Lympho-haematopoietic Cancer and Exposure to Benzene in the Australian Petroleum Industry

Technical Report and Appendices

June 2001

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Acknowledgements

The Study Team would like to acknowledge the work carried out by Dick Manuell, John Bisby, Geoff Adams, Lorna Botham, Arlene Baade and the other members of the Health Watch team at Melbourne University, including the systems analyst, Michael Scales of Wintaro. The Melbourne University team developed the Health Watch cohort and started the case-control study. The first part of the quantitative exposure assessment was carried out at Melbourne University by Deborah Glass and Dick Manuell assisted by other members of the Health Watch Team. The Project Advisory Group for the initial quantitative exposure assessment consisted of the industry occupational hygienists acknowledged below, Chris Gray of Deakin University, Georgia Sinclair (Georgia Sinclair consulting) and Tom Armstrong of Exxon in an advisory capacity.

The authors gladly acknowledge the valuable help from the AIP and several petroleum companies and in particular from, Catherine Hamilton, Sharann Johnson (BP), Graham Ward (Ampol), Wade Maxwell, Peter Clark (Mobil), Noel Tresider (Petroch Services), Simon Madin, David Hamilton (Esso) and Judy Balint, Doug Rhodes, Heather Jackson, Voytek Le Vitzki, Peter Van Schoten, Brendan Biviano and Peter Stamatovski (Shell) and Chris Church (ACTU). We also thank the many retirees and current employees from all companies who freely answered our lengthy questions about their jobs. We would also like to thank Georgia Sinclair for providing the results of pharmacokinetic modelling and evaluations of published values of dermal flux rates of benzene.

We would like to acknowledge the help from Adelaide University in providing the information associated with the new cases and controls. We also thank Dr Alison Street of the Alfred Hospital who reviewed the diagnoses for several of the cases in the study.

Continuity between the Melbourne University exposure assessment and that by Monash/Deakin was enabled by a smooth transfer of information from Melbourne to Monash achieved by Geoff Adams and advice on the structure of the database from Michael Scales.

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Glossary

ACGIH	American Conference of Governmental Industrial Hygienists, a body that publishes TLVs (recommended occupational exposure limits) in the USA.
AE	Activity Estimate – estimate of the average benzene exposure (in ppm) of a subject during an activity.
AIP	Australian Institute of Petroleum.
AML	Acute myeloid leukaemia.
ANLL	Acute non-lymphocytic leukaemia.
ALL	Acute lymphocytic leukaemia.
API	American Petroleum Institute.
AUL	Acute undifferentiated leukaemia.
BE	Base Estimate – estimate of the average benzene exposure (in ppm) for a task calculated from a series of actual occupational hygiene measurements. Basis of the exposure estimation algorithm.
Black Oil	Heavy fuel oil, such as industrial diesel oil, fuel oil, furnace oil and bunker fuel, requiring dedicated transport.
BTX	Benzene, toluene, xylene, principally an aromatic fraction derived from coke oven operations.
Case	A man from the Health Watch cohort diagnosed as having a lympho-haematopoietic cancer.
CCU	Catalytic cracking unit.
CDU	Crude distillation unit.
CE	Cumulative Estimate – estimate of the cumulative benzene exposure (in ppm-years) of a subject during their period of employment in the petroleum industry.
CI	Confidence interval in this report 95% unless other wise stated.
CML	Chronic myeloid leukaemia.
CLL	Chronic lymphocytic leukaemia.
CLR	Conditional logistic regression.
CONCAWE	The Oil Companies' European Organisation for Environment, Health and Safety.
Control	A man from the Health Watch cohort matched to a case on year of birth.
DAP	Detergent alkylate unit.
EM	Exposure Modifier applied to Base Estimates in the exposure estimation algorithm to reflect changes in exposure as a result of changes in technology, product etc.
ERDC	Energy Research and Development Corporation.

GoF	Goodness-of-Fit testing
HEE	High exposure event, unusual and probably unplanned or unsanctioned exposure.
ICD	International Classification of Diseases.
IOL	Imperial Oil Limited (Canada).
IP	Institute of Petroleum (UK).
JUHI	Joint user hydrant installation, a shared refuelling pipeline facility at airports.
LEV	Local exhaust ventilation.
LH cancer	Lympho-haematopoietic cancer, cancer of the blood forming tissue.
LPG	Liquefied petroleum gases.
Lymphatic Cancer	Term used in this study for non-Hodgkin's lymphoma & multiple myeloma.
MEK	Methyl ethyl ketone.
MM	Multiple myeloma.
NE	Not occupationally exposed to benzene
NHL	Non-Hodgkin's lymphoma.
OR	Odds ratio.
PMR	Proportional mortality ratio.
Ppm	Parts per million.
PPE	Personal protective equipment.
RPE	Respiratory protective equipment.
S & P	Storeman and packer, a union-derived job type or name.
SD	Standard deviation.
SMR	Standardised mortality ratio.
Subject	A case or control in the case-control study.
TE	Task Estimate – estimate of the average benzene exposure for a task (derived by application of EMs to a Base Estimate in the exposure estimation algorithm).
THC	Total hydrocarbons, usually C_3 to $C_{8.}$
TLV	Threshold Limit Value, an exposure limit recommended by the ACGIH.
WE	Workplace Estimate – estimate of the average benzene exposure (in ppm) of a subject during a job (standardised for a 35-hour week).
White oil products	Refined products including gasoline, diesel (distillate or automotive diesel oil), kerosenes, aviation fuels and solvents.

Executive Summary

This study was carried out in response to results obtained in the Australian Institute of Petroleum Health Watch study indicating an excess of lympho-haematopoietic cancer (LH cancer) apparently associated with exposure to benzene. Health Watch is a prospective (forward-looking) study of all-causes of mortality and cancer incidence in the Australian petroleum industry that commenced in 1980. A notable finding of the Health Watch program has been the generally low rates for most causes of mortality among the study population. The slight increase in LH cancer was one of the few adverse outcomes.

A total of 79 cases of LH cancer, satisfying the study criteria, were identified in the cohort of nearly 16 thousand male workers and retirees. These included 33 leukaemias, 31 non-Hodgkin's lymphomas (NHL) and 15 multiple myelomas (MM). The study was of the "case-control" design in which the benzene exposures of the cases and controls were compared and analysed. Five male controls were selected for each case, matched by year of birth and chosen randomly from a list of all eligible cohort members at the time of diagnosis. Subjects could be chosen as controls for more than one case and could at some future time become cases without being excluded as controls for previous cases. Based on demographic comparisons, the controls were adequately matched with the cases.

The exposure to benzene of cases and controls was estimated on an individual basis. Subjects' job histories were obtained from company records and by interview of subjects or colleagues, and their tasks with exposure to benzene were identified by colleague interview. Estimates of exposure to benzene for individual tasks were derived from company occupational hygiene exposure monitoring data and were adjusted to take account of differences in technology, products handled, era and site factors. This information was used in a computer model to derive various exposure metrics including cumulative exposure in ppm-years and average exposure intensity in ppm. Short-term high exposures were assessed in several complementary ways.

The association between the various exposure metrics and LH cancer was analysed using the statistical package Stata ®. This analysis was applied to LH cancer as a whole as well as leukaemia, leukaemia sub-groups and lymphatic cancer (non-Hodgkin's lymphoma and multiple myeloma). Analysis was also performed to examine latency and the effects of duration of employment, period of first employment, industry site type, and smoking and alcohol consumption.

Estimated lifetime cumulative benzene exposures were low for the majority of the subjects, ranging from 0.005 to 57.3 ppm-years with a mean of 4.9 ppm-years. Nearly 85 percent of subjects had estimated cumulative exposures of less than or equal to 10 ppm-years and only 3.6% were greater than or equal to 40 ppm-years. Estimates of average benzene exposure intensity (cumulative benzene exposure estimate divided by total duration of employment) ranged from 0.001 to 2.07 ppm, with a mean of 0.20 ppm. Average exposure intensity was estimated to be less than or equal to 1.0 ppm for 98 percent of subjects and less than or equal to 0.5 ppm for 90 percent of subjects. The highest average exposures were for drum filling (approximately 1.8 ppm) and rail car loading (approximately 1.6 ppm).

The results demonstrate a strong association between past benzene exposure and leukaemia as a whole and the subtypes, acute myeloid leukaemia (AML) and chronic lymphocytic leukaemia (CLL). No significant association was found between benzene exposure and lymphatic cancer (non-Hodgkin's lymphoma and multiple myeloma) or multiple myeloma alone.

The risk of leukaemia was found to be strongly associated with both cumulative exposure and average exposure intensity. These metrics are highly correlated in the study population; individuals with high exposure intensities also had high cumulative exposures, hence it is difficult to assess which of these two metrics is the more important. There was some inconclusive evidence that the risk of leukaemia is determined more by periods of high exposure than by average exposure, thus implying a non-linear relationship with exposure intensity. Those workers who had exposure to concentrated benzene or benzene/toluene/xylene were more likely to develop leukaemia than those who had similar estimated average exposures but encountered the benzene in more dilute forms such as gasoline. This might suggest that episodes of very high exposure disproportionately increased the risk of leukaemia for the benzene and benzene/toluene/xylene exposed workers. There was no evident association between leukaemia and duration of employment alone, also suggesting that exposure intensity is the more important factor. However, analysis according to high day exposures, high exposure events and lifetime average exposure intensity did not provide corroborating evidence.

Exposures more than 15 years prior to diagnosis of leukaemia were found to have very little effect, if any, and the results are consistent with a mean latency to diagnosis of around 10 years. There was no detectable association between leukaemia and duration of employment, period of first employment (pre 1965, 1965 to 1975, and post 1975) or differences in cumulative exposures in these different eras.

Leukaemia risk was found to be more closely associated with exposure in terminals compared to other industry sites, but this is probably explained by the historically higher exposures in terminals rather than any other site characteristic. No cases of leukaemia were found among workers in offices.

The data were also analysed for evidence of any association between tobacco smoking and LH cancer, lymphatic cancer or leukaemia. This analysis demonstrated that any effect of smoking must be small and could not explain the observed association between leukaemia and benzene exposure. The cases and controls were found to be very similar in their alcohol drinking histories and there was no relationship between alcohol and the risk of LH cancer, lymphatic cancer or leukaemia.

Overall the findings strongly support the need to maintain the Health Watch cohort in order to collect further cases and to examine the trend in incidence, including the delayed effect of changes in technology that are expected to be beneficial.

1. Introduction and Background

1.1. Health Watch

Health Watch is an epidemiological health surveillance program that was run by The University of Melbourne on behalf of the Australian Institute of Petroleum (AIP) from 1980 until 1998. The University of Adelaide now runs the program. The program investigates and reports on mortality and cancer incidence in the Australian petroleum industry with the aim of detecting any risk to health associated with work in the industry. It consists of a prospective cohort study of all-cause mortality and cancer incidence. The cohort consists of all employees except head office staff and those employed at sites with less than ten employees. Employees in the industry have been surveyed about every five years. The first survey was conducted from 1981 to 1983 and resulted in an original cohort of 10,979 men and 626 women. More subjects were recruited in the second and subsequent surveys. About 95 percent of eligible employees in the industry have participated in the surveys. An employee is taken into the cohort analysis after having served five years in the petroleum industry and remains in the Health Watch cohort for life. In 1998 the cohort comprised 15,732 men and 1,178 women. A 2 fold excess of leukaemia and multiple myeloma was reported for the male members of the cohort, both of these increases were statistically significant (1). Non-Hodgkin's lymphoma was not in excess.

The Health Watch program is described in more detail in Appendix 1. A background to the industry and the sources of exposure to benzene is presented in Appendix 2.

A nested case-control study of lympho-haematopoietic cancers (LH cancers) and benzene exposure was started at Melbourne University in 1988. Only men were included in the case-control study. Quantitative exposure estimation for the subjects in the case-control study started in 1995, (referred to as the ERDC study (2)) and continued since 1999 at Monash University, Department of Epidemiology and Preventive Medicine in conjunction with Deakin University's Occupational Hygiene and Public Health Departments.

Cases of lympho-haematopoietic cancer (leukaemia, multiple myeloma and non-Hodgkin's lymphoma) were identified in the cohort and their exposure to benzene was retrospectively assessed. Exposure to benzene was assessed for 65 cases and their controls at Melbourne University. 15 more cases were identified after 1998 and their exposure was assessed at Monash University.

1.2. Risk of Lympho-haematopoietic Cancers and Exposure to Benzene

Benzene is present at almost all stages of petroleum industry activity, it is one component of gasoline fuels. It occurs naturally in crude oil and gas liquids and is formed during combustion of fuels and other materials e.g. in tobacco smoke, wood smoke and coal burning. Surveys have shown that benzene is present in indoor environments from activities such as cooking and heating and is ubiquitous in community air at low concentrations (3, 4).

Benzene is an established human carcinogen within the IARC criteria (International Agency for Research on Cancer, World Health Organisation), and is associated with an increased risk of leukaemia. Other suspected outcomes are multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL).

1.2.1. Non-Hodgkin's Lymphoma

A review by Wong and Raabe reported in 2000 (5) of the exposure to benzene for 308,000 workers in a multinational study of 26 cohorts from 5 countries, found no increased rate of NHL and no differences in the rate of NHL before and after 1950 (exposures were generally higher before 1950). The results suggest that the risk of NHL is probably not associated with benzene exposure.

1.2.2. Multiple Myeloma

In 1990, Goldstein considered it reasonable to causally relate benzene exposure to multiple myeloma but that the level of proof did not reach scientific certainty (6). In discussion reported after the previous article, Landrigan raised the possibility that "relatively low cumulative exposures to benzene may produce a relatively well-differentiated cancer, such as multiple myeloma whereas higher exposures may lead to leukemia" [6]. More recent reviews have also suggested that there is evidence that multiple myeloma may be linked to benzene exposure [7, 8].

A review of hospital and population based case-control studies, however, concluded that there is no statistically significant association with benzene exposure [9]. A recent review similarly concluded that there was no evidence of an association between benzene exposure and multiple myeloma [10]. The conclusions of the article were challenged in subsequent letters [11, 12].

1.2.3. Leukaemia

There is general agreement in the scientific community that benzene can cause leukaemia in highly exposed individuals, but at present, what constitutes a safe level of exposure for benzene is unknown. The relationship between low level benzene exposure and risk of developing leukaemia is uncertain. This uncertainty results mainly from the incomplete data on the extent of exposure to benzene among the individuals in the epidemiological studies and the possibility that the exposure response relationship may be non-linear and/or there is a threshold. In addition the type of leukaemia that is caused by exposure to benzene has not been firmly established, some authorities consider that AML is the only leukaemia clearly associated with benzene exposure [13-15] but this is disputed by other researchers [8, 16].

Exposure to benzene in the Australian petroleum industry is probably an order of magnitude lower than that reported in some other industries to be associated with clearly increased risk of leukaemia [17]. The risk at lower levels has been hotly debated over the past twenty years, [7, 13, 15, 18-38]. The debate has centred on two issues: whether the exposures were underestimated in the Pliofilm™ or Chinese benzene studies; and what risk assessment model should be used to extrapolate the risk to workers exposed to lower concentrations of benzene.

1.2.4. Mechanism of benzene-induced leukaemia

In the normal formation of blood cells (haematopoiesis), the wide range of circulating blood cell types arise by division and progressive differentiation of a common stem cell type [39]. These precursor stem cells produce both myeloid stem cells and lymphoid stem cells that are committed to the production of distinct cell lineages. The myeloid stem cells produce various secondary stem cell types which further differentiate to produce, via a series of developmental stages, erythrocytes (red blood cells), thrombocytes (platelets), eosinophils, granulocytes and monocytes. The lymphoid stem cells produce plasma (B) cells, and T cells and possibly natural killer cells [39]. The bone marrow also serves a complex regulatory function in the balanced production, differentiation and release of mature cells into the circulation.

Benzene is both haematotoxic (cytotoxic) and leukaemogenic by a range of mechanisms involving the bone marrow haematopoietic cell populations [40]. The haematotoxic effects of benzene largely involve cytotoxic damage to the bone marrow stem cells or intermediately differentiated cells leading to reductions in the number/function of erythrocytes (anaemia) granulocytes (neutropenia) and platelets (thrombocytopenia). Severe cases can proceed to pancytopenia (aplastic anaemia) involving all three blood cell types. Benzene is also associated with myelodysplastic syndrome in which haematopoiesis is impaired because of stem cell disorders, resulting in pancytopenia. The syndrome is often fatal and is associated with a substantial risk of conversion to acute myeloid leukaemia [39].

The term "leukaemia" is applied to a range of malignant proliferations of cells in the blood that can involve either myeloid or lymphoid cell types, although some leukaemias involve undifferentiated cells that cannot easily be characterised in this way. Benzene has been shown to be associated with acute myeloid leukaemia, and while there is some evidence for an association with other types of leukaemia the evidence is weaker (8, 16).

The myeloid leukaemias are divided into acute (AML) and chronic (CML) forms. AMLs are heterogeneous and may involve proliferation of various representatives of the myeloid cell granulocytes or monocytes lineage [39]. The proliferating immature precursor cells accumulate in the bone marrow, as well as in circulating blood and elsewhere, thus displacing normal haematopoietic cells and causing pancytopenia. Prognosis is generally poor and while approximately 60% remission can be achieved with chemotherapy, the disease recurs in 70% to 85% of cases within 5 years. Chronic myeloid leukaemia (CML) also involves proliferation of stem cells, but unlike in AML, the cells continue to differentiate into functioning mature cells. CML progresses relatively slowly but after a mean delay of three years often accelerates into AML. Low dose chemotherapy can prolong the slow phase and cures can be achieved in many cases by bone marrow transplantation if suitable donors can be found [39].

The lymphoid (lymphocytic) leukaemias are also divided into acute (ALL) and chronic (CLL) forms. In ALL there is a proliferation of immature precursor B or T cells (lymphoblasts). Normal haematopoiesis is suppressed resulting in pancytopenia. It is sometimes difficult to distinguish ALL from AML on the basis of clinical features or cell appearance and it is then necessary to carry out immunological identification. Most cases of ALL occur in people below the age of 15 and it is much less frequent in adults. The prognosis is good in childhood cases and about 90% can be treated successfully with chemotherapy. In adults the prognosis is less optimistic. CLL involves proliferation of B cells with particular and distinctive immunological markers. It causes disruption of the immune system by mechanisms that are not well understood, leading to increased susceptibility to infection, and in some cases autoimmune attack on healthy erythrocytes and thrombocytes. It is the most common form of adult leukaemia in Western populations, occurring mostly at ages above 50 and is more common in males. Mean survival is about 4 to 6 years but the prognosis is very variable with some patients surviving 10 years or more. There is a tendency for the disease to eventually progress to a more aggressive form of acute leukaemia or lymphoma [39].

Not all leukaemias can be identified unequivocally as belonging to either myeloid or lymphatic lineages. In acute undifferentiated leukaemia (AUL), there is a proliferation of early progenitor cells with only a few chromosomal changes. These can be classified as acute non-lymphocytic cancers (ANLL) along with AML [41]. A small proportion of leukaemias defy histological categorisation and are classes as unidentifiable or unspecified.

Benzene is converted to other substances by metabolic processes in the body and these metabolites are thought to be responsible for most of the toxic effects associated with benzene exposure [40]. The major metabolic activity is in the liver where mixed function oxidase enzyme systems (cytochrome p-450) oxidise benzene to benzene oxide (an epoxide). Spontaneous rearrangements convert this to muconaldehyde, muconic acid and phenol, while other enzymes (including epoxide hydrolase) convert benzene oxide to catechol (ortho dihydroxy benzene) and further hydroxylation produces trihydroxy benzene. Phenol also undergoes further hydroxylation to produce hydroquinone (para-dihydroxy benzene) and quinone (1,4 benzoquinone). All of these compounds are to some extent conjugated in vivo with sulfate and glucuronide thus reducing their potency. The overall kinetics of benzene metabolism is saturable because the enzyme system has a finite capacity (Michaelis-Menten kinetics). At low doses the conversion rate is proportional to the dose but at higher doses the metabolic rate is independent of the dose, and other compounds can compete with benzene for the enzyme sites. Concurrent exposure to toluene for example reduces the rate at which benzene is metabolised. Benzene metabolites produced in the liver are transported to other parts of the body including the bone marrow.

There are additional metabolic enzymes present in the bone marrow that act upon benzene and its metabolites, including myeloperoxidase, DT diaphorase and quinone reductase. Myeloperoxidase converts benzene liver metabolites into more reactive (potent) metabolites including various quinones [42]. These reactions also are potentially saturable, as are the detoxification processes such as conjugate formation and deactivation by quinone reductase. The reactive metabolites of benzene cause a range of chemical changes in biological macromolecules including oxidative damage and adduct formation involving DNA, cell surface receptor sites and other intracellular target molecules. Point defects in DNA because of oxidation or adduct formation are less important than major chromosomal changes (clastogenesis) that also occur [40].

The molecular mechanisms underlying haematotoxicity as a result of exposure to benzene are not known with certainty, but its metabolites cause a variety of changes in stem cell behaviour and survival. This can involve direct toxic effects on haematopoietic cell populations, the regulatory system or regulatory signalling. These effects appear to be related to dose in a non-linear way; higher doses are disproportionately more damaging than lower doses [42].

The molecular mechanisms underlying leukaemogenesis appear to involve clastogenic effects. Leukaemia cell populations are monoclonal (resulting from a single cell or cell type) and are found to have distinct chromosomal abnormalities including breaks and deletions and disconnected strands (micronuclei). It is thought that these abnormalities are not because of direct genotoxic attack on DNA, but are the result of interference with chromosomal separation during cell division as a result of benzene metabolite induced chemical changes to the protein structures involved in separating the chromosomes. These effects also are thought to be highly non-linear with higher doses producing a disproportionately greater effect than low doses [40, 42].

1.3. Leukaemia in the Oil Producing, Refining and Distribution Industry

1.3.1. <u>Refinery Workers</u>

The majority of the studies in the petroleum industry were carried out in refineries which had relatively large populations on which to base a cohort. There were some excesses of leukaemia, but no significant excesses were found in 17 cohorts, several of which have been followed up and extended several times, [43-76][1]; and Hornstra (1989), Nakamura (1987), Enterline and Henderson (1985), all cited from [68].

Leukaemia is a relatively rare disease so that, even in refineries with large working populations, the small number of cases can make the SMRs unstable. Satin *et al* [60] found the ALL SMR for men was 260 (95% CI 112 - 512). There was a significant deficit in CLL and there was no excess in myeloid leukaemias. The authors express concern that the excess may be a result of misdiagnosis. Indeed if a single case of ALL had been removed the result would not have been significant. Similarly a significant excess of CLL in a refinery population [53] was not sustained in further follow up study [55].

It has been suggested that part of the explanation for the low rate of leukaemia may be that smoking rates, although unknown, were probably low in the cohort. Smoking rates are a possible risk factor for leukaemia [73, 77]. This was also noted in a UK study, where lung cancer rates were also low [78].

Concern has been expressed that there may have been a small group exposed to a specific hazard lost in a broader category, resulting in no significant association [79]. This question was investigated in a case-control study of leukaemia [80]. The authors matched each of the cases of leukaemia with 2 controls and examined the job for likely exposure to benzene. They found that for those cases deemed to have high or medium exposure to benzene, the risk of leukaemia approached significance when length of service was taken into account.

Twice the expected rate of leukaemia was found at the Wood River facility [81], SMR 213 (CI 117 - 358) among 3,976 white males. Rates were higher for some sub-groups but the numbers were small. The SMR for AML was elevated. Other reports have suggested that "other refinery studies could have an elevation in AML that is diluted by the summary SMR for all cell types of leukaemia combined" [79, 81]. This concern prompted the establishment of a case-control study of AML based at this refinery [82]. Each case of leukaemia was matched with 4 controls and their work histories were examined. Occupational hygienists with expertise in the industry were employed to allocate the jobs on the basis of whether the person was likely to have been exposed to a stream with >5% benzene. A great deal of careful work was put into the exposure allocations, but the work histories were not very detailed so that the conclusions were limited. In addition the intensity of exposure was assessed largely on smell and it is unlikely that this was reliable, especially at the lower end of the exposure range, as the odour threshold of benzene is estimated to be 5 ppm [83]. The overall conclusion was that, unlike the UK study, the controls had worked longer in benzene-exposed locations than the cases.

The Wood River cohort was later updated and enlarged [84]. There was a statistically significant excess of lymphocytic leukaemia for those men hired before 1940 and of myelocytic leukaemia for those hired after 1940. Manufacturing processes changed over time and in 1941 there was an increase in the percentage of benzene in some of the refinery streams to between 5 and 10%, although there were simultaneous improvements in controls to reduce exposure. The study was later updated and the excess of leukaemia cases that was observed up to the 1980s disappeared [85].

An elevated risk of LH cancers was also found for employees who started work at a refinery and chemical complex before 1946, although this decreased for those hired in later years [70, 71]. Refinery cohorts in

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[1] The highest risk to be associated with over 15 years of employment lagged by 10 years to overcome the lack of occupational histories. Recent benzene exposure measurements were low, the majority less than 1ppm.

the USA were studied and the SMRs for leukaemia were found to be 172 (statistically significant) and 97 respectively [14, 68]. One cohort study was further investigated and the SMR for lymphatic and haematopoietic cancers was found to be 133 (CI 103 - 170) [86] and the SMR for leukaemia was 139 (CI 92 - 201). This excess of leukaemia was confined to workers hired before 1950 and peaked in the 1960s. The leukaemia SMR for maintenance/craft workers was 179 (CI 111 - 273).

A significant excess of leukaemia was found for Swedish refinery operators, (CI 1.5 - 7) [87]. Again, most of the cases started work in the 1950s.

Proportional mortality studies (PMR) have been carried out based on trade union records. Since the population within which these deaths occurred could not be accurately determined an SMR study was not possible. A raised proportion of leukaemia was found [88], but the findings were challenged [89]. In a later investigation, the retirees were traced and an excess of haematopoietic and lymphatic cancers was again identified [90]. After obtaining further data from the NCI and the study was updated to 1993 for white males [91]. There was a significantly increased PMR for a number of cancers including leukaemia. A similar pattern was seen for each of the 3 individual refineries. Another union based PMR study has also found an excess of haematopoietic and lymphatic cancers in benzene exposed workers [92].

Overall, there is evidence of an association between refinery work and elevated risk of leukaemia. Some association exists for workers hired before 1950, and limited evidence of greater risk for small groups of workers with higher exposures within the refinery populations.

1.3.2. Distribution Workers

Distribution workers have been exposed to gasoline with up to 5% benzene content and some workers, have been exposed to products with higher concentrations of benzene, e.g. BTX which contains approximately 70% benzene. Four studies of the distribution sector are summarised below, the summary includes the API (USA), IOL (Canada) and IP (UK) cohorts [46, 87, 93-98]. There was an increased risk of leukaemia for tanker drivers in the latter two studies, although this was not a significant increase in the last study. The same problems arise with these studies as for the refinery cohorts namely, lack of smoking data, lack of historic exposure data and lack of documentation on the completeness of the cohort. Three of these studies were followed up with a nested case-control study to try to more accurately define job histories and hence exposures.

A case-control study for leukaemia was nested within the API distribution worker's cohort [99, 100]. There were 35 leukaemia cases overall, with 5 controls for each case. The cases and controls were categorised by job and by several quantitative gasoline exposure indices [101, 102]. The study found no significant difference between the exposures of the cases and the controls by any of the metrics: duration of exposure, cumulative exposure or frequency of peak exposure.

In the IOL study cases of lympho-haematopoietic cancers were identified and exposures to benzene for cases and a selection of controls were assessed in detail [103]. There was no exposure response evident for leukaemia with lagged or unlagged exposures. The increased detail available on work histories identified tanker drivers, for whom the OR for leukaemia was 1.09. The measure of exposure most closely associated with risk was duration of employment. The study had insufficient power to demonstrate a risk at low levels of exposure [104].

The nested case-control study in the IP cohort, identified 91 cases of leukaemia, each matched to 4 controls [105, 106] and their benzene exposure was rated [107, 108]. For those exposed for more than 5 ppm-years, there was some evidence that exposure to benzene resulted in an increased risk of leukaemia but the correlation was strongest for those employed for more than 10 years in the industry. There was some evidence that those workers with a "peaky" exposure had an increased risk of leukaemia, (Section 2.9). There was no significantly increased risk with measures of cumulative exposure, maximum intensity or mean intensity. The study was criticised by Wong and Raabe, on the basis that many of the job histories (47%) were uncertain [109].

In a study of seamen on tankers, individuals were identified from census data and cross-linked with the Swedish Cancer Register [110]. Experts were used to identify the probable jobs and type of cargoes for the individuals. An increased incidence of lymphatic and haematopoietic cancers was found among seamen exposed to cargo vapours from gasoline and other light petroleum products.

Overall therefore, there is some evidence of increased mortality from leukaemia among petroleum product distribution workers.

1.3.3. Upstream Workers

Upstream workers include those involved in oil field exploration and drilling, in production, stabilisation and preparation of crude oil and gas for pipeline and tank-ship transportation. These workers have not been intensively studied, probably because the exposure to benzene is generally low. Typically crude oil contains less than 1% benzene and in addition most production work takes place in the open air, even at sea, where winds can be expected to be effective in reducing exposure.

A case-control study based on petroleum company records found 69 cases of leukaemia [(111)]. Each of these was matched with 4 controls. A positive association was found between oil and gas fieldwork and AML compared to non-production work. This was the first time that such an association has been reported for upstream workers. There was no clear association between refinery work and risk of AML.

The mortality of one upstream cohort has been examined [(112, 113)]. Analysis by specific group gave small numbers of cancer cases with wide confidence intervals and there were problems in assigning workers to specific groups as most had held multiple jobs. There was significant excess of AML among men employed before 1940 in production and pipeline jobs.

In summary, the link between upstream work and leukaemia has not been established.

1.4. Exposure Assessment in the Petroleum Industry

Numerous epidemiological cohort studies have been carried out on workers in the petroleum industry all over the world. Most have been retrospective studies where the cohorts have been assembled from all workers employed during a specific period and the mortality and exposure status of the workers determined. A few, such as Health Watch, have been prospective studies, where the cohort has been assembled from current workers, and the individuals followed prospectively into the future. Prospective studies allow the collection of more detailed occupational and smoking histories.

There have been some studies where the health experience of the industry as a whole has been compared to that of a reference population. In these studies there has been little or no attempt to group subjects on the basis of exposure [(44, 70, 71, 73, 74, 81, 90, 114-116)]. In other studies, division has been made on the basis of hourly or non-salaried or blue collar workers compared to the rest of the cohort [(56, 81, 84, 85, 111, 117)]. In a number of studies the subjects were divided on the basis of job titles or groups, [(52, 62, 65, 81, 88, 112, 118)]. In one study a “quantitative” exposure index based on job type has been used to assess the percentage of exposed workers at each site [(43)]. In other studies some attempt has been made to group workers into semi-quantitative exposure groups [(45, 46, 48, 80, 119)].

Quantitative exposure assessment was attempted for the operations and maintenance sections of a refinery cohort, that is for those sections that were thought to be most likely to have been exposed to benzene [(58)]. The investigators estimated that 84% of benzene exposure measurements were less than 1 ppm and only 1% were greater than 25 ppm. The assessments were based on actual measured exposures all of which had sample times of less than 4 hours duration.

Exposure assessments of filling station attendants have also been carried out in parallel with an epidemiological study [(120, 121)]. The benzene exposures averaged 0.55 ppm 8-hour TWA. Multiple linear regression showed that the number of vehicles, type of fuel and season were the best predictors of exposure.

In case-control studies of leukaemia in the general population, there have been some attempts to identify which individuals were likely to have been exposed to benzene or benzene-containing materials, such as gasoline [(122-128)]. Except for Siemiatycki *et al.* and Clavel *et al.* the various authors have provided almost no explanation of how the exposure assessments were carried out.

In these various epidemiological studies in the petroleum industry establishment of health outcomes has been much more certain than categorisation or estimation of exposures. The lack of reliable exposure assessment remains a major weakness.

1.4.1. Quantitative Exposure Studies in Petroleum Industry Epidemiology

There have been three major studies that have attempted to quantitatively assess exposure to benzene in the petroleum industry. They have all followed the "source receptor" model described by Dement *et al* [129].

An exposure assessment was carried out for the API study of US petroleum industry distribution workers [101, 102] whose mortality experience was investigated [94]. The cohort was divided into generic groups including driver, loader, terminal operator and other terminal operators (and similar groups for marine operations). The "source receptor" model was used to estimate exposure to hydrocarbons. Various exposure modifiers (EMs) were determined for work situations. For example, for truck drivers, EMs included splash, submerged or bottom loading, metered or valve delivery controls, vapour recovery technology, percentage gasoline handled, fill time, delivery time etc. The changes to the EMs over time and the effect of changes on exposure was estimated. Exposure measurements were undertaken to augment those available from the companies. The period of the study was divided into eras, depending on the technology in use, and annualised average exposures were calculated from task based information and inserted into a job/era exposure matrix. Cumulative exposure and frequency of peak exposure to total hydrocarbons (THC) (defined as >500 ppm over 15-20 minutes) were then calculated for each person using the matrix information. Considerable expertise was brought to bear, for example in assessing which jobs had how many peak exposures. The authors also examined the uncertainties that arose as a result of the exposure extrapolation that took place. The uncertainties varied between different job groups but the authors did not believe that this had obscured the differences between groups which were identified by the study. The uncertainty associated with the exposure assessments, was not presented numerically but a discussion was presented in the report to the API [130].

The cohort study was followed up with a nested case-control study [100]. The land based terminal operators were divided into more specific groups for which quantitative exposures were assessed. No association was observed for all leukaemia cases or for AML alone by duration, cumulative exposure (ppm-years THC) or frequency of peak exposure.

The second study investigated the lympho-haematopoietic cancer mortality among a cohort of petroleum marketing and distribution workers employed by Imperial Oil Limited (IOL) in Canada. The mortality experience was described [96] and the exposure to benzene and total hydrocarbons was retrospectively examined for 31 LH cancer cases and 124 controls [103]. The subjects had 43 job titles and worked at 89 locations throughout Canada. The investigators used an exposure estimation algorithm similar to that used in the API study [130]. They too derived a task-based, time-dependent exposure matrix for the subjects. In an internal document [131] the investigators described in some detail, the processes by which they decided upon the EMs and the values ascribed to these modifiers. The variance of the data used in the algorithm was used to estimate the variance and confidence intervals of the historic estimates. The estimations that were made were validated by comparison with other modern data [103].

In the final study, exposure assessment was carried out for the 91 cases of leukaemia and 364 controls included in the Institute of Petroleum (IP) nested case-control study [107, 108]. The cases and controls were identified from among the 23,000 workers in the UK oil distribution cohort [98]. The exposure assessment task force based their model on that of the IOL study and considered six modifying factors. Many of the workers were described as *Terminal Operators* and the tasks that they carried out were ill defined. The investigators produced a Base Estimate (BE) of exposure for these workers, based on a list of tasks and products which changed over time and from site to site. They used non-UK-derived data to validate their exposure estimates. The analysis of the IP case-control study has been described by Rushton and Romaniuk [106].

1.5. Project Objectives

The principal objectives of this project were to:

1. Extend the case-control study by applying the benzene exposure assessment used in the ERDC study, in the Health Watch program, to the new LH cancer cases and controls;
2. Develop a new metric for benzene exposure based on frequency of high exposure days;
3. Investigate the extent of infrequent and unusual high exposures;
4. Gather more data to further validate uncertain BEs used in the ERDC study;
5. Estimate the association between cumulative exposure to benzene and the relative risk of LH cancer, leukaemia and its sub-types.
6. Examine the effect of high exposures on risk.

2. Methods

2.1. Case Identification, Case-control Definitions and Diagnoses

This investigation is a case-control study nested within the Health Watch cohort study.

2.1.1. Definition of Cases

All cases were male members of the Health Watch cohort, who had:

first diagnosis of LH cancer (ICD 9 200, 202-208) after entering the Health Watch cohort in 1980;

and diagnosis confirmed by pathology report, cancer registration, letter from medical practitioner, or death certificate;

and had reported LH cancer to Health Watch either by self or by family, **or** were lost to contact by Health Watch, **or** were deceased.

2.1.2. Definition of Controls

Five male controls were selected for each case, matched by year of birth. The controls were chosen randomly from a list of all eligible cohort members. The protocol for the case-control study stated that only cohort members at the time of diagnosis of the case were eligible to be controls. The selection was made at Melbourne University and later by the cohort management team at the University of Adelaide.

2.2. Numbers of Cases and Controls

The original exposure assessment (ERDC study) was carried out at Melbourne University for 390 subjects, comprising 65 cases and their controls. Eighty workers were identified as cases by searching the cancer registries and through self-report. One of these cases could not be used because he did not self-report the disease, and was not considered lost to follow-up. Thus, the final number of cases studied was 79. Age-matched controls for these cases were selected from the remaining pool of workers, giving a total of 474 subjects for analysis with confirmed job histories. To develop appropriately age-matched case-control sets, five workers were used as controls in multiple sets. As a result of random selection 4 of these individuals were used in two case-control sets, and one was used in three sets.

2.3. Overview of the Exposure Assessment Process

The exposure assessment was based on that described in the ERDC report [(2)]. The approach is summarised in Appendix 3. The new subjects were added to the original exposure database and their exposures were assessed in the same manner as the original subjects, by one of the two original members of the exposure assessment team.

The exposure of many of the additional subjects were satisfactorily estimated using pre-existing information, gathered during the first survey. There were, however, some new jobs for which more information from the relevant site was needed. The contacts made in the first survey were used to gather information by telephone from these sites. There were in addition, some new sites identified for which suitable contacts had to be identified.

2.4. Subject Job Histories

2.4.1. Source of the Information

The following information had been collected at various Health Watch surveys

- Survey 1 – current job held at time of survey (1981)
- Survey 2 – current job held at time of survey (1986)
- Survey 3 – history of all jobs held in the oil industry until survey time (1991)
- Survey 4 – current job held at time of survey (1996)

In 1994, the Health Watch investigators endeavoured to obtain complete job histories from all members of the cohort who were no longer working in the petroleum industry and who had not therefore been interviewed in the third survey. Subjects may have given different dates or different job and task titles at different surveys and this resulted in some difficulty in defining one coherent job history for each subject. To resolve this, a program was run which developed a job history using the information which was given at the closest time to the job in question. For example, if at Survey 1 in 1981, the subject had reported that job A was their current job, but later, in survey 3, they reported that they had held job B in 1981, they were allocated job A for 1981.

2.4.2. Verifying the Job Histories

All survey questionnaires for case-control subjects were reviewed to extract any text information about jobs. All job information was checked for completeness and logical sequence. Health Watch had consent from subjects in the case-control study to obtain a copy of their work history from the petroleum companies. A printout of the job history was sent to the contact person at each company where the subject had worked. The job history did not identify whether the subject was a case or a control. The contact person was asked to check the history against their personnel records and notify any differences. In the early years of the study, this corrected job history was then sent to the subject for confirmation. This step was later abandoned.

The job histories obtained from the companies provided information about which sites the subject had worked at, when they had worked there and the broad job classification, but usually lacked sufficient detail to identify which specific tasks or which units they had worked on. Furthermore, they were not always complete, especially for those workers who retired in the early 1980s or who were employed before computerisation of personnel records. Early paper records had been archived in off-site storage and were not available. Very limited information was available on subjects who had worked for companies such as Amoco, Golden Fleece and Total, which were taken over by other petroleum companies during the period of interest.

The information provided in this initial job-list was cross-checked with the company information and with that provided by the subjects at each survey in which the subject had participated. Discrepancies that were discovered were rectified and additional details added when available. Where there was a conflict between the company record and the subject's recall taken from the Heath Watch surveys, the more detailed record was used. This was usually the job information obtained by interview during the Health Watch surveys which were carried out prior to disease diagnosis.

2.4.3. Job History Information provided to Exposure Assessment Team

For each job in each job history, the company, site and time period was identified. The job histories did not contain names or identify whether the subject was a case or a control. For each subject the information contained the company, site, job title and area of work for each calendar period in years and months. The job titles used by the subjects were obtained from the questionnaires.

Only 10 of the original 390 subjects had incomplete job histories. For these subjects their date of first employment in the petroleum industry was known but no information was available on their early jobs. It was assumed that the subjects had been doing their first known job since their date of first employment. Two among the 84 new subjects had included early jobs in their job histories that the companies had no record of. Where a subject had held more than one job, but information was not available about when the second job started, the period of employment was split equally between the two jobs. If hours of work were missing, 40 hours per week was used as a default until 1973 and from 1974, at which time there was a union hours of work agreement, after which the hours were assumed to be 35 a week. Jobs outside the petroleum industry were not included in the exposure assessment.

Some jobs were divided into different activities carried out concurrently. For example, a subject with the job title *Storeman and Packer* at a terminal, might have spent time filling drums, preparing drums in the drum laundry, filling rail cars and sweeping the yard. Each of these would be a separate activity or task in terms of potential exposure. For most people the hours of work on each activity was also noted by the Health Watch interviewer. One notable exception was for subjects with the job title *Driver* where the division of hours between loading, unloading and driving activities was rarely given. For subjects with the job title *Refinery Operator* who looked after more than one unit, the time spent on each unit would be listed as a separate activity. However, if they worked on six or more units or were regularly rotated between units, they had usually been coded as *Refinery Operator Plantwide*. At some refineries units were grouped together into areas and refinery operators were assigned to an area. For those refineries information on the area that an operator worked in was sometimes available from the written comments in the questionnaire or could be deduced from the coding and knowledge of the site practices. For subjects with the job title *Supervisor* the time spent on the plant and the time spent in the office were usually noted separately. The activity could be further split into tasks. For the supervisor, the time on the plant could be supervising in a particular unit, taking samples or performing other tasks such as paperwork.

A variety of job titles had been used by subjects to describe essentially the same job and tasks. Individual subjects in different Australian states doing broadly the same job could be identified by three or more separate titles. This depended on company job title allocations, union affiliations and traditional state practices. There was also considerable variation in tasks undertaken by people bearing similar job titles. The term used by the subject was retained as far as possible but the job titles were examined by the petroleum industry occupational hygienists who agreed that some of the job titles were synonyms. Appendix 4 gives a complete list of the job titles and the activity group to which each was allocated.

Each of the individual subject's activities was categorised by the occupational hygienists into one of the activity groups in Table 1. Appendix 5 describes the tasks that might be carried out by subjects within an activity group. This grouping led to the choice of questionnaire used at the site and the likely tasks that the subjects carried out. Appendix 6 lists the combination of the tasks associated with each activity group. Only those tasks thought to be associated with a likelihood of exposure to benzene have been identified. The remaining tasks, for example, paperwork have been grouped as *Other*.

The collaborating occupational hygienists from each petroleum company were asked to identify for the subjects from their company, those tasks which were considered to result in no occupational exposure to benzene and those where only bystander or background exposure was likely. Appendix 7 sets out the definitions for "not occupationally exposed" and "background" that were used in the study.

A list of refinery units where subjects had worked at some stage was also compiled with the help of the company hygienists. These refinery units were then categorised by the petroleum industry occupational hygienists into those units where benzene was not present in the stream or products and those units where it might be expected to be present, these are listed in Appendix 8. It should be noted that this is not a complete list of all units at all refineries but only those represented in the study and some units may now be shutdown.

Table 1: Activity Groups

Group	Description
Aircraft Refuelling	Time spent on tarmac, loading truck and refuelling or on tank farm duties.
Drum Filling	Filling drums with refined products.
Drum Laundry and Preparation	Receipt of drums, inspection and cleaning, spray painting and preparation for filling.
Fitting	Work done by fitters, welders, machinists, their helpers, trainees and foremen where "hands-on".
Laboratory	Any laboratory work including sample collection excluding office or supervisory work.
Office	Work in an office, canteen, etc away from exposure.
Non-exposed Sites	Work at Castrol sites, the Kwinana Nitrogen Company plant or at units detached from refineries and not using benzene-containing materials.
Other Refinery	Activities not classified elsewhere including time in control rooms or operating “non-benzene units” (Table 121), instrument & electrical work, rigging, labouring, security, white-collar plantwide activity
Other Terminal	Activities not classified elsewhere including lubricating oil blending and filling, forklift and packaged good driving, stores, yard work, security and white-collar plant-wide activity.
Other Upstream	Activities not classified elsewhere including wireline work, heliport, radio operations, stores, security and white-collar plant-wide activity.
Rail Car Loading	Rail car loading only
Refinery Operations	Process operations on refinery units where benzene could occur (Table 122) done by operators or their supervisors.
Road Tanker Driving	All tanker driving, including loading and unloading, regardless of load.
Road Tanker Loading	Road tanker loading where not done by a driver of vehicle.
Supervision	Work of a supervisory nature with no hands-on exposure, but close to others with hands-on exposure.
Tank Farm Operations	Work in the tank farm of a refinery or a terminal, includes API separators, pipeline and blending, pumping, sampling, pigging, dewatering and gauging.
Unclassified	Insufficient information to categorise the activity.
Upstream Operations	Oil production operations, both offshore and onshore.
Vehicle Maintenance	Work done by mechanics (not rig mechanics) and their supervisors (if hands-on).
Wharf and Jetty Operations	Loading and unloading ships and barges including bunker fuels.

