Benzene

Major Uses and Sources of Emissions

Benzene occurs naturally in fossil fuels and is produced incidentally in the course of natural processes and human activities that involve the combustion of organic matter such as wood, coal and petroleum products. The main industrial use of benzene is as a starting material for the synthesis of other chemicals. Most benzene feedstock is imported, but some is manufactured at an Australian steelworks as a by-product of coal coking. Large quantities of benzene are produced during the refining of petroleum and retained as a component of petrol. Petrol vehicle emissions are the predominant source of benzene in the environment. (NICNAS, 2001) In the past, benzene has been widely used as a multipurpose organic solvent, however, this use has been actively discouraged.

Effects of Chronic Human Exposure

The critical human health effects from long term exposure to benzene are bone marrow depression and leukaemia, specifically acute non-lymphocytic leukaemia (also known as acute myeloid leukaemia). Benzene is classified as a human carcinogen. It is considered to be a genotoxic carcinogen for which no threshold has been established. (NICNAS 2001, US EPA 2000, WHO 2000)

There are four key occupational cohort studies demonstrating an association between benzene and leukaemia for which the exposures have been assessed in detail. These are the Goodyear Pliofilm, the Chemical Manufacturers Association (CMA), Dow Chemical and the Chinese Factory Worker cohorts.

The conclusions of recently published health reviews and the basis for their risk estimations are summarised below.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS), Benzene, Priority Existing Chemical Assessment Report No. 21 (2001)

It is well documented through numerous epidemiological studies that the principal human health hazards are bone marrow depression and leukaemia, particularly AML (ANLL). In the absence of evidence to the contrary, genotoxic carcinogens such as benzene are assumed to have a non-threshold mechanism of action. As a ‘safe’ or ‘no effect’ level therefore cannot be identified, quantitative risk estimation is used to express the cancer risk (probability) in numerical terms.

There was an excess mortality from cancer of the blood and lymphatic system in four large cohorts for which detailed benzene exposure assessments are available (Pliofilm, CMA, Dow Chemical, and Chinese Factory Worker cohorts) and a significant trend with cumulative exposure in all but the smallest cohort (the Dow Chemical cohort). As such, it is widely accepted that these studies provide sufficient evidence of a clear dose-response relationship between benzene exposure and the broad category of all cancers of the blood and lymphatic system. In addition, the Pliofilm study has the

advantage of limited if any co-exposure to other potentially carcinogenic compounds and a very long follow-up period.

NICNAS considered the Pliofilm cohort as the most reliable data set on which to establish the risk estimates. Data from the most recent follow-up of the Pliofilm cohort indicate that the risk for leukaemia is significantly elevated at cumulative exposures >50 ppm-years. However, this finding derives from a single cohort study with insufficient statistical power to rule out the possibility of some increase in leukaemia risk at lower exposures.

The additional risk for leukaemia attributable to environmental exposure to benzene can be predicted by low-dose extrapolation of the quantitative estimates for occupational exposure to benzene. Crump (1994) and USEPA (1998a) both predict the number of additional leukaemia cases at two lifetime exposure levels, namely 1 ppm and 1 ppb, however, only the latter is relevant for exposure to benzene in the general environment (table 1).

Table 1: Predicted human leukaemia risk from continuous lifetime exposure to 1 ppb benzene, based on the occupational risk estimates based on the Pliofilm cohort (from Crump (1994) and USEPA (1998a))

Mathematical model	Exposure estimate[#]	Additional lifetime leukaemias per 100,000 population*	Data source
Linear	Crump & Allen (1984, unpublished)	2	Crump (1994)
	Paustenbach et al. (1992)	2	
Nonlinear (AUC-dependent) [†]	Crump & Allen (1984, unpublished)	2	Crump (1994)
	Paustenbach et al. (1992)	1	
Nonlinear (intensity-dependent)	Crump & Allen (1984, unpublished)	2	Crump (1994)
	Paustenbach et al. (1992)	0.00002	
Proportional hazards regression	Crump & Allen (1984, unpublished)	0.2	Paxton et al. (1994b)
	Paustenbach et al. (1992)	0.4	
	Rinsky et al. (1981, 1987)	0.9	

[†] AUC = area under the curve = cumulative exposure
* Rounded to one significant figure
[#] There are several exposure estimates for the Pliofilm cohort

With the exception of one outlier which is 4-5 orders of magnitude lower than the remaining predictions, the risks shown in the table do not differ by more than one order of magnitude, irrespective of the choice of model and exposure estimate. It is therefore reasonable to base

the risk characterisation on the most conservative prediction, that is, a lifetime leukaemia (AML) risk equivalent to 2 additional cases of leukaemia per 100,000 population at 1 ppb.

By extrapolation, the lifetime leukaemia (AML) risk equivalent for increasing exposure levels can be calculated as follows:

0.5 ppb ~ 1 additional leukaemia / 100,000 population

1 ppb ~ 2 additional leukaemia/ 100,000 population

2 ppb ~ 4 additional leukaemia / 100,000 population

5 ppb ~ 10 additional leukaemia / 100,000 population

10 ppb ~20 additional leukaemia / 100,000 population

20 ppb ~ 40 additional leukaemia / 100,000 population

The NICNAS estimated that the average 24 hour lifetime exposure to benzene, from all sources (including an estimated ambient air component of 11%), of an individual not exposed to environmental tobacco smoke living in an urban area of an Australian city is 5.2 ppb. The predicted excess lifetime risk of leukaemia is therefore 1/10,000, or 1.2% of the lifetime risk of contracting leukaemia of any cause (1 in 118, or 85/10,000 population, based on 1996 incidence figures for Australia (AIHW, 1999)).

