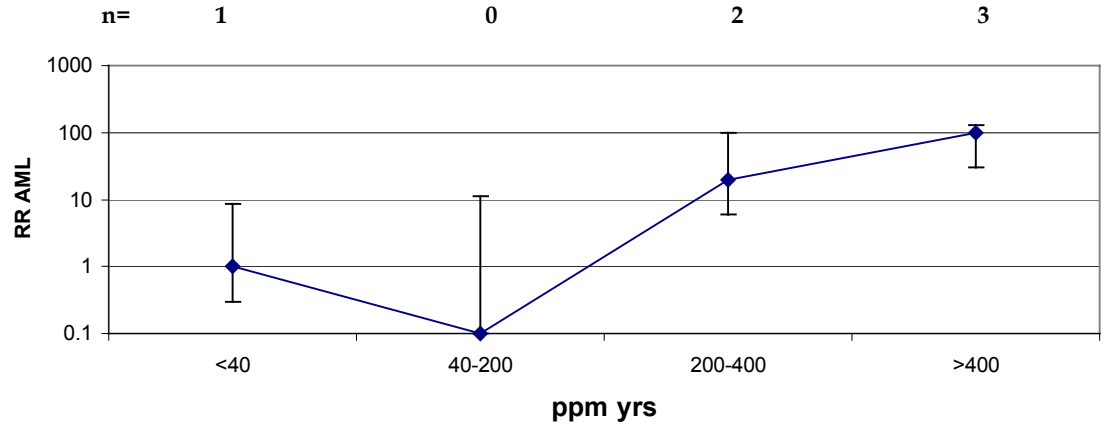
	Effect	Dose Range
Acute Toxicity		
	CNS	
	Death	20000ppm 5-10 mins
	Dizziness, tremor	250-3000 ppm
	Coma	700- 3000 ppm
	Respiratory	
	Irritation of URT	33-59 ppm
Repeated Dose		
	CNS	
	Dizziness	50-60 ppm
	Impaired motor reaction time	0.56-1.8ppm
	Haematological	
	Bone marrow toxicity (Decreased WCC)	LOAEL 7.6ppm
	Immune System	
	↑IGM↓IGA↓IGG	3-57 ppm
	Cardiovascular	
	Hypertension, Minor ECG changes	20ppm

Table 2 Benzene Risk and subsequent risk of haematological malignancy and related disorders in 11,177 workers, Shanghai China (Song Nian Yin *et al* 1997)

Benzene Poisoning	Persons	Person Years	All Haematological disorders	RR (95%CI)	ANLL/ MDS	RR (95%CI)
No	11177	122620	7	1.0	3	1.0
Yes	103	848	3	**42.3** (10.7-167.0)	2	**70.6** (11.4-439.3)

Figure 1 Benzene Dose Response Relationships (Hayes *et al*)

Pliofilm Cohort



3.1 China

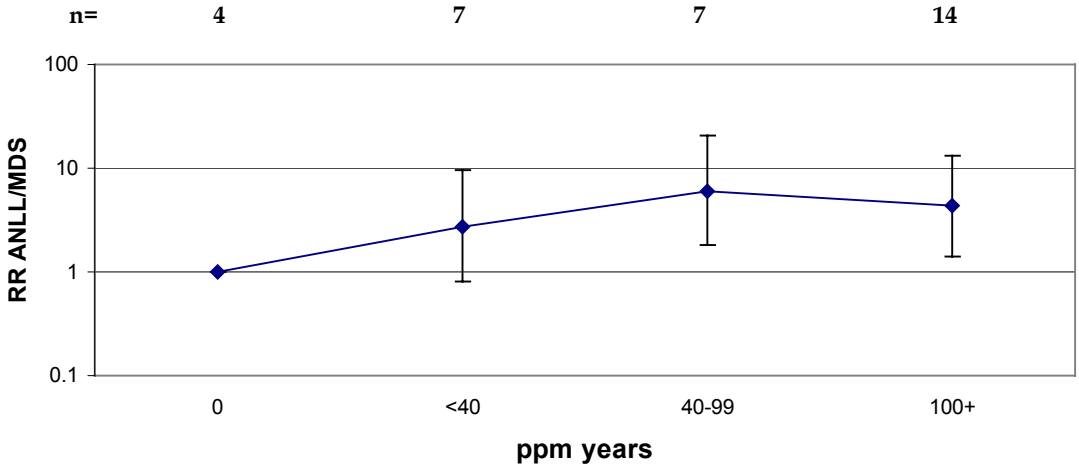


Table 3 Predicted Human Leukaemia Risk from continuous lifetime exposure to 1 ppb benzene, based on occupational exposure in Pliofilm cohort

Mathematical Model	Exposure Estimate	Additional lifetime leukaemia deaths/10^5 pop
Linear	Crump & Allen (1984)	2
	Paustenbach (1992)	2
Non Linear (AUC)	Crump & Allen (1984)	2
	Paustenbach (1992)	1
Non Linear (AUC)	Crump & Allen (1984)	2
	Paustenbach (1992)	0.00002
Proportional hazards regression	Crump & Allen (1984)	0.2
	Paustenbach (1992)	0.4
	Rinsky (1981,1987)	0.9

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