2.5. Site and Job Characterisation

2.5.1. Site Information

In the initial exposure assessment, each site still operating where subjects were or had been located was contacted and asked to complete a brief site assessment form (Appendix 9). This sought a site contact for liaison and some brief information about the activities, technology and products handled. Each site was then followed-up with a visit or telephone calls. Where possible, questionnaires were completed for sites no longer operating by interviewing men who used to work there about the specific jobs of interest.

A questionnaire was prepared to expand on the information on each of the sites gathered in the initial site assessment based on a questionnaire devised by Pearlman and others for the IP study. This sought information on the history of the site, the major changes in staffing, plant, product and technology. The sources of the products handled over the period of interest were identified when possible, so that for example, gasoline was traced to the refineries of origin.

2.5.2. Percentage of Benzene in Gasoline

A report was prepared by a consultant summarising the available information on the benzene content of gasoline produced in each Australian refinery over the years (Annex A to the ERDC Report (2)). The benzene content varied with the type of gasoline. Typically unleaded gasoline contained more reformate blend stock (and hence more benzene) than leaded, however this occurred only from 1988. The proportion of regular, premium leaded, unleaded and premium unleaded gasoline was known on a yearly Australia-wide basis. This proportion was used at each site to derive an average benzene concentration for the gasoline handled at that site. One company sold some high benzene gasoline until about 1970. This is thought to have contained approximately ten percent benzene.

2.5.3. Information Sources

Information about jobs, activities, tasks and sites came from interviews with employees and ex-employees including retirees. The interviews were carried out without naming the subjects about whom information was being sought or revealing whether the subject was a case or control.

There were four major sources of information:

- Current employees at petroleum company sites. These employees were mainly interviewed during site visits.
- Readers of company and AIP newsletters. Information articles on the retrospective exposure assessment project were placed in company and AIP newsletters and readers asked to contact Health Watch if they were able to provide more detail on the information requested. These individuals were followed-up initially by telephone and some were later visited at their homes. They were mainly retirees.
- Health Watch cohort members. For sites which were closed or where more information was needed the Health Watch cohort database was used to identify members who had worked at that site during the period of interest. These employees or ex-employees were then contacted by telephone.
- Other individuals identified by personal recommendation either via one of the other sources or from the petroleum company occupational hygienists. These individuals were initially contacted by telephone and some were visited. They were mainly employees or ex-employees.

2.5.4. Task, Technology and Product Information

Job-specific questionnaires were prepared seeking information on the tasks, technology and products for relevant job activities. A list of the job specific questionnaires is given in Table 2. The questionnaires were again based on those devised by Pearlman and others for the IP study. The questionnaires were piloted by the two interviewers together (to aid consistency) and modified before use. The questionnaires were as closed and structured as possible to try to ensure consistency between the two interviewers. There was only one interviewer for the second group of subjects whose job exposure was assessed at Monash University.

The company occupational hygienist identified those subjects who were not occupationally exposed and those who had only background (bystander) exposure. These assessments were checked at the site.

Interviewees were asked whether these subjects were likely to have had hands-on exposure. If exposure was likely or there was doubt the appropriate job specific questionnaire was completed.

Information was sought on the nature of each job held by each subject. For example, information was sought on the mix of tasks that an operator might have performed. This allowed the correct choice of questionnaire. The appropriate questionnaires were then used to establish for each exposed subject, the details of all tasks during which he might have been exposed to benzene or benzene containing materials. Information was sought about the frequency and duration of the task, about the products handled and the technology in use, and any changes to these factors that had taken place over the years of interest. Anecdotal information was also sought, for example, about spills, skin contact and cleaning regimes. The interviewees were also asked whether there were any other possible sources of exposure to benzene.

Table 2: List of Job Specific Questionnaires

Aircraft Refuellers
Drum Filling
Drum Laundry & Preparation
Electricians
Fitters/Welders/Machinists
Instrument Fitter
Laboratory Staff
Rail Car Loading
Road Tanker Drivers
Upstream, Tank Farm and Refinery Unit Operators
Vehicle Maintenance
Wharf/Jetty Operators
Other Site Staff

2.6. The Long Term Average Exposure Assessment Model

The exposure of individuals to benzene or benzene-containing materials, in the petroleum industry occurred in some, but not all tasks/jobs. Measured benzene exposure data were available for a number of current tasks and jobs but not for all sites and not for many past exposures. In addition, the technology used, the products handled and other factors may have differed between sites or have changed over time so that the available measured data would not be applicable to all situations. Where no measured data were available the benzene exposure had to be estimated by extrapolation from recent data using an estimation model.

The model used in this study was an extension of that developed for the IOL study [103] and used by the IP study [107, 108]. In those two studies a Base Estimate was calculated from a representative set of benzene measurements. A multiplicative model was then used to adjust the BEs to account for changes in those factors that were considered to affect exposure, for example, by the application of local exhaust ventilation or by an increase in the average number of loads per day for tanker drivers. Knowledge of the applicable exposure scenarios allowed extrapolation to time periods for which measured data were not available or to sites where measurements had not been made.

Health Watch has had a high participation rate, good job descriptions from living study subjects and exposure condition information from co-workers. These factors allowed good precision in allocating the tasks carried out to the subjects in the study. This allowed a task-based approach to be used more extensively than in the IOL and IP projects, where exposures went back to the early years of the century. The task-based approach was necessary because time on specific tasks varied over time and between sites [132].

The individuals in the study may have carried out their various tasks more or less frequently between sites and over time. In addition the technology changes that have taken place were (by and large) associated with a specific task rather than having an effect on the whole job. For these reasons, separate tasks were identified for each site/subject/activity time period. For example, a worker with the job title *Storeman and Packer* might have worked in two separate areas: the drum filling shed where he filled drums and loaded them on to trucks, and the rail car gantry where he filled rail tank cars. The time spent in each area was classed as a separate activity. The first activity *Drum Filling* had two tasks associated with it *Filling* and *Other* and the second activity *Rail Car Loading,* one task *Rail Car Loading.*[2] For the purposes of the exposure assessment the job of *Driver* had only one activity assigned namely, *Road Tanker Driving* which consisted of two tasks: *Tanker Loading* and *Driving and Unloading*. Changes in the loading technology did not normally affect exposure during unloading and driving.

There were four levels in the estimation process, Task, Activity, Workplace and Cumulative Dose. The estimates of exposure from the individual tasks, the Task Estimates (TE), were summed to give an Activity Estimate (AE) for each job activity. For activities that had only one task, e.g. office work, the AE was the same as the TE.

The Base Estimate (BE) of exposure for a particular task was obtained from occupational hygiene measurements taken by the petroleum companies or from data in the literature. The methodology is described in more detail in the next Section. If the BE related to a different exposure scenario than that being assessed, it required adjustment by one or more of the exposure modifiers (EMs) to reflect the difference. These EMs were identified for each task, site and time period. The combination of tasks and EMs were specific to each job title, site and time period, depending on when changes took place to the plant, the product handled, etc.

The exposure algorithm is discussed in more detail together with a worked example in Appendix 10. The cumulative estimate of exposure(CE) sums the average daily exposure multiplied by the years in that job. The controls' jobs were truncated at the date of diagnosis of their corresponding case.

2.7. Development of the Base Estimates

2.7.1. Sources of Data for the Base Estimates

Data for the BEs were obtained primarily from the participating petroleum companies in Australia. The criteria for acceptability of data are presented in Appendix 11. For tasks where there were little or no Australian measured data, estimates were based on data taken from the literature, principally from CONCAWE documents [133-135]. Other sources used were from the open literature [136-142].

Monitoring data were also sought from the Risk Management Division of the New South Wales Work Cover Authority and some data were supplied. However, little of it could be incorporated, as there was insufficient detail on the circumstances of the monitoring to allow comparison with other data.

Refinery and terminal background values were taken from exposures measured on employees carrying out jobs that were considered by the petroleum industry occupational hygienists to have been non-exposed e.g. at lubricating oil and grease manufacturing plants in refineries and at lubricating oil blending units at terminals.

Exposure monitoring data from the New South Wales CSIRO and Victorian Environmental Protection Authorities were used for the urban and rural background [143, 144].

2.7.2. Additional Exposure Data Collection

Further personal exposure data were collected by members of the team from Deakin University in 1999 and 2000 to augment those BEs that were thought to be uncertain. The methods of sampling and analysis and the newly acquired data are outlined in Appendix 12.

In most cases the results provided reasonable validation for the existing BE values. In some cases there were differences that could be explained by technology changes, for example the *Rail Car Loading* that

[2] Task definitions were detailed in [2] and the possible combination of tasks for each Activity Group in Appendix 6.

was investigated involved bottom loading with vapour recovery and exposures were minimal, whereas previous values from which the BEs were derived were for older technology without vapour recovery.

2.7.3. Base Estimate Generation

All data provided by the occupational hygienists were screened in collaboration with the company Occupational Hygienist to ensure correct job/task attribution and attribution to the correct technology and type of site. The hygienists were also asked to ensure that the measurements were typical for that job. Only personal exposure measurements were included. Data from non-Australian sites, from contractors and observers were excluded except for *Tank Cleaning* where this was the only data available. Where data had been normalised to an 8-hour average these were identified and the mean exposure measurement was used in the calculation.

The data used for the BEs were tabulated for each task, converted to units of ppm where necessary. The data were collected on tasks where petrol, avgas (aviation gasoline) and other products were handled. In order to make the data comparable they were normalised to 3 percent benzene for gasoline, 0.1 percent benzene for crude oil, and 100 percent of the load as a single product where appropriate e.g. *for Road Tanker Loading*. This assumes a linear relationship between concentration and exposure.

A value of half the limit of detection was inserted where the results were below the limit of detection. This insertion was needed to facilitate statistical analysis. The true value would have between zero and the limit of detection, and a value of half the limit of detection was used as an approximation [145]. This value was chosen because some of the BEs were based on heavily censored data or data that were highly skewed, GM >3. The detection limit varied between companies and over time for several reasons. Firstly, the mass detection limit varies as a result of the sensitivity of the analysis technique and as a result of the sampling technique (passive samplers generally sample at a lower effective flow rate than active samplers). Secondly the detection limit varies inversely with the sample time. The varying limits of detection made introduced some uncertainty in the arithmetic mean exposures. In addition these assume a log-normal distribution of data and in some cases this is only an approximation of the distribution of the data. Occupational exposure data are often log-normal in distribution [146]. When only small numbers of data points are available they are more likely to be clustered at the lower end of the exposure distribution. Larger data sets are more likely to capture the full range of exposures.

Unpublished data by Coker shows that wind speed has a major effect on exposure. Measured exposures were reduced by an order of magnitude at wind speeds of 15 kph when compared to measured exposures at 0 kph. This is confirmed by Kromhout who showed high variability in jobs carried out outdoors [147]. Many of the tasks under consideration take place in the open air. Occupational hygiene surveys usually take place over one or two days. A series of samples collected on consecutive days may underestimate the exposure variability since they may reflect only a limited set of conditions, activities and practices which are inherent in the process [148]. The full range of exposures may then not be encompassed if only small data sets are examined.

The arithmetic means of the data sets were used for the BEs as these were considered to be the best measures of long-term exposure [149]. The geometric standard deviation was also calculated and a test for log-normality was performed, where there were sufficient data, using the SPSS computer package.

Where data were collected over less than ten minutes and were below the limit of detection, they were excluded, as the limit of detection was often very high because of the short sampling period. When the BE was to be applied to a non-task based job, i.e. where it was used to represent the daily exposure, samples of less than 180 minutes duration were excluded. In most cases the mean of the short-term measurements was higher than that of the long-term measurements perhaps because specific high exposure tasks had been monitored. The exception to this was the exposure data collected for the job title *Terminal Fitter* where the tasks were examined by experienced petroleum industry hygienists and accepted as a reasonable cross-section of the tasks that a fitter might perform. A mean of all the data was used to calculate the BE.

For some tasks, monitoring data were available from a number of sites. The data were tested for homogeneity using analysis of variance. Where no significant differences between sites were found the BE was estimated from the mean of all the data.

After the BEs had been generated, they validated by comparison to data from the literature[3]. In some cases it was decided that the validation data did not support the original BE. These BEs and the validation data were examined by collaborating occupational hygienists and some of the possible validation data were rejected as being of poor quality, poorly described or not relevant. Two literature based BEs, *Driving and Unloading* and *Mechanic* were changed as a result of more literature data being found which varied from the original data. A mean of the new and old data set means was taken. In two other cases, *Reformer Operator* and *Refinery Fitter* removal of two outliers from the BE data resulted in BEs that were closer to the validation data from the literature.

The data used were compiled onto a spreadsheet and then a quality check was performed. Ten percent of the values were compared to the original source. Where errors were found the section was re-compiled and re-checked to ensure accuracy.

2.7.4. Exposures Considered to be Background

All office-based subjects were allocated either urban or rural background values depending on where they were sited. Workers at Castrol sites and the Kwinana Nitrogen Company were also allocated urban or rural background values as it was confirmed by a retired chemist from Castrol and the occupational hygienist responsible for Kwinana Nitrogen Company that there was no benzene at these sites. The additional background exposure data collected at refineries confirmed that exposure was very low in offices.

Table 3: Additional Background Exposure Data Collected at Australian Sites

Situation	**Benzene ppm**
Outdoors, background	0.009
Outdoors, background	0.008
Outdoors, background near tank farm	0.059
Canteen room, workers in overalls, no smoking	0.007
Canteen room, unoccupied	<0.001
Canteen room, workers in overalls, no smoking	<0.001
Office, clerical	<0.001
Office, clerical	<0.001
Office, clerical	<0.001
Office, clerical	<0.001

Diligent efforts were made to ensure that those office workers who had reason to visit plant operations had this time allocated to the appropriate task in another Activity Group. Jobs away from the site and jobs where no product containing benzene was involved were allocated the *Urban Background* or *Rural Background* value as the BE. The effect of active or passive smoking in offices or airport refuelling standby rooms was not considered.

For areas of terminals and refineries where no substances containing benzene were handled (for example, lubricating oil blending and filling units, packaged goods stores and utilities), the appropriate *Terminal* or *Refinery Operator NE* (not exposed) BE was used. For exploration and upstream processing the rural background value was used as the BE for jobs with no specific exposure to benzene.

LPG and black oil drivers were allocated the *Urban Background* BE as the majority of their time was off site and they were not directly exposed to products containing benzene.

The BE for *Airport Background* exposure was calculated from exposure measurements for refuellers working with jet fuel or with avgas that contained no benzene.[4]

[3] More details of the process of validation and the validation data are presented in Glass and Gray (submitted for publication)

[4] Only one Australian refinery produced avgas from 1954 to 1979 and it contained no benzene.

Control rooms were considered to be at ten percent of the exposure for general work in the area unless the air was scrubbed or the control room was remote from the unit – in which case it was given the *Urban Background* BE value.

2.7.5. <u>Work and Exposure at Overseas Sites</u>

Where overseas sites were nominated in job histories they were treated as though they were Australian and local values were applied to the variables. Activity exposure had to be calculated for one refinery fitter, one terminal fitter, a wharf and jetty operator and an aircraft refueller where task times were not known. The means of appropriate activity exposure values from subjects working over a similar time period were used.

2.8. Exposure Modifying Factors (EMs)

There were many factors that influenced exposure to benzene in the workplace. Some of these were identified as resulting in significant differences in exposure between workplaces/individuals or over time. These factors were used to adjust for differences between the actual exposure situations and that of the Base Estimates. Each task had different factors as the important determinants of the extent of exposure by intensity or time.

2.8.1. <u>Exposure Modifying Factors Considered for Use</u>

Experts involved with the IOL study listed a number of factors as important modifiers of exposure to benzene, (Appendix 13), [131]. Not all these EMs could be used in the IOL study, or this study, as they were either not quantifiable or considered to have a negligible effect.

The following were considered by the IOL experts, important exposure modifying factors: fuel components and percentage, ambient and fuel temperature, wind speed and direction, refuelling time and rate [150]. Distance from pump and orientation were the most important determinants of exposure. The dominant effect of wind speed and direction made temperature effects hard to detect. At 2 feet (approximately 600 mm) from the source in a reverse wind the total hydrocarbon exposure was less than 2000 times the exposure in parallel wind measurements.

CONCAWE reported 2 studies that compared exposures in London and southern Italy; Scotland and Greece. They concluded that temperature did not have a big influence on mean exposures. The arithmetic mean exposure in the cool climates was 2.01 ppm and 1 ppm respectively for London and Scotland (temperature ranges -1°C to 17.5°C and 8°C to 15°C). The arithmetic mean exposure in the warm climates was 1.61 ppm and 1.1 ppm respectively for southern Italy and Greece (temperature ranges 6°C to 30°C and 25°C to 33°C).

Appendix 13 shows the factors that were considered relevant in this study. These factors were considered at the site, with the serving employees and/or in consultation with the relevant company occupational hygienist.

2.8.2. <u>Exposure Modifying Factors Used</u>

On the basis of the information collected from the sites, some of the proposed EMs were not used in the analysis. Reasons for exclusion included:

- The factor had not changed over the years or between sites and therefore would have been a constant in the calculation, e.g. in Australia, as far as ascertainable service station tanks have always been vented remotely from the delivery point;
- The effect of the factor was too small to be worth considering e.g. the type of work clothing or the effect of an urban or rural background on terminal exposures;
- Adequate data could not be collected on the factor without disproportionate effort, e.g. number of calm days, wind direction, strength and variability, volumes of material handled;
- Data were too uncertain or could not be quantified for use, e.g. attitude to health and safety; use of standard operating procedures; seasonal changes in use of personal protective equipment; reliability of engineering controls; incident frequency and most data on the use of benzene-containing products as cleaning materials.

Adequate data could not be collected on some of the EMs without recourse to the individual subject, e.g. amount of overtime, frequency of spills, exposure to unusual incidents, and for drivers, the percentage of loads of gasoline or benzene. For some of these EMs an average figure was used based on information collected from the site for a hypothetical average worker doing that job or task. More precise information might have been available in some cases by interviewing the subject or a work mate who carried out the same or comparable tasks and naming the individual, but this was not carried out as it could have introduced recall bias.

2.8.3. Quantification of Exposure Modifying Factors

The EM values were derived by using methods based on underlying principles and known factors:

Site Factors

Some of the factors were based on the information provided at the sites, for example, the time spent on loading was based on interviews which asked for the number of loads per day. The value used for time taken to load was standardised as an arithmetic mean of the values given for all the tanker drivers. A value for the proportion of gasoline or benzene carried was obtained from interview data. These values were then used directly to modify the BEs. It was assumed that there would be a linear relationship between exposure and number of loads, % benzene in the gasoline and proportion of gasoline in the load. These assumptions were also made in the IP and IOL studies.

Technology Factors

The values ascribed to technology changes were derived by asking the company occupational hygienists to individually estimate the effect of a change compared to the baseline or technology that gave rise to the least exposure. The individual estimates were then tabled and a single value agreed in a round table meeting. These factors included the effect of open and closed drains for dewatering bulk tanks, drum filling technology, sampling and gauging technology, rail and road tanker loading technology.

The hygienists considered that there had been more exposure in drum laundries in the past. The exposure measurements referred to more modern laundries. Drum laundries and drum preparation areas were categorised on the basis of how close they were to the drum filling area, how well ventilated they were and the time period. The petroleum company OHs then allocated a ratio of 1 for low, 2 for medium and 4 for high background.

Top splash loading was found to result in approximately 3 times as much exposure to THCs as spear loading, according to an investigation by the American Petroleum Institute [151]. A USA EPA study estimated that splash loading results in 2.4 times the exposure of submerged fill or bottom loading of VOCs (volatile organic compound) without vapour recovery [152]. Losses during loading were thought to have been reduced by a factor of three going from top splash to submerged loading according to a report by the API but this factor was probably derived from the API report [153].

Exposure to benzene had been measured for contractors testing the atmosphere during crude and ballast tank cleaning. Exposure was also measured for the crude tank cleaner and data were available for gasoline tank cleaning. The ratio between the two operations at crude tanks was applied to the gasoline tank cleaning to derive a value for a gas tester at a gasoline tank.

Working Practice Factors

It was decided to increase past exposures by extrapolation, to reflect legislative or work practice changes where no data were available for a more data driven approach. The refinery and terminal exposures were considered to be era related; pre 1975 being twenty percent higher than post 1975, to allow for changes in general exposure as a result of responses to environmental regulations on hydrocarbon emissions. The introduction of internal floating rafts in storage tanks was thought to have more than halved storage tank emissions around this time [153]. Although there were significant reductions in fugitive emissions at terminals and refineries at this time many of these were from tank tops and stacks remote from the worker's breathing zone. The pre-1975 increase affects the exposure of instrument fitters, fitters, mechanics, refinery unit operators, tank farm operators and terminal operators (when not loading rail cars, tankers, barges, filling drums, sampling, gauging etc.). It also applies to supervisors, engineers and other staff for their time on site.

Terminal fitters were considered to have been exposed to more benzene before 1975 compared to the period after this date. Proposed occupational health and safety legislation and greater awareness of health and safety issues resulted in changes in work practices such as the use of cleaning solvents, line purging procedures and more automated equipment. An arbitrary value of 1.5 times as much exposure was chosen in the absence of measured data for a more data driven approach.

Supervisors, engineers, managers etc. were given the appropriate site background BE for the period when they were considered to be on the site (as opposed to being in the site office) but not hands-on. This BE was derived from exposure monitoring on refinery or terminal operators who were not exposed to benzene directly in their job. For any period when supervisors were hands-on they have been given the BE associated with the trade or unit where they were exposed. Where the hands-on time was not known (this was usually the case), they have been allocated the exposure corresponding to the workers being supervised for ten percent of the period when they were on site. This was similar to the value used in the IP study for supervisors of large sites (108).

2.9. Peak or Episodic Exposure Rating Index for Benzene

There is both toxicological and pharmacokinetic evidence for a non-linear relationship between the concentration of benzene or its metabolites in the human body and the risk of gene damage leading to leukaemia. The API suggested in their evidence to the ACGIH TLV committee that several genes were probably affected giving a multistep model and that some of the steps were non-linear[5] so the exposure response relationship is likely to be non-linear (40). It has been considered that there is sufficient evidence from animal experiments to suggest that there were increased adverse haematotoxic effects from short high rather than cumulative exposures (42). This would mean that long exposure to low levels of benzene is not equivalent in outcome to short high exposures and that this would be consistent with a threshold of effect.

In order to investigate this possibility in an epidemiological study, it is necessary to assess peak or episodic high exposures for individuals independently of cumulative exposure. This requires a suitable independent episodic exposure index. Such an index might involve the frequency of exposure exceeding some threshold concentration over an appropriate averaging time. Just what this averaging time should be has been problematic until recently.

A physiologically based pharmacokinetic was developed by Georgia Sinclair in collaboration with another member of the study team. This was used to examine the time course of benzene and its primary metabolites in various tissues including the bone marrow (154). Simulations were carried out using the model to compare constant and "peaky" exposure scenarios. The results indicated that the body and its enzyme systems have the capacity to damp the metabolite dose that is delivered to the target organs from short-term high exposures, i.e. short-term variations in exposures, within a day, do not markedly affect the dose to the target organ which appears to be averaged over several hours. The usual occupational hygiene definition of a peak exposure (from less than fifteen minutes to one hour in duration) is thus not appropriate in respect of exposure to benzene. For this reason it was decided to consider only high daily doses and to ignore short periods of high exposure except to the extent that they contribute to the 8 hour TWA exposure.

On this basis "peak" exposure indices can be derived from the frequency distribution of daily exposures if this is known. Three such approaches have been taken. The first approach, involved identifying those individual subjects who had or hadn't handled concentrated benzene or benzene/toluene/xylene (BTX) and analysing the outcome on this dichotomous basis. The second approach the "daily exposure assessment method" described next, used estimates of the frequency of the different mean daily exposures for individuals based on the combination of tasks they performed. The third approach added infrequent perhaps accidental but potentially high exposures to the daily exposures. The two latter approaches are described in the next Section.

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[5] The evidence of non-linearity include: benzene metabolism is not proportional to dose but is enzyme dependent and therefore rate limited; cytotoxic effects are proportional to the product of two metabolites: haematotoxic effects are not well predicted by cumulative dose: genotoxicity is non-linear *in vitro* and *in vivo* and that the epidemiology supports a threshold effect.

2.10. The Daily Exposure Assessment Model

2.10.1. Days of High Exposure Identified from Job History

Since the exposure response models suggest that the daily rate of dose is important it was decided to discriminate between individuals on this basis. Workers who handled benzene did not typically do so on a daily basis; they only handled the product a few times a year. Other workers such as *Drum Fillers* and *Wharf and Jetty* workers have also had variable daily exposures. *Drum Fillers* may have filled gasoline one day and mainly diesel the next; and *Wharf and Jetty* may have had elevated exposures on a small number of days every year, when the arrival or departure of a ship demanded intensive loading or unloading work. For these workers the days spent on different combinations of tasks were allocated from an assumed 250 working days a year. All other workers were allocated 250 days per year at the mean exposure calculated from the existing exposure assessment method.

2.10.2. Additional High Exposure Events

Subjects may also have experienced infrequent but potentially high exposures (High Exposure Events or HEEs) for example from spills. The potential for this to have occurred was identified for each group of workers. This was considered important because these infrequent exposures would be unlikely to be represented in the BEs. The probable exposure from such events was estimated using additional exposure data and simulated exposures. The data were then allocated to groups of workers based on job activities and era considerations.

The HEEs could add considerably to the upper range of the distribution of daily exposures and as such might contribute disproportionately to the risk of LH cancer if the risk is dependent on "peak" exposures rather than long term cumulative exposure. However, the HEEs would be unlikely to make a major contribution to the cumulative exposure of most petroleum workers because they were relatively infrequent events.

Identification of High Exposure Events

The exposures that were considered were identified from the anecdotal reports collected during the site visits. These were collated and allocated to a job group e.g. a double fill for drum fillers with meters. These exposures were examined and modified by an experienced occupational hygienist from the industry. The list was then sent to the collaborating industry occupational hygienists. Their opinion was canvassed in a telephone survey and their individual replies collated. The collated replies were examined by a panel of 3 industry hygienists and a consensus reached on:

- the probability of the exposure,
- the group(s) of workers affected,
- the frequency for a particular exposure,
- the era over which the high exposures might have occurred,
- how long the exposure would have lasted on each occasion,
- the extent of skin exposure if any.

Assessment of Extent of Exposure from High Exposure Events (HEE)

The probable total exposure by inhalation, and where appropriate from skin exposure was considered for HEEs. Some exposures were simulated in the laboratory and new data gathered to estimate exposure from these HEEs, (Table 4). The likely exposure from inhalation and through the skin was then calculated using simulated data as explained in Section 2.12 and estimated as an equivalent 8-hour TWA (inhalation only exposure), using a spread sheet, (Table 5). The total exposure was added to the BE for the appropriate number of days. Where exposures were considered to have occurred less then once every 2 years they were not included.

The frequency of the various HEEs could not be assessed with accuracy and they could not be assigned to individuals. Instead reasonable frequency estimates were obtained from the company hygienists so that possible contribution of HEEs to groups of workers could be examined in the outcome analysis.

In the event some HEEs that were considered were not included for the following reasons:

1. Some activities were thought to be so unlikely or infrequent that they could not be allocated to any individual, e.g. siphoning gasoline by mouth.
2. Some activities occurred too infrequently to be included in the model, e.g. major spillages during gasoline delivery that probably occurred less than once every 20 years for any one driver.
3. Activities which were already represented in the BE data, e.g. fitter breaking lines containing gasoline.
4. Activities that were thought to result in low exposures, e.g. handling benzene as a reagent in a fume cupboard.

Table 4: High Exposure Events Where New Data Collected

HEE	**Examples**	**New Data Obtained**
Spills	Substantial spillages of benzene-containing products: double fills or over fills, damaged stock return, failed couplings, tanker overflows.	Measured: - Drum filling spills, product recycle and drum cleaning and coupling leaks.
Cleaning	Using gasoline or other benzene-containing product for washing: trucks, tools, components and equipment, outside of drums, overalls, hands, floors (mopping).	Simulated - measurements of washings, tools and hands.
Switch	Exposure during product switch: draining benzene-containing product, mopping out tankers from the top, entering compartments after draining and/or rinsing.	Exposure data was obtained for draining tanks only.
Clothing	Benzene-containing product on clothing: extensive splashes of overalls, gasoline soaked gloves in vehicle cab.	Simulations carried out.
Laboratories	Use of benzene or high benzene products in laboratories.	Some new data and simulations carried out.
Ingestion	Siphoning gasoline by mouth.	Estimated by theoretical calculation only.
Maintenance	Maintenance work on equipment carrying benzene-containing product: pumps, meters, pigs, other equipment, tanks and lines.	New data was obtained.

Table 5: Incidental High Exposure Events Included in Daily Exposure Assessment Model

Job	High Exposure Event (HEE)	Frequency per person	Site	Changes over time?	Comments	Exposure ppm[6]
Drum Fillers	Extensive splashes of overalls	1 per year		Stopped early 1990s	From occasional drum overfills during metered delivery.	3.43
Fitters	Extensive splashes of overalls	1 per year	Terminals Refineries	Pre 1970	Arms and top of legs.	3.43
Fitters & Mechanics	Washing hands in gasoline	2 per day	Terminals Refineries	Pre 1950	Practice widespread.	0.35
Fitters & Mechanics	Washing hands in gasoline	1 per day		1950-1980	A few individuals continue.	0.17
Fitters & Mechanics	Washing tools	4 mins per day 15 mins Friday	Terminals Refineries	Pre 1975	Used gasoline until about 1975, kerosene thereafter.	0.20 0.76
Fitters & Mechanics	Washing components and equipment	15 mins per day	Terminals Refineries	Stops 1975	Practice widespread then fewer individuals. After 1975 used proprietary cleaners or kerosene.	1.34
Mechanics	Washing overalls	1 per week, 10 mins exposure		Stops 1955 Co provides overalls weekly	Friday left to soak in gasoline for half an hour, pick out, drain, wear next Monday.	0.67
Lab technicians, samplers (not chemists)	Washing hands in LVN	2 mins 2 per day	Terminals Refineries	Pre 1965	LVN (1% benzene) at this time.	0.11
Lab technicians, samplers (not chemists)	Washing components and equipment	15 mins per day washing fuel oil sample bottles in gasoline	Refinery only	Stops 1990	After 1990, only mineral turps used.	1.34
Lab technicians, samplers (not chemists)	Washing hands in benzene	2 mins once per week	Refineries C & D	Pre 1980	Benzene not gasoline for hand washing.	5.71
Rail Car Loader	Tanker overflow	1 per year, Top dipped				1.88
Road Tanker Filler	Tanker overflow	1 per year, Top dipped				1.88
Youngest Storeman & Packer for about 5 years[7]	Washing floors (mopping)	Wash floor with LVN 1 hour per week, Fridays	Esso Grease & lubes only	Stops 1972	Rest used kerosene or nothing.	3.93

[6] This includes exposure by inhalation added to exposure through the skin calculated as an 8-hour equivalent exposure.

[7] This HEE was not used and the only subject in the study employed at an Esso Lubes plant before 1972 was a Leading Hand.

2.11. The Database

Microsoft Access, a relational database, was used to record data for each subject, company, site, area, activity, and Activity Group. The choice of Activity Group drove the choice of tasks available. The time stated for an activity by a subject was allocated between tasks, based on the information gathered at the site about the frequency and duration of each task. The associated technology, the proportion of each benzene containing product handled and the percentage of benzene in those products handled were also entered. A diagram of the database is presented in Appendix 14.

As the data were entered into the database, a set of coding rules was developed and documented. If there was a change in the task mix or technology in an activity, the activity was split at the start of the calendar year when the change took place.

Refinery Unit Operators, Wharf and Jetty Operators and *Tank Farm Operators* usually performed several tasks as part of their jobs. However, since the data collected on the time spent on each of the separate tasks were not robust and the BE for refinery unit operators and tank farm operators included time spent sampling, dipping etc., their jobs were not separated into individual tasks and EMs were not applied. The exception was when the frequency of the tasks or the products handled were considered unusual, for example, in the past more dips and samples were taken and at some sites benzene had been handled. The extra tasks/exposures were then added to the standard BE for that unit in the database calculation.

Data about individual sites, such as the products handled, the source of products for each site, their benzene content by source and year, the type of technologies associated with tasks and their EM values, the BEs and their products and technologies were entered into the database as look-up tables. The Activity Estimate (AE), Workplace Estimate (WE) and Cumulative Estimate (CE) could then be calculated using relatively simple equations.

The database was restructured to allow the daily exposures to be calculated. Subject work histories were recorded in a custom-designed Microsoft Access database. To cope with the need to accurately record a great variety of information about the subjects' work histories, a family of hierarchically linked datasets was used. At the highest level, jobs held by each subject during the analysis period were listed in a *Job* dataset. Job titles, company names, and job contract duration were stored in this dataset. Below the *Job* dataset, two linked datasets - *DayBlock* and *DayBlockTask* - were used to describe the yearly variations in task distribution which occurred in certain job types (Section 2.10). Researchers recorded daily combinations of tasks in *DayBlockTask*, and subsequently recorded the yearly frequency of each of these daily task combinations in *DayBlock*. Each task recorded in *DayBlockTask* had further information stored about it in *ActivityTask*, including the relevant exposure estimate (ppm), and three subject-, task-, and history-sensitive modifiers to the exposure estimate. These modifiers respectively adjusted for historical differences in petroleum product concentrations and industry technology, as well as considering task-specific variations in petroleum product mixtures.

2.11.1. <u>Database Checking</u>

The data associated with the original subjects were entered on a site-by-site basis and then checked by examining the data on an activity basis to ensure consistency. When all the data were entered, a random sample of 10% of the individuals were selected by the computer and their jobs were reassessed from the original site questionnaire information. When an error was found all other jobs at that site or of that type were checked.

Changes were made to the records for 5 of 40 subjects that were checked. For two drivers their load time had been entered as 7.5 hours per week, instead of 6.25 for a period prior to 1965. Checks revealed two other drivers at that site to whom this applied. One person had the BEs for drum preparation and drum laundry reversed for the two tasks. One refinery operator had a catalytic cracker BE (0.11) rather than the crude unit BE (0.16) allocated. One Refinery Tank Farm operator had been allocated the Terminal Tank Farm BE. Further checking revealed another case of this. One driver had 24 hours rather than 2.4 hours per week loading for part of his exposure. None of these changes, except the last, would have altered the extent of exposure by a large amount.

The data associated with the new subjects was also checked. This showed that nine small changes were required such as changing 100% gasoline to 75% for one person.

2.12. Skin Exposure

Dermal absorption can contribute to the total uptake of benzene, particularly as direct contact with petroleum products is known to occur during loading, sampling and equipment maintenance. Vapour absorption through the skin is likely to be negligible, as shown for toluene and xylene, for which 1-2% of body burden is from contact with the vapour and the remainder is from inhalation (155). Dermal absorption of benzene vapour was not considered in this study.

Dermal uptake from contact with liquids containing benzene may be relatively important for those workers exposed to low airborne concentrations of benzene (32). The amount of benzene absorbed through the skin depends on the length of contact, the percentage of benzene in the liquid and the area in contact. In this industry, under most circumstances, contact with benzene was from splashes of gasoline on the skin rather than prolonged immersion.

The literature on the dermal flux rate of benzene was reviewed by Georgia Sinclair using scientific literature and technical reports. The rate at which benzene enters the human body when the skin is in contact with petroleum is not known with great certainty. Franz determined the flux of concentrated benzene through human skin *in vivo*, and the flux of concentrated benzene and benzene as a 5% portion of gasoline, through epidermal human skin *in vitro* (156). Unfortunately it is not clear which *in vitro* experiments were undertaken using full thickness skin (epidermis and dermis), or just epidermal skin (stratum corneum and viable epidermis). Blank and McAuliffe measured the flux of concentrated benzene and 5% benzene in gasoline through the stratum corneum of human skin *in vitro* (157). These experiments involved continuous benzene skin contact (infinite dose) over four hours. The Blank and McAuliffe data was excluded on the basis of the lack of a complete set of flux data and the lack of applicability of the infinite dose data to industrial situations. Lodén determined the flux of benzene, *in vitro*, over a 13.5 hour period, through full thickness human skin (158). The flux value was determined to be 0.00165 mg/cm^2/min[8]. Hanke *et al*. in a 1961 paper reprinted in 2000, determined the flux of benzene through human skin *in vivo* over a period of between 1 and 1.25 hours. The flux value was determined to be 0.0067 mg/cm^2/min[8] (159).

Table 6: Values for Flux Coefficient of Benzene in Skin (*F*) (Data selected by G Sinclair)

Duration of skin contact	*F* (mg/cm^2/min)	Reference
30 seconds	0.0035	Franz (1984)
30 seconds	0.0052	"
1 minute	0.03	"
3 minutes	0.018	"
10 minutes	0.0052	"
1 hour	0.0042	"
1.25 hours	0.0067	Hanke *et al*. (1961)
2 hours	0.004	Franz (1984)
4 hours	0.0038	"
13.5 hours	0.00165	Lodén (1986)

The benzene dermal flux data suggest that the uptake rate declines dramatically over the first few minutes of contact. This can be explained in terms of Fick's Law of diffusion; as the concentration of benzene in the skin increases, the concentration gradient driving the diffusion declines. Values of flux for dermal absorption of benzene through the skin for various contact times are given in Table 6. The duration of direct skin contact with petroleum products for the subjects in his study varied considerably, but was mostly of only a few minutes or less. Splashes, hand washing and brief immersion would all result in short term contact because of the rapid evaporation rate. More prolonged contact was reported during washing of components (up to about 15 minutes) but this was relatively uncommon. For these

[8] Data recalculated in different units

reasons the one-minute flux rate of 0.03 mg/cm^2/minute for concentrated benzene was used throughout the dermal uptake calculations.

The majority of the skin contact with benzene-containing products for the subjects in this study involved gasoline with approximately 3% benzene content. There is little data on skin uptake of benzene from petroleum. Blank and McAuliffe reported that the infinite dose flux rate of benzene from 5% benzene in gasoline was approximately 3.3% of that from concentrated benzene. In the absence of more reliable data it was assumed that the benzene flux rate was proportional to the benzene concentration.

The benzene uptake (S milligrams) for a particular skin contact was estimated from the expression:

$S = F \times A \times B / 100 \times t$ where *F* is the flux coefficient (mg/cm^2/minute)
A is the skin contact area (cm^2)
and *B* is the benzene content of the product (%)

The skin uptake was then expressed as an equivalent 8 hour inhalation exposure. Assuming a typical respiration rate of 0.6 m^3/hour for an average male doing light work, then an inhalation exposure of 1 ppm (3.18 mg/m^3) would result in a maximum benzene uptake of 15.3 mg over 8 hours. Thus a skin uptake of X mg would be equivalent to an 8 hour inhalation exposure of X/15.3 ppm.

Table 7 shows the calculated exposure through the skin as an 8 hour TWA equivalent for inhalation exposure the workers who were routinely, most frequently and heavily exposed. The nature of the exposure, frequency and length of each exposure were drawn up in discussion with 2 experienced hygienists from the industry. The BE to which the exposure would have been added is also shown. Some of these activities would have occurred 3-4 times a year e.g. handling hoses on the wharf. Others on a daily basis e.g. loading gasoline. Some exposures would have been much less likely after 1960 when PVC gloves were introduced. For most subjects in the study therefore, skin exposure was unlikely to have contributed much to their daily exposure. Hence these exposures have not been included in the study.

Skin exposure was, however, included for the high exposure events analysis in this study, (Section 2.10.2).

Table 7: Calculated Exposure through the Skin for Subjects Handling Gasoline in the Study

Job Group	**Job**	**Frequency**	**Time skin wet** (mins)	**Time per day** (mins)	**Extent of Exposure**	**BE**	**Skin Exposure** daily equivalent
Terminal Fitters	Opening lines/valves	1 x week	10	10	Palms & fingers	0.67	0.18
Refinery Fitters	Opening lines/valves	1 x month	10	10	Palms & fingers	0.35	0.18
Terminal Fitters at Wharf	Hose work (not Chicksan arms)	Not every day	2	2	Fingers	0.11	0.02
Mechanics	Work on gasoline engines[9]	3 times per week	10	10	Palms & fingers	6.60[9]	0.18
Drum Fillers[10]	When filling gasoline	5 x day, not every day	10	50	Palms & fingers	4.69 3.52	0.92
Truck Loaders[10]	Top loading pre 1960	10 x day	5	50	Palms & fingers	1.76	0.92
Truck Drivers[10]	Top loading pre 1960	3 x day	5	15	Palms & fingers	1.76	0.27
Samplers, Chemists, Tank Farm Operators	Dip samples	Not every day	5	5	Palms & fingers	0.67	0.09
Rail Car Loaders[10]	When filling gasoline	Not every day	5	5	Palms & fingers	3.77	0.09

[9] Most mechanics worked on diesel trucks not petrol engines, BE adjusted for petrol work

[10] Most operators would have worn leather gloves pre 1960 so skin exposed, after 1960 most wore PVC gloves so no exposure.

2.13. Metrics Used to Compare Cases and Controls

A number of qualitative and quantitative metrics were selected with which to analyse the outcome of the study, as itemised below. These metrics included periods of employment, type of site, as well as benzene exposure. The effects on odds ratios of self reported smoking history and alcohol consumption were also examined as these factors were possible confounders.

2.13.1. Exposure Metrics

The association between LH cancer, lymphatic cancer (NHL and MM) or leukaemia and sub types of leukaemia and the following exposure metrics (described in Section 4) were examined:

1. Continuous cumulative exposure to benzene (ppm-years).
2. Cumulative exposure by quintiles and geometric exposure groups.
3. The time frame for exposure to benzene, (to test for latency).
4. Duration of employment (years).
5. Start date and era in the industry pre 1965, 1965-1975 and post 1975.
6. Site type e.g. terminal, refinery, office etc.
7. Odds ratios for subjects handling concentrated benzene or BTX.
8. Odds ratios for subjects who did not handle concentrated benzene or BTX.
9. Frequency of high days exposure to benzene with differing cut-offs.
10. Frequency of high days exposure and high event exposure
11. Intensity of exposure to benzene (ppm) (cumulative exposure divided by duration).
12. Highest benzene exposure intensity job ever held (ppm).
13. Smoking and alcohol.

2.13.2. Smoking Data

Subject smoking habits were assessed during the Health Watch surveys at three different periods. Survey 1 was conducted between 1981 and 1983, Survey 2 between 1985 and 1987, and Survey 3 between 1990 and 1992. Not all subjects completed surveys at each of the intervals, but in combination, smoking data was available for all but seven subjects. The survey recorded subjects' smoking status at the time of survey, the age at which they started smoking, and, if they were ex-smokers (or smokers who resumed the habit after a long period of abstention) the age at which they stopped smoking. The frequency of consumption was also recorded as packs per day. A single smoking score was calculated which estimated pack-years up to the date of case diagnosis. Subjects who reported their smoking status as "current" at the time of survey were assumed to have continued smoking until the case diagnosis date.

2.13.3. Alcohol Data

Subject alcohol habits were assessed on the same surveys as smoking; three blocks of data were collected for each subject between 1981 and 1992. The same information was collected about alcohol habits as about smoking habits, with subjects reporting whether they were current or previous drinkers, at what age they first started drinking, and where applicable, when they stopped drinking. Subjects' average frequency of alcohol consumption during previous and current drinking eras was recorded in standard drinks/day. Using all available data, drink-year scores were calculated for all but 2 subjects. Scores were calculated up to the time of diagnosis of the case set. Subjects who reported that they were current drinkers were assumed to have continued drinking alcohol at the reported frequency until the case diagnosis date.