Air Quality Guidelines for Europe, *2nd edition* -WHO Regional Office for Europe, 2000 (WHO 2000)

The WHO assessments concluded that the carcinogenicity of benzene has been established both in humans and in laboratory animals. An increased mortality from leukaemia has been demonstrated in workers occupationally exposed to benzene.

Because benzene is characterized as a genotoxic carcinogen and recent data gathered in humans and mice suggest mutagenic potential *in vivo*, establishment of exposure duration and concentration in the human exposure studies was considered to be of major importance for the calculation of cancer risk estimates.

WHO has stated that the most thorough and well investigated study, which has also been the main study used for quantitative risk assessment, and is on workers that used to be employed in the manufacture of rubber film, known as the "The Goodyear Pliofilm cohort studies". They noted that significant exposures to other substances at the studied facilities were probably not a complicating factor, but that exposure estimates for this cohort vary considerably. There have been several quantitative cancer risk assessments conducted on this cohort Rinsky et al. (1981), Crump & Allen (unpublished report prepared for the Occupational Safety and Health Administration in 1984) and Paustenbach et al. (1992). WHO have also considered that the CMA cohort study (Wong 1987a, 1987b) and the more recent US NCI and CAPM Chinese cohort study (Hayes et al 1997) as being suitable for carcinogenic risk assessment estimations.

They concluded that benzene is carcinogenic to humans and no safe level of exposure can be recommended. For purposes of guideline derivation, the WHO decided to use the 1994 risk calculation of Crump (of the Pliofilm cohort) rather than to derive new estimates. It was

recognized that this use of existing analyses of the most recently updated cohort ruled out the inclusion of certain of the analyses noted earlier.
The geometric mean of the range of estimates of the excess lifetime risk of leukaemia at an air concentration of 1 $\mu g/m^3$ is 6×10^{-6}. The concentrations of airborne benzene associated with an excess lifetime risk of 1/10 000, 1/100 000 and 1/1 000 000 are 17, 1.7 and 0.17 $\mu g/m^3$, (5.3, 0.53, 0.053 ppm) respectively.

International Programme on Chemical Safety, Environmental Health Criteria Document No. 150, Benzene (1993).

The document concludes that the most frequently reported health effect of benzene is bone marrow depression leading to aplastic anaemia. At high levels of exposure a high incidence of these diseases is probable. Benzene is a well-established human carcinogen. Epidemiological studies of benzene-exposed workers have demonstrated a causal relationship between benzene exposure and the production of myelogenous leukaemia. The IPCS Task Group was of the opinion that the epidemiological evidence is not capable of distinguishing between a small increase in mortality from leukaemia in workers exposed to low levels of benzene, and a non-risk situation.

In their assessment of human health risks from benzene they have used the Goodyear Pliofilm, and CMA cohort studies as well as other epidemiological studies such as Decoufle et al (1983), a retrospective cohort of male chemical workers in the USA employed between 1947-1968; Paci et al (1989), a cohort of shoe workers (males and females) in Florence, Italy and; Yin et al (1987a, b), a large retrospective cohort study of 28,460 Chinese factory workers.

They concluded that a time-weighted average of 3.2 mg/m^3 (1 ppm) over a 40-year working career has not been statistically associated with any increase in deaths from leukaemia. Because benzene is a human carcinogen, however, exposures should be limited to the lowest level technically feasible.

Commission of European Communities, Council Directive on Ambient Air Quality: Assessment and Management Working Group on Benzene Position paper (1998)

The Working Group stated that most authorities agree that benzene should be classified as a known human genotoxic carcinogen. There are open questions about its mechanism of action, particularly at low doses, but at present no threshold for effects has been identified. It is not possible to estimate precisely the risks associated with exposure to environmental benzene. The largest body of evidence is concerned with exposure of industrial workers to relatively high concentrations for relatively short periods of time. There are many uncertainties when extrapolating from these data to exposure of the whole population to lower concentrations over a lifetime.

The Working Group noted that WHO in developing its 1996 guidelines used a linear model to extrapolate the available data. They noted the uncertainties in the assessment but did not feel it possible to recommend any other way of modelling the data. An ad hoc group of experts in 1998, which reviewed evidence published since WHO carried out their work, was of the view that this evidence does not allow the uncertainties identified by WHO to be removed. That is, it is still not possible to say what is the best model for extrapolating from worker exposure to environmental exposure of the whole population.

Because benzene is characterised as a genotoxic carcinogen and recent data gathered in humans and mice suggest mutagenic potential in vivo, establishment of exposure duration and concentration in the human exposure studies is of major importance for the calculation of cancer risk estimates.