2.14. Statistical Methods

Statistical analysis was performed using the statistical package Stata ® produced by the Stata Corporation, 702 University Drive East, College Station, Texas 77840, USA. The principal test employed was matched case-control modelling using Conditional Logistic Regression (CLR). CLR is appropriate because the outcome variable (cancer/no cancer, or case/control status) is a binary (dichotomous) variable and many of the explanatory variables are continuous (quantitative). Conditional, rather than unconditional, logistic regression was used because the controls were matched with cases in individual strata of one case and five controls. CLR exploits the variability observed within matched sets to estimate the conditional likelihood of being a case, rather than a control, given the exposures. Relative risks of cancer are expressed as odds ratios, averaged across all the matched sets in the data. An odds ratio (OR) of 1.0 indicates no association between exposure and the incidence of cancer; if OR > 1, then there is a positive association, and subjects who are exposed have higher risks of cancer than the baseline group to which they have been compared.

The statistical variability in OR values is expressed using a 95% confidence interval (CI). The CI shows the range of feasible values which the OR might have, consistent with the observed data. If the 95% CI for the OR includes the value 1.0, then the observed association is not statistically significant; in other words, the observed data could have arisen by chance even if the exposed subjects had the same risk of cancer as the unexposed group.

An exposure variable (e.g. cumulative career exposure to benzene, average intensity of exposure, years of employment, pack-years of cigarettes) can be measured either as a continuous (numerical) quantity or as a categorical (qualitative) grouped variable. In the simplest case, the exposure can be a binary variable taking only two levels, exposed or not exposed. In this case, the unexposed group is usually taken as the reference category, and CLR estimates the risk as an OR for the exposed group relative to the unexposed group. In other cases, there are several, perhaps ordered, categories of exposure—for example, subjects can be grouped into categories of cumulative career exposure (< 0.5 ppm-year, 0.5 to 1.0 ppm- year, 1.0 to 2.0 ppm- year, etc). When using this type of variable in CLR, one of the categories (usually the first, or the least exposed) is nominated as the baseline, or reference category, and the CLR estimates odds ratio for all the other categories *relative to the common baseline category*. Thus, for example, if there are six categories of increasing cumulative exposure, the first will be the reference category and the CLR will report five ORs (one for each of the remaining five categories of exposure) and each of these will be the relative risk of cancer for subjects within that category, relative to the risk of cancer in the baseline or reference group.

The odds ratio estimate reported by CLR has a different interpretation when the predictor variable is continuous (e.g. exact number of ppm-years exposure, or exact computed pack-years of smoking exposure). In this case, a single value of OR is reported, and this represents the relative increase in risk of cancer for a unit increase in the exposure variable. An odds ratio estimate of OR 1.025 per ppm-year, for example, implies that the risk increases by 2.5% for each ppm-year increase in lifetime cumulative exposure. This interpretation reveals an important assumption about the odds ratio estimates made by CLR when the exposure variable is continuous: a critical assumption is that the increase per extra unit of exposure is the same *at all levels of exposure*. In other words, the value OR 1.025 assumes that the risk increases by 2.5% for each ppm-year when the exposure is very low *and* by 2.5% for each ppm-year when the exposure is very high.

Sometimes, this assumption is not true. In particular, if the true effect of exposure acts as a threshold (no increased risk up to a particular level of exposure, but marked increase in risk at levels above this fixed value), then the CLR model in which exposure is measured purely on a continuous scale will be wrong. To avoid this pitfall of continuous exposure analysis, we have chosen often to use an ordered categorical measure of exposure (e.g. geometric exposure groups, or quintiles of exposure). If the resulting odds ratio estimates show an approximately linear increase in relative risk as exposure increases, then the continuous model of exposure is valid.

A typical table of results from CLR analysis is shown below. In this case the explanatory variable is Cumulative Exposure which has been stratified into exposure groups with ranges (ppm-years) as shown in column 2. The Min and Max columns indicate the actual minimum and maximum values of cumulative exposure for subjects in each exposure group. Odds Ratios for the particular disease in question are expressed relative to group 1, which is assigned the baseline OR value of 1.00. The 95% confidence intervals of the Odds Ratios are given in the last 2 columns. In this example, the odds ratio estimates show no consistent upward trend in relative risk with increasing exposure category: a “plateau” of non-significant slightly elevated risk can be seen for categories 2, 3, 4 and 5; then a sudden, and steep increase in relative risk is seen for the highest category of exposure.

Table 8: Example of CLR Analysis

Conditional (fixed-effects) logistic regression				Number of obs =		474
Exposure group	Cum ppm-years	Min	Max	Odds Ratio	95% Conf. Interval	
1	< 1	0.005	0.999	1.00*		
2	1 - 2	1.03	1.98	1.57	0.71	3.46
3	2 - 4	2.02	4.00	1.92	0.91	4.04
4	4 - 8	4.04	7.92	1.48	0.66	3.33
5	8 - 16	8.04	15.97	1.65	0.72	3.80
6	> 16	16.77	57.31	**4.86**	**1.86**	**12.72#**

*Odds ratios are relative to Group 1
#Statistically significant results are shown in bold

The overall regression model for this example analysis is shown below. Here the Odds Ratio of 1.021 indicates that the Odds Ratio increases by 2.1% for each additional exposure group above group 1. That is, the risk of cancer in Group 2 is 2.1% greater than that in Group 1, the risk in Group 3 is 2.1% greater than that in Group 2, the risk in Group 4 is 2.1% higher than in Group 3 and so on. This implies a log-linear (exponential) relationship between exposure and risk for the disease in question rather than a linear relationship.

Table 9: Example of Overall Regression Model in CLR Analysis

Conditional (fixed-effects) logistic regression		Number of obs =	474
case	Odds Ratio	95% Conf. Interval	
Exposure group	**1.02**	**1.01**	**1.08**

The results presented in these two tables, which describe the same data in different ways, can illuminate the underlying assumptions of the CLR models. In Table 8, each of the ORs are computed relative to the single baseline category (< 1.0 ppm-year). In Table 9, the pair-wise relative risk (of each group with its lower neighbour) is averaged across all five steps in the exposure categorisation. Because the three intervening steps are very much lower than the final, largest step, the resulting average is lower than obtained by the direct comparison of the highest group with the lowest. This difference between the direct high/low ratio and the average-step figure reveals the false assumption of a continuous increase in risk. The highest exposure category is associated with a much greater risk than can be explained on the basis of the simple exponential model described in the second table. This may be evidence of stronger non-linearity than the exponential model predicts, or may be because of confounding by other risk factors in the highest exposure group.

3. Results of the Exposure Assessment

3.1. Demographics of Cases and Controls

The 79 cases in the study include 31 non-Hodgkin's lymphomas, 33 leukaemia and 15 multiple myeloma cases (Table 10). Of the 33 leukaemia cases, there were nine for which the sub-type was not clear. A histopathologist reviewed the information on the nine indeterminate leukaemias and they have been categorised using the FAB system (Table 10). The largest single group were 11 CLLs. The 5 “other” leukaemias were a Hairy Cell leukaemia, 2 acute undifferentiated leukaemias and 2 unspecified lymphocytic leukaemias.

Table 11 shows the demographics of the cases and controls. The cases and controls were similar in most respects. There was a similar proportion of subjects who have never smoked in each group but more current and fewer ex-smokers among the controls. There was a higher percentage of controls with more than 20 years in the industry[11]. Figure 1 shows the distribution of year of first employment in the petroleum industry. Figure 2 shows that about half the cases were diagnosed after 1990.

Table 10: Type of Cancer by Highest Level of Evidence for the Decision

	Histology	Drs letters	Cancer registry	Death certificate	Total	Percent
Type of LH cancer	**39**	**17**	**14**	**9**	**79**	**100.0**
NHL	14	6	5	6	**31**	**39.2**
MM	8	4	2	1	**15**	**19.0**
Leukaemia	17	7	7	2	**33**	**41.8**
Leukaemia type	**17**	**7**	**7**	**2**	**33**	**100.0**
CLL	5	5		1	**11**	**33.3**
CML	1	1	4		**6**	**18.2**
ALL	2				**2**	**6.1**
AML	6	1	1	1	**9**	**27.3**
Other	3		2		**5**	**15.2**

[11] For controls employed after the date of diagnosis of their case, the years of employment are truncated to that date.

Table 11: Comparison of Cases and Controls

Characteristic	Cases n = 79		Controls n = 395	Chi-square OR	P	95% CI
Age in years mean	54		54			
range	26-79		26-76			
standard deviation	11		11			
Majority of career						
Office worker	16 (20%)		105 (27%)	-	-	-
Non-Office worker	63 (80%)		290 (73%)	1.43	< 0.24	0.79 - 2.58
Smoking n & (%)[12]						
Never	28 (35%)		125 (32%)	-	-	-
Previous (Ex)	21 (27%)		166 (42%)	0.56	< 0.06	0.31 - 1.04
Current	30 (38%)		103 (26%)	1.30	< 0.37	0.73 - 2.32
Alcohol number & (%)						
Never	16 (20%)		79 (20%)	-	-	-
Previous (Ex)	2 (3%)		10 (3%)	0.99	< 0.99	0.20 - 4.94
Current	61 (77%)		305 (77%)	0.99	< 0.97	0.54 - 1.81
Country of birth n & (%)[12]						
Australia	56 (71%)		259 (66%)	-	-	-
UK	14 (18%)		75 (19%)	0.86	< 0.65	0.46 - 1.64
Other	9 (11%)		60 (15%)	0.69	< 0.34	0.32 - 1.48
No. years employment				[13]		
<10	13 (16%)		60 (15%)	1.0	-	-
10-20	25 (32%)		139 (35%)	0.83	0.64	0.37 - 1.83
20-30	27 (34%)		131 (33%)	0.96	0.93	0.40 - 2.33
30-40	12 (15%)		60 (15%)	0.95	0.93	0.34 - 2.68
>40	2 (3%)		5 (1%)	1.88	0.49	0.31 - 11.4
Start work in industry						
Before 1975	58 (73%)		294 (74%)	-	-	-
1975 or later	21 (27%)		101 (26%)	1.05	< 0.85	0.61 - 1.82
Start work in industry	Leukaemia	Lymphatic[14]				
Before 1975	27 (82%)	31 (67%)	294 (74%)	0.65[15]	< 0.35	0.26 - 1.61
1975 or later	6 (18%)	15 (33%)	101 (26%)	1.41[16]	< 0.30	0.73 - 2.72

[12] One control did not record smoking data or country of birth.

[13] Analysis done by CLR

[14] Lymphatic cancer included non-Hodgkin's lymphomas and multiple myelomas

[15] Values for leukaemia

[16] Values for lymphatic cancer

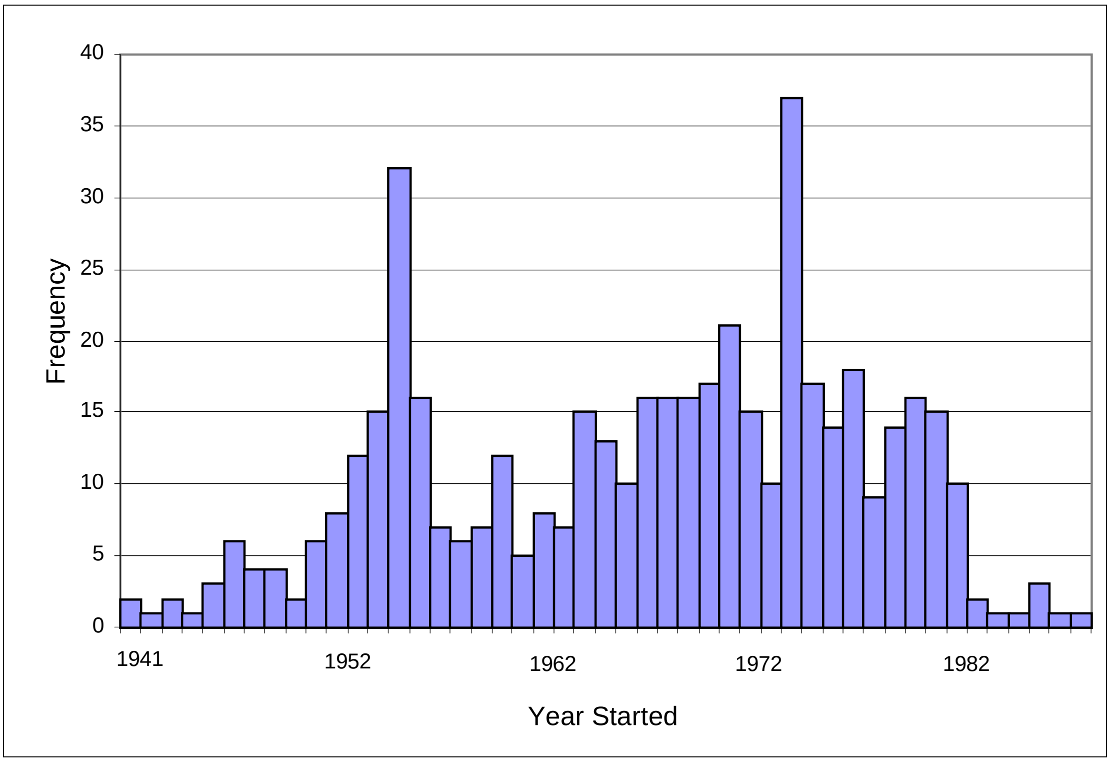


Figure 1: Start Date of the Subjects

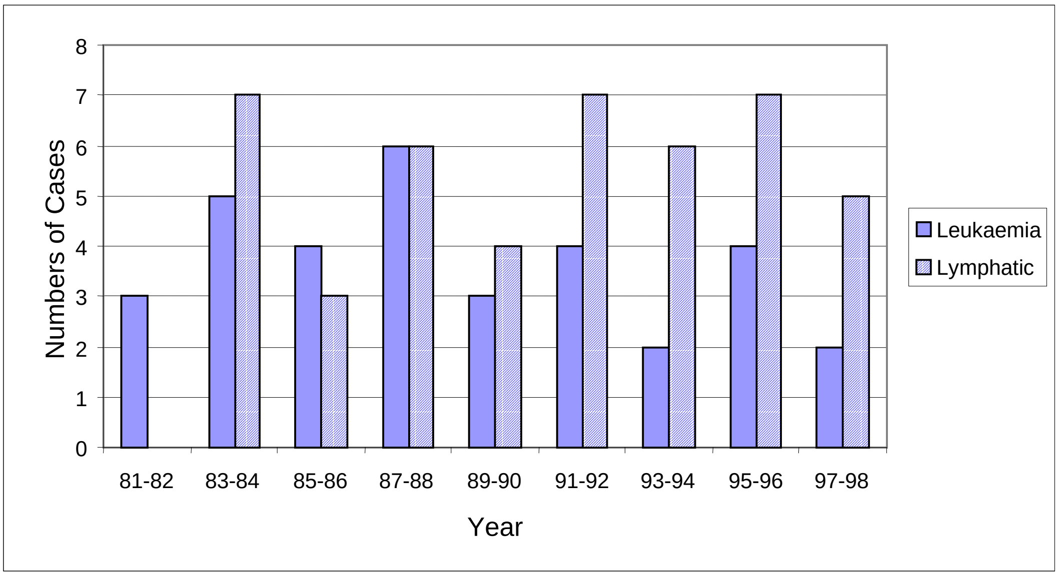


Figure 2: Cases by Date of Diagnosis[17]

[17] One lymphatic cancer was diagnosed in 1999, this was not included in this figure as other cases may have been diagnosed in that year but were not notified to Health Watch.

3.2. Exposure Assessment

3.2.1. Site Information

The individual sites in the case-control study were categorised by type and whether they had been visited. Forty-six sites were visited (ten refineries, thirty-one terminals and five airports). Sixty-seven sites were closed, 45 had office staff only, 39 were overseas, and one was unclassifiable. A further eleven sites were listed by subjects as combination of sites (Ampol Botany/Banksmeadow) or sites which had changed ownership (e.g. Mobil Spotswood is the former Esso Spotswood site). Twenty-seven sites were open but not visited (eight lubricating oil terminals, six other terminals, two airports, three offshore and eight onshore production operations). For almost all of the non-visited sites, telephone contact was made with current employees, ex-employees or retirees from that site or with others who had working knowledge of the site.

Site assessment questionnaires were filled out for all sites visited and for most of the other sites. A few sites had been closed for some time and no reliable information could be found for two of them (Shell Essendon Airport and Shell Cooma Depot). These sites were allocated information based on other sites of similar type, size and period.

3.2.2. Benzene Content of Products

Gasoline

From about 1961 Australian refinery production accounted for over ninety percent of local gasoline consumption. There were two grades of gasoline, premium or super and regular, both contained lead. As unleaded gasoline was phased in from 1985 the regular grade was discontinued and the use of premium grade gasoline was proportionally reduced. By 1995 unleaded gasoline accounted for sixty percent of sales. Premium unleaded gasoline currently accounts for about two percent of sales. The benzene content of premium leaded and unleaded gasoline depends on the benzene in the crude, the refinery process units and the percentage of reformate[18] in the gasoline. Typically unleaded gasoline contained more reformate blend stock (and hence more benzene) than leaded, however this was made only from 1988. Reformers have been in use at all refineries since the 1950s and these were the major determinant of benzene concentration (Tresider personal communication). The composition of the reformer product varies with the operating conditions and over time, consequently the percentage of benzene in gasoline varied with the originating refinery and the time period, but was usually between one and five percent by weight. The 1968 Victorian Benzene Regulations stipulated a statutory limit of five percent by volume for gasoline [(2)], this is equivalent to approximately six percent by weight [(160)].

The measured benzene percentage for each type of gasoline was attributed to the year in which the measurement was made and for each year before that for which no measurement was available. For the 1950s and 1960s the benzene percentage for each type of gasoline was assumed to be the same as the earliest values measured for that refinery in 1974. Values of 2.9 percent for premium leaded gasoline, 2.0 percent for regular and unleaded gasoline and 3.8 percent for premium unleaded gasoline were used as default values for the benzene content for all the sites that sourced gasoline from overseas. These values were based on a mean of the earliest Australian refinery data for each type of gasoline.

The source refinery for gasoline was identified for each site. Where gasoline was obtained from more than one source, a 50:50 split was assumed. The amounts of the different types of gasoline handled each year at each site was not able to be determined. The proportion of regular, premium leaded, unleaded and premium unleaded gasoline was known on a yearly Australia wide basis. This proportion was used to derive an average benzene concentration for the total gasoline handled at that site.

Before 1970, some terminals belonging to one company added approximately 5-7.5% benzene to the gasoline, making 7-12% benzene gasoline (depending on the refinery source). According to the terminal information this was not a continuous process and was only added to the super grade. Two drivers in the case-control study could have had exposure to this gasoline and their exposure was calculated in proportion to the amount of super fuel. Super accounted for approximately half the gasoline used in 1955 but declined to about 20% by 1970.

[18] Reformate is the product of the reformer, a refinery unit

Aviation Fuels

There are two main types of aviation fuel; avgas, which may contain benzene; and jet fuel which is kerosene. The jet fuel JP1 in use in Australia, contains no benzene.

There were four main sources of avgas in Australia. Prior to 1955 all avgas was imported. When the Refinery A came on stream it produced, and still produces, avgas without benzene (Tresider personal communication). Refinery D started to produce avgas in 1980 and this contained between one and three percent benzene (Jackson personal communication) – a value of two percent was used for the benzene content of Refinery D avgas. Refinery F started to produce avgas with one-percent benzene in 1987 (Johnson personal communication). Some avgas is still imported particularly for use in the Northern Territory.

The specification for avgas has not changed markedly over the years and the freezing point requirement sets a limit on the possible benzene content (Tresider personal communication). A value of two-percent benzene was used as the default value for all the sites that sourced avgas from overseas.

Benzene

Where concentrated benzene was used it was assumed to be 100 percent benzene. If the source was a coke oven or coal gasification by-product, known as BTX or "Benzole" it was assumed to be 70 percent. In the 1960s there was a product known as “Benzol” brought by road tanker from the Morwell gas plant to the Refinery A. This was a by-product of the Lurgi process, but according to current sources at the refinery this was cresol and did not contain benzene (Clark personal communication). The senior chemist from the Gas and Fuel Corporation at the time states that it was mainly straight chain aliphatics and may have had cresols and phenols but very little benzene (Hartmann personal communication).

Other Products

The percentage of benzene in crude oil is approximately 0.1 percent for oil sourced from the Middle East, Indonesia and the Bass Strait (Tresider personal communication). Reformate composition varies from week to week and from reformer to reformer, and ranges from five to twelve percent benzene, but was usually about eight percent (Tresider personal communication). CCU intermediate was approximately four percent and light virgin naphtha (LVN) was one percent benzene. Solvent X55, a form of LVN, used as a laboratory cleaning solvent, has changed in formulation over the years from approximately one percent to 0.3 percent benzene at the time that the BE data were collected, to currently 0.1% benzene (Jackson personal communication).

3.2.3. Subject Information

The pool of 468 workers assessed had between them 1477 jobs, 2182 activity lines, and 3457 tasks allocated. They came from 238 sites (Appendix 9 to the ERDC Report [(2)]). Many sites, 136 of 238, had only one subject, and for 85 of the sites, the subject had only one job with one activity. Figure 3 shows the distribution of subjects by longest worked site type and Figure 4 shows the frequency distribution of total workers' time by site type. Figure 5 shows the distribution of number of subjects by site, and Figure 6 shows the distribution of activities by site. The number of activities per worker ranged from 1 to 20 with an average of 4.7 activities (Figure 7). The refineries had larger numbers of subjects and more activities per subject. Twenty-three of the subjects were employed before 1950, and only five after 1985. Figure 8 shows the percentage of the subjects' total years worked by activity. Office work was the largest single activity, accounting for nearly 25% of the years worked by subjects in the study.

The exposure status of subjects was checked at the site for all sites except those classified as being "Office-only" or "Non-exposed". Some distribution terminal sites were classified as office-only for the purposes of this study because only office workers from that site were subjects in the case-control study. Sites classified as "Non-exposed" included the Kwinana Nitrogen Company on a site adjacent to Refinery F and all Castrol sites. These sites did not handle benzene-containing products. Job specific questionnaires were completed for all exposed employees at all visited sites. Questionnaires were also completed for the exposed employees at most of the closed sites and the sites not visited. Only part of the information on the exposure of employees from smaller depots was obtained. In some cases this came from current company employees who had knowledge of the site but who may not have worked there themselves. The tasks carried out by employees are described in Appendix 5.

Appendix 6 gives a table of the tasks associated with each activity group. Only those tasks thought to be associated with a likelihood of exposure to benzene have been identified. The remaining tasks, such as paperwork, have been grouped as *Other*. Not all tasks were performed at all sites or by all members of an Activity Group. The allocation of a task, its time, the product handled and technology were all identified at a site level. Any changes over time were included in the database.

Where a subject was one of a group that took turns to carry out a job, such as unloading tank ships at regional terminals, the time spent per year has been divided between the eligible workers and the proportion attributed on a weekly basis. For example, between 1965 and 1974 a fitter from Site 19, a terminal would go to Coode Island to help to unload a benzene tanker every three months. However, this could be any one of six fitters. For any individual this corresponds to approximately 0.32 hours per week averaged over the period of the job.

Table 12 shows a summary of the subjects by Activity Group, the number of tasks and the range of times spent on them. Subjects often had more than one activity at a time. For example, for a refinery operator who worked on more than one unit, the time spent on each unit was classed as an activity. At some refineries operators were rotated at regular intervals around the different processing units and the time spent on individual units was not available from either their job histories or from refinery records. These operators have been classified as *Refinery Operator Plantwide.*

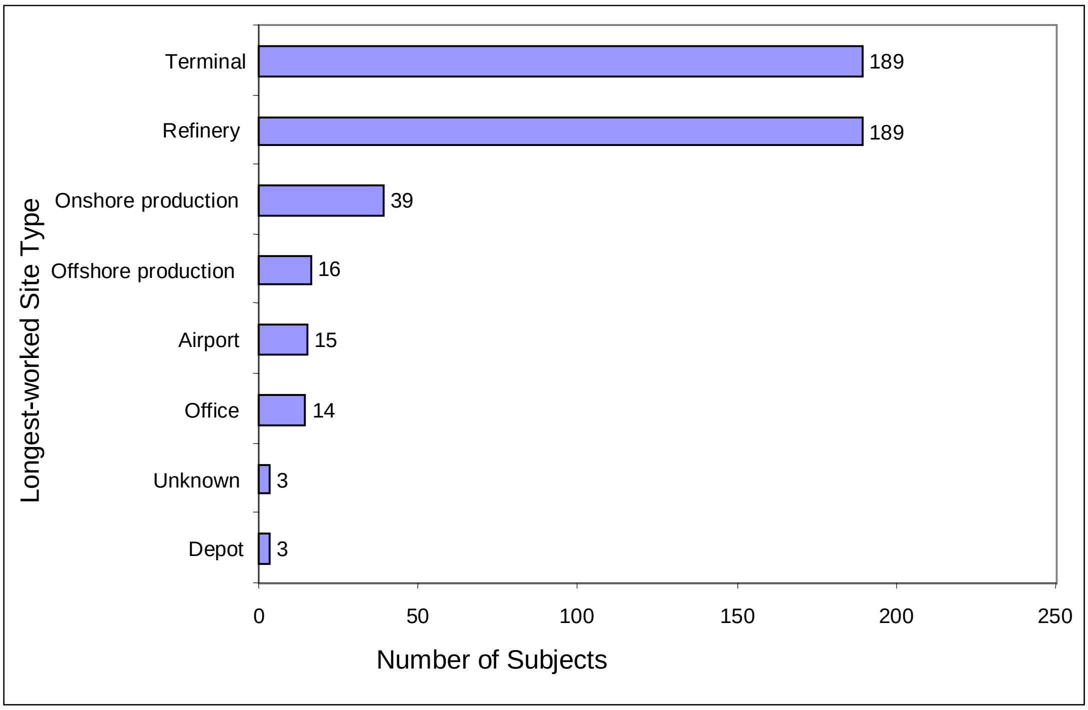


Figure 3: Number of Subjects by Longest Worked Site Type

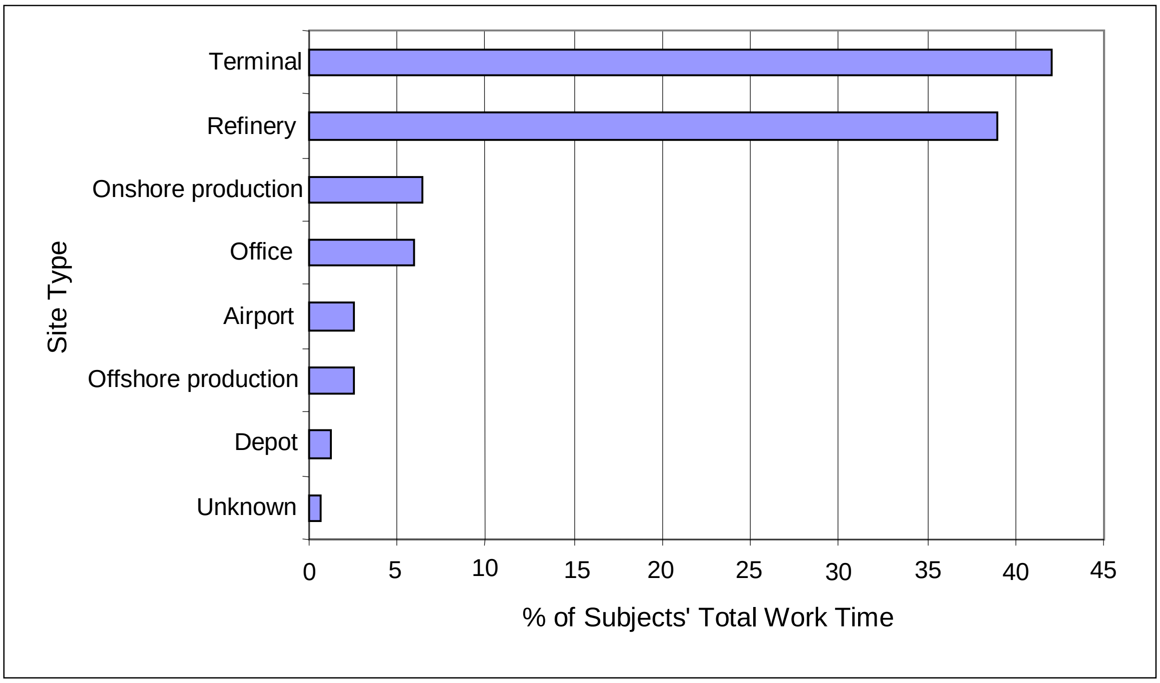


Figure 4: Total Subjects' Time by Site Type

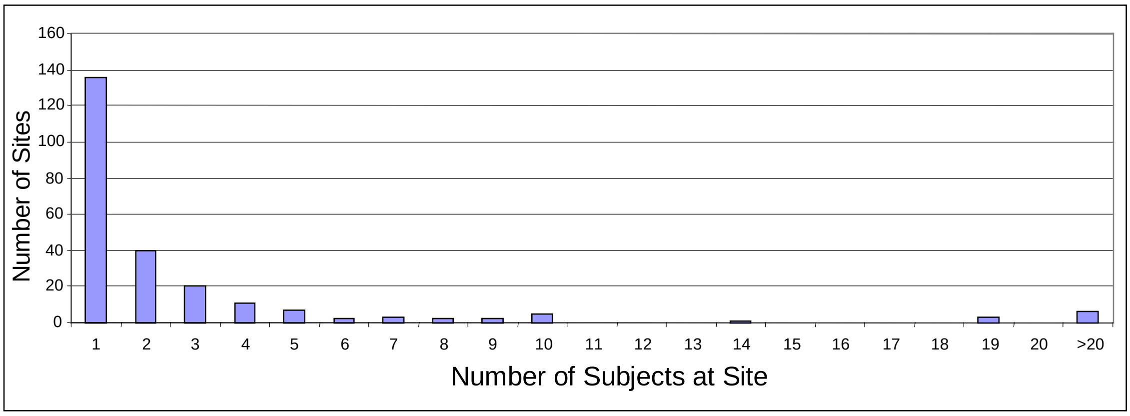


Figure 5: Number of Subjects by Site

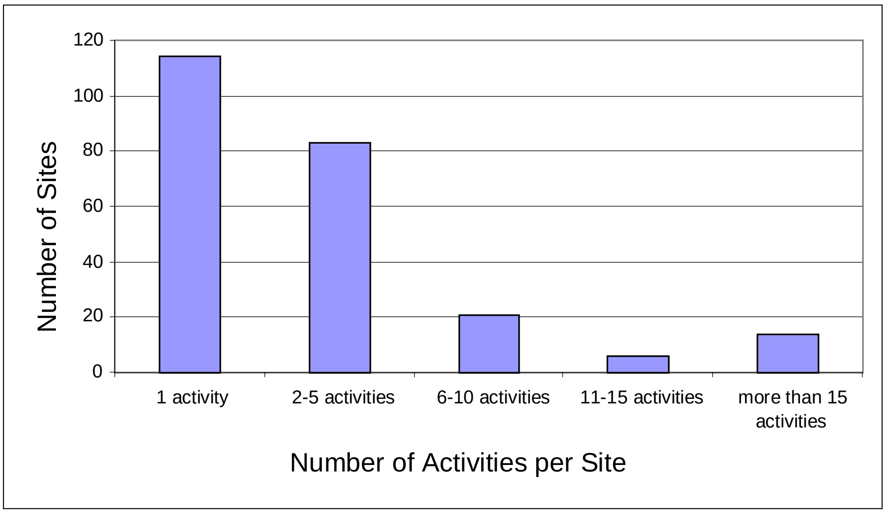


Figure 6: Number of Activities by Site

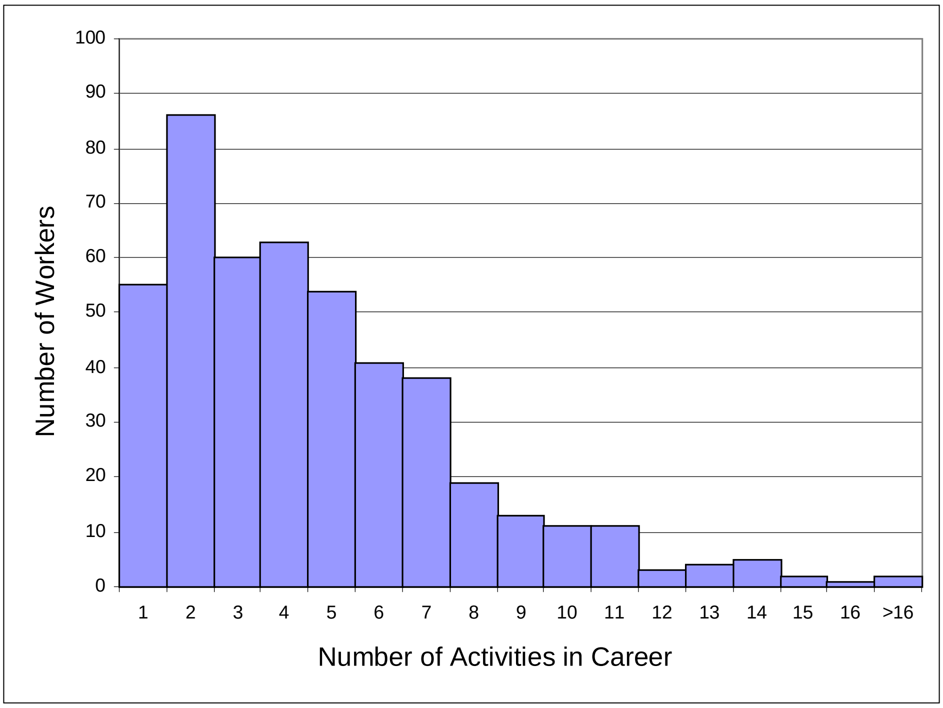


Figure 7: Distribution of Activities in Career

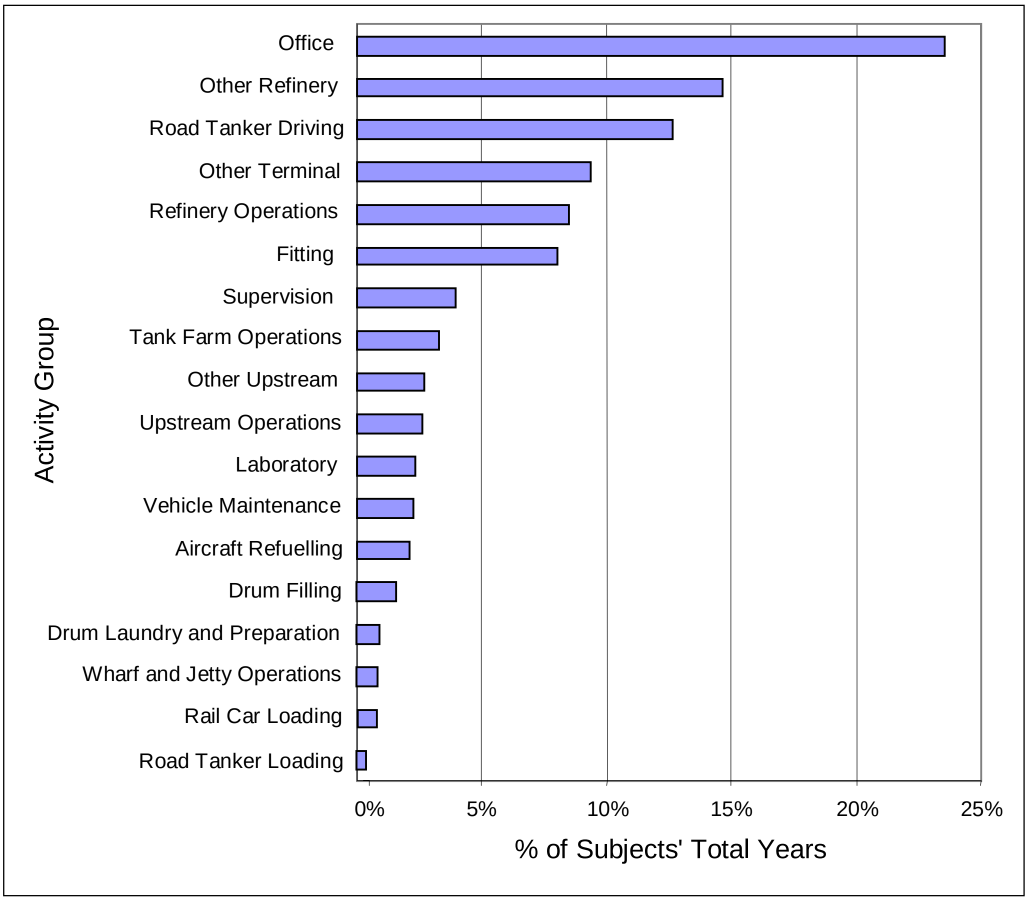


Figure 8: Distribution by Activity Group

Table 12: Summary of Subjects by Activity Group, Number of Tasks, and Range of Times (hours per week)

Group	Task	Number of workers	Minimum time per week[19]	Maximum time per week
Aircraft Refuelling	Other	36	2	49.88
	Refuelling	15	0.12	8.33
	Sampling	6	0.4	3.75
	Tanker loading	13	0.01	8.33
Drum Filling	Filling	64	0.08	27
	Other	58	0.5	40
Drum Laundry and Preparation	Other	24	3	60
Fitting	Barge loading	7	0.5	3.3
	Gauging	1	0.25	0.25
	Other	145	2	50
	Product	82	0.03	13
	Rail car cleaning	1	0.7	0.7
	Tank cleaning	46	0.03	8
Laboratory	Other	54	1	45
	Sampling	11	0.003	1
	Washing glassware	7	0.25	5
Office	Other	515	2	60
	Sampling	1	0.25	0.25
Other Refinery	Gauging	1	5.62	5.62
	Other	432	0.7	60
	Sampling	1	1.25	1.25
Other Terminal	Other	175	1	65
Other Upstream	Other	67	2	50
Rail Car Loading	Rail car loading	28	0.2	47
Refinery Operations	Dewatering	53	0.01	3
	Gauging	53	0.01	5.62
	Line pigging	1	0.03	0.03
	Other	259	2.9×10^{-10}	44
	Sampling	105	0.02	5
	Separator cleaning	24	0.5	35
	Tank cleaning	2	3	3
Road Tanker Driving	Other	167	2.161	70
	Tanker loading	117	0.001	11.25
Road Tanker Loading	Other	5	2	7
	Tanker loading	22	0.6	45

continued

[19] Some infrequent activities averaged on a weekly basis result in low minimum times

Table 12 continued

Group	Task	Number of workers	Minimum time per week[20]	Maximum time per week
Supervision	Gauging	2	1	1
	Mechanical work	5	0.5	4.5
	Other	244	0.2	45
	Product	3	0.35	1.5
	Rail car loading	2	0.15	0.4
	Sampling	1	2	2
	Tank inspection	1	1	1
	Tanker loading	12	0.14	4
Tank Farm Operations	Dewatering	51	0.15	10
	Gauging	76	0	7.5
	Interceptor cleaning	14	0.1	5
	Line pigging	4	0.005	0.3
	Other	72	0.18	43.7
	Sampling	52	0.01	10
	Tank cleaning	12	0.1	1.6
Upstream Operations	Dewatering	6	0.01	0.5
	Gauging	11	0.01	0.16
	Interceptor cleaning	24	0.03	0.5
	Line pigging	36	0.01	0.5
	Other	45	8.5	55.13
	Sampling	33	0.5	1.4
Vehicle Maintenance	Mechanical work	48	0.3	40
	Other	14	4	28
Wharf and Jetty Operations	Barge loading	2	1.6	10
	Dipping and gauging	13	0.1	3
	Line pigging	2	0.007	0.01
	Other	27	0.353	50
	Product	33	0.06	15
	Sampling	14	0.02	2.5

[20] Some infrequent activities averaged on a weekly basis result in low minimum times

3.3. Episodic High Exposure

Those workers with a likelihood of episodic high exposures included: subjects handling benzene or BTX, drum fillers not using local exhaust ventilation, workers in quality control laboratories with poor ventilation, and barge workers handling gasoline or other high benzene content products.

Certain sites, and jobs at those sites, were identified as having handled concentrated benzene or BTX during the time periods of interest to this study. From their job histories, twelve subjects were known to have had such jobs at those sites during the relevant time period and so had a high likelihood of having handled benzene or BTX. When calculating the cumulative exposure estimate for these subjects it was assumed that they had handled benzene and the time spent handling benzene was averaged over the group of all possible workers at that site who were involved in the specific tasks. Table 13 shows the combinations of sites, tasks and time periods for those subjects who were likely to have handled benzene or BTX. The table shows only the tasks involving the handling of benzene or BTX; the subjects also had other tasks that are not displayed. There were relatively few of these subjects and for most of them the product was handled intermittently, typically three to four times per year. They thus appear to have handled the product for a very short time when averaged on a weekly basis. These subjects come within the episodic exposure definition. The Yarraville subjects were exposed to benzene at Coode Island. The fitters took it in turn to visit the site, as did laboratory workers.

Table 13: Subjects Handling Benzene or BTX by Company and Site

Company	Site	Area	Started	Finished	Group	Product	Task	Time[21]	Technology Used
Mobil	Yarraville	Plantwide	1-Jan-65	1-Jan-78	Fitting	Benzene	Product Loading/Unloading	0.32	Flexible hose
Mobil	Yarraville	Laboratory	1-Apr-69	1-Jul-81	Laboratory	Benzene	Sampling	0.003	Open sampling
Shell	Corio	DAP	1-Jan-75	1-Apr-84	Refinery Operations	Benzene	Gauging	0.83	Diptape gauging
		DAP benzene receipt	1-Jan-75	1-Apr-84	Refinery Operations	Benzene	Dewatering	0.01	Open drain dewatering
			1-Jan-75	1-Apr-84	Refinery Operations	Benzene	Line pigging	0.03	Pig retrieval
			1-Jan-75	1-Apr-84	Refinery Operations	Benzene	Sampling	0.03	Open sampling
BP	Altona	Drum Bank (Drum Filling Shed)	1-Nov-70	1-Jun-75	Drum Filling	BTX	Filling	0.44	Stub displaced vapour
			1-Nov-70	1-Jun-75	Wharf and Jetty Operations	BTX	Line pigging	0.007	Pig retrieval
			1-Nov-70	1-Jun-75	Wharf and Jetty Operations	BTX	Product Loading/Unloading	0.64	Flexible hose
			1-Nov-70	1-Jun-75	Wharf and Jetty Operations	BTX	Sampling	0.02	Open sampling
Ampol (Total)	Matraville	Plantwide	1-Feb-60	1-Oct-84	Fitting	Benzene	Tank cleaning	0.07	Gas test scrape and hose
			1-Oct-54	1-Feb-60	Fitting	Benzene	Tank cleaning	0.07	No gas test scrape and hose
			1-Oct-54	1-Oct-84	Fitting	BTX	Tank cleaning	0.03	Gas test scrape and hose
Ampol (Total)	Matraville	CDU	1-Nov-67	1-May-84	Refinery Operations	Benzene	Gauging	0.03	Diptape gauging
			1-Nov-67	1-May-84	Refinery Operations	Benzene	Sampling	0.06	Open sampling
			1-Nov-67	1-May-84	Refinery Operations	BTX	Gauging	0.01	Diptape gauging
			1-Nov-67	1-May-84	Refinery Operations	BTX	Sampling	0.02	Open sampling
Shell	Gore Bay	Plantwide	1-May-61	1-Apr-62	Fitting	Benzene	Product Loading/Unloading	0.06	Flexible hose
		Tank farm	1-Apr-60	1-May-61	Wharf and Jetty Operations	Benzene	Product Loading/Unloading	0.06	Flexible hose
BP	Newcastle	Drum filling	1-Dec-75	1-Jan-79	Drum Filling	BTX	Filling	0.32	Stub no LEV Open filling
		Unloading tank ships	1-Dec-75	1-Jan-79	Wharf and Jetty Operations	BTX	Line pigging	0.01	Pig retrieval
			1-Dec-75	1-Jan-79	Wharf and Jetty Operations	BTX	Product Loading/Unloading	0.3	Flexible hose
BP	North Fremantle	Dock	1-Mar-61	1-Jun-65	Wharf and Jetty Operations	Benzene	Product Loading/Unloading	0.2	Flexible hose
		Drum filling	1-Mar-61	1-Jun-65	Drum Filling	BTX	Filling	0.08	Stub no LEV Open filling
		Tank Farm	1-Mar-61	1-Jun-65	Tank Farm Operations	Benzene	Gauging	0.01	Diptape gauging
			1-Mar-61	1-Jun-65	Tank Farm Operations	Benzene	Sampling	0.01	Open sampling
BP	North Fremantle	Drum platform	1-Jan-56	1-Jun-56	Drum Filling	BTX	Filling	0.08	Stub no LEV Open filling
		Gantry	1-Jan-59	1-Nov-70	Road Tanker Driving	BTX	Tanker loading	0.002	Fill metered Top Load
BP	Whinstanes	Tank farm	1-Mar-59	1-Jan-65	Tank Farm Operations	BTX	Gauging	0.25	Diptape gauging
			1-Jan-65	1-May-75	Tank Farm Operations	BTX	Gauging	0.25	Side gauging
			1-Mar-59	1-May-75	Tank Farm Operations	BTX	Sampling	0.25	Open sampling
Shell	Gore Bay	Plantwide	1-Jan-54	1-Jul-60	Fitting	Benzene	Product Loading/Unloading	0.03	Flexible hose

[21] Average number of hours per week – calculated from the time spent on the task in a year and averaged over all workers who may have performed the task

3.4. The Base Estimates Used

3.4.1. Introduction

Most of the BEs were derived from data provided by the collaborating Occupational Hygienists. Data were collected by sampling for benzene not by extrapolation from THC measurements. In some cases data from the literature were used where there was no or insufficient local data. Where possible the BE data were validated by comparison to other data from the literature (paper submitted for publication). Table 14 summarises the values calculated for each BE. The product and the technology associated with the BE are also given. Where there was no exposure-specific technology associated with the BE, e.g. for background exposures, the term "*no technology*" has been used in the Table. All BEs were derived either from monitoring data provided by the petroleum companies, from published data found in the literature or from data collected by Deakin University at Australian petroleum company sites. Specific comments on the calculation of each of the BEs are given in Appendix 15.

For many BEs, the exposure data were found to have an approximately log-normal distribution. Statistical tests of normality confirmed this. For some BEs, where large numbers of data were available more apparent outliers were found than for smaller sets of data from other sites [161, 162]. Data from several sites were pooled provided that they were within the distribution of the rest of the data.

In some data sets the distribution was heavily censored, i.e. much of the data was below the limit of detection. The choice of method and equipment used for sampling and analysis affect the limit of detection. The limit of detection for benzene has been reduced over the years by an order of magnitude. These factors probably account for most of the apparent clustering of data in low exposed jobs. For example, in the monitoring data used for calculation of the *Refinery Operator NE* BE the limits of detection in various samples were 0.01, 0.02, 0.03, 0.05, 0.07, 0.09, 0.1 and 0.2 ppm.

Further information on specific BEs is included in Appendix 15. Details of the statistical analysis are given in Annex B to the ERDC report [2].

Table 14: Base Estimates Used in this Study

Base Estimate	Task	Product	Technology	Benzene ppm
Airport Background	Other		No technology	0.08
Area 2 – Refinery A	Other		No technology	0.14
Area 3A & B – Refinery A	Other		No technology	0.23
Barge Loading	Barge loading	Gasoline	Flexible hose barge loading	2.21
CCU	Other		No technology	0.16
CDU	Other		No technology	0.11
DAP General Work pre 89	Other		No technology	1.86
DAP Head Operator pre 89	Other		No technology	0.74
DAP Maintenance	Other		No technology	1.02
Dewatering	Dewatering	Gasoline	Open drain dewatering	0.63
Driving & Unloading	Other		No technology	0.16
Drum Filling: Stub, Enclosed	Filling	Gasoline	Stub, no LEV, enclosed filling	4.69
Drum Filling: Stub, Open	Filling	Gasoline	Stub, no LEV, open filling	3.52
Drum Filling: Spear, Open	Filling	Gasoline	Spear, no LEV, open filling	3.52
Drum Filling: Stub, LEV	Filling	Gasoline	Stub, LEV	1.55
Drum Laundry	Other		No technology	0.39
Drum Preparation	Other		No technology	0.14
Gauging[22]	Gauging	Gasoline	Dip tape gauging	4.20
Instrument Fitter	Other		No technology	0.48
Interceptor Cleaning[22]	Interceptor cleaning		Interceptor cleaning	0.12
Lab Bench High	Other		No technology	0.75
Lab Bench Low	Other		No technology	0.15
Lab Other High	Other		No technology	0.09
Lab Other Low	Other		No technology	0.09
Lab Washing Glassware[22]	Washing glassware	X55	Solvent washing	0.40
Mechanic	Other		Non-gasoline solvent	0.33
Mogas Blending	Other		No technology	0.42
Offshore Operators	Other		No technology	0.02
Onshore Operators	Other		No technology	0.06
Pigging[22]	Line pigging	Gasoline	Pig retrieval	4.20
Rail Car Loading FTD	Rail car loading	Gasoline	Fill tube, dip stick	3.77
Rail Car Loading FTM	Rail car loading	Gasoline	Fill tube, metered	3.77
Rail Car Loading SFD	Rail car loading	Gasoline	Spear fill, dip stick	3.77
Rail Car Loading SFM	Rail car loading	Gasoline	Spear fill, metered	3.77

continued

[22] Short term task normally less than 1 hour in duration

Table 14 continued

Base Estimate	Task	Product	Technology	Benzene ppm
Refinery Fitter	Other		No technology	0.35
Refinery Fitter calculation[23]	Other		No technology	0.36
Refinery Operator NE	Other		No technology	0.07
Refinery Operator Plantwide	Other		No technology	0.08
Reformer	Other		No technology	0.39
Refuelling calculation[23]	Other		No technology	0.40
Refuelling with Avgas[22]	Refuelling	Avgas	Over-wing refuelling	1.65
Road Tanker Loading BMN	Tanker loading	Gasoline	Bottom loading, metered, no vapour recovery	0.55
Road Tanker Loading BMV	Tanker loading	Gasoline	Bottom loading, metered, vapour recovery	0.55
Road Tanker Loading FD	Tanker loading	Gasoline	Fill tube, dip stick	1.76
Road Tanker Loading FM	Tanker loading	Gasoline	Fill tube, metered	1.76
Road Tanker Loading SD	Tanker loading	Gasoline	Spear, dip stick	1.76
Road Tanker Loading SM	Tanker loading	Gasoline	Spear, metered	1.76
Rural Background	Other		No technology	0.001
Sampling[22]	Sampling	Gasoline	Open sampling	0.67
Separator Skimming[22]	Separator cleaning		Separator cleaning	0.12
Ship Dip/Gauge[22]	Dipping and gauging ships	Gasoline	Dip tape, hatch	5.41
Ship Loading/Unloading	Product load out/receipt	Gasoline	Flexible hose jetty work	0.11
Sour Water	Other		No technology	0.06
Tank Cleaning 1	Tank cleaning	Gasoline	Gas test, scrape and hose	0.15
Tank Cleaning 2	Tank cleaning	Crude	Gas test	0.30
Tank Cleaning 3	Tank cleaning	Crude	Gas test, scrape and hose	2.01
Tank Farm – Refinery	Other		No technology	0.14
Tank Farm – Terminal	Other		No technology	0.36
Terminal Fitter	Other		No technology	0.67
Terminal Fitter calculation[23]	Other		No technology	1.00
Terminal Operator NE	Other		No technology	0.14
Upstream Fitter	Other		No technology	0.04
Urban Background	Other		No technology	0.005
Wharf calculation[23]	Other		No technology	0.20

[23] This BE was derived by calculating the exposure of similar workers from the period and applied to a worker where job details were unavailable

3.5. Modifying Factors Used

Modifying factors were applied to less than 160 tasks out of a total of 3457 tasks identified. One reason for this was that unlike other studies in the petroleum industry, there were no pre 1940 subjects using old technologies. For example, among the subjects who were tanker drivers, there was only one driver who used top splash loading.

3.6. Exposure Analysis

3.6.1. Distribution of Activity Exposure Estimates

The mean activity exposure estimates (ppm) for each of the Activity Groups are shown in the

Table 15, together with the standard deviation and the minimum and maximum estimated exposures. Table 16 shows the distribution of Activity Exposure estimates for the different Activity Groups. Except for the Activity Groups *Drum Filling* and *Rail Car Loading*, the majority of exposure estimates were less than 1.0 ppm. Overall, 89.9 percent of Activity Exposure estimates were less than 0.5 ppm and 95.3 percent were below 1.0 ppm. Figure 8 shows the most common Activity Groups were for low exposed workers such as *Office, Other Refinery and Other Terminal.*

Table 15: Activity Exposure Estimates by Activity Group

Activity Group	Frequency	Mean (ppm)	Standard Deviation	Minimum (ppm)	Maximum (ppm)
Aircraft Refuelling	36	0.26	0.34	0.07	1.25
Drum Filling	57	1.48	1.01	0.15	5.7
Drum Laundry & Preparation	23	0.71	0.51	0.14	1.87
Fitting	144	0.49	0.32	0.001	1.2
Laboratory	52	0.39	0.53	0.001	2.11
Office	513	0.01	0.02	0.001	0.19
Other Refinery	418	0.09	0.10	0.001	0.74
Other Terminal	175	0.14	0.03	0.01	0.16
Other Upstream	67	0.005	0.01	0.001	0.04
Rail Car Loading	27	1.67	1.03	0.38	4.29
Refinery Operations	147	0.66	5.97	0.01	72.57[24]
Road Tanker Driving	168	0.22	0.14	0.001	0.74
Road Tanker Loading	23	0.52	0.51	0.07	2.47
Supervision	160	0.12	0.17	0.001	1.32
Tank Farm Operations	74	0.42	1.03	0.01	8.5
Upstream Operations	45	0.04	0.02	0.001	0.06
Vehicle Maintenance	34	0.69	0.43	0.14	1.68
Wharf and Jetty Operations	31	0.40	0.72	0.001	3.66
All Groups	**2194**	**0.46**	**0.72**	**0.001**	**72.57**

[24] Short term exposure handling benzene

Table 16: Numbers of Subjects in Exposure Bands according to Activity Group

Activity Group	**≤0.05**	**≤0.1**	**≤0.5**	**≤1**	**≤5**	**>5**	**Total**
Aircraft Refuelling		26	3	6	1		36
Drum Filling			4	16	36	1	57
Drum Laundry and Preparation			12	6	5		23
Fitting	14	6	72	33	19		144
Laboratory	8	17	9	15	3		52
Office	484	23	6				513
Other Refinery	33	362	18	5			418
Other Terminal	9		166				175
Other Upstream	67						67
Rail Car Loading			1	9	17		27
Refinery Operations	4	24	116	2		1	147
Road Tanker Driving	29		133	6			168
Road Tanker Loading		2	13	6	2		23
Supervision	36	63	56	3	2		160
Tank Farm Operations	2	4	62	1	4	1	74
Upstream Operations	16	29					45
Vehicle Maintenance			18	9	7		34
Wharf and Jetty Operations	8	5	12	2	4		31
Total	**710**	**561**	**701**	**119**	**100**	**3**	**2194**

3.6.2. Distribution of Cumulative Benzene Exposure Estimates

The cumulative benzene exposure estimates ranged from 0.005 to 57.3 ppm-years, with a mean of 4.9 ppm-years. The duration of employment ranged from 4.2 to 41.7 years, with a mean of 20.2 years and standard deviation of 8.9 years. Approximately one-third of the cumulative estimates were less than one ppm-years and nearly 85 percent were less than or equal to 10 ppm-years (Table 17). Figure 9 shows the frequency distribution of the cumulative benzene exposure estimates for the 474 subjects in the study. Figure 10 shows more detail of the cumulative benzene exposure estimates below 2.5 ppm-years.

Table 17: Cumulative Benzene Exposure Estimates Distribution

Cumulative Exposure (ppm-years)	**Percentage of Subjects**
≤0.5	24.1%
>0.5 - ≤1.0	8.9%
>1.0 - ≤5.5	39.5%
>5.5 - ≤10.0	12.7%
>10.0 - ≤20.0	10.8%
>20.0 - ≤40.0	3.6%
>40.0	0.6%

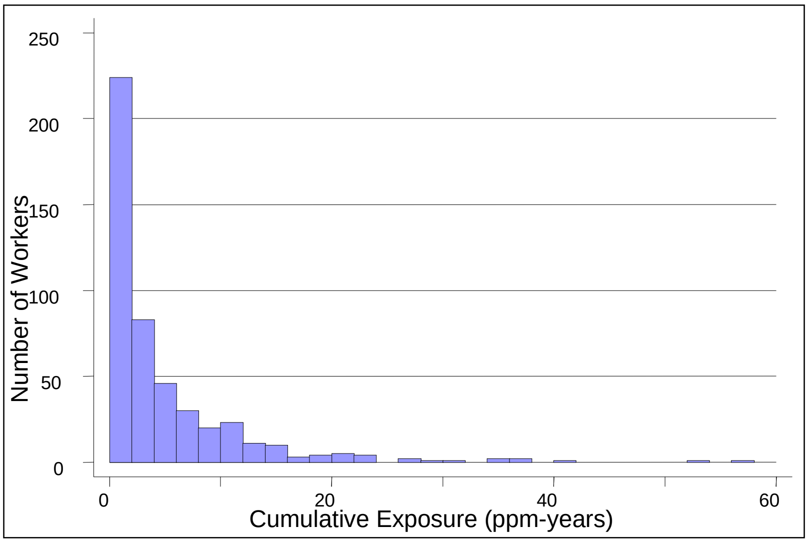


Figure 9: Cumulative Benzene Exposure Estimates Distribution

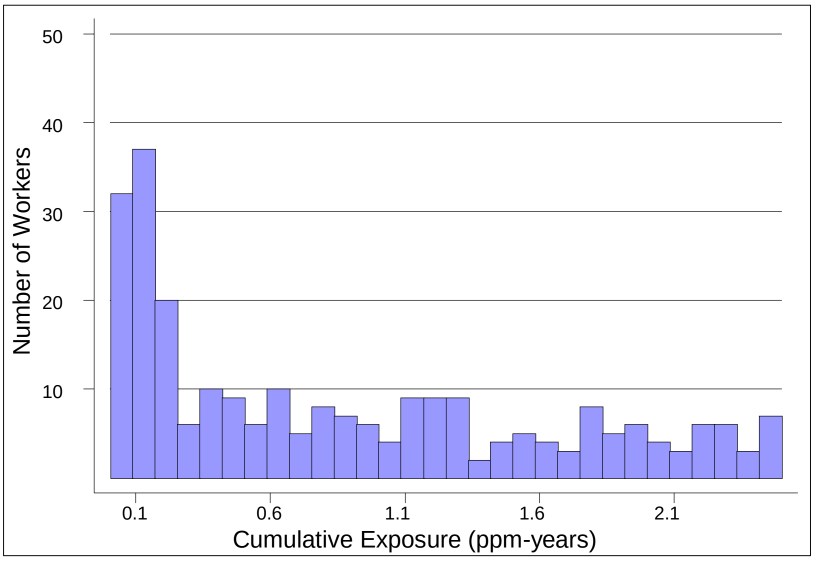


Figure 10: Cumulative Benzene Estimates Distribution Below 2.5 ppm-years (expanded scale)

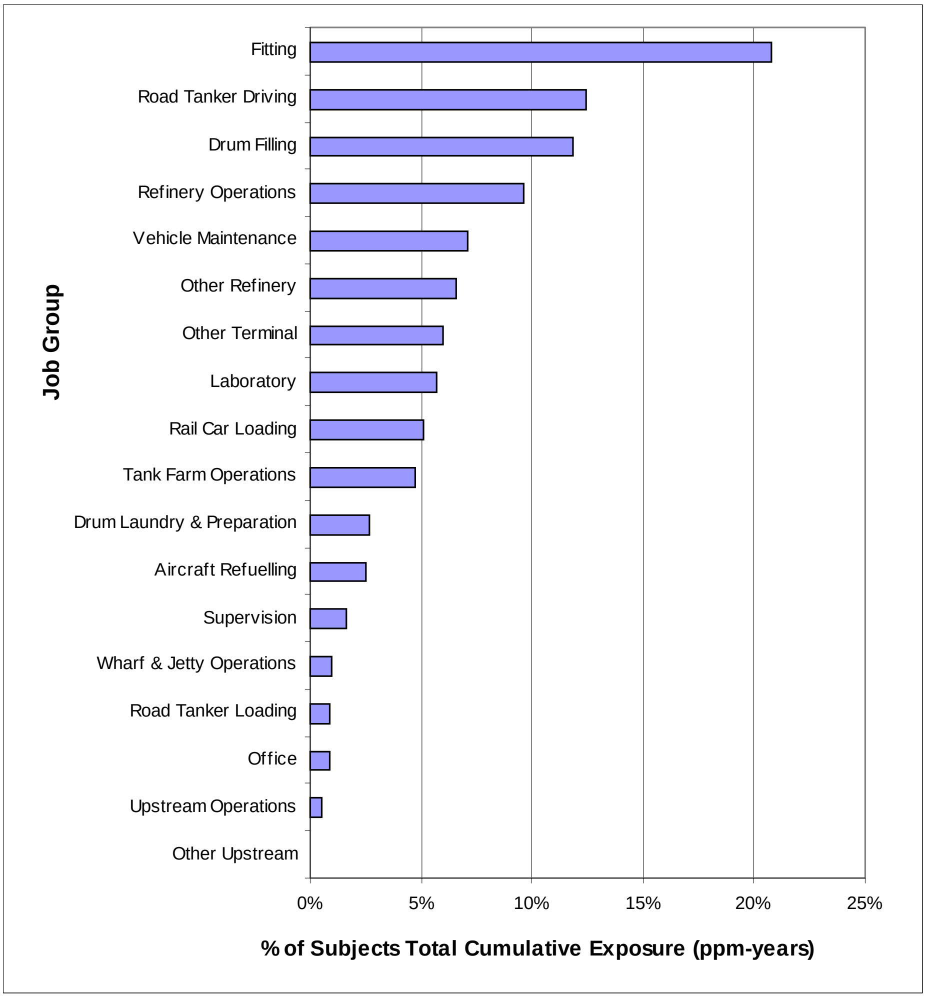


Figure 11: Cumulative Exposure to Benzene Distribution by Job Group

3.6.3. Distribution of Exposure Intensity

Estimates of average benzene exposure intensity (cumulative benzene exposure estimate divided by duration of employment) ranged from 0.001 to 2.07 ppm, with a mean of 0.20 ppm. The distribution of exposure intensities is shown in Table 18 and illustrated in Figure 12 and Figure 13. Average exposure intensity was estimated to be less than or equal to one ppm for 98 percent and less than or equal to 0.5 ppm for 90 percent of subjects. Average exposure intensities by job are shown in Figure 14. The highest exposures were for *Drum Filling* and *Rail Car Loading*.

Table 18: Long-term Exposure Intensities Distribution

Exposure Intensities (ppm)	Percentage of Subjects
≤0.01	17.1%
>0.01 - ≤0.05	11.4%
>0.05 - ≤0.1	22.2%
>0.1 - ≤0.5	40.3%
>0.5 - ≤1.0	7.2%
>1.0 - ≤2.0	1.7%
>2	0.2%

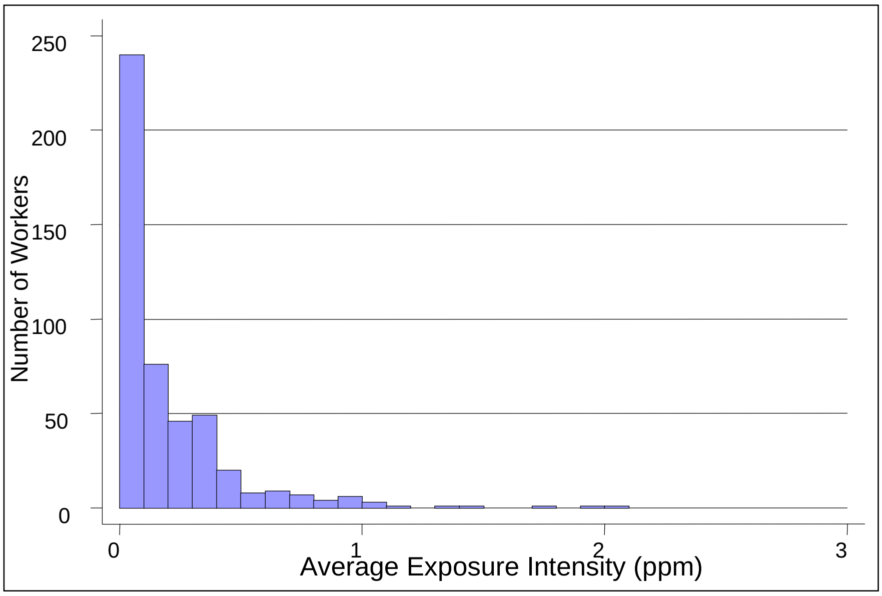


Figure 12: Long-term Average Benzene Exposure Intensity Distribution

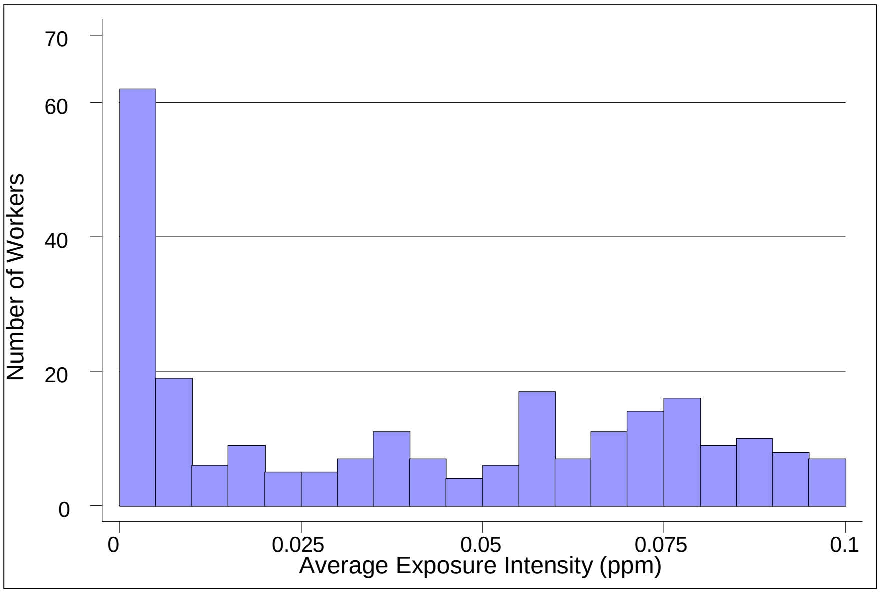


Figure 13: Long-term Average Intensity Distribution, Exposures less than 0.1 ppm (expanded scale)

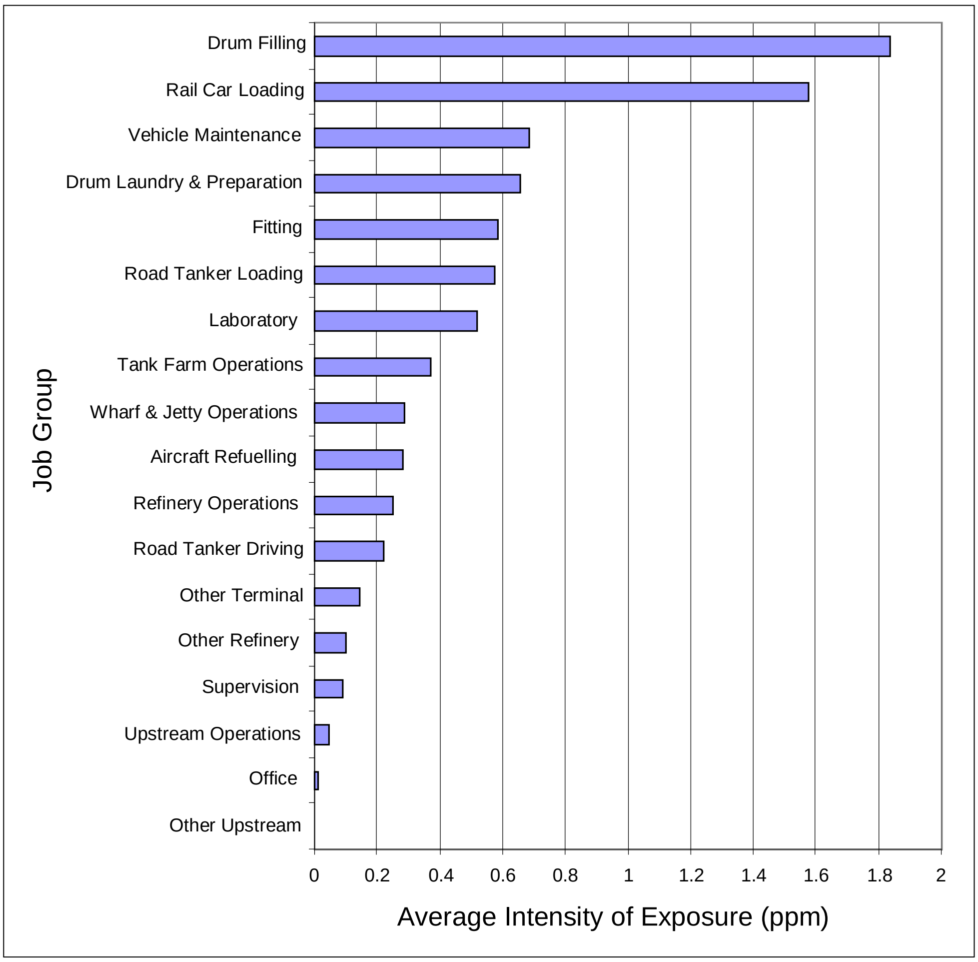


Figure 14: Average Exposure Intensity (ppm) by Job Group

3.6.4. Distribution of Daily Exposures

High Exposure Days

Figure 15 shows the exposures in ppm for each day contributed by the population to the study. For example, the first bar indicates that 24% of the population's total workdays were days with exposures of 0.01 ppm or less.

High Exposure Days and High Exposure Events

Some workers in the industry occasionally experienced rare, brief, high-exposure episodes, usually as a result of accidents, or when washing floors, hands, or tools, with gasoline or benzene (Section 2.10.2). With additional information from company occupational hygienists, the exposure estimate database was extended to include data about these events. The increase that each of the high exposure events would cause in daily benzene concentration was estimated. The estimated yearly frequency of these events was then included in the existing exposure estimate database, and a separate set of cumulative exposure estimates were developed for subjects, taking the high exposure events into account. Most of these events were experienced by *Fitters* and *Mechanics* (Table 19). Figure 15 also shows the exposures with the HEEs added.

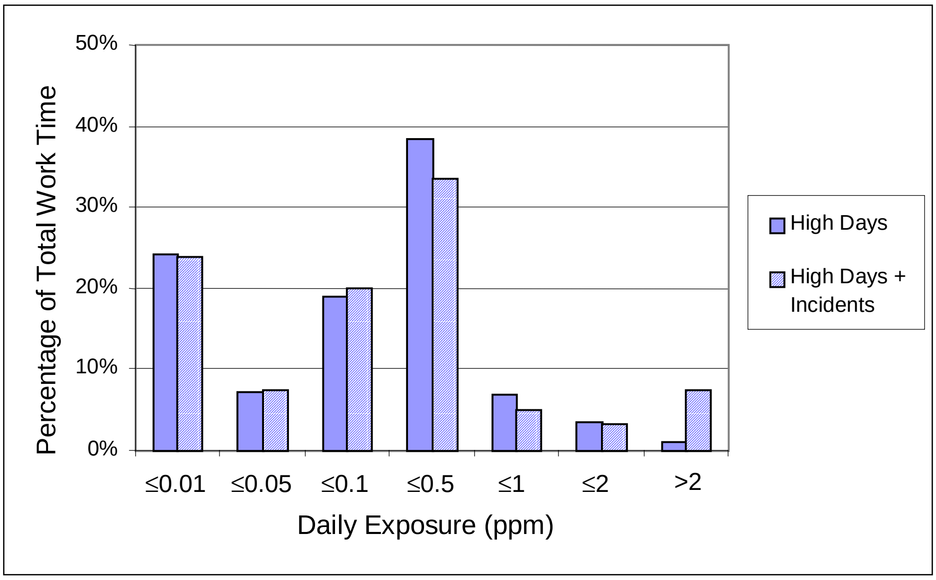


Figure 15: Daily Exposures by Percentage of Work Time(from Day Block File) including the contribution of high exposure days and events

Table 19: High Exposure Events by Job Group

Group	% of total HEEs
Fitting	69.1%
Vehicle Maintenance	16.7%
Laboratory	8.3%
Office	1.5%
Refinery Operations	1.5%
Other Refinery	1.1%
Supervision	0.8%
Other Terminal	0.8%
Road Tanker Driving	0.1%
Others	0.1%

3.6.5. Cumulative Exposure Groupings

Across the 474 subjects included in the analysis (79 cases and 395 matched controls), the lifetime cumulative exposures had a mean of 4.9 ppm-years, with a standard deviation of 7.1 ppm-years. These cumulative exposures are from inhalation alone and do not include the high exposure events. The distribution is shown in Table 20 and illustrated in Figure 16 and Figure 17.

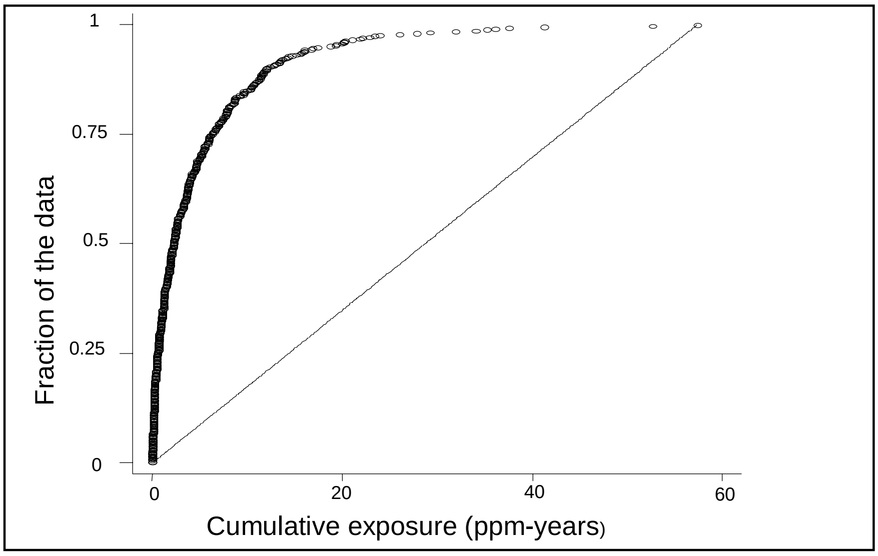


Figure 16: Lifetime Cumulative Exposure Distribution for all Subjects

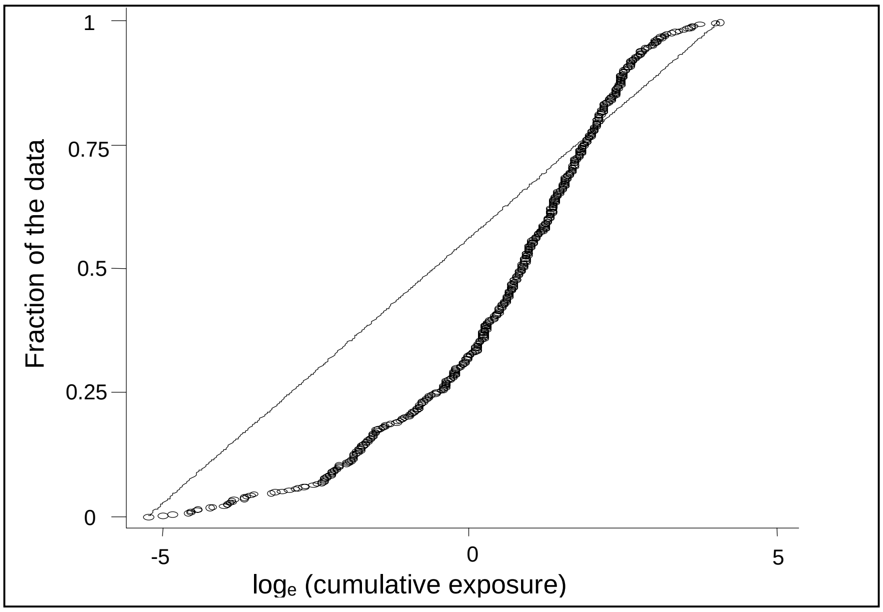


Figure 17: Lifetime log$_e$ Cumulative Exposure Distribution for all Subjects

Table 20: Lifetime Cumulative Exposures Distribution for all 474 Subjects Combined

Percentile	Centile
0	0.01
5	0.04
25	0.56
50	2.26
75	6.33
95	18.86
100	57.31

Exposure Distribution by Age of Subjects

The distribution of cumulative exposure in ppm-years was highly age-dependent as shown in the table and figures below.

Table 21: Lifetime Cumulative Exposures Distribution by Age Group for All Subjects

Age Group	Mean Cumulative Exposure (ppm-years)	Standard Deviation	Minimum (ppm-years)	Median (ppm-years)	Maximum (ppm-years)
Up to 40	2.56	4.2	0.005	0.8	22.1
41 to 50	3.20	4.9	0.011	1.6	34.0
51 to 60	6.48	8.3	0.010	4.0	52.7
61 to 75	6.28	8.4	0.010	3.5	57.3

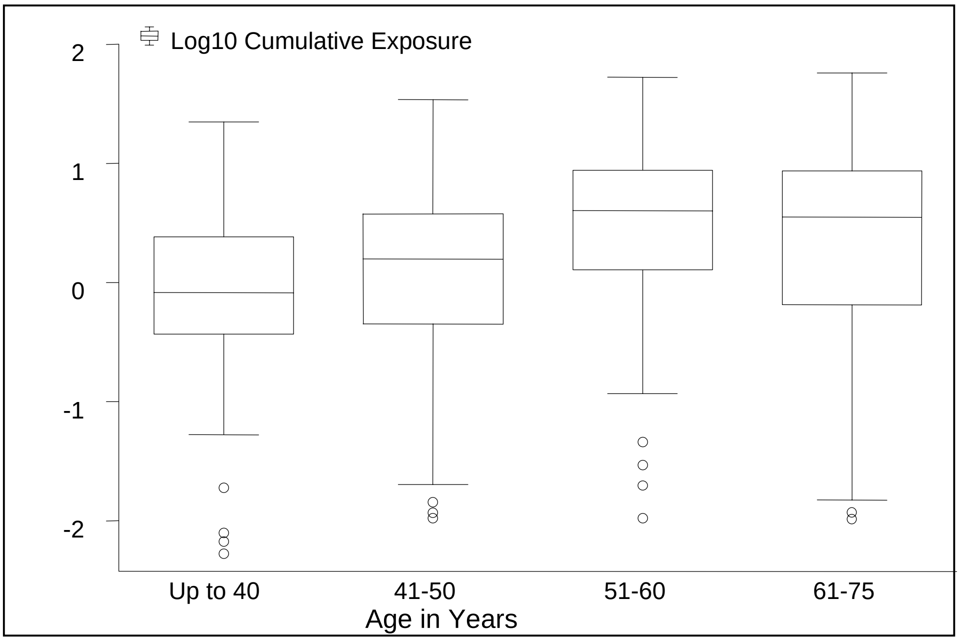


Figure 18: Lifetime Cumulative Exposures Distribution by Age Group for all Subjects (ppm-years)

The average intensity of exposure shows that older workers have had slightly higher average exposures than younger workers reflecting perhaps the phasing out of exposure to benzene and BTX and the reduction in exposure as a result of technological changes such as the introduction of bottom loading. However, this slight difference might also be explained by changes in the structure of the workforce and a greater emphasis on white collar work in recent years.

Table 22: Lifetime Average Exposure Intensity Distribution by Age Group for All Subjects

Age Group	Mean Intensity of Exposure (ppm)	Standard Deviation	Minimum (ppm)	Median (ppm)	Maximum (ppm)
Up to 40	0.19	0.31	0.001	0.07	1.76
41 to 50	0.19	0.29	0.001	0.09	2.07
51 to 60	0.22	0.23	0.001	0.15	1.13
61 to 75	0.20	0.26	0.001	0.10	1.48

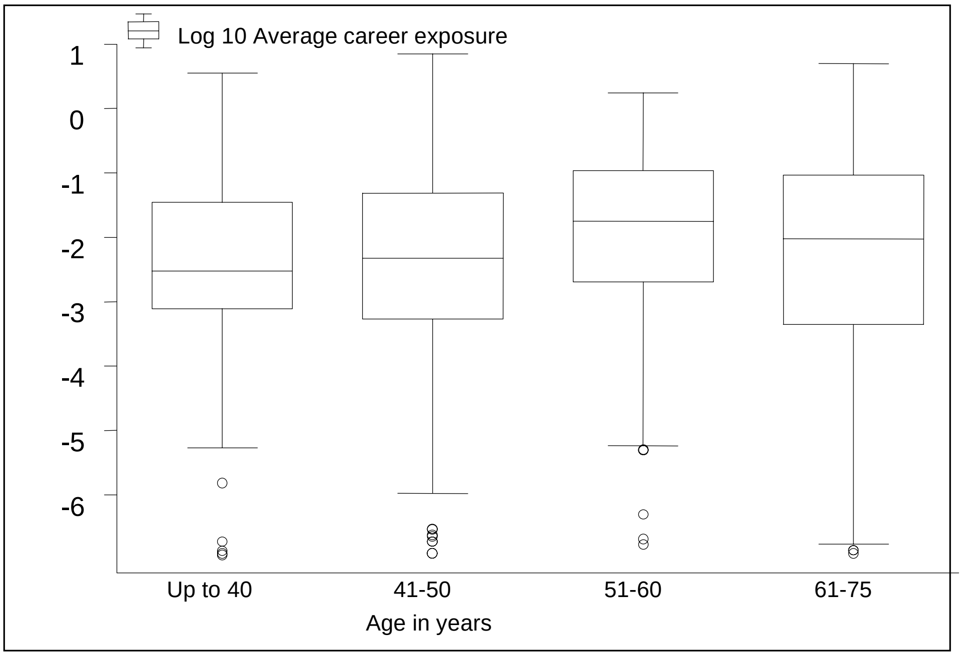


Figure 19: Lifetime Average Intensity of Exposure by Age Group for all Subjects

<u>Selection of Exposure Sub Groups</u>

Conditional logistic regression requires the exposures to be grouped into bands of increasing exposure. Two methods of grouping were employed:

- quintiles of cumulative exposure, which divides the entire 474 subjects into five groups of equal size, each with about 95 members (Table 23, Figure 20 and Figure 21).
- six groups of cumulative exposure, based on geometric steps of actual ppm-years values. The cut-points, selected arbitrarily, were in powers of two (Table 24 and Figure 22).

This second categorisation of cumulative exposure has the advantage of a broad base of 156 subjects in the “less than 1 ppm-years” group. In practice, little distinction would be made between these groups. The highest exposure group, with only 27 subjects, starts at >16 ppm, this is more than double the lower limit of the highest quintile.

Table 23: Cumulative Exposure Limits within the Quintile Groupings (ppm-years)

Quintile	Control	Case	N	Distribution of cumexp within group Min	Mean	Median	Max
1	87	8	95	0.01	0.12	0.12	0.33
2	80	15	95	0.34	0.84	0.79	1.42
3	77	18	95	1.46	2.31	2.27	3.52
4	79	16	95	3.54	5.30	5.16	7.82
5	72	22	94	7.88	15.78	12.04	57.31

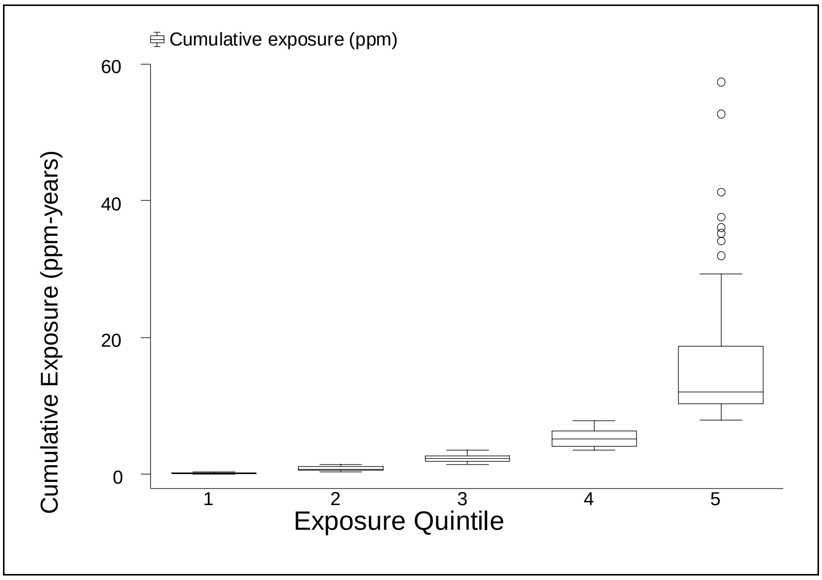


Figure 20: Quintiles of Exposure (Lifetime Cumulative Exposures in ppm-years)
(Vertical bars show range of exposures in each quintile group except for outliers)

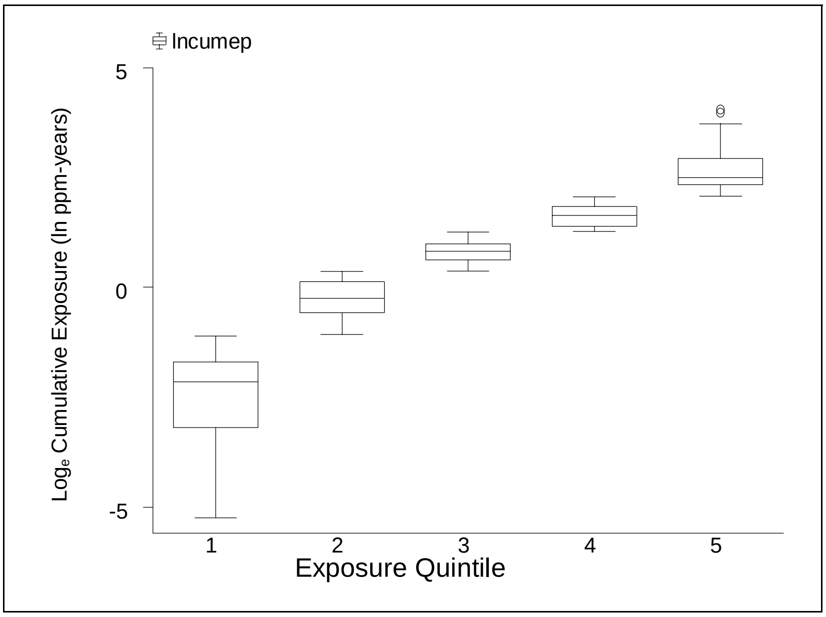


Figure 21: Quintiles of Exposure (log$_e$ Lifetime Cumulative Exposures in ppm-years)
(Vertical bars show range of exposures in each quintile group except for outliers)

Table 24: Six Geometric Exposure Groups (ppm-years)

Exposure Group	ppm-years	Control	Case	N	Distribution of cumexp within group Min	Mean	Med	Max
1	<1	138	18	156	0.01	0.33	0.20	1.00
2	1 - 2	56	12	68	1.03	1.47	1.44	1.98
3	2 - 4	67	16	83	2.02	2.93	2.78	4.00
4	4 - 8	64	12	76	4.04	5.85	5.85	7.92
5	8 - 16	53	11	64	8.04	11.35	11.27	15.97
6	>16	17	10	27	16.77	27.15	22.90	57.31

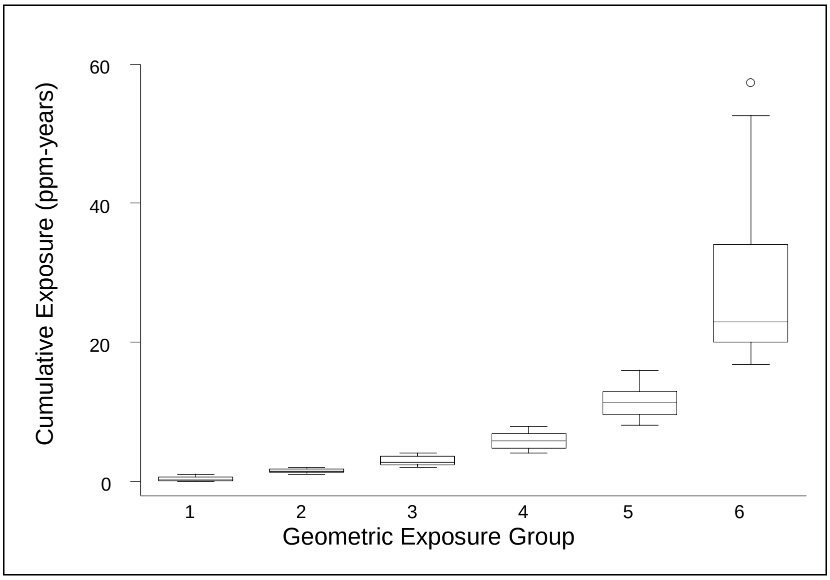


Figure 22: Geometric Exposure Groups (Lifetime Cumulative Exposures in ppm-years)
(Vertical bars show range of exposures in each quintile group except for outlier)

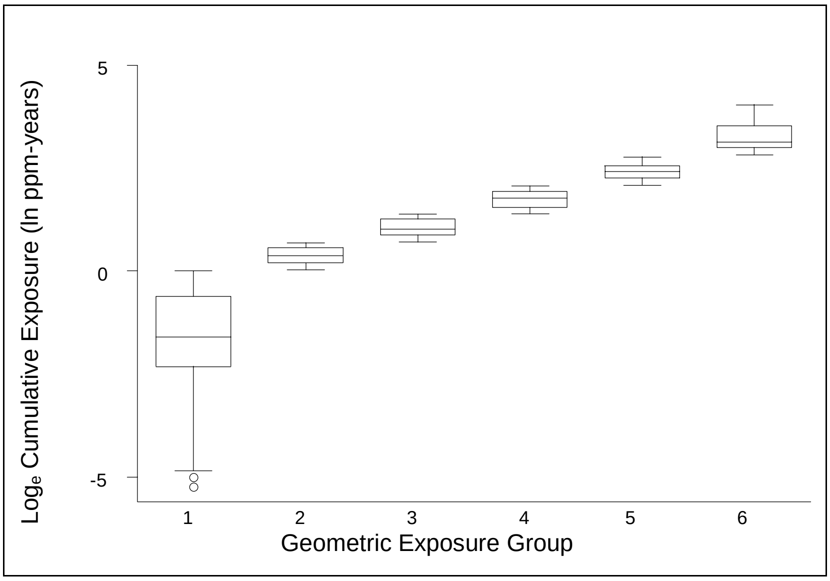


Figure 23: Geometric Exposure Groups (log$_e$ Lifetime Cumulative Exposures in ppm-years)
(Vertical bars show range of exposures in each quintile group.)