They stated that the Goodyear Pliofilm cohort was the most thoroughly studied group. It was noted that significant exposures to other substances at the studied facilities were probably not a complicating factor, but that exposure estimates for this cohort vary considerably. Three different exposure matrices have been used to describe the Pliofilm cohort, i.e., those reported by Crump and Allen (1984), by Rinsky et al. (1987), and a newer and more extensive one by Paustenbach et al. (1992). For purposes of guideline derivation, the working group chose to use the 1994 risk calculation of Crump rather than to derive new estimates.

The Working Group concluded that though it was not possible on present evidence to give a precise estimate of the risk associated with benzene it was possible to define a range within which that risk was likely to lie. The procedure followed by the WHO working group was considered to result in the highest plausible estimate of risk – an excess lifetime risk of leukaemia at an air concentration of 1 $\mu g/m^3$ of 6×10^{-6}. The lowest unit risk which the group felt was likely to be plausible was in the order of 5×10^{-8}, developed from a meta analysis of petroleum industry workers in UK and USA Wong and Raabe (1995). However, the methodology for derivation of the unit risk factor is not explained in the position paper.

The European Parliament and the European Council, when considering the proposal for a Directive on Drinking Water, agreed that an excess lifetime risk of 1 in a million should be taken as the starting point for developing limit values. Taking this as a precedent, the range of unit risks given above (6×10^{-6} to 5×10^{-8}) has been converted into annual average concentrations which would, over a lifetime, equate to an excess risk of contracting leukaemia of 1 in a million. The resultant range of concentrations is 0.21 to 20 $\mu g/m^3$. The Working Group recommends that this range should be taken as a starting point for developing proposals for a limit value, defined as an annual average concentration.

United Kingdom Air Quality Standard for Benzene (EPAQS, 1994)

The Expert Panel on Air Quality Standards (EPAQS) was set up in 1991 to advise the Government on air quality standards. In recommending a standard for benzene the Panel have considered concerns regarding the differences between past industrial cohorts and the general population. The former generally comprised fit young and middle aged males, whereas the general population of course includes also children, pregnant women, the elderly and the sick, some of whom may be unduly sensitive to toxic chemicals. The industrial cohort is potentially exposed to high concentrations for perhaps 8 hours per day, five days weekly for 40 years, whereas the general population is exposed to much lower concentrations, but throughout their lifetimes.

The Panel examined published reports of studies of leukaemia in a number of cohorts of workers exposed to benzene. While none provided wholly reliable information on the exposures of the workers, several included estimates that were felt to be reasonable.

The two studies considered most useful were those of the Pliofilm and the CMA cohort studies. Both studies showed an increased risk of non-lymphocytic leukaemias in workers with the highest exposures, estimated to have been greater than 200 parts per million (ppm) years (equivalent to 10 ppm or 10,000 ppb exposure for 20 years) in the former study.

The Panel accepted that benzene is a genotoxic carcinogen and that therefore no absolutely safe exposure level could be defined. Nevertheless, for practical purposes they believed that a concentration may be proposed at which the risks are exceedingly small and unlikely to be detectable by any practicable method. The Panel therefore adopted the pragmatic approach of recommending a target Standard that is as low as is reasonably practicable.

Based on the available epidemiological studies, the Panel determined that the risk of leukaemia in workers was not detectable when average exposures over a working lifetime were around 0.5 ppm. Allowing for a 100-fold uncertainty factor to account for the difference between working lifetime and chronological life and for inter-individual differences in sensitivity, the Panel recommended an ambient air level of 5 ppb (as a running annual average). Since benzene is a genotoxic carcinogen and since, in principle, exposure to such substances should be kept as low as practicable, the Panel further recommend a future target Standard of 1 ppb running annual average.

USEPA Carcinogenic Effects of Benzene: An Update (January 2000)

The study of Goodyear Pliofilm rubber workers at three facilities in Ohio (Rinsky et al., 1981, 1987) was considered by the USEPA to provide the best published set of data to date for evaluating human cancer risks from exposure to benzene. Compared to other published studies (Hayes et al., 1996; Bond et al., 1986; Wong, 1987; Schnatter et al., 1996; Rushton et al., 1997), it was said to have the fewest reported coexposures in the workplace to other potentially carcinogenic substances that might confound risk analysis for benzene. Except for the cohort studied by Bond et al. (1986), the Pliofilm workers, furthermore, experienced a greater range of estimated exposure to benzene than the cohorts of other studies in which efforts were made to estimate individual exposures. The value of Bond et al. (1986) for analysis of the effects of exposure to benzene was considered to be diminished by reported coexposures to styrene, arsenic, and other potentially carcinogenic substances. Hence, the Pliofilm workers are the preferred population for estimating the effects of exposure to benzene.

The USEPA assessed the National Cancer Institute and the Chinese Academy of Preventive Medicine, collaborative study in 12 cities of China (Dosemeci et al., 1994; Hayes et al., 1996, 1997). Workers were followed for an average of slightly less than 12 years. This study, one of the largest of its type ever undertaken, enabled its authors to claim detection of significantly elevated risks of hematologic neoplasms (RR = 2.2, 95% C.I .= 1.1-4.2) at low levels of exposure to benzene, average levels of less than 10 ppm.