4. Results of Risk Analysis

This chapter presents results of analysis on the following topics:

Analysis by Cumulative Exposure;

- Comparison of the exposure of cases and controls;
- Association with LH Cancer, lymphatic cancer and leukaemia;
  - Continuous Exposure
  - Quintile of exposure
  - Geometric exposure
- Cumulative exposure by leukaemia sub type;
  - Quintile of exposure
  - Geometric exposure
- Cumulative exposure and multiple myeloma;
  - Quintile of exposure
  - Geometric exposure
- Exposure time frame and LH Cancer and leukaemia;
  - Latency
  - Recent exposures
- Duration of employment;
- Period
  - Start date (pre 1965, 1965-1975, post 1975);
  - Era
- Site category;
  - Cumulative exposure
  - Longest held job

Examination of “peak” exposure and LH Cancer;

- Benzene & BTX subjects and odds ratios of LH Cancer and Leukaemia
- Days of high exposure;
- Days of high exposures and high exposure events;
- Intensity of exposure (ppm) (cumulative exposure/duration)
  - Lifetime intensity
  - Intensity of highest held job.

Risk from Smoking and Alcohol

- Smoking;
- Alcohol;

Of 79 cases of LH cancer in total, 33 were leukaemia and the remainder were either non-Hodgkin's lymphoma (NHL) or multiple myeloma (MM), which for most of the following analyses were grouped together under the rubric “lymphatic cancer”.

4.1. Analysis of Cumulative Exposure

4.1.1. Comparison of Exposures for Cases and Controls

The cumulative exposures to benzene in ppm-years of the cases were compared to those of their matched sets of controls to investigate any possible overall difference. Because the exposures followed a highly skewed distribution it was more appropriate to consider the geometric means and geometric standard deviations of the data, hence the logarithms of the cumulative exposure were taken for this comparison. The mean of $\log_e$(cumulative exposure) for the controls in each of the 79 matched sets was calculated. These were collected together in one file with the corresponding $\log_e$(cumulative exposure) for the case from each matched set. If cases had higher exposures than the controls, then the difference in the values would tend to be positive; if there had been no difference in the exposure of cases and controls, then this difference would average to zero. The summary statistics are given in Table 25.

Table 25: Exposure to Benzene ($\log_e$ ppm-years) Summary Statistics

Variable	Obs	Mean	Std. Dev.	Min	Max	Geom Mean
Controls	79	0.36	0.89	-1.80	1.86	1.43
Cases	79	0.10	1.73	-4.58	3.96	2.71
Difference	79	0.64	1.99	-5.37	4.95	1.89

In Table 25, there were 79 observations, corresponding with the 79 matched sets. Across all matched sets, the cases had a mean $\log_e$ cumulative exposure of 0.10 (or a geometric mean cumulative exposure of exp(0.10) = 2.71 ppm-years; the controls, on the other hand, had a GM cumulative exposure of exp(0.36) = 1.43 ppm-years, was obtained using the pair-wise difference statistic. The ratio of mean exposure for cases compared to matched controls was at least exp(0.19) = 1.21. The difference in the mean value of the $\log_e$(cumulative exposures) for cases and controls was analysed by t-test. The difference, 0.64 was found to be significant (95% CI 0.19 - 1.08, P = 0.0058).

4.1.2. Association of Continuous Cumulative Exposure with Disease

Table 26 shows that odds ratios for LH cancer increase with cumulative exposure OR 1.05 per ppm-year, P = 0.002. The risk however concentrates for leukaemia OR 1.10 per ppm-year, P = 0.001. The odds ratio lymphatic cancers (non-Hodgkin's lymphoma and multiple myeloma) is not elevated.

Table 26: Odds Ratios by Continuous Cumulative Lifetime Exposure (ppm-years)[25]

	Odds Ratio	P>|z|	95% Conf.	Interval
LH Cancer		Number of obs	=	474
cumexp	**1.05**	**0.002**	**1.02**	**1.08**
Leukaemia Only		Number of obs	=	198
cumexp	**1.10**	**0.001**	**1.04**	**1.16**
Lymphatic Cancer Only		Number of obs	=	276
cumexp	1.00	0.90	0.95	1.05

[25] Bold figures in the Table signify a result which is statistically significant at P < 0.05.

4.1.3. Associations of Cumulative Exposure with Disease (Unmatched)

In this stage of this analysis, the matching within the data was ignored and a simple comparison of the numbers of cases and controls in each exposure group was made to provide preliminary indications of association between LH cancer and cumulative exposure grouped by quintiles.

Table 27 displays the numbers of cases and controls in each of five quintiles of cumulative lifetime exposure. The column labelled "case:ctl ratio" shows the crude ratio of numbers of cases to controls within each exposure stratum; with five controls per case, this ratio should average 0.20. The column labelled OR shows the odds ratios for LH cancer in exposure quintiles 2, 3, 4 and 5, relative to the lowest quintile. This number was the crude (unmatched) odds ratio for disease relative to the lowest exposure group.

Figure 24 shows that the odds ratio increases across the quintiles, reaching a 3.32 for the fifth quintile (corresponding to ≥ 8 ppm-years). The vertical lines represent the 95% confidence interval for the odds ratio. Figure 25 shows the same odds ratios plotted against the midpoint of the quintiles of exposure on a linear axis. The relationship may not be log linear, (the cumulative exposure has an arithmetic scale but the underlying assumption in the CLR is that the risk compounds with increasing exposure).

Table 27: LH Cancer by Quintiles of Cumulative Lifetime Exposure (ppm-years)

Quintile	Min	Max	Control	Case	case:ctl ratio	OR#	95% Conf. Interval	
1	0.005	0.33	87	8	0.09	1.00		
2	0.340	1.42	80	15	0.19	2.04	0.82	5.07
3	1.46	3.52	77	18	0.23	**2.54**	**1.05**	**6.18**
4	3.54	7.82	79	16	0.20	2.20	0.89	5.43
5	7.88	57.31	72	22	0.31	**3.32**	**1.40**	**7.91**

Odds ratios are relative to Quintile 1

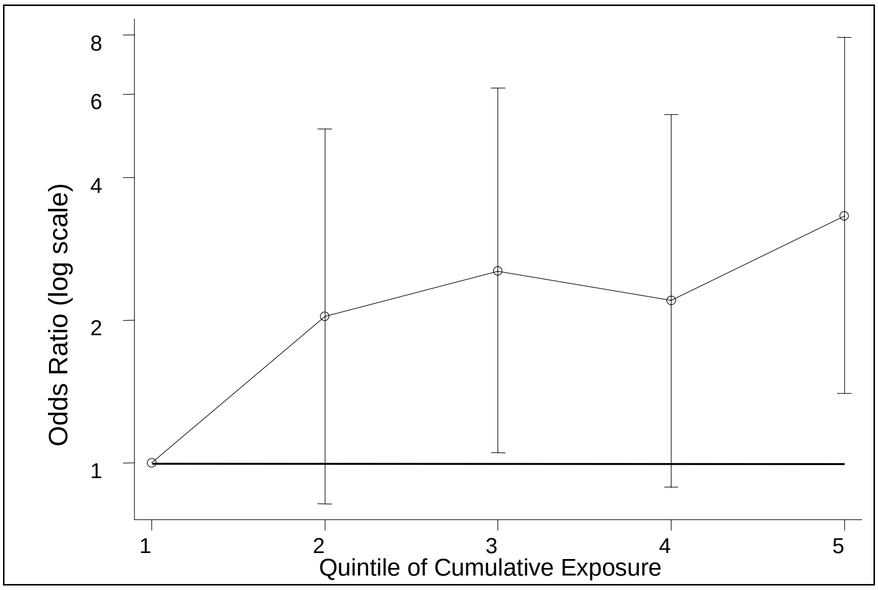


Figure 24: LH Cancer Odds Ratios by Quintiles of Cumulative Exposure

A similar increase relative to exposure group 1 is seen when exposure was grouped into 6 geometric exposure categories (Table 28). Figure 26 illustrates this upward trend in the odds ratio for increasing exposure. In this case, however, most of the elevated risk appeared to be concentrated in the highest exposure group. In Figure 27 the data are presented with the OR plotted at the mid point of the cumulative exposure group on a linear scale. In Figure 28 the same data are presented on a linear exposure scale and the horizontal lines in Figure 28 represent the range of cumulative exposures in each exposure group. The relationship between cumulative exposure and the odds ratio on a log scale was found to be approximately linear. This suggests that the exposure response relationship may actually be exponential.

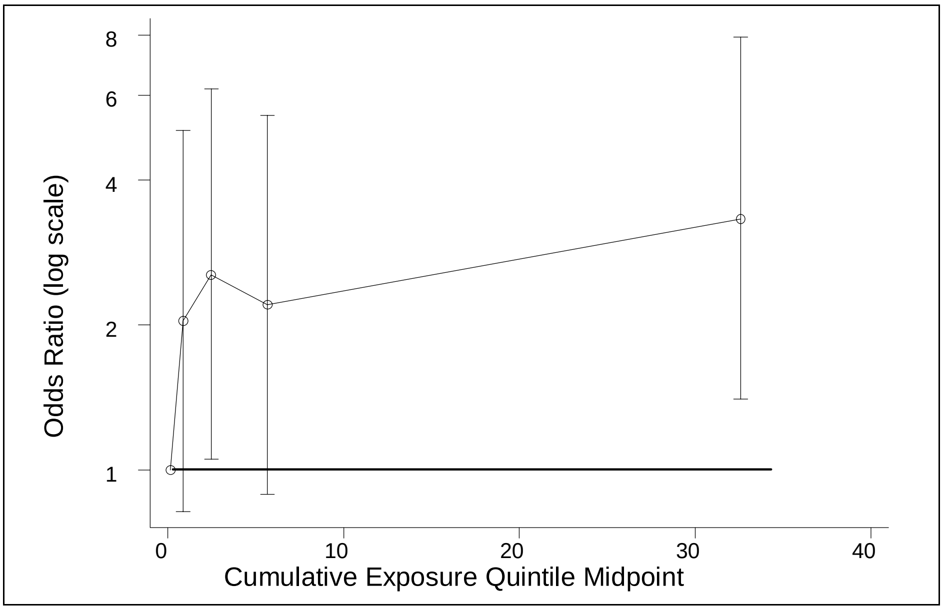


Figure 25: LH Cancer Odds Ratios by Quintiles of Cumulative Exposure ppm-years (Linear Axis)

Table 28: Cases and Controls by Geometric Cumulative Exposure Groups

Exposure group	ppm-years	Min	Max	Control	Case	Case:ctl	OR#	95% Conf. Interval	
1	< 1	0.0053	1.00	138	18	0.13	1.00		
2	1 - 2	1.03	1.98	56	12	0.21	1.64	0.74	3.63
3	2 - 4	2.02	4.00	67	16	0.24	1.83	0.88	3.81
4	4 - 8	4.04	7.92	64	12	0.19	1.44	0.65	3.16
5	8 - 16	8.04	15.97	53	11	0.21	1.59	0.70	3.59
6	> 16	16.77	57.31	17	10	0.59	**4.51**	**1.79**	**11.35**

Odds ratios are relative to Quintile 1

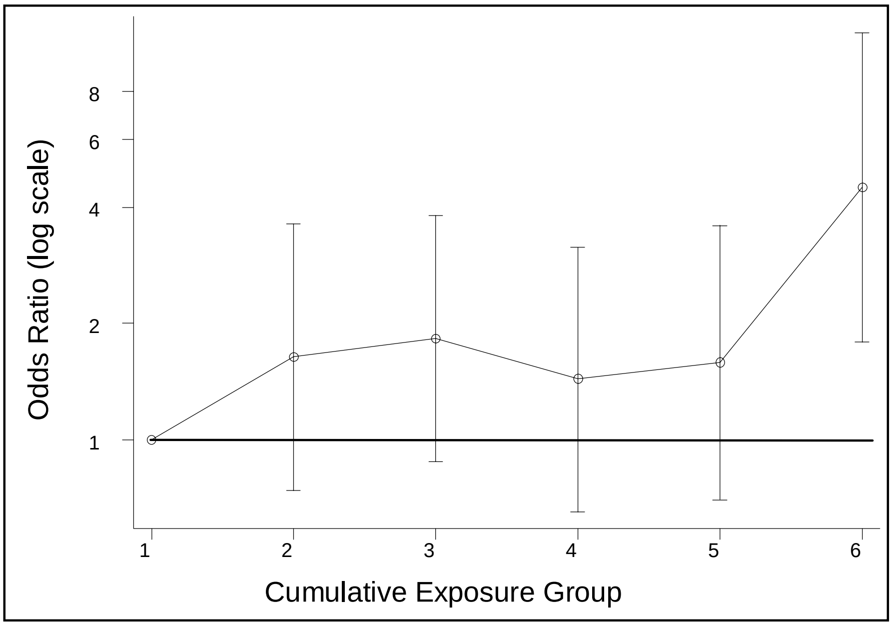


Figure 26: LH Cancer Odds Ratios by Geometric Exposure Groups

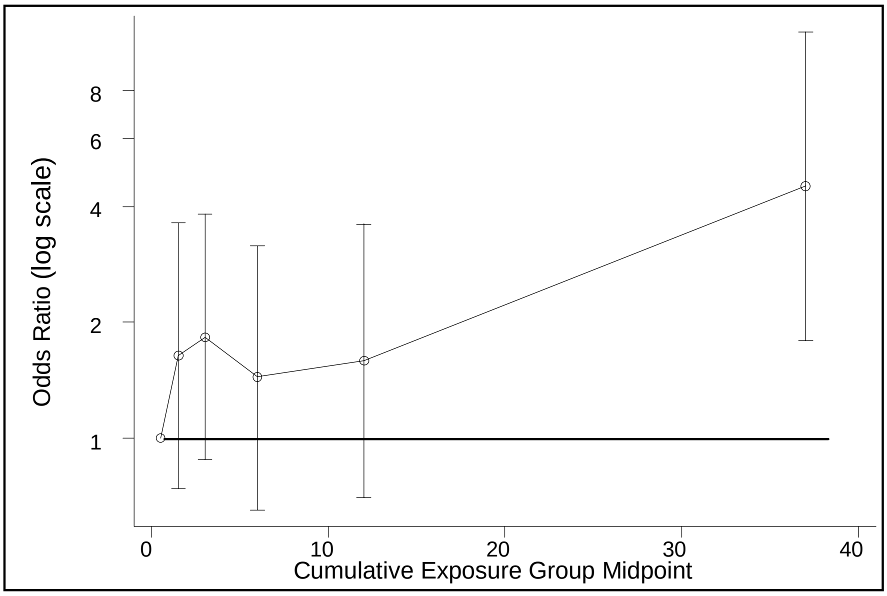


Figure 27: LH Cancer Odds Ratios by Geometric Exposure Groups (Linear Axis)
ppm-years (Relative to Group 1)

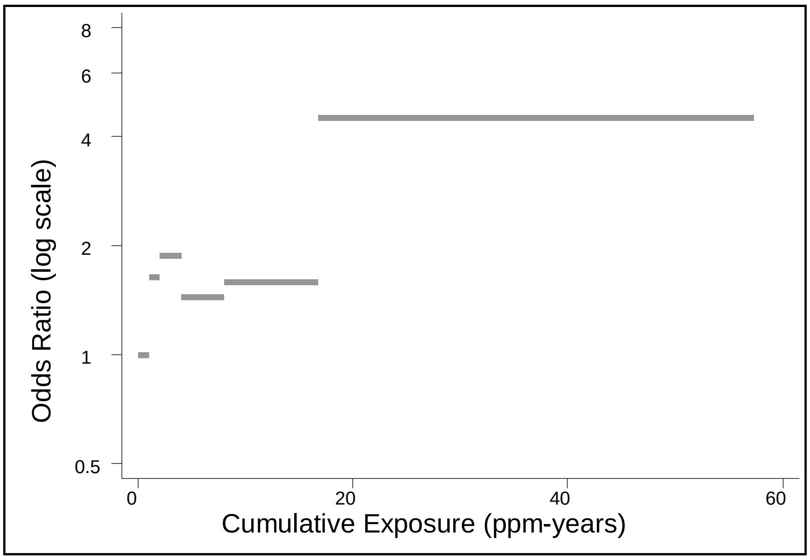


Figure 28: LH Cancer Odds Ratios by Geometric Exposure Groups (ppm-years) shown on a linear exposure scale. Horizontal bars indicate the range of exposure in each exposure group.

4.1.4. Associations of Cumulative Exposure with Disease (Matched)

The study design matched each case to 5 controls so the exposures of cases and controls were compared within the matched sets. Matched analysis was carried out by Conditional Logistic Regression (CLR).

LH Cancer by Quintiles of Cumulative Exposure

The CLR results using quintiles to categorise exposure are presented in Table 29. Relative to the lowest quintile of cumulative benzene exposure, the highest quintile shows an odds ratio of 3.3 (95% CI: 1.4 - 8.0, P = 0.007). The third and fourth quintiles also have raised ORs. These results are illustrated in the next 3 Figures.

To obtain an overall test of the association, the cumulative exposure quintiles were used as quantitative predictors (Table 30). The odds ratio of 1.28 indicates that the risk of LH cancer increases by 28% compound for each additional quintile of exposure. The P-value of 0.009 can be regarded as indicative of the significance of the association.

There appears to be little difference between the ORs with matched and unmatched analyses.

Table 29: LH Cancer by Quintiles of Cumulative Exposure

Conditional (fixed-effects) logistic regression				Number of obs = 474		
	Cumexp (ppm-years)					
Quintile	Min	Max	Odds Ratio#	P>|z|	95% Conf. Interval	
1	0.005	0.33	1.00			
2	0.34	1.42	1.88	0.17	0.76	4.64
3	1.46	3.52	**2.50**	**0.04**	**1.02**	**6.11**
4	3.54	7.82	2.25	0.08	0.91	5.58
5	7.88	57.31	**3.34**	**0.007**	**1.39**	**8.00**

Odds ratios are relative to Quintile 1

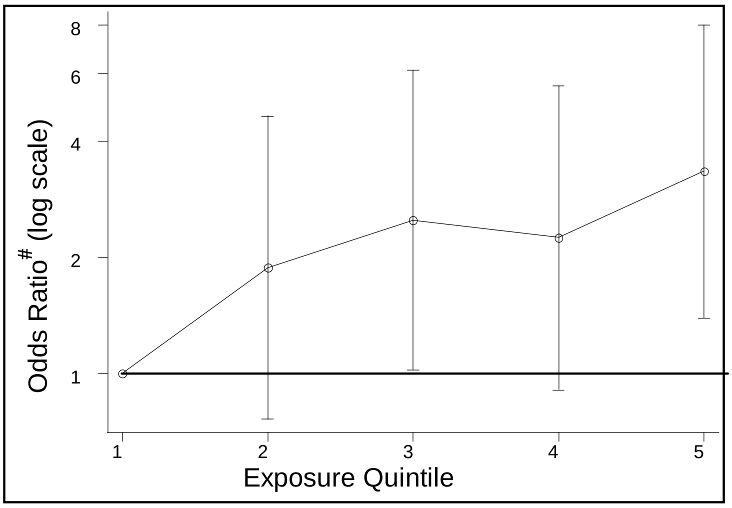


Figure 29: LH Cancer Odds Ratios by Exposure Quintiles (matched)
Odds ratios are relative to Quintile 1

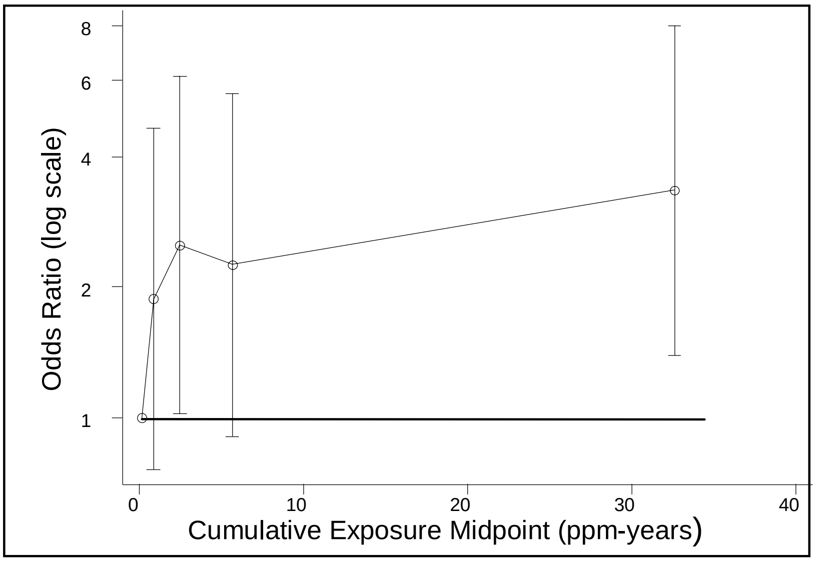


Figure 30: LH Cancer Odds Ratios and CI by Exposure Quintiles (Linear Scale) (matched)

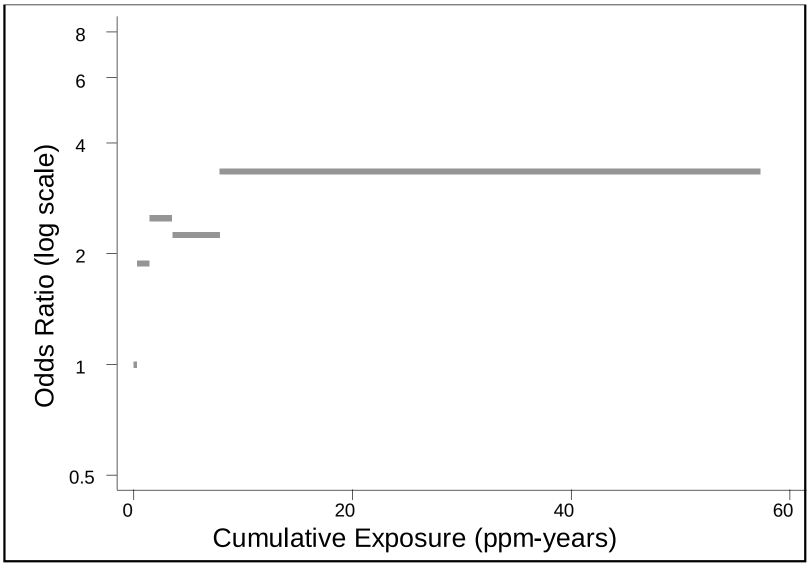


Figure 31: LH Cancer Odds Ratios by Quintile Exposures (Linear Scale) (matched)
Horizontal bars indicate the range of exposure in each exposure group.

Table 30: LH Cancer Predicted Odds Ratio by Quintiles of Exposure

Conditional (fixed-effects) logistic regression	Number of obs	=		474
	Odds Ratio	P>z	95% Conf. Interval	
Cumulative Exposure Quintile	**1.28**	**0.009**	**1.06**	**1.55**

LH Cancer by Geometric Exposure Groups

For cumulative exposure measured in geometric steps, a similar increase in risk was observed as for the analysis by quintiles (Table 31). In this case, non-significant odds ratios are seen for all but the highest benzene exposure group (≥ 16 ppm-years), for which the odds ratio, relative to the lowest group, was 4.86.

Geometric exposure groups were also used to calculate the predicted odds ratios (Table 32). The P-value of P = 0.006 indicates a significant increase in odds ratio as exposure doubles. The odds ratio of 1.04 indicates that the risk of lympho-haematopoietic cancer increases by about 4% for each doubling of benzene cumulative lifetime exposure above the exposures for Group 1 (Table 32).

Once again the relationship between the odds ratio and cumulative exposure appeared to be approximately linear when the odds ratio was plotted on a log axis (Figure 33 and Figure 34). As with the unmatched analysis described previously, this could be explained by an exponential exposure response relationship.

Table 31: LH Cancer Predicted Odds Ratios by Geometric Exposure Groups

Conditional (fixed-effects) logistic regression					Number of obs = 474		
Exposure group	Cum ppm-years	Min	Max	Odds Ratio#	P>z	95% Conf. Interval	
1	< 1	0.005	0.999	1.00			
2	1 - 2	1.03	1.98	1.57	0.27	0.71	3.46
3	2 - 4	2.02	4.00	1.92	0.09	0.91	4.04
4	4 - 8	4.04	7.92	1.48	0.34	0.66	3.33
5	8 - 16	8.04	15.97	1.65	0.24	0.72	3.80
6	> 16	16.77	57.31	**4.86**	**0.001**	**1.86**	**12.72**

Odds ratios are relative to Group 1

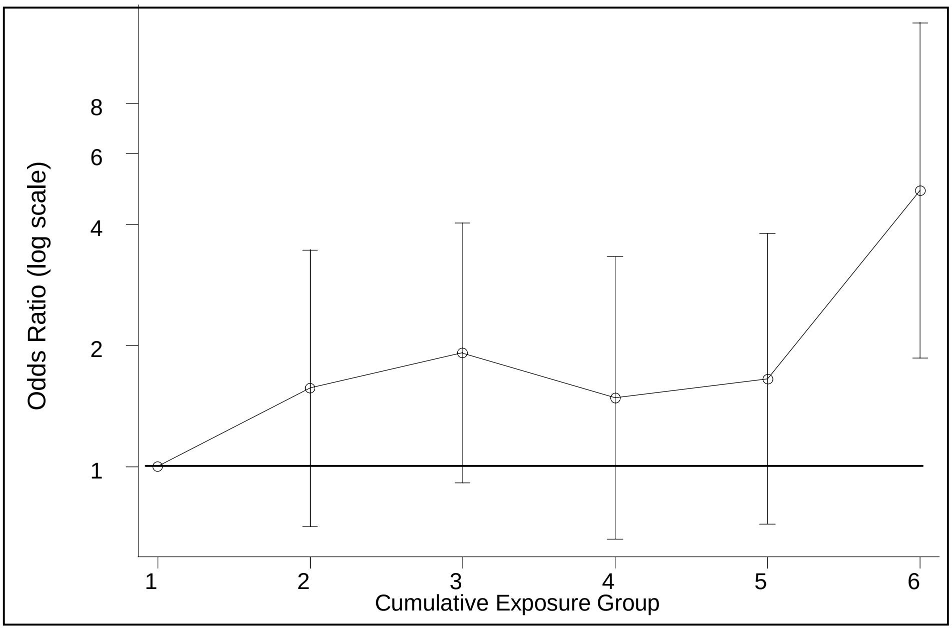


Figure 32: LH Cancer Odds Ratios by Geometric Exposure Groups (matched)

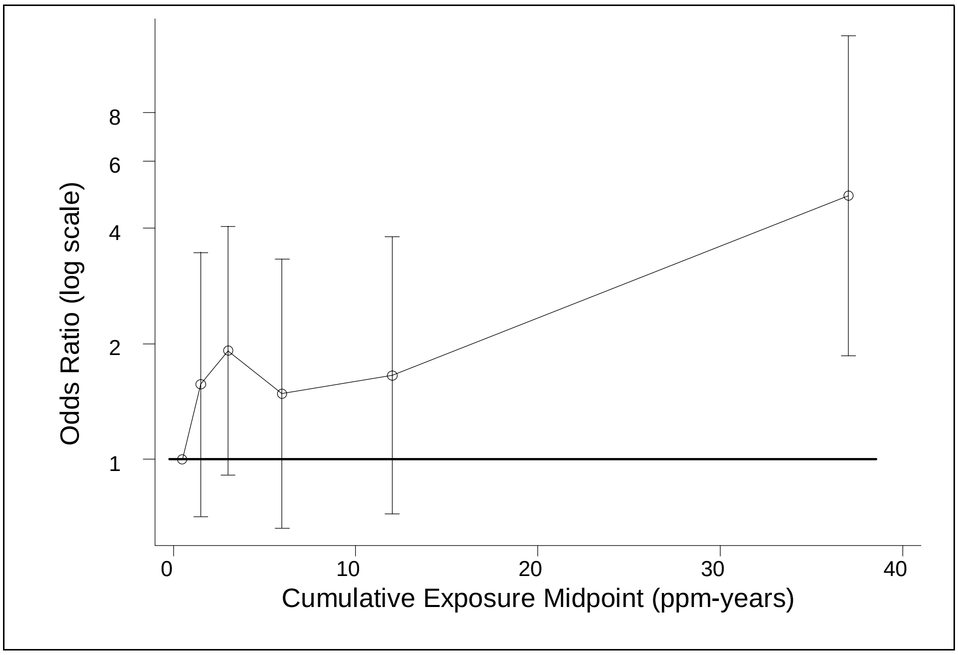


Figure 33: LH Cancer Odds Ratios and CIs by Geometric Exposure Groups (matched) (Linear Scale)

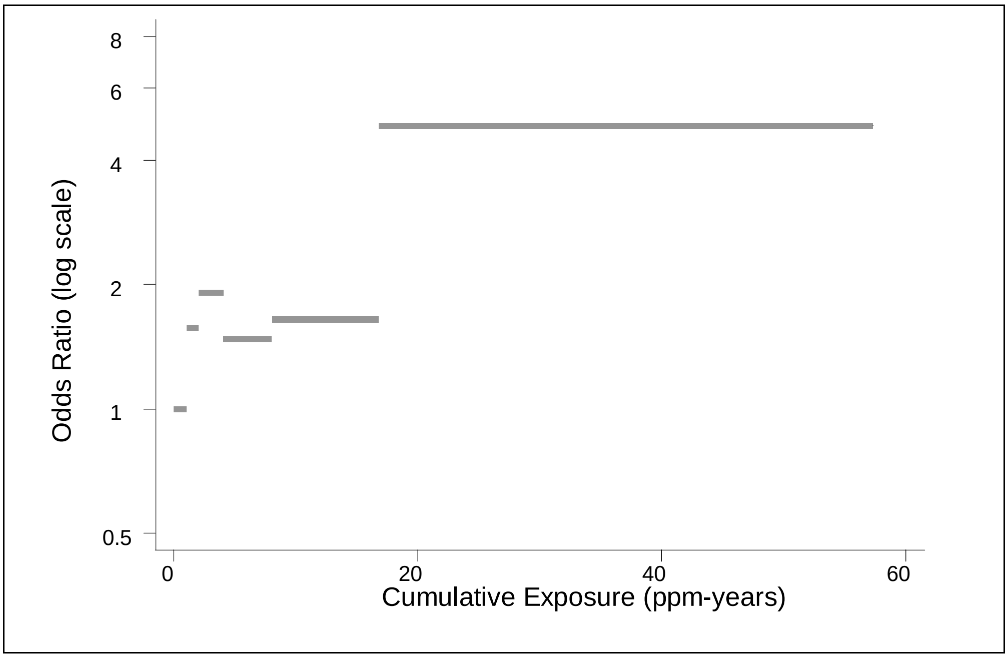


Figure 34: LH Cancer Odds Ratios by Geometric Exposure Groups (Linear Scale) (matched) Horizontal bars indicate the range of exposure in each exposure group.

Table 32: LH Cancer Predicted Odds Ratio by Geometric Exposure Groups

Conditional (fixed-effects) logistic regression	Number of obs =		474	
	Odds Ratio	P>z	95% Conf. Interval	
Geometric Exposure Group	**1.04**	**0.006**	**1.01**	**1.07**

4.1.5. Different Sub-Groups of LH Cancer - Cumulative Benzene Exposure Relationships

The unmatched case-control exposure data shown previously were separated by sub-groups of cancer in order to investigate any overall difference in cumulative exposure for cases and controls. The unmatched results for lymphatic cancer are presented in Table 33 and Table 34. For lymphatic cancer (NHL and multiple myeloma) there was no apparent increase in risk with increasing quintile of exposure. For leukaemia, Quintiles 1 and 2 were amalgamated because there was only one case in the lowest quintile. The increase for leukaemia was dramatic, the OR rising to over 22 for the top quintile of exposure. These results are illustrated in Figure 35 and Figure 36.

Table 33: Lymphatic Cancer by Cumulative Exposure Quintiles (Unmatched Data)

Quintiles	ppm-years Min	Max	Control	Case	Case:ctl	OR#	OR*[26]	95% Conf. Interval	
1	0.005	0.33	49	7	0.14	1.00	1.00		
2	0.34	1.42	47	11	0.23	1.64	1.60	0.59	4.35
3	1.46	3.52	42	8	0.19	1.33	1.32	0.46	3.83
4	3.54	7.82	44	12	0.27	1.91	1.85	0.69	5.00
5	7.88	57.31	48	8	0.17	1.17	1.16	0.40	3.33

Odds ratios are relative to Quintile 1

Table 34: Leukaemia by Cumulative Exposure Quintiles (Unmatched Data)

Quintiles	ppm-years Min	Max	Control	Case	Case:ctl	OR#	OR *[26]	95% Conf. Interval	
1 and 2	0.005	1.420	71	5	0.07	1.00	1.00		
3	1.46	3.52	35	10	0.29	4.06	**3.85**	**1.27**	**11.63**
4	3.54	7.82	35	4	0.11	1.62	1.65	0.45	6.10
5	7.88	57.31	24	14	0.58	8.28	**7.69**	**2.60**	**22.74**

Odds ratios are relative to Quintile 1

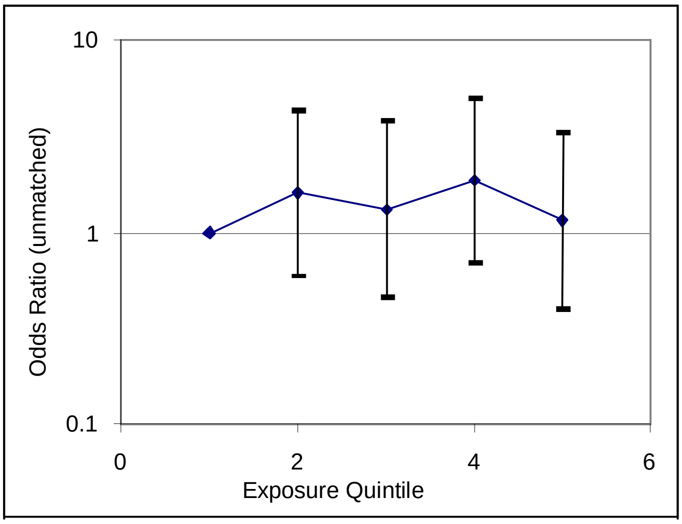


Figure 35: Lymphatic Cancer Odds Ratios by Exposure Quintiles (Unmatched Data)

[26] OR is the crude Odds Ratio without 0.5 correction: OR* has added 0.5 to each frequency to stabilise the estimate

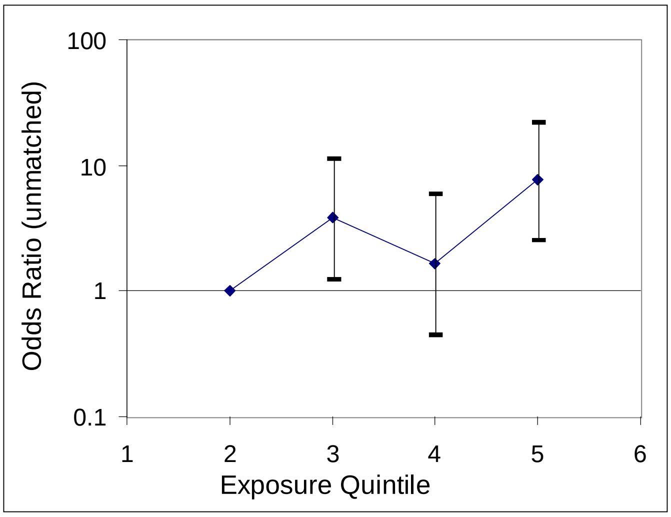


Figure 36: Leukaemia Odds Ratios by Exposure Quintiles (Unmatched Data)

The data separated by cancer type were also analysed by geometric exposure groups as shown in Table 35 and Table 36 and illustrated in Figure 37 and Figure 38.

A slight increase in risk for the highest exposure group for lymphatic cancer was seen, but this was not statistically significant. For leukaemia, however, the stabilised odds ratio was elevated for all groups above the lowest, and reached to more than 35 for the highest exposure group.

Table 35: Lymphatic Cancer by Geometric Exposure Groups (Unmatched Data)

Exposure group	**Cum ppm-years**	**ppm-years Min**	**Max**	**Control**	**Case**	**Case:ctl**	**OR#**	**OR*26**	**95% Conf. Interval**	
1	< 1	0.005	1.00	80	15	0.19	1.00	1.00		
2	1 - 2	1.03	1.98	30	6	0.20	1.07	1.11	0.40	3.03
3	2 - 4	2.02	4.00	37	8	0.22	1.15	1.18	0.47	2.96
4	4 - 8	4.04	7.92	37	9	0.24	1.30	1.32	0.54	3.22
5	8 - 16	8.04	15.97	32	5	0.16	0.83	0.88	0.31	2.52
6	> 16	16.77	57.31	14	3	0.21	1.14	1.25	0.35	4.54

Odds ratios are relative to Group 1

Table 36: Leukaemia by Geometric Exposure Groups (Unmatched Data)

Exposure group	**Cum ppm-years**	**ppm-years Min**	**Max**	**Control**	**Case**	**Case:ctl**	**OR#**	**OR*26**	**95% Conf. Interval**	
1	< 1	0.005	1.00	58	3	0.05	1.00	1.00		
2	1 - 2	1.03	1.98	26	6	0.23	4.46	**4.10**	**1.03**	**16.27**
3	2 - 4	2.02	4.00	30	8	0.27	5.16	**4.66**	**1.24**	**17.43**
4	4 - 8	4.04	7.92	27	3	0.11	2.15	2.13	0.45	10.02
5	8 - 16	8.04	15.97	21	6	0.29	5.52	**5.05**	**1.26**	**20.29**
6	> 16	16.77	57.31	3	7	2.33	45.11	**35.82**	**6.77**	**189.4**

Odds ratios are relative to Group 1

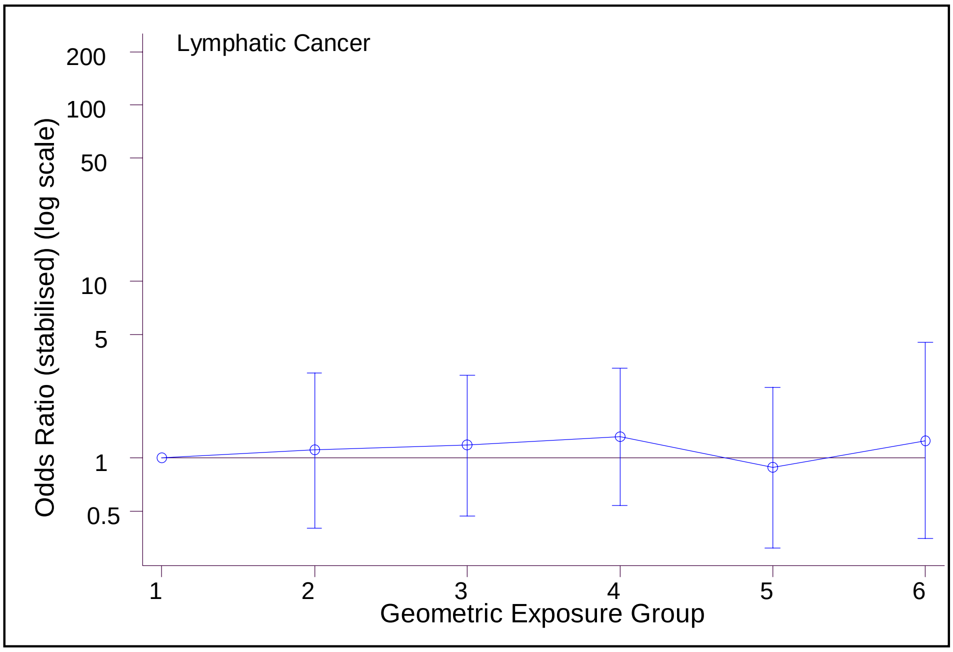


Figure 37: Lymphatic Cancer Odds Ratios by Geometric Exposure Groups (Unmatched Data)

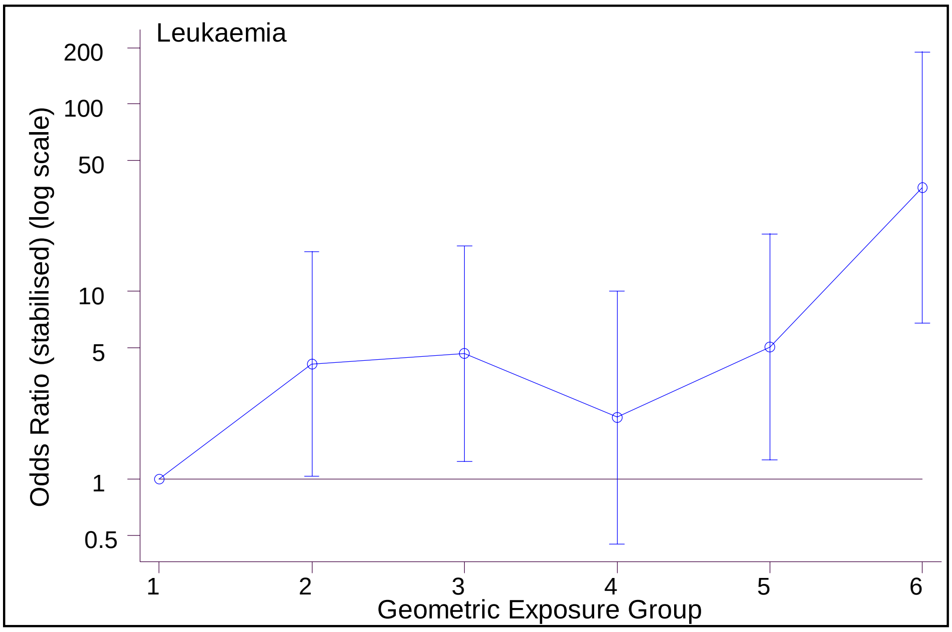


Figure 38: Leukaemia Odds Ratios by Geometric Exposure Groups (Unmatched Data)

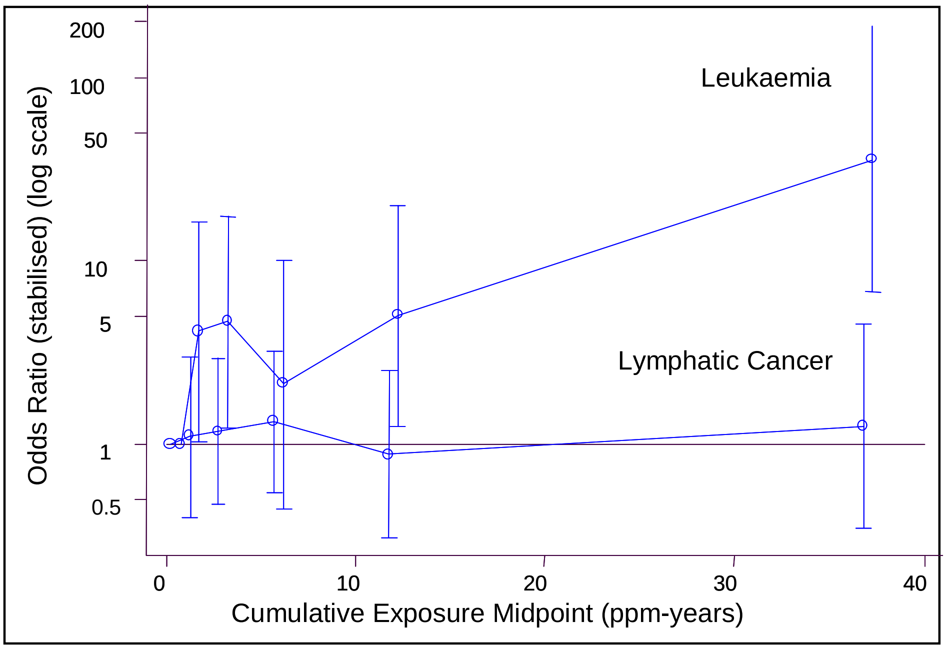


Figure 39: Lymphatic Cancer and Leukaemia Odds Ratios by Cumulative Exposure (Unmatched Data)

Interaction Between Major Cancer Type and Exposure Quintile

The interaction between cancer type and the quantitative quintile exposure variable was tested using CLR. The results are presented in Table 37. This shows the interaction between cancer type and exposure. There was a small non-significant increase in the odds ratio in the case of lymphatic cancer and a highly significant increase in the odds ratio for leukaemia (OR 1.78, 95%CI 1.18 - 2.71), that is the risk for leukaemia increases by almost 80% for each quintile of exposure.

Conditional logistic regression also showed that the risk of leukaemia was significantly associated with quintiles of cumulative exposure (OR 1.86) (Table 38).

Table 37: Major Cancer Type and Interaction with Cumulative Exposure Quintiles

Conditional (fixed-effects) logistic regression		Number of obs =	474	
Cancer Type	Odds Ratio	P>z	95% Conf. Interval	
Lymphatic cancer	1.05	0.70	0.83	1.31
Leukaemia	**1.78**	**0.006**	**1.18**	**2.71**

Table 38: Leukaemia by Cumulative Exposure Quintiles

Conditional (fixed-effects) logistic regression		Number of obs =	198	
Leukaemia	Odds Ratio	P>z	95% Conf. Interval	
Cumulative Exposure Quintile	**1.86**	**0.000**	**1.32**	**2.64**

Interaction Between Major Cancer Type and Cumulative Geometric Exposure

Stratum-specific estimates of odds ratio were calculated for cumulative benzene exposure by geometric groups. The results are presented in Table 39. For lymphatic cancers, the baseline odds ratios showed no trend or significance, indicating no relationship. For leukaemia, however, the odds ratios showed a clear increasing trend as exposure group increased and the differences between odds ratios for the two cancer groups were significant for the two highest groups of exposure; Group 5 OR 7.06 (95% CI 1.07 - 46.4, P = 0.042), Group 6 OR 86.4, (95% CI 5.4 - 1384, P = 0.002).

The estimates of odds ratios for leukaemia are presented in Table 40. For the highest exposure group the OR was 98.2 (CI 8.8 - 1090, P = <0.001). The relationship between leukaemia odds ratio and cumulative exposure is shown in Figure 40 and Figure 41.

As in the previous figures, the scale of the vertical axis in these figures is logarithmic, the OR of the highest exposure group was much larger than the other ORs. The horizontal lines in Figure 41 represent the range of cumulative exposure in each group.

The increase in risk of leukaemia with doubling of benzene cumulative lifetime exposure was highly significant; the OR = 1.65 indicates that the risk increases by 65% for each doubling of exposure (95% CI: 25% - 117%) (Table 41).

Table 39: Leukaemia and Lymphatic Cancer by Cumulative Geometric Exposure

Conditional (fixed-effects) logistic regression				Number of obs =474	
Exposure group	Exposure	Odds Ratio#	P>z	95% Conf. Interval	
Lymphatic					
1	<1	1.00			
2	1 - 2	1.06	0.90	0.38	2.95
3	2 - 4	1.16	0.75	0.45	2.98
4	4 - 8	1.28	0.60	0.51	3.22
5	8 - 16	0.84	0.76	0.27	2.55
6	> 16	1.14	0.86	0.29	4.50
Leukaemia (relative to Lymphatic Cancer)					
2	1 - 2	3.69	0.15	0.61	22.15
3	2 - 4	5.22	0.06	0.92	29.48
4	4 - 8	1.88	0.53	0.26	13.34
5	8 - 16	**7.06**	**0.04**	**1.07**	**46.43**
6	> 16	**86.41**	**0.002**	**5.40**	**1384**

Odds ratios are relative to Group 1 Lymphatic Cancer

Table 40: Leukaemia by Geometric Exposure Groups

Conditional (fixed-effects) logistic regression		Number of obs = 198		
Cumulative Exposure (ppm-years)	Odds Ratio#	P>z	95% Conf. Interval	
<1	1.00			
1 - 2	3.93	0.07	0.90	17.14
2 - 4	**6.07**	**0.02**	**1.42**	**26.01**
4 - 8	2.41	0.32	0.43	13.60
8 - 16	**5.91**	**0.02**	**1.30**	**26.97**
> 16	**98.17**	**0.000**	**8.84**	**1090**

Odds ratios are relative to Group 1

Table 41: Leukaemia Odds Ratio and CI by Geometric Exposure Groups

Conditional (fixed-effects) logistic	**regression**	Number of obs	=	198
	Odds Ratio	P>z	95% Conf. Interval	
Cumulative Exposure Group	**1.65**	**0.000**	**1.25**	**2.17**

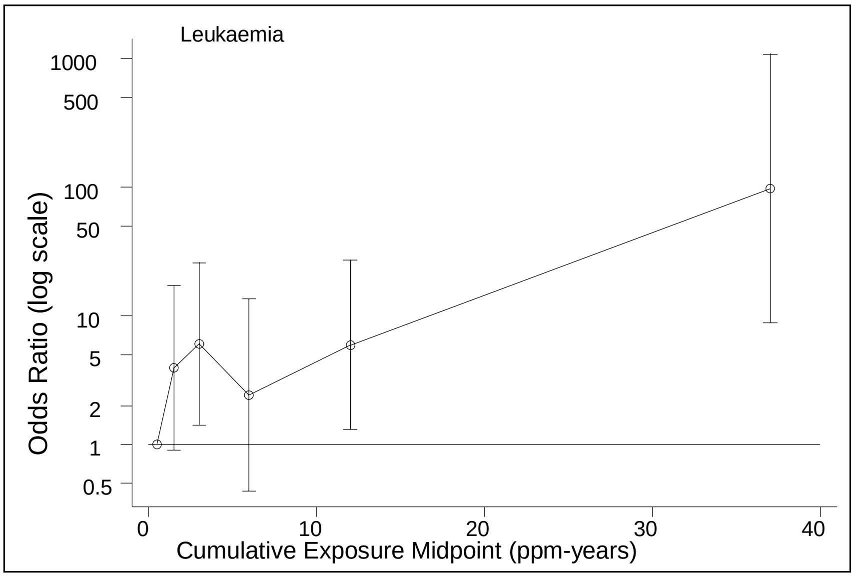


Figure 40: Leukaemia Odds Ratios by Geometric Exposure Groups (ppm-years) (Logarithmic axes)

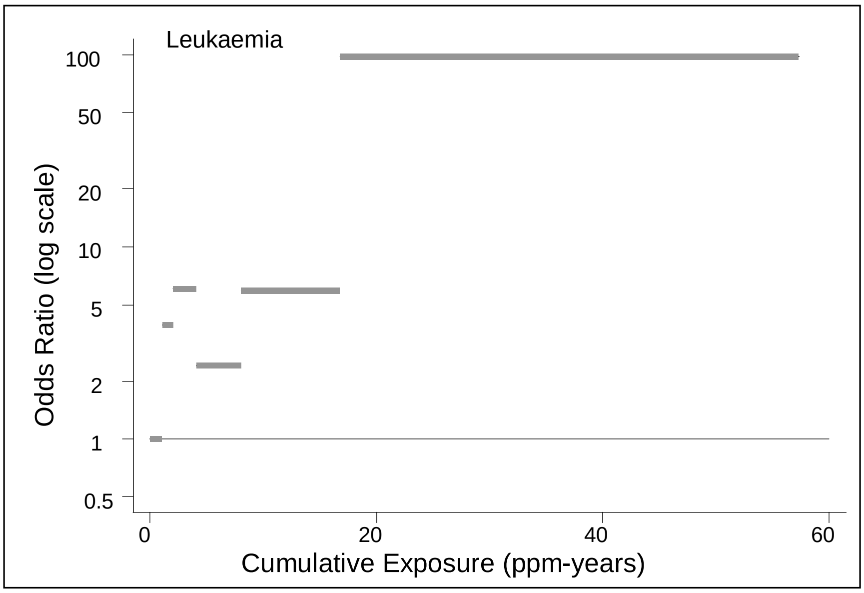


Figure 41: Leukaemia Odds Ratios by Geometric Exposure Groups (Linear Scale) Horizontal bars indicate the range of exposure in each exposure group.

4.1.6. Different Types of Leukaemia

Because of the small numbers of cases for particular leukaemia types, confidence intervals for the odds ratios would be expected to be very wide. No analysis was possible for acute lymphocytic leukaemia for which there were only 2 cases. Analysis was performed for the other leukaemia types by exposure quintile and exposure group.

Leukaemia Type by Quintile

There were 33 leukaemia cases, consisting of 9 acute myeloid leukaemias (AML), 6 chronic myeloid (CML), 2 acute lymphocytic (ALL), 11 chronic lymphocytic (CLL) and 5 other leukaemias. There were no cases of AML or CLL in the lowest quintile of exposure so that crude odds ratios could not be calculated. The small number of cases made the odds ratios unstable. The cases in the 3 lowest quintiles were amalgamated and the ORs were calculated (Table 42). There were two acute undifferentiated leukaemia cases which could be classified with the AMLs. The subtype analysis was rerun including these with the AMLs, making 11 cases of acute non-lymphocytic leukaemia (ANLL).

The ORs for two sub-groups in the highest exposure quintiles relative to quintiles 1-3 were significantly raised: AML odds ratio 4.79, (95% CI 1.05 - 21.8), ANLL OR 5.71, (95% CI 1.22 - 26.88), CLL OR 5.39, (95% CI 1.26 - 23.0).

The matched analysis in Table 43, suggests that there was an association with the highest exposure quintile for AML OR 8.89 and the association was significant for ANLL (AML and AUL) OR 8.29, (95% CI 1.31 - 52.3), CLL OR 7.2, (95% CI 1.29 - 39.7).

Table 42: Leukaemia Type Odds Ratios by Quintile (Quintiles 1-3 amalgamated)

AML	Controls	Cases	Case:Control	OR#	OR*[26]	95% Conf. Interval	
1-3	25	4	0.16	1.00	1.00		
4	14	0	0.000	0.00	0.20	0.01	3.89
5	6	5	0.83	**5.21**	**4.79**	**1.05**	**21.80**
AML+AUL (ANLL)							
1-3	32	4	0.12	1.00			
4	16	2	0.12	1.00		0.17	6.05
5	7	5	0.71	**5.71**		**1.22**	**26.88**
CML							
1-3	20	5	0.25	1.00	1.00		
4	5	0	0.000	0.00	0.34	0.02	7.11
5	5	1	0.20	0.80	1.02	0.13	7.79
CLL							
1-3	37	4	0.11	1.00	1.00		
4	10	2	0.20	1.85	1.98	0.37	10.76
5	8	5	0.62	**5.78**	**5.39**	**1.26**	**23.02**

Odds ratios are relative to Quintiles 1-3

Table 43: Leukaemia Type by Quintile CLR

AML		Number of obs	=	54
quintile	Odds Ratio[#]	P>z	95% Conf.	Interval
1-3	1.00			
4	0.00	1.00	0.00	.
5	8.89	0.055	0.95	82.84
AML+AUL (ANLL)		Number of obs	=	66
1-3	1.00			
4	1.11	0.91	0.18	6.96
5	**8.29**	**0.02**	**1.31**	**52.36**
CML		Number of obs	=	36
1-3	1.00			
4	0.00	1.00	0.00	.
5	0.78	0.84	0.07	9.06
CLL		Number of obs	=	66
1-3	1.00			
4	2.25	0.40	0.34	14.76
5	**7.15**	**0.02**	**1.29**	**39.70**

[#] Odds ratios are relative to Quintiles 1-3

Leukaemia Type by Geometric Exposure Group

There were so few cases of leukaemia in the lowest geometric exposure groups that crude odds ratios were unstable. The CLR results were similar to those derived from the analysis by quintile so they have not been presented in this report.

4.1.7. Multiple Myeloma by Cumulative Exposure

Although there was no apparent association between lymphatic cancer (MM and NHL) and benzene exposure, analysis was performed to investigate the possibility of an association for multiple myeloma alone (n=15).

The odds ratio for multiple myeloma in various quintiles are shown in Table 44 after an amalgamation of quintiles 1-3 because of the small numbers of cases. None of these are significantly elevated. Conditional logistic regression again showed no significant effect (Table 45). Similarly negative results were obtained when exposures were put into geometric groups, (analysis not presented here). There does not appear to be a relationship between exposure to benzene (assessed by cumulative exposure in quintiles or by geometric exposure group) and risk of multiple myeloma.

Table 44: Multiple Myeloma Odds Ratios by Quintiles (Quintiles 1-3 amalgamated)

	Exposure ppm-years								
MM	**Min**	**Max**	**Controls**	**Cases**	**Case:Control**	**OR#**	**OR*[26]**	**95% Conf.**	**Interval**
1-3	0.005	3.52	46	9	0.20	1.00	1.00		
4	3.54	7.82	13	4	0.31	1.57	1.63	0.46	5.80
5	7.88	57.31	16	2	0.12	0.64	0.74	0.17	3.31

Odds ratios are relative to Group 1-3

Table 45: Multiple Myeloma by Quintiles

Multiple Myeloma		Number of obs = 90		
quintile	Odds Ratio#	P>z	95% Conf.	Interval
1-3	1.00			
4	1.56	0.54	0.38	6.47
5	0.67	0.64	0.12	3.62

Odds ratios are relative to Group 1-3

4.2. Exposure Time Frame and LH Cancer

4.2.1. Analysis of Latency for LH Cancer

The effect of latency on LH cancer rates was investigated by using various periods of lagging of cumulative exposure.

The database contained two dates for each job: date at start of job and date at finish of job. In addition, the date of diagnosis was available for each case set. The finish date was set equal the date of diagnosis if a job was known to have continued beyond diagnosis (this was usually more relevant for the controls, using the diagnosis date of the matched case).

To compute lagged exposure, dates at five, ten and fifteen years prior to the date of diagnosis were taken, and for each subject, a job finish date was recomputed which was either the actual finish date or the new lagged date of diagnosis, whichever was earlier. The job duration was then recalculated as the months between the start date and new finish date (or zero, if the latter preceded the job start date).

Cumulative exposure was then computed in the same manner as before, by multiplying the task exposure by the job duration and days-per-year, then aggregating over jobs to the subject level, giving four cumulative exposure figures:

No lagging:	lifetime cumulative exposure (as before)
5 years:	cumulative exposure prior to 5 years before diagnosis
10 years:	cumulative exposure prior to 10 years before diagnosis
15 years:	cumulative exposure prior to 15 years before diagnosis

Because these quantities were strictly decreasing for each subject, we can also define the interval exposures:

recent exposure within 5 years of diagnosis
exposure within 10 years of diagnosis
exposure within 15 years of diagnosis
exposure interval 5 & 10 years prior to diagnosis
exposure interval 10 & 15 years prior to diagnosis

Because some periods of exposure have been discounted different cut-points have been used for the cumulative exposure estimates. These groups were based on fixed cut-points of 0.5, 1, 2, 4, 8 ppm-years, these were the upper limits of the cumulative exposure data. The exposure groups that were formed were therefore, ≤0.5, >0.5 ≤1, >1 ≤2, >2 ≤4, >4 ≤ 8 and >8 ppm-years. The results of this analysis, for unmatched data, are shown in Table 46. In Figure 42 the odds ratios of the cumulative exposure groups are plotted with different lag periods. A lag of 15 years means that all exposures within 15 years of diagnosis were ignored.

An attenuation in the observed peak odds ratio was found as the lag increased. This can be seen clearly in a line graph of the odds ratios against lagging (years before diagnosis) (Figure 43). The horizontal axis (lagging) is shown in reverse sequence to emphasise that this was time prior to diagnosis.

For all exposure ranges (relative to the reference range of ≤ 0.5 ppm-years) the odds ratio increased as the lagging was reduced. The all-lifetime exposure showed the greatest association with LH cancer incidence, and the earlier exposures (15 years or more before diagnosis) were the least associated with LH cancer.

This was further analysed by conditional logistic regression and the results are presented in Table 47. The odds ratios for exposure 15 years or more before diagnosis were increased but not significantly although they did but fit the patterns set by previous lags.

Table 46: LH Cancer Odds Ratios for Lagged Exposure by Groups (ppm-years)

	Cut-point	Controls	Cases	Case:ctl	OR#	95% Conf. Interval	
No lagging	<0.5	104	10	0.10	1.00		
	0.5 - 1	34	8	0.24	2.45	0.89	6.70
	1 - 2	56	12	0.21	2.23	0.91	5.48
	2 - 4	67	16	0.23	**2.48**	**1.06**	**5.80**
	4 - 8	64	12	0.19	1.95	0.80	4.77
	>8	70	21	0.30	**3.12**	**1.39**	**7.03**
5 years	<0.5	123	14	0.12	1.00		
	0.5 - 1	40	9	0.22	1.98	0.80	4.91
	1 - 2	46	11	0.24	2.10	0.89	4.96
	2 - 4	66	14	0.21	1.86	0.84	4.14
	4 - 8	61	12	0.20	1.73	0.75	3.96
	>8	59	19	0.32	**2.83**	**1.33**	**6.03**
10 years	<0.5	160	25	0.16	1.00		
	0.5 - 1	40	10	0.26	1.60	0.71	3.60
	1 - 2	36	7	0.19	1.24	0.50	3.10
	2 - 4	63	9	0.149	0.91	0.40	2.07
	4 - 8	56	13	0.23	1.49	0.71	3.10
	>8	40	15	0.38	**2.40**	**1.16**	**4.97**
15 years	<0.5	204	40	0.20	1.00		
	0.5 - 1	32	4	0.12	0.64	0.21	1.90
	1 - 2	41	9	0.22	1.12	0.50	2.48
	2 - 4	56	9	0.16	0.82	0.38	1.79
	4 - 8	29	6	0.21	1.06	0.41	2.71
	>8	33	11	0.33	1.70	0.79	3.64

Odds ratios are relative to Cut-point 1

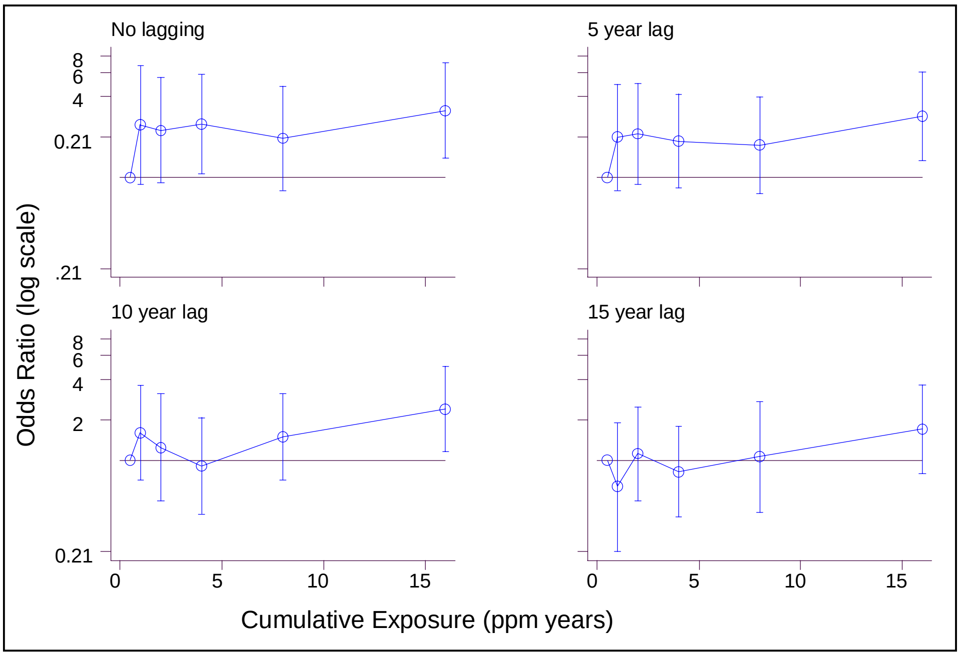


Figure 42: LH Cancer Odds Ratios by Cumulative Exposure by Various Lag Periods

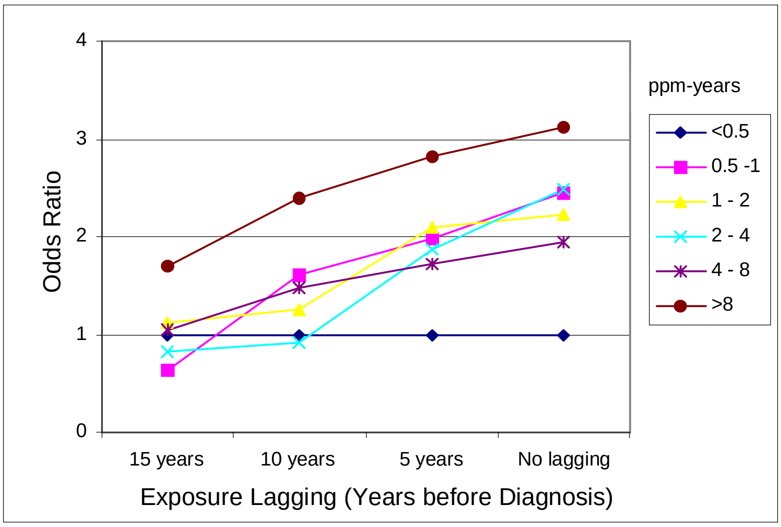


Figure 43: LH Cancer Odds Ratios and the Effect of Exposure Lagging for Various Cumulative Exposures

Table 47: LH Cancer by Lagged Cumulative Exposure

LH Cancer		Number of obs =	474	
Exposure ppm-years	Odds Ratio#	P>|z|	95% Conf.	Interval
No lag - Cumulative Lifetime Exposure				
<0.5	1.00			
0.5 - 1	2.32	0.11	0.83	6.48
1 - 2	2.10	0.10	0.86	5.11
2 - 4	**2.47**	**0.04**	**1.06**	**5.79**
4 - 8	2.00	0.13	0.81	4.95
> 8	**3.11**	**0.007**	**1.37**	**7.06**
Exposure 5 years or more Prior to Diagnosis				
<0.5	1.00			
0.5 - 1	1.87	0.19	0.74	4.72
1 - 2	2.02	0.12	0.84	4.84
2 - 4	1.91	0.12	0.85	4.29
4 - 8	1.80	0.18	0.77	4.22
> 8	**2.82**	**0.008**	**1.31**	**6.04**
Exposure 10 years or more Prior to Diagnosis				
<0.5	1.00			
0.5 - 1	1.60	0.26	0.71	3.64
1 - 2	1.28	0.61	0.50	3.28
2 - 4	0.10	1.00	0.43	2.29
4 - 8	1.58	0.26	0.71	3.51
> 8	**2.58**	**0.02**	**1.18**	**5.61**
Exposure 15 years or more Prior to Diagnosis				
<0.5	1.00			
0.5 - 1	0.62	0.40	0.20	1.89
1 - 2	1.13	0.76	0.50	2.57
2 - 4	0.84	0.69	0.36	1.95
4 - 8	1.09	0.87	0.41	2.89
> 8	1.82	0.16	0.79	4.23

Odds ratios are relative to cut-point <0.5 ppm-years

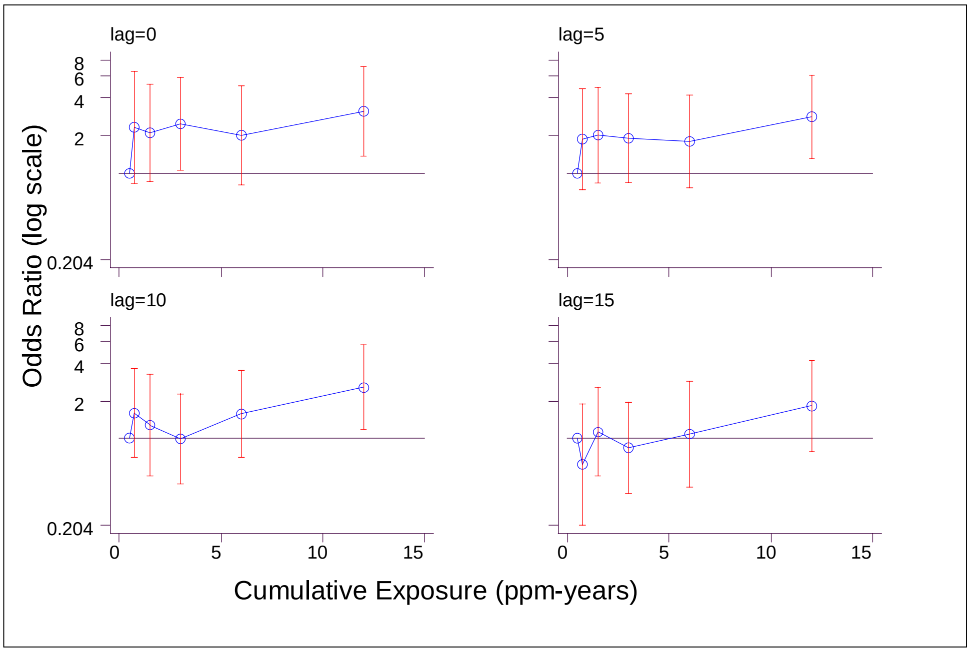


Figure 44: LH Cancer Odds Ratios by Cumulative Exposure for Different Lag Periods

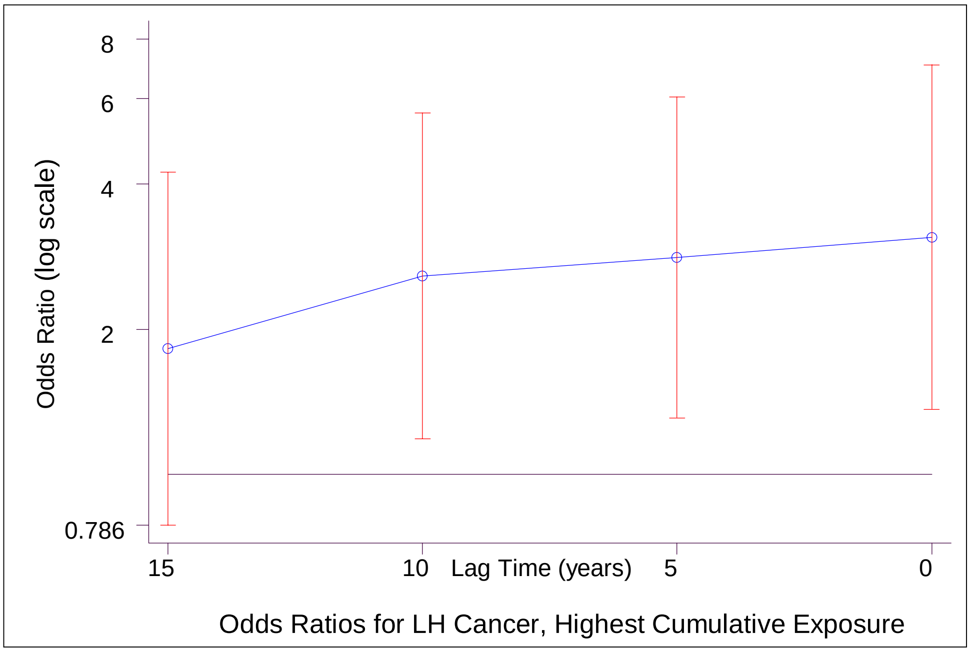


Figure 45: LH Cancer Odds Ratios and the Effect of Exposure Lagging for Cumulative Exposures of 8 ppm-years or more. A lag of 15 years means that all exposures within 15 years of diagnosis were ignored.

4.2.2. LH Cancer and the Effect of Recent Exposures

The observation of a decrease in odds ratio with increasing lag implies that the LH risk from benzene exposure dissipates over time. This can be verified by looking at the risks associated with recent exposure only. For example, the analysis in Table 48 shows the association with exposure within the five years preceding diagnosis. Although the odds ratios were not statistically significant, the 3- to 4-fold risk of LH cancer in the higher exposed groups is worthy of note.

The results for exposures within 10 years of diagnosis are presented in Table 48. In this case, the odds ratios were greater and the P-values confirmed a strong significance. In the highest exposure group (over 8 ppm-years) the odds ratio represents an almost 7-fold risk, with a 95% CI from 2.1 to 22.5.

When all exposures within 15 years of diagnosis were examined, the LH cancer odds ratios were again increased significantly, for example in the highest exposure group (>8 ppm-years) the odds ratio was 6.43 (CI 2.35 - 17.09).

Table 48: LH Cancer by Proximity of Cumulative Exposure

LH Cancer		Number of obs = 474		
Exposure ppm-years	Odds Ratio#	P>|z|	95% Conf.	Interval
Within 5 years of diagnosis				
< 0.5	1.00			
0.5 - 1	0.92	0.84	0.38	2.21
1 - 2	1.57	0.27	0.71	3.48
2 - 4	**3.03**	**0.03**	**1.10**	**8.36**
4 - 8	3.02	0.21	0.53	17.11
> 8	3.97	0.27	0.34	46.45
Within 10 years of diagnosis				
< 0.5	1.00			
0.5 - 1	**2.27**	**0.02**	**1.14**	**4.54**
1 - 2	**2.21**	**0.05**	**1.00**	**4.89**
2 - 4	1.47	0.41	0.59	3.64
4 - 8	**3.94**	**0.006**	**1.48**	**10.47**
> 8	**6.83**	**0.002**	**2.07**	**22.51**
Within 15 years of diagnosis				
< 0.5	1.00			
0.5 - 1	**2.58**	**0.03**	**1.11**	**6.00**
1 - 2	**4.01**	**0.000**	**1.85**	**8.70**
2 - 4	2.26	0.09	0.89	5.72
4 - 8	**3.81**	**0.004**	**1.54**	**9.42**
> 8	**6.34**	**0.000**	**2.35**	**17.09**

Odds ratios are relative to cut-point <0.5 ppm-years

For exposures in the period 5 to 10 years prior to diagnosis (Table 49) there are again significant increases in LH cancer odds ratios. In the highest exposure group the odds ratio of 22 is significant (P = 0.008) but has a very high standard error, and a correspondingly wide confidence interval from 2.2 upwards.

For exposures in the period 10 to 15 years prior to diagnosis (Table 49) the odds ratios are even higher particularly for the higher exposures.

An analysis was also carried out to compare exposure within the more recent 15 years with that more than 15 years prior to diagnosis. This is presented in Table 50. The odds ratio associated with exposure within the past 15 years peaks at OR = 8.98 (95% CI 2.97 - 27.13, P < 0.001), whereas none of the post-15 year odds ratios is significantly elevated.

Table 49: LH Cancer by Recent Cumulative Exposures
Five to Ten Years Preceding Diagnosis

LH Cancer		Number of obs = 474		
Exposure ppm-years	Odds Ratio#	P>|z|	95% Conf.	Interval
Between 5 & 10 years prior to diagnosis				
<0.5	1.00			
0.5 - 1	**2.28**	**0.02**	**1.13**	**4.62**
1 - 2	0.90	0.81	0.40	2.05
2 - 4	**2.55**	**0.05**	**1.00**	**6.53**
4 - 8	2.52	0.10	0.85	7.51
> 8	**22.28**	**0.008**	**2.24**	**221.3**
Between 10 & 15 years prior to diagnosis		Number of obs = 474		
<0.5	1.00			
0.5 - 1	**2.05**	**0.03**	**1.07**	**3.94**
1 - 2	1.38	0.43	0.62	3.04
2 - 4	1.66	0.28	0.66	4.18
4 - 8	**3.46**	**0.03**	**1.13**	**10.59**
> 8	**25.03**	**0.004**	**2.76**	**227.0**

Odds ratios are relative to cut-point <0.5 ppm-years

Table 50: LH Cancer Latency - Cumulative Exposure
Less than and Greater than Fifteen Years Preceding Diagnosis

LH Cancer		Number of obs = 474		
ppm-years	Odds Ratio#	P>|z|	95% Conf.	Interval
Within 15 years of diagnosis				
<0.5	1.00			
0.5 - 1	**3.00**	**0.01**	**1.26**	**7.17**
1 - 2	**5.50**	**0.000**	**2.36**	**12.79**
2 - 4	**2.89**	**0.04**	**1.05**	**7.92**
4 - 8	**5.30**	**0.001**	**1.95**	**14.43**
> 8	**8.98**	**0.000**	**2.97**	**27.13**
More than 15 years prior to diagnosis				
0.5 - 1	0.33	0.06	0.10	1.07
1 - 2	0.69	0.40	0.29	1.65
2 - 4	0.39	0.05	0.15	1.01
4 - 8	0.48	0.18	0.16	1.41
> 8	0.74	0.55	0.27	1.99

Odds ratios are relative to cut-point <0.5 ppm-years

Table 51 illustrates the effect of various lagging periods on LH cancer odds ratio. The odds ratio peaks at around 10 to 15 years prior to diagnosis. Exposures more than 15 years prior to diagnosis appear to make a negligible contribution to LH cancer risk (Figure 46 and Figure 47). This would appear to be mostly as a result of an increased risk of leukaemia for more highly exposed workers. This is shown in the differences in the odds ratios for the most highly exposed workers, OR 5.09, (95% CI 1.0 - 26.0, P = 0.05) for lymphatic cancer (Table 52) and OR 34.12, (95% CI 4.1 - 285, P = 0.001) for leukaemia (Table 53). Figure 48 shows leukaemia is most strongly associated with benzene exposures in the period upto 15 years before diagnosis. In the case of lymphatic cancer there is an apparent association involving a deficit of cases with exposures more than 15 years before diagnosis. There is no known explanation for such an effect, lymphatic cancer was not associated with benzene exposure in other analyses in this study.

A complete analysis for latency in leukaemia similar to that presented in Section 4.2 for LH cancers as a whole, would be of interest. This analysis was attempted but there were too few leukaemia controls in the higher exposure groups for the CLR model to converge. The best groupings available were those shown in "Recent vs Past", i.e. up to 15 years and then over 15 years (Table 53).

Table 51: LH Cancer Latency - Cumulative Exposures in Various Time Intervals

LH Cancer		Number of obs = 474		
	Odds Ratio#	P>|z|	95% Conf.	Interval
Within 5 years				
<0.5	1.00			
0.5 - 1	0.71	0.52	0.25	2.01
1 - 2	2.00	0.23	0.65	6.19
2 - 4	3.62	0.10	0.79	16.55
4 - 8	2.06	0.59	0.15	27.52
> 8	2.89	0.65	0.03	296.3
Between 5 & 10 years				
0.5 - 1	1.81	0.20	0.73	4.48
1 - 2	0.44	0.19	0.13	1.50
2 - 4	0.89	0.89	0.17	4.54
4 - 8	0.56	0.58	0.07	4.30
> 8	2.33	0.61	0.09	57.65
Between 10 & 15 years				
0.5 - 1	2.25	0.07	0.95	5.31
1 - 2	2.40	0.13	0.77	7.43
2 - 4	1.63	0.49	0.40	6.60
4 - 8	3.67	0.16	0.61	22.28
> 8	23.74	0.03	1.45	388.7
More than 15 years				
0.5 - 1	0.38	0.13	0.11	1.33
1 - 2	0.64	0.36	0.25	1.66
2 - 4	0.44	0.11	0.16	1.22
4 - 8	0.58	0.35	0.18	1.82
> 8	0.65	0.46	0.21	2.02

Odds ratios are relative to cut-point <0.5 ppm-years

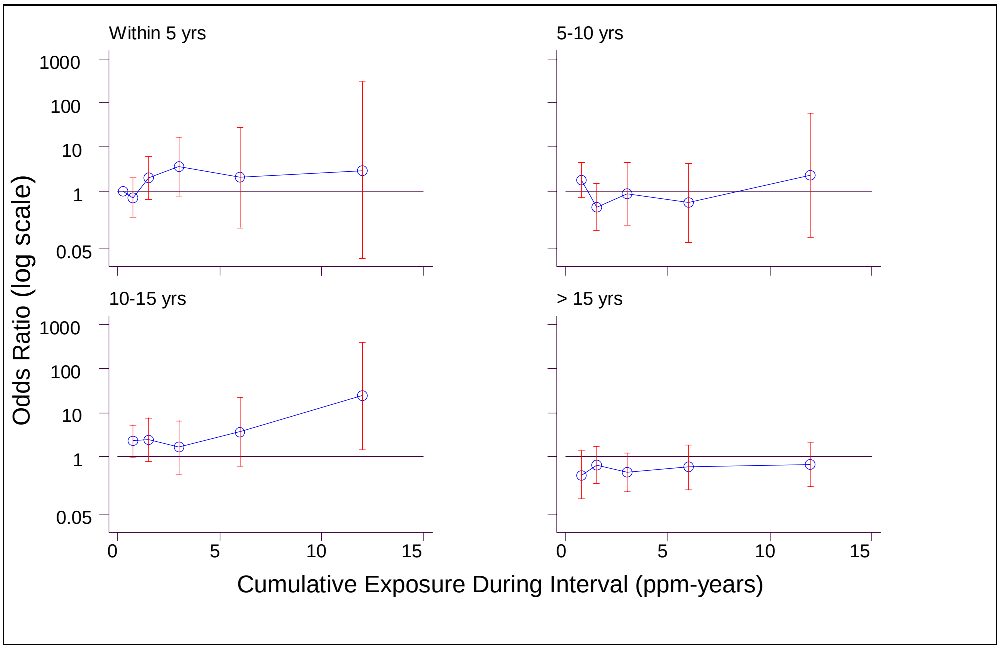


Figure 46: LH Cancer and Cumulative Exposure by Lag Interval

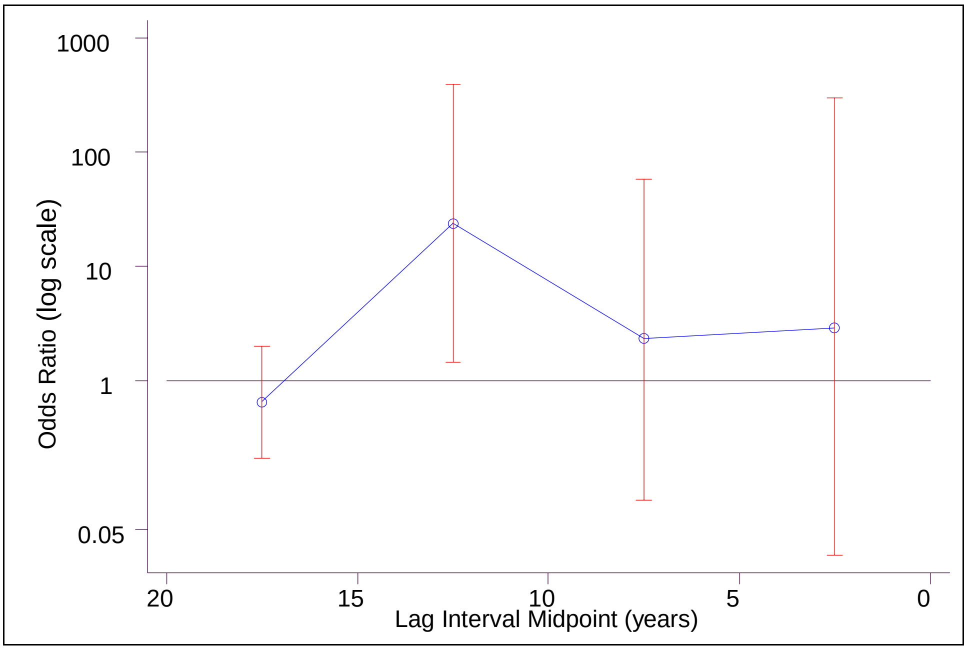


Figure 47: LH Cancer by Lag Interval for the Highest Exposure Group

Table 52: Lymphatic Cancer Latency by Years Prior to Diagnosis

Lymphatic Cancer		Number of obs = 276		
ppm-years	Odds Ratio[#]	P>|z|	95% Conf. Interval	
Within 15 years of diagnosis				
<0.5	1.00			
0.5 - 1	2.90	0.06	0.93	8.98
1 - 2	**5.47**	**0.004**	**1.74**	**17.19**
2 - 4	**3.86**	**0.05**	**1.00**	**14.83**
4 - 8	**7.18**	**0.004**	**1.86**	**27.67**
> 8	**5.09**	**0.05**	**1.00**	**25.96**
More than 15 years prior to diagnosis[27]				
0.5 - 1	**0.20**	**0.05**	**0.04**	**0.99**
1 - 2	**0.27**	**0.04**	**0.08**	**0.94**
2 - 4	**0.24**	**0.02**	**0.07**	**0.81**
4 - 8	0.24	0.08	0.05	1.20
> 8	**0.15**	**0.02**	**0.03**	**0.72**

[#] Odds ratios are relative to cut-point <0.5 ppm-years

Table 53: Leukaemia Latency by Years Prior to Diagnosis

Leukaemia		Number of obs = 198		
ppm-years	Odds Ratio[#]	P>|z|	95% Conf. Interval	
Within 15 years of diagnosis				
<0.5	1.00			
0.5 - 1	**8.22**	**0.02**	**1.30**	**51.88**
1 - 2	**12.15**	**0.005**	**2.15**	**68.62**
2 - 4	5.17	0.11	0.70	38.11
4 - 8	**12.44**	**0.02**	**1.60**	**96.63**
> 8	**34.12**	**0.001**	**4.08**	**285.09**
More than 15 years prior to diagnosis				
0.5 - 1	0.73	0.75	0.11	4.99
1 - 2	2.68	0.17	0.66	10.89
2 - 4	0.53	0.50	0.08	3.40
4 - 8	0.91	0.90	0.18	4.53
> 8	**6.18**	**0.04**	**1.05**	**36.26**

[#] Odds ratios are relative to cut-point <0.5 ppm-years

[27] Odds ratios significantly less than expected

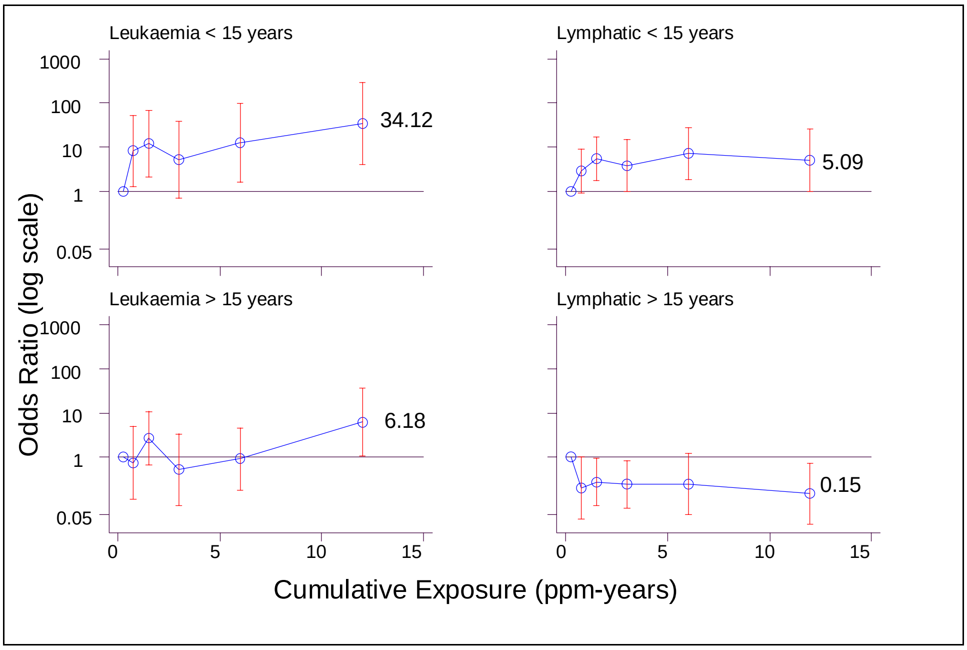


Figure 48: Cancer Type and Odds Ratios by Lag Period

4.3. Duration of Employment

Duration of employment (in participating companies) was examined as a possible determinant of LH cancer risk. The duration of employment was defined as the difference between the earliest start date and the latest finish date for each subject, truncated by date of diagnosis. The resulting distribution of employment duration among the 474 subjects is summarised below. The mean duration of employment was 20.36 years (SD 8.98), with a maximum 43 years and minimum 4.3 years[28].