The USEPA report drew attention to substantial uncertainties and potential weaknesses of the study. The major potential problem was the development of exposure estimates for the benzene-exposed and unexposed workers. According to the authors (Dosemeci et al., 1994), only 38% of the 18,435 exposure estimates were based upon actual measurements of benzene concentrations; the remainder were numbers generated by factory industrial hygienists based upon their estimates of benzene concentrations. During the earliest period, only 3% of the exposure estimates were based on actual measurements.

Also, the derivation of the cohort from many different factories across China suggested the possibility that this cohort was exposed to mixtures of many different chemicals. In addition, it is important to analyse lifestyle and socioeconomic factors impacting this cohort and to determine how they differ from those of workers in similar occupational settings in Western countries.

The USEPA used the Goodyear Pliofilm study as reported by Rinsky et al (1981, 1987) for their quantitative risk estimation.

They estimated a range of 2.2×10^{-6} to 7.8×10^{-6} as the increase in the lifetime risk of an individual who is exposed for a lifetime to 1 ug/m^3 benzene in air. This is based on a linear model and is dependent on which exposure measurements were used (ie Crump and Allen, 1984 or Paustenbach et al. 1993). This extrapolates to air concentrations of 1.3 to 4.5 ug/m^3 for a risk level of 1 in 100,000).

Canada Priority substances list assessment report on benzene (1993)

The report states that on the basis of available data, carcinogenicity is potentially the most sensitive endpoint for the assessment of "toxic" to humans for benzene under Canadian Environmental Protection Act. In numerous case studies, and in the majority of epidemiological studies conducted to date, associations between leukemia and exposure to benzene in occupationally exposed populations have been observed. In addition, there was a clear exposure-response relationship in the Goodyear Pliofilm worker population for which exposure has been the most extensively characterized (Rinsky *et al.,* 1987). They stated that, information in only three Studies (Bond *et a*l., 1986; Wong, 1987a, 1987b; Rinsky *et a*l., 1987) was considered sufficient to form the basis of a quantitative assessment of carcinogenic potency, although the numbers of deaths due to leukemia were small in each investigation. The other studies are less relevant owing to limitations that include poor characterization or description of the basis for estimation of exposure, concomitant exposure to substances other than benzene, and/or the low number of observed cases.

In recent studies, benzene has also been carcinogenic in two species of experimental animals, inducing a wide variety of tumours following inhalation and ingestion. Available data on the mechanisms of action of benzene also indicate that induction of leukemia by this compound is biologically plausible. Benzene has been classified, therefore, in Group I ("Carcinogenic to Man") of the classification scheme developed by the Bureau of Chemical Hazards for use in the derivation of the "Guidelines for Canadian Drinking Water Quality" (Health and Welfare Canada, 1989b).

As stated in the large number of assessments of the toxicity of benzene, most of the human health-exposure data has been obtained from retrospective epidemiological studies relating to occupational settings. It is accepted that there are difficulties in relating these studies usually in fit healthy adults to the population in general which consists of all ages and various levels of health and infirmity.

In considering the recent risk assessments for benzene the Canadians decided to use the Goodyear Pliofilm (Rinsky et al 1997), CMA (Wong 1987a, 1987b), and Dow chemical (Bond et al 1986) cohort studies for their evaluation as they were thought to have the best benzene exposure

assessments and relatively large cohorts. In addition, the Pliofilm study has the advantage of limited if any co-exposure to other potentially carcinogenic compounds and a very long follow-up period.

The Canadians estimated that for AML, the $TD_{0.05}$ (the lower confidence limit of the benchmark dose that corresponds to a 5% increase in mortality) is calculated at 4.6 ppm, based on an early report on the Pliofilm cohort (Rinsky et al, 1987), the exposure estimates by Crump & Allen (1984, unpublished) and a linear-quadratic mathematical model.

Summaries of the key studies of the carcinogenicity of benzene in humans

The Goodyear Pliofilm cohort assessments

An excess incidence of leukaemia in rubber workers at two Goodyear facilities in Ohio, USA was reported in a preliminary paper by Infante et al. (1977) and in more detail by Rinsky et al. (1981). Depending on its definition, this cohort comprises 1165-1212 male workers employed from 1936-75 in the manufacture of Pliofilm, which is a material made from rubber hydrochloride (Paxton et al, 1994a; Rinsky et al, 1987). The manufacturing process used large volumes of benzene as a solvent and there was no exposure to other known carcinogenic substances. The last worker joined the cohort in 1965 and the most recent follow-up was in 1987.

Excluding deaths before 1950, Rinsky et al. (1987) identified 15 deaths from lymphatic and haematopoietic cancers versus 6.6 expected [Standardised Mortality Rate (SMR) = 2.27 (1.27-3.76)] and 9 deaths from leukaemia versus 2.7 expected [SMR = 3.37 (1.54-6.41)].

In a later analysis that included deaths between 1940-50, Paxton et al. (1994a) identified 21 deaths from lymphatic and haematopoietic cancers versus 9.51 expected [SMR = 2.21 (1.37-3.38)] and 14 deaths from leukaemia versus 3.89 expected [SMR = 3.60 (1.97-6.04)]. Neither of these analyses considered smoking or other potential confounders. The individual exposure histories of the cohort members were reconstructed after the plants closed in 1975, from fairly detailed monitoring and health surveillance data and other information on record.

The results reproduced in the table suggest a strong dose-response relationship of risk increasing with cumulative exposure, no matter which estimate is used, and indicate that there is a significantly elevated risk for leukaemia (according to 2 of the 3 available exposure estimates) at a cumulative dose >50 ppm-years, corresponding to a long-term average exposure of 1.25 ppm over 40 years.

Table e2 SMRs (95% CI) for leukaemia in the Pliofilm cohort, analysed by cumulative exposure as estimated by Crump & Allen (1984, unpublished), Paustenbach et al. (1992) and Rinsky et al. (1987)(from Paxton et al, 1994a)

Cumulative Exposure (ppm-years)	**Exposure estimate**		
	Crump & Allen	**Paustenbach et al.**	**Rinsky et al.**
0-5	0.88 (0.02-4.89)	1.33 (0.03-7.43)	1.97 (0.41-5.76)
>5-50	3.25 (0.88-8.33)	1.79 (0.22-6.45)	2.29 (0.47-6.69)
>50-500	4.87 (1.79-10.63)*	2.80 (0.76-7.16)	6.93 (2.78-14.28)
>500	10.34 (2.13-30.21)**	11.86 (4.76-24.44)**	20.00 (0.51-111.4)

* $p < 0.05$, ** $p < 0.01$

The major distinction between the three exposure estimates is the disregard by Rinsky et al. (1987)

for the likely increase in exposure levels during and in the aftermath of World War II because of wartime conditions and longer working hours. In addition, only Paustenbach et al. (1992) have given consideration to the potential for dermal exposure.

As the SMR was not significantly different from unity at cumulative exposures ≤50 ppm-years for any of the three exposure estimates, the authors concluded that the results of the analysis were consistent with a threshold model for benzene-induced leukaemia. However, the power of the analysis was insufficient to support this conclusion. The upper 95% confidence limits given in Table 2 range from 6.45- 8.33 in the >5-50 ppm-year exposure category and from 4.89-7.43 the 0-5 ppm-year category. In either case, the upper limits are well above unity irrespective of the exposure estimate used. Therefore, it cannot be excluded that a cumulative exposure level ≤50 ppm-years is also associated with an excess mortality from leukaemia.

Wong and Raabe (1995) reanalysed the findings of Paxton et al. (1994a) by cell type (AML and MM), using the Rinsky et al. (1987) exposure estimate which in general is the lowest of the three. He found no relationship between cumulative exposure and the risk of MM, whereas the SMR for AML showed a clear dose response. (Table 3)

Table.3 Wong (1995) reanalysis for AML of Paxton et al 1994a findings

Cumulative exposure	**SMR (95% CI)**	**Statistical significance**
<200 ppm-years	0.91 (0.02-5.11)	Not significant
200-400 ppm-years	27.21 (3.29-98.24)	p <0.01
>400 ppm-years	98.37 (20.28-287.65)	p <0.01
Total cohort	5.03 (1.84-10.97)	p <0.01

The author concluded that there was no significant increase in the risk of AML for cumulative exposure to benzene <200 ppm-years, above which the risk rose sharply to a very substantial SMR of 98.37 for >400 ppm-years. However, as the 95% upper confidence limit in the lowest exposure group was 5.11, an increase in mortality from AML at a cumulative exposure <200 ppm-years cannot be ruled out.

The Chemical Manufacturers Association (CMA) cohort study

The CMA cohort is considered to be a suitable study to support findings from the Goodyear Pliofilm study. The SMR for leukaemia was elevated (2.6) in workers with a cumulative exposure of ≥720 ppm-months (that is, ≥60 ppm-years), but it was not significantly different from unity and therefore could have been due to chance.

The Chemical Manufacturers Association sponsored a study of 4602 male chemical workers who were employed for ≥6 months from 1946-75 at 7 US plants (Wong, 1987a, 1987b). Two comparison groups were used: the general US population and 3074 unexposed male workers employed at the same plants at the same time as the cohort. Smoking or other potential confounders were not considered. The vital status of all subjects was followed up until the end of 1987 and the findings compared to average and peak exposures as determined from available air monitoring data and employment records obtained from the participating companies.

There were 19 deaths from cancer of the blood and lymphatic system in the exposed workers compared to 3 in the unexposed group. In the exposed group, 7 of the observed cases were diagnosed with leukaemia and the remaining 12 with lymphoma. The subjects with leukaemia comprised 1 case with acute lymphatic leukaemia, 2 with chronic lymphatic leukaemia, 1 with unspecified lymphatic leukaemia, 2 with chronic myeloid leukaemia and 1 with unspecified acute leukaemia. In the unexposed workers, all 3 cases were diagnosed with lymphoma. The SMRs for all cancers of the blood and lymphatic system were 0.91, 1.47, and 1.75, and for leukaemia 0.97, 0.78 and 2.76 for cumulative exposures of less than180, 180-719 or ≥720 ppm-months respectively, but none of the ratios was significantly different from unity. The RRs for all cancers of the blood and lymphatic system were 2.10, 2.95 and 3.93 respectively for the same cumulative exposure groups, with $p = 0.02$ for trend. The RRs for leukaemia were indefinite as there were no cases in the unexposed workers, with $p = 0.01$ for trend with cumulative exposure. There was no correlation with peak levels or duration of exposure.