To examine the relation between duration of employment and the incidence of LH cancer, quintiles of duration were calculated and analysed by conditional logistic regression. The quintiles were evenly spaced in this case (Table 54). The cut-points fall about every seven years, except for the last category of longest duration. The conditional logistic regression for association with LH cancer is summarised in Table 55. There is no evidence of any association between duration of employment and the incidence of LH cancer: although the highest quintile of duration shows a slightly elevated odds ratio, OR = 1.23, the associated confidence interval and the P-value indicates that this is statistically significant. Table 56 shows an increased OR for increasing durations of employment reaching OR 1.59 for the longest employed. The associated confidence intervals and P-values show that none of the increases were statistically significant however.

Figure 49: Duration of Employment for all Subjects in the Case-control Study

[28] This duration is less than the minimum Health Watch cohort entry criterion of work duration 5 years, as this is a control whose exposure was truncated by the date of diagnosis of the matched case.

Table 54: Duration of Employment in Quintiles

Quintiles of Duration	**N**	**Duration (years)** **min**	**max**
1	95	4.3	11.2
2	95	11.2	16.9
3	95	17.0	22.4
4	95	22.5	28.9
5	94	29.0	43.0

Table 55: LH Cancer by Quintiles of Employment Duration

LH Cancer		Number of obs = 474		
Duration (years)	Odds Ratio#	P>|z|	95% Conf.	Interval
<11	1.00			
>11 < 17	1.01	0.97	0.46	2.24
>17 < 22.5	0.80	0.62	0.33	1.95
>22.5 < 29	1.05	0.92	0.42	2.61
> 29	1.23	0.66	0.48	3.12

Odds ratios are relative to duration < 11 years

Table 56: Leukaemia by Quintiles of Employment Duration

Leukaemia		Number of obs = 198		
duration (years)	Odds Ratio#	P>|z|	95% Conf.	Interval
<11	1.00			
>11 < 17	1.23	0.72	0.38	3.97
>17 < 22.5	1.57	0.48	0.45	5.53
>22.5 < 29	0.97	0.97	0.23	4.16
> 29	1.59	0.53	0.37	6.85

Odds ratios are relative to duration < 11 years

4.4. Analysis by Start Date and Era

4.4.1. Analysis by Start Date

The subjects were divided into three groups by their start date in the industry. The three eras were pre 1965, 1965-1975 and post 1975. The earliest subject started in January 1941 and the latest in December 1990.

Unmatched analysis in Table 57 suggested that the odds ratios for LH cancer and leukaemia may have been lower in later eras. Conditional logistic regression (matched analysis) in the next Table also suggested that LH cancer and leukaemia were related to start date (Table 58 and Table 60). After adjusting for quantitative cumulative exposure, however, the apparent associations vanished (Table 59 and Table 61). The ORs for leukaemia were 1.02 (post-75) and 0.96 (1965-1975) compared to pre 1965, with P-values 0.976 and 0.965. Clearly the suggestion of association seen in Table 58 and Table 60, was attributable to confounding; the early starters simply having higher cumulative exposure.

Any further investigation of whether the risk of leukaemia is associated with start date would be better carried out by examination of the rates in the entire Health Watch cohort.

Table 57: Cancer Odds Ratios by Start Date in Industry

	Control	Case	OR[#]	95% Conf.	Interval
LH Cancer					
pre 1965	147	34	1.00		
1965-75	161	27	0.73	0.42	1.26
post 1975	87	18	0.89	0.48	1.68
Leukaemia					
pre 1965	63	15	1.00		
1965-75	60	12	0.84	0.36	1.94
post 1975	42	6	0.60	0.22	1.67
Lymphatic Cancer					
pre 1965	84	19	1.00		
1965-75	101	15	0.66	0.31	1.37
post 1975	45	12	1.18	0.52	2.65

[#] Odds ratios are relative to pre 1965 figures

Table 58: LH Cancer by Start Date in Industry

Conditional (fixed-effects) logistic regression	Number of obs = 474			
Era Start	Odds Ratio[#]	P>|z|	95% Conf.	Interval
pre 1965	1.00			
1965-75	0.64	0.19	0.33	1.25
post 1975	0.75	0.52	0.31	1.81

[#] Odds ratios are relative to pre 1965 figures

Table 59: LH Cancer by Start Date in Industry and Cumulative Exposure Quintile

Conditional (fixed-effects) logistic regression		Number of obs = 474		
Era start	Odds Ratio#	P>|z|	95% Conf.	Interval
pre 1965	1.00			
1965-75	0.77	0.47	0.38	1.55
post 1975	0.98	0.97	0.38	2.51
CE Quintile 2	1.83	0.19	0.74	4.54
CE Quintile 3	**2.46**	0.05	**1.00**	**6.05**
CE Quintile 4	2.20	0.09	0.88	5.52
CE Quintile 5	**3.22**	0.01	**1.32**	**7.89**

Odds ratios are relative to pre 1965 figures

Table 60: Leukaemia by Start Date in Industry

Conditional (fixed-effects) logistic regression		Number of obs = 198		
Era Start	Odds Ratio#	P>|z|	95% Conf.	Interval
pre 1965	1.00			
1965-75	0.65	0.42	0.22	1.88
post 1975	0.41	0.19	0.11	1.55

Odds ratios are relative to pre 1965 figures

Table 61: Leukaemia by Start Date in Industry and Cumulative Exposure Quintile

Conditional (fixed-effects) logistic regression		Number of obs = 198		
Era start	Odds Ratio#	P>|z|	95% Conf.	Interval
pre 1965	1.00			
1965-75	1.02	0.98	0.28	3.71
post 1975	0.96	0.97	0.19	4.92
CE Quintile 2	3.68	0.25	0.40	33.85
CE Quintile 3	**12.74**	**0.02**	**1.42**	**114.6**
CE Quintile 4	5.74	0.15	0.53	61.58
CE Quintile 5	**27.02**	**0.004**	**2.88**	**253.6**

Odds ratios are relative to pre 1965 figures

4.4.2. Analysis by Cumulative Exposure Divided into Eras

Each subject's job history was divided into 3 eras; pre 1965, 1965-1975 and post 1975. The relevant period of time and associated exposure was allocated to one of these eras. The cumulative exposures were higher after 1975 on average, although some of the highest exposures (maximum values) occur before 1965.

Table 63 to Table 65 show no significant association between LH cancers, leukaemia or lymphatic cancers and era of exposure. This indicates that it is cumulative exposure rather than era that was associated with an increased risk of LH cancer.

Table 62: Era and Cumulative Exposure

Variable (ppm-years)[29]	Obs	Mean	Std. Dev.	Min	Max
CE pre-1965	474	1.27	3.75	0.00	31.76
CE 1965-1975	474	1.26	2.34	0.00	18.69
CE post-1975	474	2.32	3.33	0.01	25.03
CE quintile pre-1965	474	2.34	1.74	1.00	5.00
CE quintile 1965-1975	474	2.94	1.47	1.00	5.00
CE quintile post-1975	474	3.00	1.41	1.00	5.00
CE geom. Group pre-1965	474	1.84	3.51	0.50	16.00
CE geom. Group 1965-1975	474	1.97	3.02	0.50	16.00
CE geom. Group post-1975	474	3.20	3.87	0.50	16.00

Table 63: LH Cancer and Cumulative Exposure by Era

Conditional (fixed-effects) logistic regression		Number of obs = 474		
Era[30]	Odds Ratio	P>|z|	95% Conf.	Interval
CE pre 65	0.99	0.86	0.91	1.08
CE 65-75	1.13	0.06	0.99	1.30
CE post 75	1.05	0.20	0.97	1.13

Table 64: Leukaemia and Cumulative Exposure by Era

Conditional (fixed-effects) logistic regression		Number of obs = 198		
Era[30]	Odds Ratio	P>|z|	95% Conf.	Interval
CE pre 65	1.05	0.49	0.92	1.20
CE 65-75	1.15	0.23	0.92	1.43
CE post 75	1.11	0.13	0.97	1.27

Table 65: Lymphatic Cancer and Cumulative Exposure by Era

Conditional (fixed-effects) logistic regression		Number of obs = 276		
Era[30]	Odds Ratio	P>|z|	95% Conf.	Interval
CE pre 65	0.95	0.50	0.83	1.09
CE 65-75	1.05	0.63	0.86	1.29
CE post 75	1.02	0.70	0.92	1.12

[29] There are N = 474 for each variable in this table --- this is the whole sample. Each person had a valid (sometimes zero) value for the cumulative exposure in each era.

[30] These are three separate CLRs, each with cumulative exposure measured as geometric groups and fitted as a continuous variable. Each OR can be interpreted as the relative increase for each additional exposure group.

Table 66: Odds Ratios for Cancers by Era and Cumulative Exposure

	LH cancer				Leukaemia				Lymphatic Cancer			
pre-1965	Controls	Cases	OR[#]	95% CI	Controls	Cases	OR[#]	95% CI	Controls	Cases	OR[#]	95% CI
< 0.5	301	55	1.00		127	22	1.00		174	33	1.00	
0.5 - 1	17	6	1.93	0.73 - 5.12	5	1	1.15	0.13 - 10.36	12	5	2.20	0.73 - 6.65
1 - 2	21	4	1.04	0.34 - 3.15	9	1	0.64	0.08 - 5.32	12	3	1.32	0.35 - 4.93
2 - 4	21	6	1.56	0.60 - 4.05	10	3	1.73	0.44 - 6.80	11	3	1.44	0.38 - 5.44
4 - 8	20	2	0.55	0.12 - 2.41	9	1	0.64	0.08 - 5.32	11	1	0.48	0.06 - 3.84
> 8	15	6	2.19	0.81 - 5.89	5	5	**5.77**	**1.54 - 21.60**	10	1	0.53	0.06 - 4.26
1965-1975												
< 0.5	230	40	1.00		99	14	1.00		131	26	1.00	
0.5 - 1	47	10	1.22	0.57 - 2.62	15	5	2.36	0.74 - 7.49	32	5	0.79	0.28 - 2.21
1 - 2	48	8	0.96	0.42 - 2.18	23	2	0.62	0.13 - 2.90	25	6	1.21	0.45 - 3.24
2 - 4	42	6	0.82	0.33 - 2.06	18	1	0.39	0.05 - 3.18	24	5	1.05	0.37 - 3.00
4 - 8	22	9	**2.35**	**1.01 - 5.48**	9	6	**4.71**	**1.46 - 15.26**	13	3	1.16	0.31 - 4.37
> 8	6	6	**5.75**	**1.77 - 18.72**	1	5	**35.36**	**3.84 - 325.2**	5	1	1.01	0.11 - 8.98
post-1975												
< 0.5	128	12	1.00		57	2	1.00		71	10	1.00	
0.5 - 1	71	15	**2.25**	**1.00 - 5.08**	28	7	**7.13**	**1.39 - 36.56**	43	8	1.32	0.48 - 3.60
1 - 2	71	14	2.10	0.92 - 4.79	34	5	4.19	0.77 - 22.80	37	9	1.73	0.64 - 4.62
2 - 4	61	17	**2.97**	**1.34 - 6.61**	26	9	**9.87**	**1.99 - 48.91**	35	8	1.62	0.59 - 4.47
4 - 8	45	15	**3.56**	**1.55 - 8.17**	15	6	**11.40**	**2.09 - 62.30**	30	9	2.13	0.79 - 5.77
> 8	19	6	**3.37**	**1.13 - 10.04**	5	4	**22.80**	**3.32 - 156.8**	14	2	1.01	0.20 - 5.14

[#] Odds ratios are relative to < 0.5 ppm-years

4.5. Analysis by Industry Site Type

4.5.1. Cumulative Exposure and Site Type

Each site where a subject worked was allocated to a site type. The period of time and associated exposure for each subject, was then allocated to that site type. If a subject worked in the office at a terminal or refinery he was included as an office worker rather than being assigned to a site type. The site types are listed in Table 67. Depots have been included in the "Terminal" category.

Table 67 shows CLR done simultaneously, i.e. adjusting for possible confounding variables. A small but significant excess risk of LH cancer was associated with time spent at terminals compared to other sites.

The mean exposure at terminals was clearly higher than that at other sites, followed by that at refineries (Table 68). The distribution of exposures is shown in Table 69, most exposures were low but there was a high tail of exposures at these types of sites. Exposure at upstream and offices site was low as expected. The odds ratio for LH cancer in the highest exposure group at terminals was significantly raised, OR 2.78 (95% CI 1.43 - 5.39, P = 0.002) (Table 70). The odds ratio for leukaemia in the highest exposure group at terminals was substantially and significantly raised, OR 7.05 (95% CI 2.52 - 19.75, P = <0.000) (Table 71).

Table 67: LH Cancer Odds Ratios by Site Type

Conditional (fixed-effects) logistic regression	Number of obs = 474			
	Odds Ratio	P>|z|	95% Conf.	Interval
Airport	1.14	0.10	0.98	1.33
Office	0.00	NA	NA	NA
Upstream	0.09	0.15	0.00	2.48
Refinery	1.02	0.54	0.95	1.10
Terminal	**1.05**	**0.004**	**1.02**	**1.08**
Unknown	1.74	0.82	0.02	198.9

Table 68: Cumulative Exposure by Site Type (ppm-years)

Variable	Obs	Mean	Std. Dev.	Min	Max
Airport	474	0.16	1.23	0.00	21.79
Office	474	0.03	0.53	0.00	11.52
Upstream	474	0.04	0.18	0.00	1.80
Refinery	474	1.61	3.46	0.00	34.04
Terminal	474	3.01	6.89	0.00	57.31
Unknown	474	0.003	0.05	0.00	1.12

Table 69: Site Type and Cumulative Exposure Group*

Exposure Group	N	Min	Max
Airports			
1	452	0.00	0.46
2	6	0.50	1.00
3	8	1.09	1.98
4	3	2.14	3.63
5	3	5.81	6.16
6	2	9.93	21.79
Offices			
1	472	0.00	0.48
2	1	0.67	0.67
6	1	11.52	11.52
Upstream			
1	458	0.00	0.46
2	11	0.50	0.90
3	5	1.11	1.80
Refineries			
1	299	0.00	0.44
2	23	0.53	0.95
3	42	1.03	1.97
4	53	2.03	3.90
5	27	4.04	7.82
6	30	8.04	34.04
Terminals			
1	314	0.00	0.49
2	11	0.52	1.00
3	17	1.07	1.98
4	26	2.02	3.96
5	51	4.39	7.92
6	55	8.07	57.31
Unknown			
1	473	0.00	0.23
3	1	1.12	1.12

Note: There were N = 474 for each variable in this table --- this is the whole sample. Each person had a valid (sometimes zero) value for the cumulative exposure in each site type.

Key to exposure groups

Group	Exposure (ppm-years)
1	<0.5
2	0.5 - 1
3	1 - 2
4	2.- 4
5	4 - 8
6	>8

Table 70: LH Cancer by Site Category and Exposure Group[31]
Bivariate CLR only (i.e. not simultaneous)

Exposure Group	Odds Ratio#	P>|z|	95% Conf.	Interval
Refineries				
1	1.00			
2	1.46	0.49	0.50	4.25
3	0.68	0.44	0.26	1.81
4	1.43	0.33	0.70	2.93
5	0.88	0.81	0.29	2.62
6	0.54	0.34	0.15	1.92
Terminals				
1	1.00			
2	2.53	0.19	0.62	10.26
3	1.93	0.27	0.60	6.23
4	0.83	0.78	0.24	2.92
5	1.18	0.69	0.53	2.65
6	**2.78**	**0.002**	**1.43**	**5.39**

Odds ratios are relative to Group 1

Table 71: Leukaemia by Site Category and Exposure
Bivariate CLR only (i.e. not simultaneous)

Exposure Group	Odds Ratio#	P>|z|	95% Conf.	Interval
Refineries				
1	1.00			
2	1.87	0.52	0.28	12.34
3	0.34	0.31	0.04	2.68
4	1.64	0.33	0.60	4.45
5	0.57	0.60	0.07	4.74
6	0.58	0.62	0.07	5.10
Terminals				
1	1.00			
2	0.00	1.00	0.00	NA
3	2.15	0.37	0.40	11.58
4	0.61	0.64	0.07	5.02
5	0.73	0.69	0.16	3.44
6	**7.05**	**0.000**	**2.52**	**19.75**

Odds ratios are relative to Group 1

[31] The analyses for Airports, Office, Upstream and Unknown sites have been omitted from the table as the numbers in each group were very small

4.5.2. Analysis by Site of Longest Held Job

The previous Section provided some evidence that risk of leukaemia was associated with work at terminals but the analysis in this Section shows that this was more closely related to the cumulative exposure rather than to any other aspect of the site type. This is a rather crude measure of exposure. There is a wide range of observed unmatched ORs: airport workers have OR = 3.5 for leukaemia, but this was not statistically significant (P = 0.08). Interestingly, upstream workers had an OR of 0.3 relative to terminal workers, and this dropped to an OR of 0.2 for leukaemia alone. This is statistically significant (P = 0.023) for all LH cancers, but not for leukaemia alone.

Table 72: Category of Longest Held Job and Odds Ratios for Cancers

Site of longest job	**Control**	**Case**	**OR#**	**95% CI**
LH Cancer				
Airport	11	5	1.73	0.57 - 5.26
Office	10	0	0.00	-
Upstream	52	4	**0.29**[27]	**0.10 - 0.86**
Refinery	166	29	0.66	0.39 - 1.12
Terminal	156	41	1.00	
Leukaemia				
Airport	4	4	3.78	0.91 - 15.87
Office	5	0	0.00	-
Upstream	20	1	0.19	0.02 - 1.46
Refinery	68	10	0.56	0.26 - 1.18
Terminal	68	18	1.00	
Lymphatic Cancer				
Airport	7	1	0.55	0.06 - 4.67
Office	5	0	0.00	-
Upstream	32	3	0.36	0.10 - 1.28
Refinery	98	19	0.74	0.38 - 1.45
Terminal	88	23	1.00	

Odds ratios are relative to Terminal

Table 73: LH Cancer by Site of Longest Held Job

Conditional (fixed-effects) logistic regression		Number of obs = 474		
Longest Site	Odds Ratio#	P>|z|	95% Conf.	Interval
Airport	1.71	0.34	0.57	5.14
Office	0.00	1.00	0.00	NA
Upstream	**0.28**[27]	**0.02**	**0.10**	**0.84**
Refinery	0.65	0.11	0.38	1.10

Odds ratios are relative to Terminal

Table 74: Leukaemia by Site of Longest Held Job

Conditional (fixed-effects) logistic regression		Number of obs = 198		
Longest Site	Odds Ratio#	P>|z|	95% Conf.	Interval
Airport	3.97	0.08	0.84	18.75
Office	0.00	1.00	0.00	
Upstream	0.18	0.11	0.02	1.50
Refinery	0.58	0.20	0.25	1.33

Odds ratios are relative to Terminal

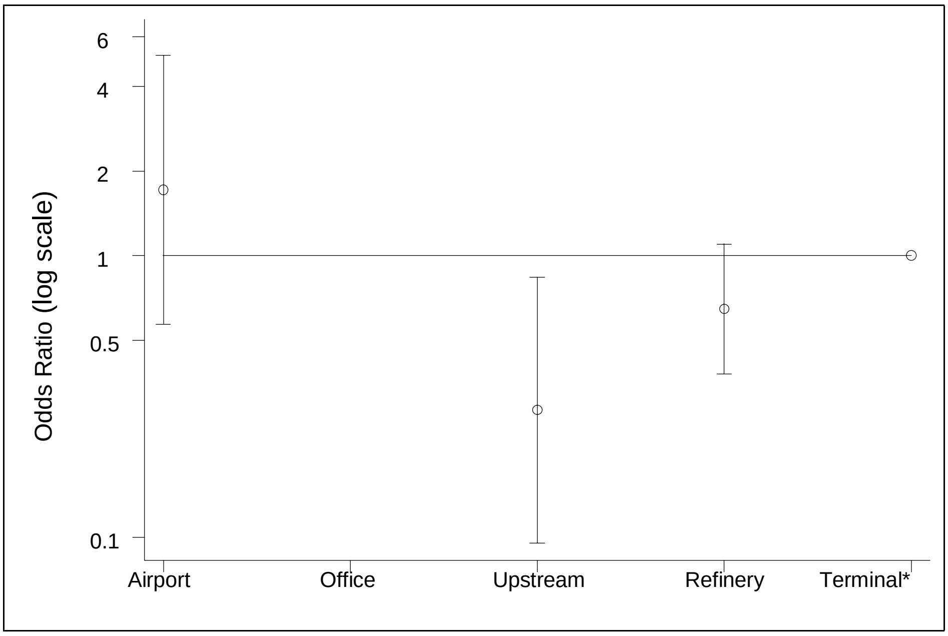


Figure 50: LH Cancer Odds Ratios for Longest Held Job (Compared to Terminals)

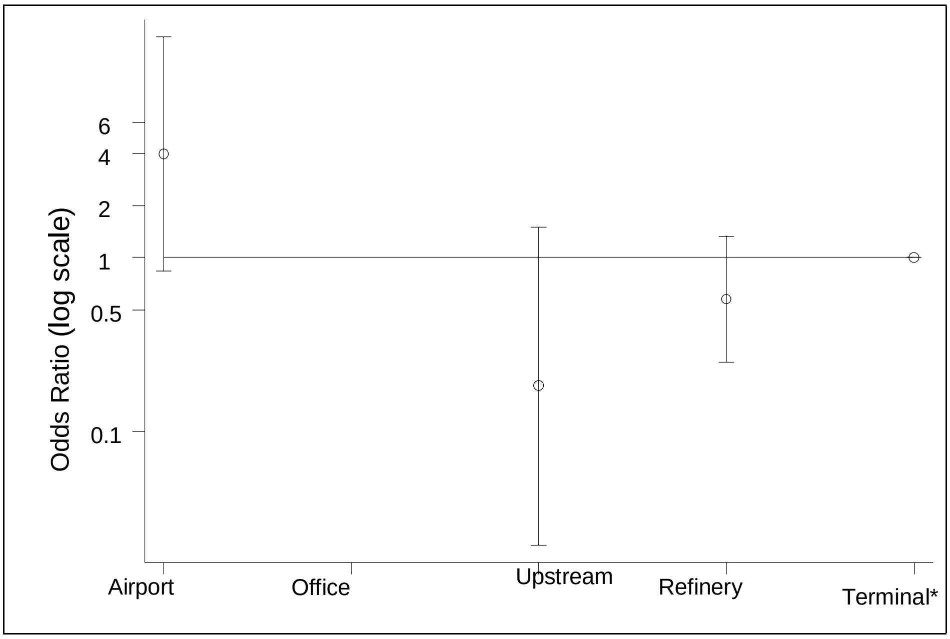


Figure 51: Leukaemia Odds Ratios for Longest Held Job (Compared to Terminals)

4.6. Contribution of High Exposures

Analysis of the contribution of high exposure to the various cancer types was done four ways:

1. Subjects who had worked at some time with concentrated benzene (CB) or Benzene/Toluene/Xylene (BTX) were identified and the risk of cancer was compared to that of workers who had not carried out this type of work.
2. High day exposures were identified by separating out tasks that had higher Base Estimates of exposure and these were used in the calculation of day exposures above selected thresholds (Section 2.10.1).
3. The high day exposures were extended by adding in the high exposure events referred to in Section 2.10.2.
4. Exposure intensity (cumulative exposure divided by duration of exposure) was computed by subject lifetime and for the highest exposed job as exposure indices.

4.6.1. Subjects with Exposure to Concentrated Benzene and/or BTX

Twelve subjects were identified as having worked at some time with concentrated benzene or BTX (CB/BTX). Their case/cancer status is presented in Table 75. The crude odds ratios indicate a strong association for LH cancer (OR 3.82, 95% CI 1.24 - 11.81). The conditional logistic regression for this binary variable shows a significant association for LH cancer with CB/BTX (OR 3.57, 95 CI 1.13 - 11.25, P = 0.03).

The crude odds ratios for leukaemia, however, indicate an extremely strong association (OR 12.62, 95% CI 2.69 - 59.29) (Table 75). The CLR for leukaemia alone also showed a very strong association (OR 12.50, 95% CI 2.43 - 64.43, P = 0.003) (Table 76).

There were no cases of lymphatic cancer among subjects exposed to CB/BTX.

When cumulative exposure was taken into account, there was still an apparent residual risk associated with exposure to CB/BTX. For LH cancer the residual risk of benzene exposure corresponded to an odds ratio of 1.8 (CI 0.5 - 6.52) (Table 77). For leukaemia analysed with the continuous cumulative exposure variable the residual risk of benzene exposure corresponded to an odds ratio of 4.2 (CI 0.66 - 27) (Table 79). When the risk of exposure to CB/BTX was analysed taking into account the geometric cumulative exposure groups, the effect remained (Table 80).

Table 75: Cancer Odds Ratios and Exposure to CB/BTX

CB/BTX Exposure	Controls	Cases	Case:Control	OR	OR*[26]	95% Conf. Interval	
LH Cancer							
No	388	74	0.19	1.00	1.00		
Yes	7	5	0.71	3.75	**3.82**	**1.24**	**11.81**
Leukaemia only							
No	163	28	0.17	1.00	1.00		
Yes	2	5	2.50	14.55	**12.62**	**2.69**	**59.29**
Lymphatic only							
No	225	46	0.20	1.00	1.00		
Yes	5	0	0.000	0.00	0.44	NA	NA

Table 76: LH Cancer and Exposure to CB/BTX

Conditional (fixed-effects) logistic regression Number of obs = 474				
	Odds Ratio	P>|z|	95% Conf. Interval	
CB/BTX	**3.57**	**0.03**	**1.13**	**11.25**

Table 77: LH Cancer and CB/BTX Exposure by Continuous Cumulative Exposure

Conditional (fixed-effects) logistic regression		Number of obs = 474		
	Odds Ratio	P>|z|	95% Conf.	Interval
CB/BTX	1.81	0.36	0.50	6.52
Cumulative exposure	**1.05**	**0.01**	**1.01**	**1.08**

Table 78: Leukaemia and Exposure to CB/BTX

Conditional (fixed-effects) logistic regression		Number of obs = 198		
	Odds Ratio	P>|z|	95% Conf.	Interval
CB/BTX	**12.50**	**0.003**	**2.43**	**64.43**

Table 79: Leukaemia and CB/BTX Exposure by Continuous Cumulative Exposure

Conditional (fixed-effects) logistic regression		Number of obs = 198		
	Odds Ratio	P>|z|	95% Conf.	Interval
CB/BTX	4.21	0.13	0.66	26.97
Cumulative exposure	**1.08**	**0.01**	**1.02**	**1.15**

Table 80: Leukaemia and Exposure to CB/BTX by Geometric Exposure Groups

Conditional (fixed-effects) logistic regression		Number of obs = 198		
Cumulative Exposure Group	Odds Ratio#	P>|z|	95% Conf.	Interval
Group 1, no CB/BTX	1.00			
CB/BTX	5.03	0.125	0.64	39.56
2	4.05	0.064	0.92	17.75
3	**6.29**	**0.014**	**1.46**	**27.09**
4	2.52	0.297	0.44	14.27
5	**5.16**	**0.039**	**1.09**	**24.39**
6	**68.33**	**0.001**	**5.52**	**846.14**

Relative to Group 1

4.6.2. Analysis of Risk Excluding Subjects Exposed to CB/BTX

The twelve subjects with exposure to concentrated benzene or benzene/toluene/xylene (CB/BTX) were all found to be in the highest cumulative exposure group. All 12 had cumulative exposures in excess of 16 ppm-years, and 5 had cumulative exposures in excess of 32 ppm-years. This group also had a substantial excess of leukaemia (5 cases) but no lymphatic cancers. Four of the 5 leukaemia cases in this group had estimated cumulative exposure in excess of 32 ppm-years compared to only one of the CB/BTX exposed controls. The CB/BTX exposed subjects represent a group with high risk of leukaemia and the potential for episodes of very high exposure compared to the subjects exposed only to gasoline[32]. Therefore it was of interest to exclude the subjects with CB/BTX exposure and analyse the risk of leukaemia for the remaining cases and controls.

The results for all leukaemia cases and controls were presented previously in Table 40 and the results obtained after excluding the CB/BTX exposed cases and controls are presented Table 81.

[32] Most exposures were based on BEs measured when gasoline was being handled and normalised to 3% benzene. The exposure for CB/BTX was extrapolated by multiplying the relevant BE by 100/3 for concentrated benzene and 70/3 for BTX.

The major effect of this exclusion was to reduce the leukaemia odds ratio for the highest exposure group (>32 ppm-years) from 98 to 39 (CI 3.04 - 501). This is illustrated in Figure 52. There was very little difference in the estimated cumulative exposures between the non-CB/BTX exposed group (mean 32.67 ppm-years, median 29.85 ppm-years) and the CB/BTX exposed group (mean 32.25 ppm-years, median 28.08 ppm-years). In fact, the mean and median exposure of the CB/BTX exposed group was slightly lower than that of the non-CB/BTX exposed group. The difference in odds ratios for the highest exposure group with and without the CB/BTX exposed subjects is not of itself statistically significant. However it is a large difference which if real cannot be explained in terms of differential exposures as estimated. A possible explanation is that episodic high exposures might have increased the risk of leukaemia for CB/BTX exposed workers suggesting that there is a non-linear relationship between risk of leukaemia and intensity of exposure to benzene.

Table 81: Leukaemia by Geometric Exposure Groups Excluding Subjects Exposed to CB/BTX

Conditional (fixed-effects) logistic regression		Number of obs = 166		
Cumulative Exposure Group	Odds Ratio[#]	P>|z|	95% Conf.	Interval
1	1.00			
2	3.91	0.07	0.89	17.12
3	**6.08**	**0.02**	**1.41**	**26.12**
4	2.40	0.32	0.42	13.63
5	**5.86**	**0.03**	**1.25**	**27.40**
6	**39.03**	**0.01**	**3.04**	**501**

[#] Relative to Cumulative Exposure Group 1

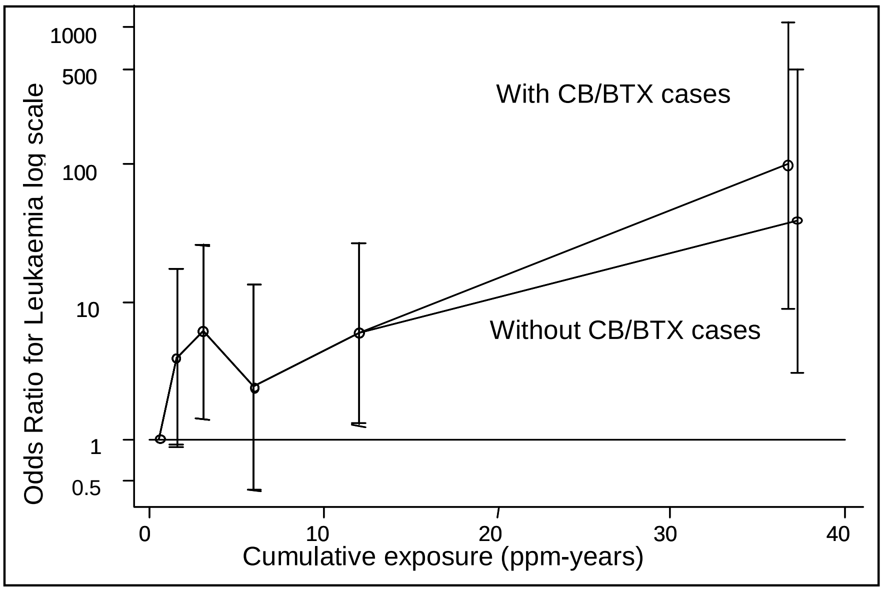


Figure 52: Comparison of ORs for Leukaemia with and without CB/BTX Exposure

Note: The points on the graph are plotted at the mid-point of the range of exposures in each exposure group. The highest exposure groups have been offset slightly for clarity. This does not imply any difference in exposure.

4.6.3. High Day Exposures

The data were structured to permit identification of high day exposures according to job. The algorithm used to calculate cumulative exposure aggregated the exposures from each job as daily averages. This allowed cut points to be introduced in order to calculate “truncated” cumulative exposures including only those daily exposures in excess of certain values. This algorithm was repeated for a range of daily exposure cut-offs. As the cut-off value increased, the magnitude of the final cumulative sum for each subject decreased as expected. However, if it was the high day exposures that were important, then a steeper gradient in the risk per unit exposure would be expected since the higher cut-off exposures would all have occurred at high daily exposures and would be expected to be more carcinogenic per unit exposure.

A range of cut-offs was used to examine the peak exposure hypothesis: the lowest chosen was 0.1 ppm per day, which was around the median of the daily exposures calculated according to jobs. The highest cut-off selected was 2.0 ppm per day, which was limited by diminishing power in the analysis. In between, cut-offs of 0.2, 0.4 and 1.0 ppm per day were selected. These values were used to calculate truncated cumulative exposures as a surrogate peak exposure metric.

Table 82: Truncated Cumulative Exposures (ppm-years) and Effect of Cut-off for Leukaemia Cases and Controls

Cut-off	Number of Subjects	Mean Exposure	Standard Deviation	Min	Max
0.0	162	4.88	7.27	0.01	52.66
0.1	105	6.95	8.23	0.04	52.66
0.2	78	8.21	8.97	0.30	52.11
0.4	55	8.98	10.31	0.06	51.85
1.0	23	12.63	12.93	0.06	45.19
2.0	17	6.13	7.18	0.06	21.30

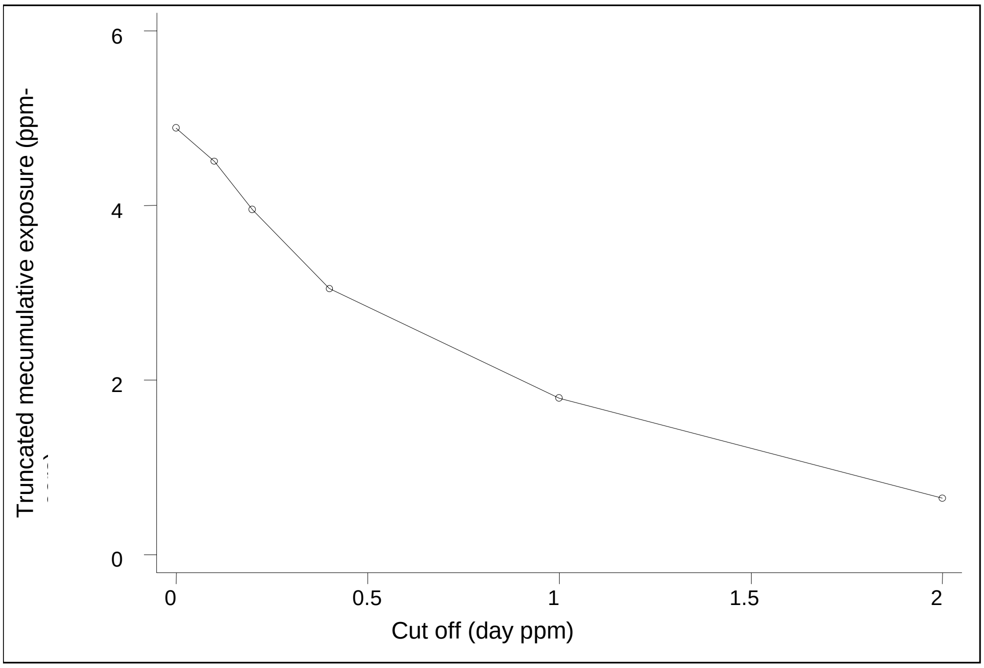


Figure 53: Effect of Increasing Cut-off on Average Truncated Cumulative Exposure (ppm-years) for Leukaemia Cases and Controls

Conditional logistic regressions were repeated on the matched data, using increasing peak daily exposure cut-off values. The models fitted used ungrouped cumulative lifetime benzene exposure, rather than quintiles or other groupings, so that odds ratios could be compared between models. Table 82 shows mean and standard deviation of truncated cumulative exposures by subject. The five cut-offs are shown, together with the unmodified cumulative lifetime exposure, which is labelled as “0.0”. The column of means shows the gradual decrease in the truncated cumulative exposure as the cut-off point increases.

Conditional logistic regression analyses were run for each of these six cut-off models. Table 83 shows the estimated odds ratio from each model for the leukaemia cases and their matched sets, with the corresponding standard error, P-value and confidence interval. The first row in the table shows the same model as previously seen for cumulative exposure modelled as a continuous predictor variable. The P-value of 0.002 confirms a significantly increasing risk with increasing lifetime exposure to benzene, measured at all levels over all exposures. The OR of 1.09 indicates that the risk of leukaemia increases by 9% for each additional cumulative ppm-year of exposure.

The next five rows show the results for progressively increasing cut-offs in daily exposure. If it were the high day exposures that were important in the carcinogenic process, then a corresponding increase in the odds ratio per unit cumulative exposure would be observed indicating that the risk was greater at the higher daily exposure levels.

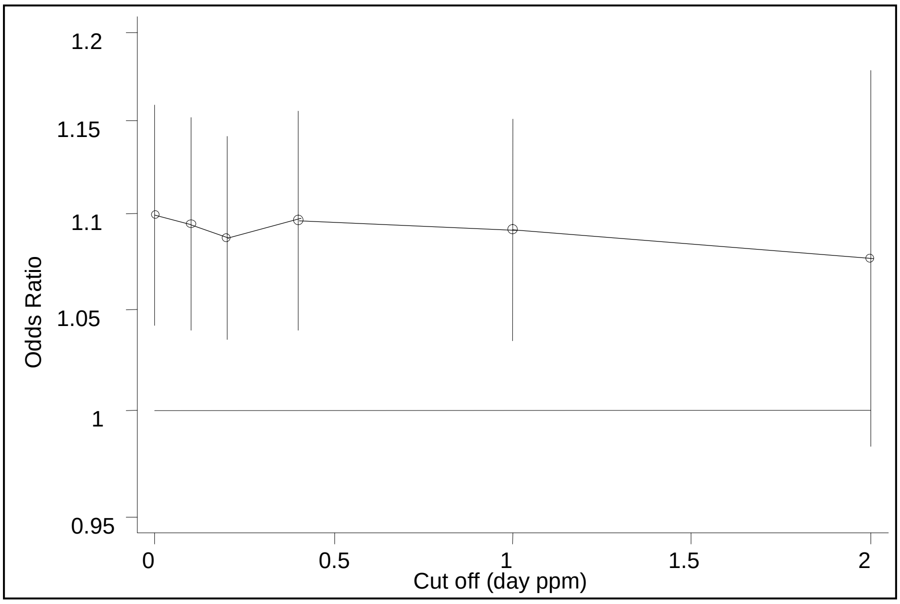
Table 83: Leukaemia by Cut-off in Mean Daily Exposures (ppm)

Cut-off	Odds Ratio#	P>|z|	95% Conf.	Interval
0.0	1.099	0.001	1.042	1.159
0.1	1.094	0.001	1.040	1.152
0.2	1.087	0.001	1.035	1.141
0.4	1.096	0.001	1.040	1.155
1.0	1.091	0.001	1.034	1.151
2.0	1.076	0.111	0.983	1.178

per ppm-year

The table above shows no trend towards increasing carcinogenicity of cumulative benzene exposure as the lower daily exposures were discounted. The odds ratio estimate of 1.09 per ppm-years is replicated almost precisely as the cut-off increases. A non-significant reduction in the estimated odds ratio to 1.076 occurred at the highest cut-off of 2.0 ppm per day—but this is possibly a reflection of a loss of power within this data set rather than any change in the effective potency at the highest exposure intensity.

Figure 54: Leukaemia Odds Ratios and Absence of Effect of Increasing Cut-off (up to 2 ppm) (Logarithmic axes)



4.6.4. <u>High Days and High Exposure Events</u>

Subjects may also have experienced infrequent but potentially high exposures (High Exposure Events or HEEs) e.g. from spills, Section 3.6.4. The probability of exposure to an HEE was assessed on the basis of the job group rather than on information about a specific individual. The numbers of leukaemia and lymphatic cancer cases with and without high exposure events are shown in Table 84.

The CLR analyses in Table 85 and Table 86 confirm that it was the cumulative exposures rather than the HEEs that predict most or all of the risk. Table 85 shows that the odds ratio for LH cancer and lymphatic cancer did not increase when the high exposure events were added. The OR for leukaemia increased but the increase was not statistically significant. Table 86 shows the change in the effect of HEEs when they are included in a model with Cumulative Exposure. There is no clear effect of the HEE variable on cancer status, nor can any clear interactions of HEE and cumulative exposure be discerned.

The results in Table 87 are from the conditional logistic regression of the continuous exposure variable that represents cumulative exposure plus the total career exposure from HEEs. Most subjects' cumulative exposures were only marginally increased by HEEs, but some were increased substantially. Leukaemia was associated with having experienced a high exposure event, OR 1.10 (95% CI 1.04 - 1.16, P = 0.001). This may be because those workers at risk of high exposure events were also those who were more highly exposed and therefore at increased risk of leukaemia, e.g. *Drum Fillers*.

Table 84: Proportion of Cases and Controls with a High Exposure Event in their career

Had HEE	**Leukaemia**		**Lymphatic Cancer**		**Total**
	Controls	Cases	Controls	Cases	
No	125	23	177	37	362
Yes	40	10	53	9	112

Table 85: Cancer and Whether Ever had a High Exposure Event in Career (Matched)

Conditional (fixed-effects) logistic regression				
	Odds Ratio	P>|z|	95% Conf.	Interval
LH Cancer			Number of obs = 474	
Did not have HEE	1.00			
Had HEEs	1.03	0.92	0.28	1.14
Leukaemia			Number of obs = 198	
Did not have HEE	1.00			
With HEEs	1.39	0.45	0.59	3.26
Lymphatic Cancer			Number of obs = 276	
Did not have HEE	1.00			
With HEEs	0.80	0.60	0.36	1.81

* Reference category = Did not have HEE in career.