Based on the RRs and their trend with cumulative exposure, the author concluded that workers exposed to benzene exhibited a significant excess of deaths from leukaemia as well as from the broader category of all cancers of the blood and lymphatic system when compared with workers who were not exposed to the chemical.

Ireland et al. (1997) conducted an extended mortality study in production personnel from one of the plants included in the CMA-sponsored study. The workers were stratified into three categories based on cumulative exposure, the SMR for leukaemia was: incalculable (0.0-5.9) for less than12 ppm-months (n = 666), SMR 2.5 (0.3-8.9) for12-72 ppm-months (n = 378) and SMR 4.6 (0.9-13.4) for ≥72 ppm-months (n = 164) compared to the regional population, with no clear dose-response relationship.

The Dow Chemical cohort

This cohort comprised 956 male chemical workers employed at a single site in Michigan, USA, between 1940 and 1982. The workers were exposed to benzene in chlorobenzene or alkylation plants which used benzene as a raw material, or in an ethyl cellulose plant where benzene was used as a solvent (Bond et al, 1986; Ott et al, 1978). They were followed up until the end of 1982. The average exposure duration and length of follow-up were 7 and 26 years respectively. Each job entry was assigned an exposure intensity level on the basis of job classification and representative personal air monitoring data.

The analysis accounted for co-exposure to arsenic, asbestos or high levels of vinyl chloride. Smoking or other potential confounders were not considered. There were 6 deaths from cancer of the blood and lymphatic system against 4.8 expected, including 4 cases of myelogenous leukaemia against 0.9 expected, and 4 from skin cancer (3 melanomas and 1 squamous cell carcinoma) against 0.9 expected, using concurrent US white male mortality rates as reference values.

The excess of myelogenous leukaemia was statistically significant ($p = 0.011$; SMR and 95% CI not stated) and the risk for skin cancer was significantly elevated (SMR = 4.41 (1.21-11.38)).

There were no significant trends with either work area, cumulative exposure or duration of exposure. Of the 6 cases of blood and lymphatic system cancer, 4 had been exposed to <500 ppm-months and 2 to ≥1000 ppm-months. In the case of myelogenous leukaemia, cumulative exposures varied from 18-4211 ppm-months. The 4 cases of skin cancer all occurred in workers with exposures <500 ppm-months, but otherwise had no unusual or common characteristics.
The authors concluded that their study provided support for an association between exposure to benzene and myelogenous leukaemia.

US National Cancer Institute (NCI) and Chinese Academy of Preventive Medicine (CAPM) Chinese factory workers cohort study

The US National Cancer Institute and the Chinese Academy of Preventive Medicine have collaborated to follow up on a large cohort study commenced in 1982 to assess the risks of specific bone marrow disorders in relationship to occupational benzene exposure (Hayes et al, 1997). The final cohort comprises 74,828 male and female benzene-exposed workers employed from 1972 to 1987 in 672 factories in 12 cities in China and 35,805 unexposed workers. The subjects were followed until the end of 1987, for an average of approximately 11 years. RRs were determined for incident cancer of the blood and lymphatic system, non-Hodgkin's Lymphoma (NHL), leukaemia, ANLL, a diagnosis of either ANLL or Myelo Dysplastic Syndromes (MDS), and leukaemia other than ANLL, with stratification by age and sex. Smoking or other potential confounders were not considered. The exposed workers held permanent jobs in the painting, printing, footwear, rubber and chemical industries. Exposure levels were estimated from available area monitoring data, detailed production and process information, and employee records.

There is doubt about the true exposures in the Chinese cohort as reported by Dosemeci et al (1994) and Hayes et al (1997). It should be noted that personal monitoring in a subset of the Chinese cohort measured current exposure levels which were reported to be 'much higher than expected' compared to the estimates that were made in the course of the main study

There were 58 specified cancers of the blood and lymphatic system and 18 other bone marrow disorders (2 cases of agranulocytosis, 9 of aplastic anaemia and 7 of MDS) in the cohort, compared to 13 and 0 respectively in the control group.

When the cohort was divided into three categories according to the estimated average benzene exposure level, the RRs for all cancer of the blood and lymphatic system and ANLL/MDS were elevated in all categories, with a positive trend for increasing average exposure, as shown below.

Table 4 Relative risk and exposure levels

	Estimated average exposure			
Cancer type/RR	<10 ppm	10-24 ppm	>25 ppm	Trend
Blood and lymphatic system	2.2 (1.1-4.2)	3.1 (1.5-6.5)	2.8 (1.4-5.7)	p = 0.003
ANLL/MDS	3.2 (1.0-10.1)	5.8 (1.8-18.8)	4.1 (1.2-13.2)	p = 0.01

The RR for NHL was 4.7 (1.2-18.1) in workers exposed to ≥25 ppm, but was not elevated in the lower average exposure categories.

When the cohort was divided into three categories according to the estimated cumulative benzene exposure level, the RR for all cancer of the blood and lymphatic system was elevated in all

categories, whereas the RRs for leukaemia and ANLL/MDS were elevated at cumulative exposures ≥40 ppm-years.

Table 5 Relative risk and cumulative exposure (duration × concentration)

Estimated cumulative exposure				
Cancer type/RR	<40 ppm-years	40-99 ppm-years	≥100 ppm-years	Trend
Blood and lymphatic system	2.2 (1.1-4.5)	2.9 (1.3-6.5)	2.7 (1.4-5.2)	p = 0.004
Leukaemia	1.9 (0.8-4.7)	3.1 (1.2-8.0)	2.7 (1.2-6.0)	p = 0.04
ANLL/MDS	2.7 (0.8-9.5)	6.0 (1.8-20.6)	4.4 (1.4-13.5)	p = 0.01

The RR for NHL was not elevated in any of the three cumulative exposure categories, but NHL was linked to duration of exposure. None of the RRs were related to the year of initial employment in the study factories. ANLL/MDS was linked to recent exposure (<10 years prior to diagnosis), whereas NHL was linked to distant exposure (≥10 years prior to diagnosis).

Overall mortality rates in the Chinese cohort have been reported by (Yin et al, 1987b) and the average latency period of fatal leukaemia in benzene-exposed workers was estimated at 11-12 years, with a range from 10 months to 50 years.

The authors concluded that the results suggest an association between benzene exposure and a spectrum of blood cancers and related disorders, with an increase in cancer risk at cumulative exposures <40 ppm-years and a tendency, although not strong, for the risk to rise with increasing levels of exposure. It should be noted that personal monitoring in a subset of the Chinese cohort measured current exposure levels which were reported to be 'much higher than expected' compared to the estimates that were made in the course of the main study (Rothman et al, 1996). As such, the historical exposure levels used to determine the dose-response relationship may have been grossly underestimated (Budinsky et al, 1999; USEPA, 1998a Wong, 1999).

Summary of Carcinogenicity Studies

The Pliofilm cohort is considered to be the most suitable for the determination of the carcinogenic (potency /dose relationships)of benzene. In addition, the Pliofilm cohort has the advantage of limited if any co-exposure to other potentially carcinogenic compounds and a very long follow-up period. However, it does suffer from uncertainty about actual exposure levels, particularly prior to 1950, which is important as there are no cases of leukaemia in workers first employed after that year (USEPA, 1998, NICNAS 2001).

Based on an unpublished assessment of individual exposures in the Pliofilm cohort, Rinsky et al. (1987) determined SMRs for leukaemia that increased exponentially with cumulative exposure, starting from near unity at a cumulative exposure <40 ppm-years. More recent dose-response analyses that include other, more comprehensive exposure assessments indicate that the risk for leukaemia is significantly elevated at a cumulative exposure level above, but not below 50 ppm-years, corresponding to an average exposure level of 1.25 ppm over 40 years (Paxton, 1994b). Moreover, whatever exposure estimate was used, the number of observed cases of leukaemia was consistently below the expected number in all workers whose long-term exposure never exceeded 15 ppm (Schnatter et al, 1996). However, because of the limited statistical power resulting from the size of the Pliofilm cohort, these results do not rule out the possibility of an increased risk

of leukaemia at exposure levels lower than those cited above.

In the CMA cohort, the SMR for leukaemia was elevated (2.6) in workers with a cumulative exposure of ≥720 ppm-months (that is, ≥60 ppm-years), but it was not significantly different from unity and therefore could have been due to chance. In a subset of the CMA cohort, the SMR for leukaemia was 4.6 in workers with a cumulative exposure of ≥72 ppm-months (6 ppm-years), but again did not differ significantly from unity. There was no clear dose-response relationship in the Dow Chemical cohort and there is doubt about the true exposures in the Chinese cohort as reported by Hayes et al 1997.

Modes of Action

Several reviews of benzene metabolism and the proposed mechanisms of toxicity have been published (Ross, 1996; Snyder, 2000; Snyder et al, 1993; Snyder and Hedli, 1996; Yardley-Jones et al, 1991).

Exposure to benzene can result in haematotoxicity, immunotoxicity and carcinogenicity in humans and animals. Haematotoxicity resulting from chronic benzene exposure can present as anaemia, aplastic anaemia, leukopenia, lymphocytopenia, thrombocytopenia, or pancytopenia (Aksoy, 1989). While the liver is the initial site for the biotransformation of benzene, hepatotoxicity is not a consequence of benzene exposure. Subsequently, these metabolites become localised within the bone marrow (Rickert et al, 1979) where they undergo activation by peroxidase enzymes, which are present in bone marrow. While individual benzene metabolites appear not to induce bone marrow toxicity, the combination of phenol and hydroquinone have been shown to induce the same effects on bone marrow as benzene (Eastmond et al, 1987). This effect appears to be due to the ability of phenol to act as a co-oxidant in the activation of metabolites.

Subsequent changes in cellular function result in altered growth factor production with inhibition of bone marrow stem cell proliferation, differentiation and maturation. The formation of reactive oxygen species damage cells and result in DNA adduct formation, DNA base modification, chromosomal aberrations. Damaged cells not deleted by apoptosis and which possess activated oncogenes or damaged tumour suppressor genes may begin to proliferate as clonal lines, which may result in leukaemia in humans or solid tumours in animals.

Humans exhibit differences in the expression and activity of several enzymes involved in the metabolism of benzene, the most notable of which occurs with NQO1, an enzyme which is responsible for converting quinones to their corresponding hydroquinones and affords protection against quinone-adduct and reactive oxygen species formation within cells. Thus the expression of genetic polymorphisms may modulate the sensitivity of an individual or ethnic group to the effects of benzene exposure.

Non Cancer Endpoints

Effects of long term human exposure

Tsai *et al.* (1983) examined the mortality from all cancers and leukaemia, in addition to haematological parameters in 454 male workers exposed to benzene for 1-21 years in a refinery from 1952-1978. The median air concentration was 0.53 ppm in the work areas of greatest exposure to benzene. The average length of employment in the cohort was 7.4 years. The analysis of overall mortality in this population revealed no significant excesses. A subset of 303 workers was followed for medical surveillance. Up to four haematological tests per year showed all parameters to be within normal limits in this group.

Collins *et al*. (1997) used routine data from Monsanto's medical/industrial hygiene system to study 387 workers with daily 8-hour time-weighted exposures (TWA) averaging 0.55 ppm benzene (range = 0.01 – 87.69 ppm; based on 4213 personal monitoring samples, less than 5% of which exceeded 2 ppm). There was no increase in the prevalence of lymphopenia (decreases in lymphocyte numbers), an early, sensitive indicator of benzene toxicity, or other measures of haematotoxicity.

Rothman *et al* (1996) studied a small number (44) of Chinese workers heavily exposed to benzene (31 ppm, 2 - 329 ppm range) and showed decreases in white blood cell counts and absolute lymphocyte counts and other blood parameters when compared to matched unexposed controls. In a much smaller subgroup of 11 of the 44 workers, with a recorded lower median exposure to benzene of 7.6 ppm (1 -20 ppm range), only the absolute lymphocyte count was decreased compared to the controls. Their results support the use of the absolute lymphocyte count as the most sensitive indicator of benzene-induced hematotoxicity.

Summary of benzene non-cancer health effects

The No Observed Adverse Effect Level (NOAEL) for haematotoxicity in humans was established by Tsai *et al* (1983) at 0.53 ppm, and by Collins *et al* (1997) at 0.55 ppm, from long-term worker exposure studies, with daily 8 hours exposures, 5 days per week. NICNAS (2001) also conclude NOAELs to be around the 0.5 ppm level and a LOAEL at 7.6 ppm in a subgroup of 11 exposed workers (Rothman *et al* 1996).

Although the study by Tsai *et al.* (1983) is a free-standing NOAEL of 0.53ppm, the endpoint examined is a known sensitive measure of benzene toxicity in humans. The recent results of Collins *et a*l. (1997) that included a NOAEL of 0.55 ppm and of Rothman *et a*l. (1996) that included a LOAEL of 7.6 ppm are consistent with those of Tsai *et a*l. (1983)

Effects Of Laboratory Animal Exposure To Benzene

A number of animal studies have demonstrated that benzene exposure can induce bone marrow damage, changes in circulating blood cells, developmental and reproductive effects, alterations of the immune response, and cancer at multiple organ sites. With respect to long term exposure toxicity, haematological changes appear to be the most sensitive indicator.

Aoyama (1986) showed that a 14 day exposure of mice to 50 ppm of benzene resulted in significantly reduced blood leukocyte (white blood cell) count. Mice have been shown to be more sensitive than rats to the haematotoxic and leukaemic effects of benzene.

Keller and Snyder (1988) reported a NOAEL of 10 ppm for bone marrow toxicity to foetal mice.

Ward *et al*. (1985) exposed rats and mice of both sexes up to 300 ppm benzene, 6 hours/day, 5 days/week for 13 weeks. No effects on blood values were found for mice and rats at 1, 10, or 30 ppm, decreases in white blood cells (lymphocyte percentages, leukocyte and platelet counts) were observed in male and female mice at 300 ppm Histological changes in mice included myeloid hypoplasia of the bone marrow. Effects were less severe in the rats.

Cronkite *et al*. (1989) exposed mice up to 3000 ppm benzene 6 hours/day, 5 days/week for up to 16 weeks. No effects were observed at 10 ppm. Decreased leukocyte counts were observed in the 25 ppm exposure group. Higher concentrations of benzene produced dose-dependent decreases in blood lymphocytes and bone marrow cellularity.

Laboratory animal reproductive or developmental toxicity
Kuna and Kapp (1981) found malformations in foetuses from pregnant rats which were exposed 6 hours/day during gestation to a concentration of 500 ppm. In this study, a concentration of 500 ppm produced malformations in foetuses but 50 ppm resulted in lower foetal weights measured on day 20 of gestation. No foetal effects were noted at an exposure of 10 ppm (32 mg/m^3).

Coate *et al*. (1984) exposed groups of 40 female rats up to 100 ppm benzene for 6 hours/day during gestation. A significant decrease was noted in the body weights of foetuses at 100 ppm. No effects were observed at 40 ppm or below (a NOAEL of 40 ppm).

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