Table 86: LH cancer, High Exposure Event status and Cumulative Exposure (Matched)

Conditional (fixed-effects) logistic regression			Number of obs = 474	
	Odds Ratio#	P>|z|	95% Conf.	Interval
HEE model			Number of obs = 474	
Did not have HEE	1.00			
Had HEEs	1.03	0.92	0.58	1.84
HEE and Cumexp model			Number of obs = 474	
Did not have HEE	1.00			
Had HEEs	0.56	0.11	0.28	1.14
Cumulative Exposure	**1.07**	**0.00**	**1.03**	**1.11**

Relative to Subjects without HEEs

Table 87: Effect of Cumulative Exposure including additional ppm contributed by High Exposure Events (Matched)

Conditional (fixed-effects) logistic regression[33]				
	Odds Ratio#	P>|z|	95% Conf.	Interval
LH Cancer			Number of obs = 474	
Cumulative Exposure + HEE exposure	**1.05**	**0.002**	**1.02**	**1.08**
Leukaemia only			Number of obs = 198	
Cumulative Exposure + HEE exposure	**1.10**	**0.001**	**1.04**	**1.16**
Lymphatic only			Number of obs = 276	
Cumulative Exposure + HEE exposure	1.00	0.92	0.95	1.05

Relative to without HEEs

[33] CE is a continuous variable, so OR is relative increase per ppm-year increase in cumulative exposure.

4.6.5. Intensity of Exposure

Intensity of Exposure over Lifetime

At the simplest level, a lifetime average intensity of exposure is cumulative lifetime exposure divided by duration of employment. The units of intensity are ppm.

Intensity (ppm) = Cumulative exposure (ppm-years) / Total Duration of Employment (years)

The lifetime mean intensity of exposure for all subjects was 0.23 (SD 0.30, CI 0.00 - 2.33) and the distribution had a strong positive skew (Figure 55). The distribution of $\log_e$ intensity was more symmetrical (Figure 56). The exposure intensity was divided into quintiles as described previously with ranges as shown in Table 88.

The question that was to be addressed was whether intensity of exposure was more important than cumulative exposure in predicting the incidence of LH cancer. Unfortunately, this question is very difficult to answer using the definitions used in this data set, since intensity and cumulative exposure are so closely related. This is not really surprising, since intensity has been computed directly from cumulative exposure and duration of employment.

To illustrate the strength of this association, the scatter plot (Figure 57) shows exposure intensity (in ppm) vs observed values of cumulative exposure (in ppm-years). The graph shows a number of important features of these data. First, the data stretch in a narrow band from low exposure/low intensity up to high exposure/high intensity. Any attempt to estimate the effect of one of these variables while controlling for the other is difficult, given the relatively narrow range of exposures within any "slice" through this band of data. Second, the cases are clearly clustered to the top of this band of data, which is consistent with the high odds ratios found by CLR using either metric of exposure. This clustering, compared to the position of the controls was more pronounced for the leukaemia cases than for the lymphatic cancer cases.

The results of conditional logistic regression for LH cancer and leukaemia are shown in

Table 89 and Table 90 respectively. There was a strong association between leukaemia risk and average career exposure intensity.

Table 88: Quintiles of Exposure Intensity

Quintile exposure intensity	N	Intensity (ppm) min	max
1	95	0.001	0.02
2	95	0.02	0.08
3	95	0.08	0.18
4	95	0.18	0.38
5	94	0.38	2.33

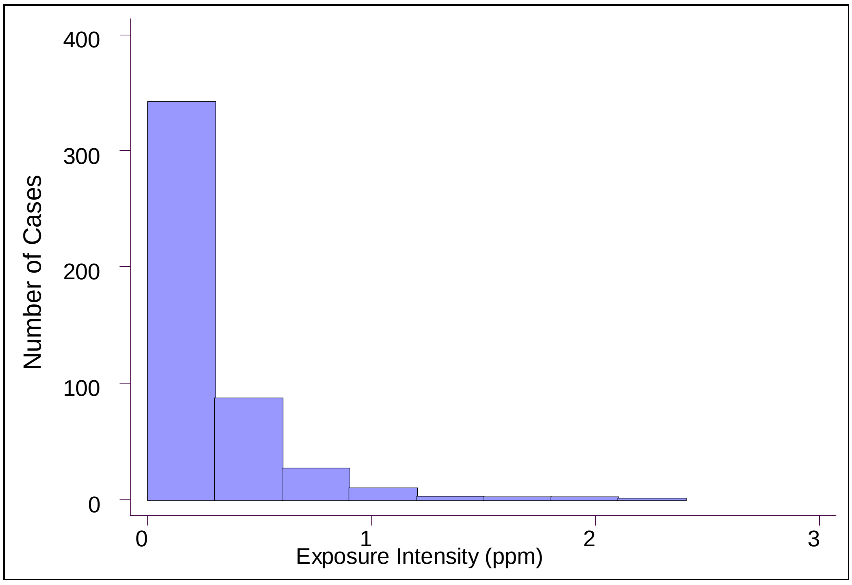


Figure 55: Subjects' Lifetime Average Exposure Intensity
(Cumulative Exposure divided by Duration)

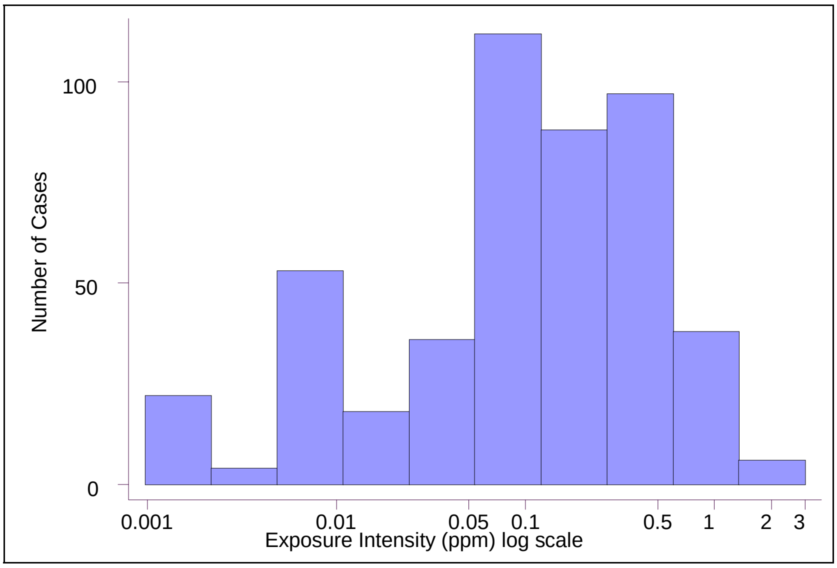


Figure 56: Exposure Intensity Distribution on Logarithmic Scale for all Subjects
(Cumulative Exposure Divided by Years of Exposure)

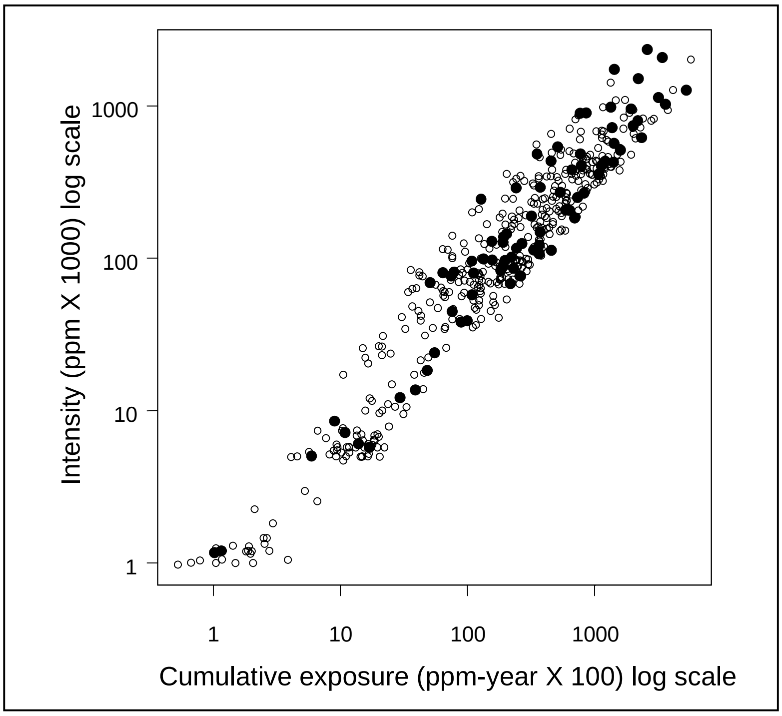


Figure 57: Scatterplot Comparing each of the 474 Subjects' Exposure Intensity (in ppm) vs Cumulative Exposure (ppm-years). Logarithmic scales are used for both axes. Cases are marked on the graph with a black circle, and controls with an open circle.

Table 89: LH Cancer by Intensity Quintile

Conditional (fixed-effects) logistic regression		Number of obs = 474		
Exposure Intensity Quintile	Odds Ratio#	P>|z|	95% Conf.	Interval
Quintile 1	1.00			
Quintile 2	1.13	0.78	0.47	2.73
Quintile 3	**2.38**	**0.04**	**1.05**	**5.42**
Quintile 4	1.08	0.87	0.43	2.73
Quintile 5	**3.02**	**0.01**	**1.36**	**6.70**

Relative to Quintile 1

Table 90: Leukaemia by Intensity Quintile

Conditional (fixed-effects) logistic regression		Number of obs = 198		
Exposure Intensity Quintile	Odds Ratio#	P>|z|	95% Conf.	Interval
Quintile 1	1.00			
Quintile 2	2.93	0.36	0.30	29.01
Quintile 3	**13.91**	**0.02**	**1.56**	**123.74**
Quintile 4	3.46	0.31	0.31	38.21
Quintile 5	**27.50**	**0.00**	**3.11**	**242.80**

Relative to Quintile 1

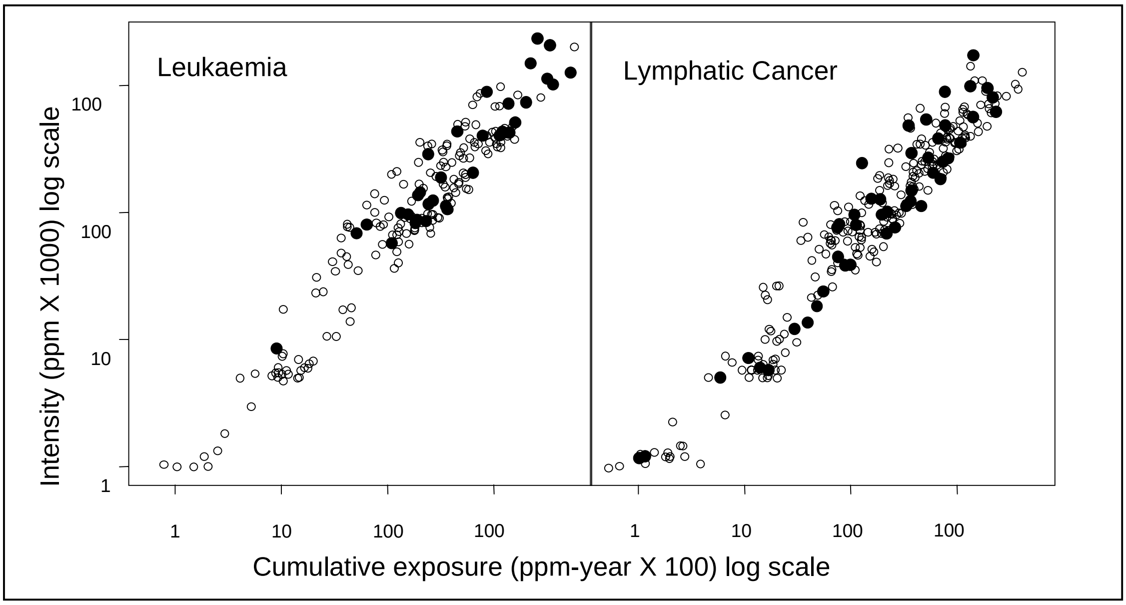


Figure 58: Comparison of each of the Leukaemia and Lymphatic Cancer Cases' and their Controls' Exposure Intensity (in ppm) vs Cumulative Exposure (ppm-years).

Intensity of Exposure of Highest Exposed Job Held

This analysis examined the association between LH cancer and the intensity of the highest exposed job that was held by each subject. The exposure intensities, which ranged from less than 0.1 ppm up to about 4.9 ppm maximum, were divided into quintiles (Table 91) and geometric exposure groups (Table 93).

The unmatched ORs for LH cancer by quintiles of exposure intensity of highest exposed job are shown in Table 92. No consistent association was apparent in this case. The unmatched ORs for LH cancer, leukaemia and lymphatic cancer by geometric groups of exposure intensity of highest exposed job are shown in Table 94. This showed an apparent association for LH cancer and leukaemia, but not for lymphatic cancer. The CLR analyses (Table 95 and Table 96) confirmed these results and showed a significant exposure response relation for leukaemia, which peaked at OR = 20 (CI 1.6 - 270) in the highest exposure group of > 3.2 ppm (based on small numbers). If a CLR carried out for leukaemia and intensity of highest exposed job, and duration is taken into account, (Table 97) the ORs decrease slightly. This suggests that the intensity of the job is important but that duration of the job also has an effect.

The CLR results for all LH cancer were non-significant with both exposure groupings.

Table 91: Quintiles of Exposure Intensity of Highest Exposed Job Ever Held (ppm)

Intensity Quintile	**n**	**min ppm**	**max ppm**
1	95	0.001	0.05
2	95	0.05	0.11
3	95	0.11	0.29
4	95	0.29	0.58
5	94	0.60	4.88

Table 92: LH Cancer by Exposure Intensity Quintile for Highest Exposed Job Ever Held

Conditional (fixed-effects) logistic regression		Number of obs = 474		
Exposure Intensity Quintile	Odds Ratio[#]	P>|z|	95% Conf.	Interval
1	1.00			
2	1.19	0.70	0.49	2.88
3	**2.37**	**0.03**	**1.07**	**5.24**
4	1.54	0.33	0.65	3.68
5	2.16	0.06	0.97	4.81

[#] Relative to Quintile 1

Table 93: Geometric Exposure Intensity Groups of Highest Exposed Job Ever Held (ppm)

Intensity Group	**ppm**	**n**	**Min ppm**	**Max ppm**
1	< 0.1	175	0.001	0.01
2	0.1 - 0.2	82	0.10	0.20
3	0.2 - 0.4	62	0.20	0.40
4	0.4 - 0.8	85	0.41	0.80
5	0.8 - 1.6	47	0.80	1.56
6	1.6 - 3.2	18	1.61	2.63
7	> 3.2	5	3.49	4.88

Table 94: Odds Ratios by Geometric Intensity Group of Highest Exposed Job Ever Held

Exposure Intensity Group	Control	Case	OR	95% CI
LH Cancer				
1	157	18	1.00	
2	63	19	**2.63**	**1.30 - 5.34**
3	50	12	2.09	0.94 - 4.64
4	72	13	1.57	0.73 - 3.39
5	37	10	**2.36**	**1.01 - 5.53**
6	13	5	**3.35**	**1.07 - 10.50**
7	3	2	5.81	0.91 - 37.15
Leukaemia				
1	65	5	1.00	
2	26	9	**4.50**	**1.38 - 14.7**
3	25	4	2.08	0.52 - 8.38
4	31	4	1.68	0.42 - 6.68
5	11	6	**7.09**	**1.84 - 27.3**
6	6	3	**6.50**	**1.24 - 34.1**
7	1	2	**26.00**	**2.00 - 338.7**
Lymphatic Cancer				
1	92	13	1.00	
2	37	10	1.91	0.77 - 4.74
3	25	8	2.26	0.84 - 6.07
4	41	9	1.55	0.62 - 3.92
5	26	4	1.09	0.33 - 3.62
6	7	2	2.02	0.38 - 10.8
7	2	0	0.00	-

Table 95: LH Cancer by Geometric Intensity Group of Highest Exposed Job Ever Held (ppm)

Conditional (fixed-effects) logistic regression		Number of obs = 474		
Exposure Intensity Group	Odds Ratio[#]	P>|z|	95% Conf.	Interval
1	1.00			
2	**2.50**	**0.01**	**1.24**	**5.02**
3	2.10	0.07	0.94	4.69
4	1.55	0.27	0.71	3.39
5	2.24	0.06	0.97	5.17
6	3.14	0.05	0.99	9.93
7	5.47	0.07	0.87	34.50

[#] Relative to Group 1

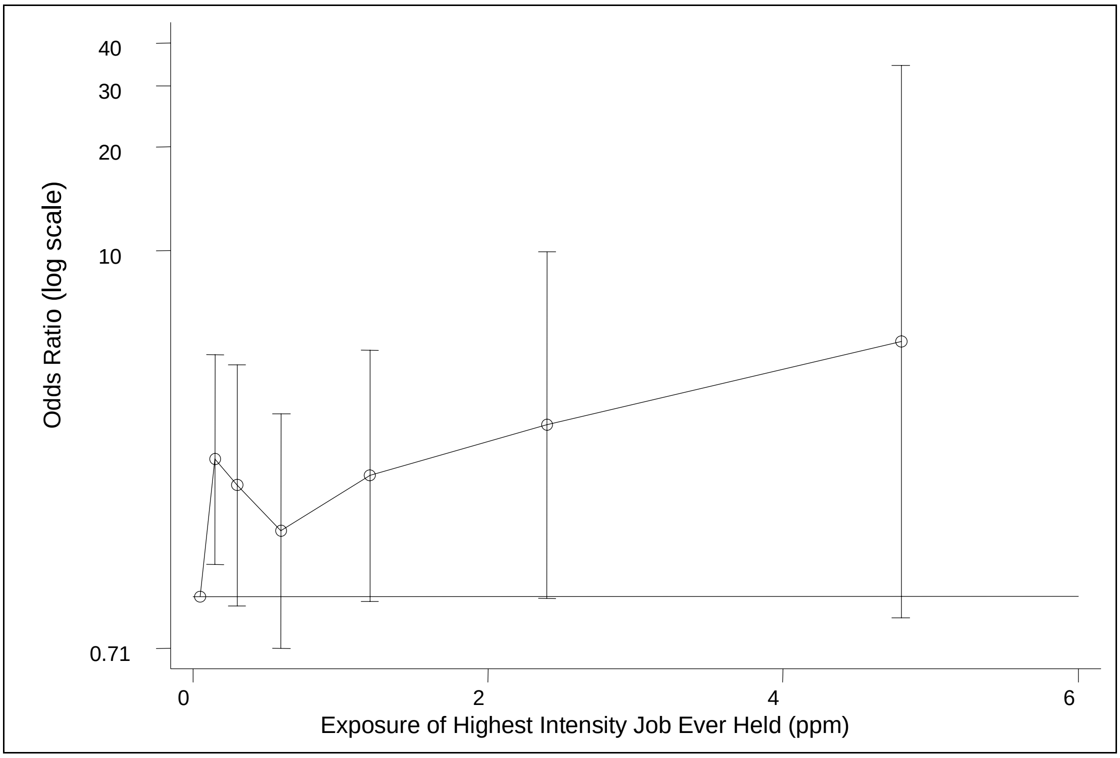


Figure 59: LH Cancer Odds Ratios by Highest Exposed Job (ppm) in Geometric Intensity Groups

Table 96: Leukaemia by Geometric Intensity Group of Highest Exposed Job Ever Held (ppm)

Conditional (fixed-effects) logistic regression		Number of obs = 198		
Exposure Intensity Group	Odds Ratio#	P>|z|	95% Conf.	Interval
1	1.00			
2	**3.93**	**0.02**	**1.22**	**12.65**
3	2.20	0.29	0.51	9.39
4	1.57	0.55	0.37	6.67
5	**6.58**	**0.01**	**1.69**	**25.72**
6	**5.62**	**0.05**	**1.01**	**31.21**
7	**20.43**	**0.02**	**1.55**	**270.2**

Relative to Group 1

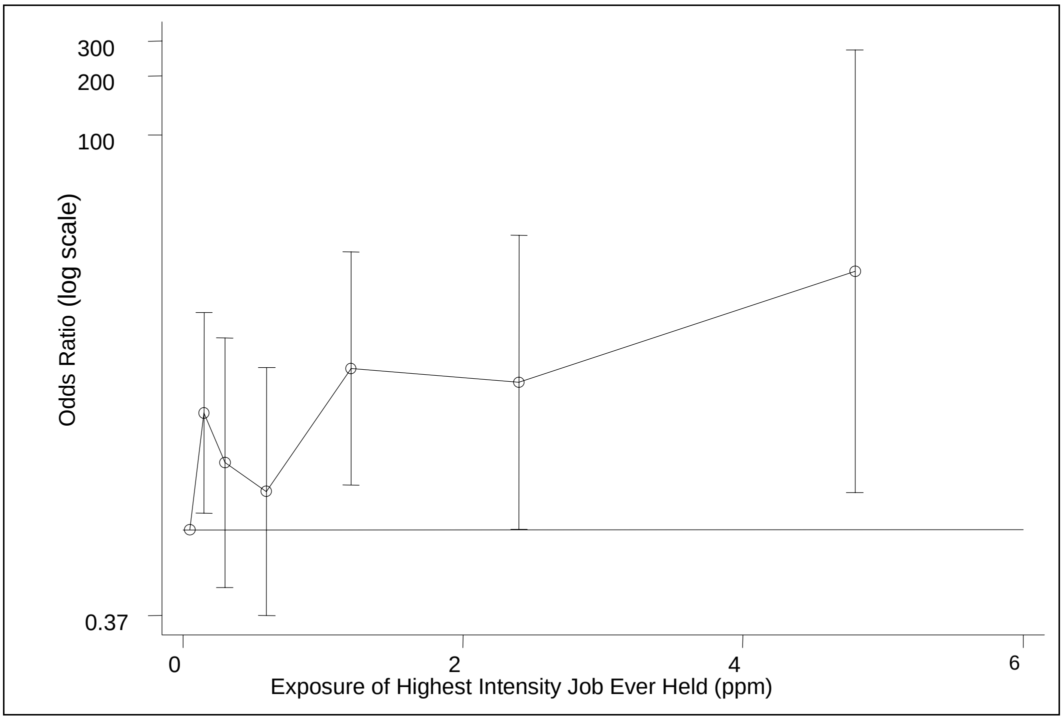


Figure 60: Leukaemia Odds Ratios by Highest Exposed Job (ppm) in Geometric Intensity Groups

Table 97: Leukaemia by Intensity of Highest Exposed Job (ppm) Controlling for Career Duration.

Conditional (fixed-effects) logistic regression		Number of obs = 198		
Exposure Intensity Group	Odds Ratio#	P>|z|	95% Conf.	Interval
Career Duration	1.00			
2	**3.84**	**0.03**	**1.16**	**12.69**
3	2.16	0.30	0.49	9.35
4	1.52	0.58	0.34	6.70
5	**6.34**	**0.01**	**1.54**	**26.18**
6	**5.58**	**0.05**	**1.00**	**31.04**
7	**19.56**	**0.03**	**1.41**	**270.8**

Relative to Group 1

4.6.6. Co-linearity of Intensity and Cumulative Exposure

Unfortunately it is difficult to disentangle the effect of intensity of highest job exposure from that of cumulative exposure. This is shown in the scatter plot (Figure 61). Table 98 and Table 99 show the results of CLR analysis for the intensity groups together with the cumulative exposure. For leukaemia, the highest job exposure intensity has no significant effect, but the effect of cumulative exposure is even stronger than when fitted by itself.

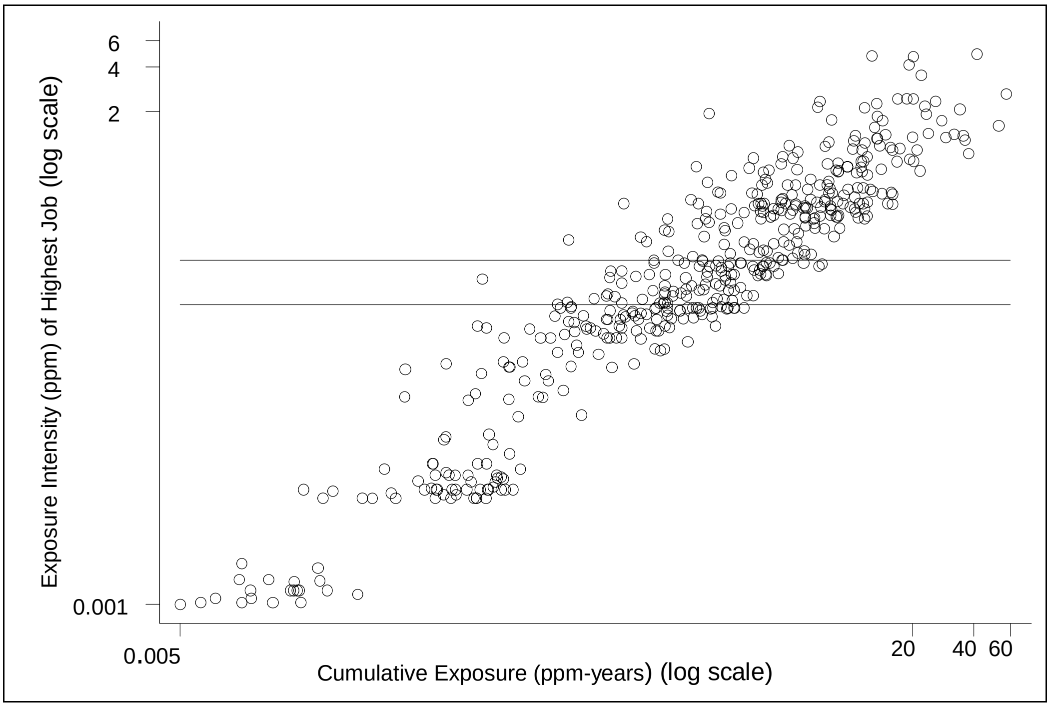


Figure 61: Scatterplot Comparing Cumulative Exposure and Exposure Intensity of Highest Exposed Job Ever Held (ppm)

Table 98: LH Cancer by Intensity of Highest Exposed Job and Cumulative Exposure

Conditional (fixed-effects) logistic regression[34]	Number of obs = 474			
Exposure Intensity (ppm)	Odds Ratio	P>|z|	95% Conf.	Interval
<0.1	1.00			
0.1 - 0.2	2.12	0.11	0.84	5.35
0.2 - 0.4	1.86	0.29	0.58	5.95
0.4 - 0.8	1.30	0.68	0.38	4.45
0.8 - 1.6	1.68	0.48	0.40	7.08
1.6 - 3.2	2.25	0.34	0.43	11.92
> 3.2	3.70	0.25	0.40	34.61
Cumulative exposure (ppm-years)				
0.5 -1	1.85	0.26	0.63	5.43
1 - 2	1.37	0.58	0.46	4.08
2 - 4	1.43	0.56	0.43	4.76
4 - 8	1.22	0.78	0.30	4.96
> 8	1.74	0.47	0.39	7.86

Table 99: Leukaemia by Intensity of Highest Exposed Job and Cumulative Exposure

Conditional (fixed-effects) logistic regression[34]		Number of obs = 198		
Exposure Intensity (ppm)	Odds Ratio	P>|z|	95% Conf.	Interval
<0.1	1.00			
0.1 - 0.2	1.21	0.79	0.30	4.89
0.2 - 0.4	0.51	0.47	0.08	3.19
0.4 - 0.8	0.24	0.18	0.03	1.98
0.8 - 1.6	0.61	0.67	0.06	6.18
1.6 - 3.2	0.44	0.54	0.03	6.10
> 3.2	1.55	0.79	0.06	37.89
Cumulative exposure (ppm-years)				
0.5 -1	8.99	0.10	0.66	122.0
1 - 2	10.27	0.05	0.99	106.2
2 - 4	**19.08**	**0.02**	**1.51**	**240.2**
4 - 8	12.62	0.09	0.71	225.5
> 8	**57.88**	**0.01**	**2.77**	**1208**

In view of the strong co-linearity between cumulative exposure and exposure intensity, goodness-of-fit and stepwise regression techniques were used to compare the effect of the two exposure metrics.

[34] The baseline is the lowest exposure for each variable, and the ORs are average over levels of the other variable.

Goodness-of-Fit Tests

Goodness-of-fit (GoF) testing was carried out in order to try to establish whether cumulative exposure or intensity of exposure was then better predictor of the risk of leukaemia. CLR was carried out for intensity and leukaemia in matched sets, OR = 7.83 (95%CI 2.46 - 24.88, P < 0.000). Similar analysis for cumulative exposure and leukaemia in matched sets gave OR = 1.10 (95%CI 1.04 - 1.06, P = 0.001).

The odds ratios cannot be compared since different units are used in the two measurements. Comparison can be made, however, of the "standardised odds ratios" which are the z-values of log-odds divided by log-odds standard error. These two values were found to be almost indistinguishable (3.49 and 3.47, respectively). The values of psuedo-R^2 are 0.1403 and 0.1420 respectively, also effectively indistinguishable.

Goodness-of-fit analysis was carried out for exposure intensity (unmatched analysis) giving an odds ratio of 7.41 (95%CI 2.49 - 22.09, P < 0.000), Hosmer-Lemeshow $Chi^2(8)$ = 13.44, Prob > chi^2= 0.098. Similar analysis for cumulative exposure gave an odds ratio of 1.09 (95%CI 1.04 - 1.14, P 0.001), Hosmer-Lemeshow chi2(8) = 9.96, Prob > Chi^2 = 0.27.

Both predictor variables show "non-significant" goodness-of-fit using the Hosmer-Lemeshow test. The P-value of 0.098 for intensity of exposure is closer to being "statistically significant" (i.e. further away from a "good fit") than the comparison P-value of 0.268 for cumulative exposure.

However these goodness-of-fit statistics need to be interpreted carefully, since they are based on unconditional regressions which ignore the matching inherent in the case-control study design, even though these exposure measures were treated in the same unmatched way.

Stepwise Regression

To use stepwise regression, both quantitative variables (intensity and cumulative exposure) were fitted into one model. Table 100 shows that under these circumstances, neither is significant, despite both variables being highly significant when considered separately. The stepwise routine in Stata ® chose intensity of exposure as the first variable to remove from the full model. The P-value associated with this removal was P = 0.365. The remaining variable in the stepwise model was cumulative exposure, with its highly significant predictive properties. Stata ® probably favoured cumulative exposure rather than intensity because the two P-values of 0.32 and 0.36 were compared, and the larger (i.e. "less significant") value of P=0.365 corresponding with intensity of exposure was selected as the variable to remove.

The difference between these P-values is small and to rule unequivocally in favour of cumulative exposure based solely on this evidence overstates its value.

Table 100: CLR for Cumulative Exposure and Intensity for Leukaemia (matched)

Conditional (fixed-effects) logistic regression			Number of obs = 198	
	Odds Ratio	P>|z|	95% Conf.	Interval
Cumulative exposure	**1.05**	**0.32**	**0.95**	**1.16**
Intensity	**2.80**	**0.36**	**0.30**	**25.88**

Table 101: Stepwise Regression for Cumulative Exposure and Intensity for Leukaemia (matched)

Conditional (fixed-effects) logistic regression			Number of obs = 198	
p = 0.3651 >= 0.2000 removing intensity				
	Odds Ratio	P>|z|	95% Conf.	Interval
Cumulative exposure	**1.099**	**0.001**	**1.04**	**1.16**

Neither the goodness-of-fit statistics nor the stepwise conditional logistic regression algorithm provided unequivocal evidence that would distinguish between the contributions to leukaemia risk of cumulative exposure and exposure intensity.

4.7. Effect of Smoking and Alcohol

4.7.1. Smoking

Smoking Behaviour and LH Cancer

The data were analysed for evidence of any association between smoking and leukaemia and lymphatic cancer (non-Hodgkin's lymphoma and multiple myeloma). In the first analysis, smoking status (never, previous or current) was examined for cases and controls. The results of this analysis are shown in Table 102. There was no consistent pattern in the results and "previous" smokers appear to have a lower risk of both leukaemia and lymphatic cancer than "never" smokers. Conditional-logistic regression was carried out with results as shown in Table 103. This analysis does not show a significant association with previous or current smoking.

Analysis was then carried out using “pack-years” as a quantitative metric of cumulative smoking. The distribution of smoking (pack years) for subjects is shown in Figure 62. Table 104 shows quintiles of smoking used in the analysis. The results are tabulated in Table 105 and illustrated in Figure 63. The results again show no significant effect of smoking on LH cancer or leukaemia.

Table 102: LH Cancer Rates and Smoking Experience

Smoker	Control	Case	OR#	95% Conf	Interval
LH Cancer					
Never	125	28	1.00		
Previous	166	21	0.56	0.31	1.04
Current	103	30	1.30	0.73	2.32
Leukaemia					
Never	48	11	1.00		
Previous	70	8	0.50	0.19	1.33
Current	47	14	1.30	0.54	1.27
Lymphatic Cancer					
Never	77	17	1.00		
Previous	96	13	0.61	0.28	1.34
Current	56	16	1.29	0.60	2.78

Odds Ratios relative to Never Smoked

Table 103: Smoking Experience

Conditional (fixed-effects) logistic regression			Number of obs = 473	
Smoker	Odds Ratio#	P>|z|	95% Conf.	Interval
Never Smoked	1.00			
Previous Smoker	0.56	0.06	0.30	1.03
Current Smoker	1.29	0.39	0.73	2.29

Odds Ratios relative to Never Smoked

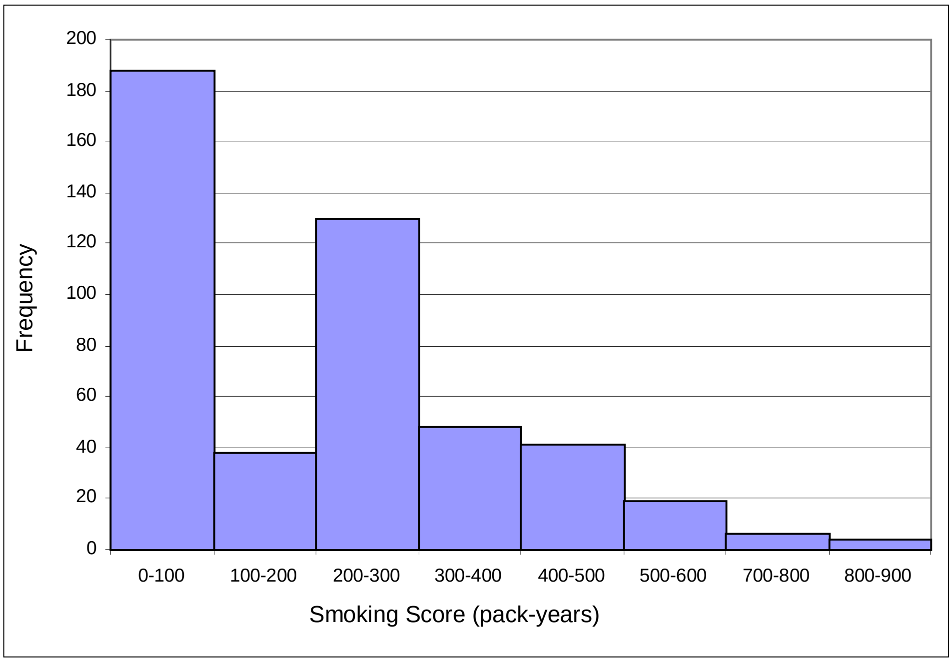


Figure 62: Distribution of Smoking Scores (pack-years)

Table 104: Smoking Score Quintiles (pack-years)

Smoking Score Quintile	Numbers[35]	Mean (pack/years)	Minimum (pack/years)	Maximum (pack/years)
1	153	0.0	0.0	0.0
2	66	100.7	14.6	146.0
3	135	266.4	175.2	292.0
4	48	364.1	321.2	365.0
5	70	524.6	438.0	876.0

Table 105: LH Cancer by Quintiles of Smoking (pack-years)

Conditional (fixed-effects) logistic regression		Number of obs = 472		
Smoking Quintile	Odds Ratio#	P>|z|	95% Conf.	Interval
1	1.00			
2	0.53	0.16	0.22	1.28
3	0.96	0.90	0.53	1.76
4	1.17	0.70	0.52	2.62
5	0.75	0.48	0.35	1.65

Odds Ratios relative to Smoking Quintile 1

35 Many individuals share the same value of packyear. This makes for a very uneven quintile distribution.

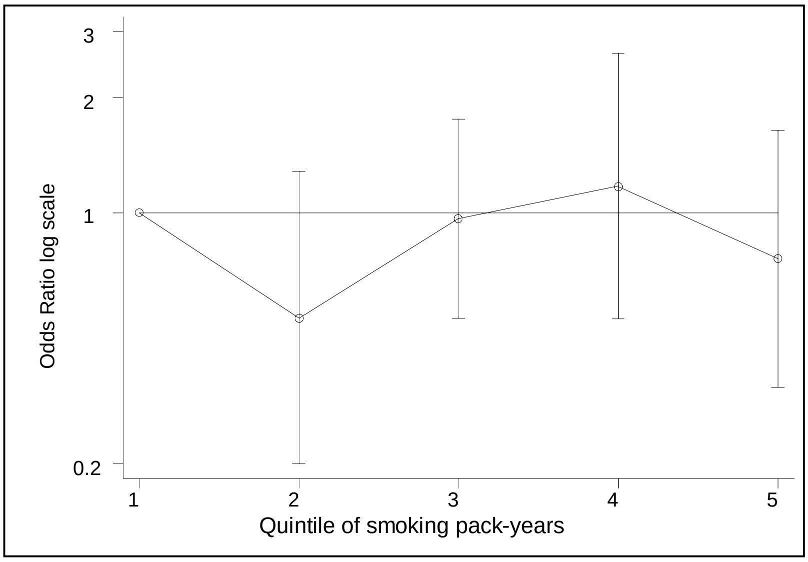


Figure 63: LH Cancer and Smoking
(Smoking pack years have been grouped into quintiles, according to numbers of subjects)[36]
(ORs are relative to Quintile 1)

[36] Unless otherwise stated, vertical bars on graphs in this document indicate 95% confidence intervals

Interaction of Smoking and Cumulative Exposure Group

Conditional (fixed-effects) logistic regression was carried out to examine the risk associated with smoking and exposure (Table 106 and Table 107). The results showed that smoking did not confound or change the effect of cumulative exposure on risk of LH cancer or leukaemia. The lack of effect on LH cancer suggested that analysis for lymphatic cancer alone was unnecessary.

Table 106: LH Cancer and Effect of Smoking and Cumulative Exposure

Conditional (fixed-effects) logistic regression		Number of obs = 473		
Cumulative Exposure Group	Odds Ratio#[37]	P>|z|	95% Conf.	Interval
Never Smoked[38] Cumexp Group 1	1.00			
Previous Smoker	0.57	0.08	0.30	1.06
Current Smoker	1.27	0.43	0.71	2.27
2	2.26	0.12	0.80	6.40
3	1.97	0.14	0.80	4.86
4	**2.44**	**0.04**	**1.03**	**5.75**
5	1.81	0.20	0.72	4.53
6	**2.95**	**0.01**	**1.29**	**6.76**

Odds Ratios relative to Never Smoked and Cumulative Exposure Group 1

Table 107: Leukaemia and Effect of Smoking and Cumulative Exposure

Conditional (fixed-effects) logistic regression		Number of obs = 198		
Cumulative Exposure Group	Odds Ratio# [37]	P>|z|	95% Conf.	Interval
Never Smoked[38] Cumexp Group 1	1.00			
Previous Smoker	0.34	0.06	0.11	1.06
Current Smoker	0.85	0.74	0.32	2.27
2	12.86	0.06	0.88	188.78
3	**9.74**	**0.04**	**1.08**	**87.79**
4	**20.04**	**0.01**	**1.96**	**204.37**
5	7.41	0.11	0.62	88.54
6	**38.32**	**0.002**	**3.81**	**385.89**

Odds Ratios relative to Never Smoked and Cumulative Exposure Group 1

[37] ORs differ from those in Table 102 because cases are matched to controls and adjusted for Smoking status and Exposure Group

[38] The "Previous smoker" and "Current smoker" are averaged over the six cumulative exposure groups. Equally, the "Cumulative Exposure Group 2" is averaged over the three smoking groups

4.7.2. Alcohol

Alcohol Drinking Rates and LH Cancer

The data were analysed for evidence of any association between alcohol and LH Cancer. In the first analysis, drinking status (never, previous or current) was examined for cases and controls for LH cancer, leukaemia and lymphatic cancer (non-Hodgkin's lymphoma and multiple myeloma). The results of this analysis are shown in Table 108. There were no significant associations for any cancer type. Analysis was then carried out using a drinking score (standard drink-years) as a quantitative metric of cumulative alcohol consumption. The distribution of alcohol score for subjects is shown in Figure 64. Table 110 shows quintiles of alcohol score used in the analysis. Conditional-logistic regression was carried out with results as shown in Table 109 and Table 111.

This analysis showed no evidence of an association between drinking alcohol and LH cancer or leukaemia. The baseline level was taken as "current drinker", since this was the most prevalent group.

Table 108: Alcohol Experience Odds Ratios for LH Cancer, Leukaemia and Lymphatic Cancer

Drinker	Control	Case	OR#	95% Conf	Interval
LH Cancer					
Never	79	16	1.00		
Previous	10	2	0.99	0.20	4.94
Current	305	61	0.99	0.54	1.81
Leukaemia					
Never	32	7	1.00		
Previous	5	1	0.91	0.09	9.10
Current	128	25	0.89	0.36	2.25
Lymphatic Cancer					
Never	47	9	1.00		
Previous	5	1	1.04	0.11	10.03
Current	177	36	1.06	0.48	2.36

Odds Ratios relative to Current Drinker

Table 109: Alcohol Experience and LH Cancer

Conditional (fixed-effects) logistic regression		Number of obs = 473		
Drinker status	Odds Ratio#	P>|z|	95% Conf.	Interval
Previous Drinker	1.02	0.96	0.55	1.88
Current Drinker	1.00	1.00		

Odds Ratios relative to Current Drinker

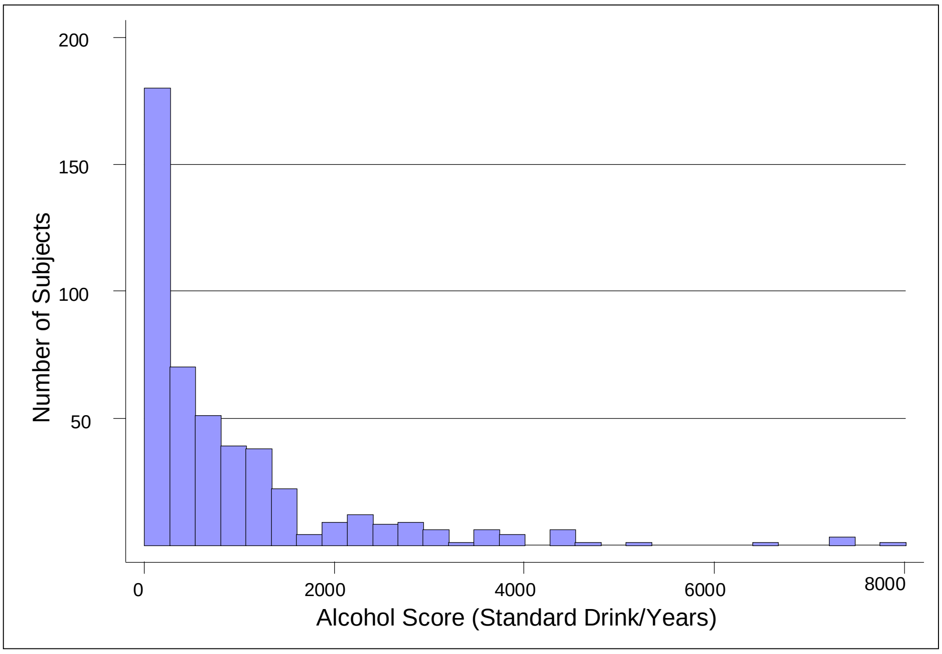


Figure 64: Alcohol Score Distribution amongst Subjects

Table 110: Quintiles of Alcohol Drinking Score (standard drink-years)

Alcohol Score Quintile	Mean (standard drink-year)	Min (standard drink-year)	Max (standard drink-year)
1	0	0	0
2	177	52	312
3	546	364	728
4	1032	780	1300
5	2778	1404	8008

Table 111: LH Cancer Odds Ratios by Drink-Year Quintiles

Conditional (fixed-effects) logistic regression	Number of obs = 318			
Alcohol Score Quintile	Odds Ratio[#]	P>|z|	95% Conf. Interval	
1	1.00			
2	1.12	0.77	0.53	2.37
3	1.22	0.61	0.57	2.59
4	0.91	0.81	0.41	1.99
5	0.80	0.59	0.35	1.80

[#] Odds Ratios relative to Quintile 1

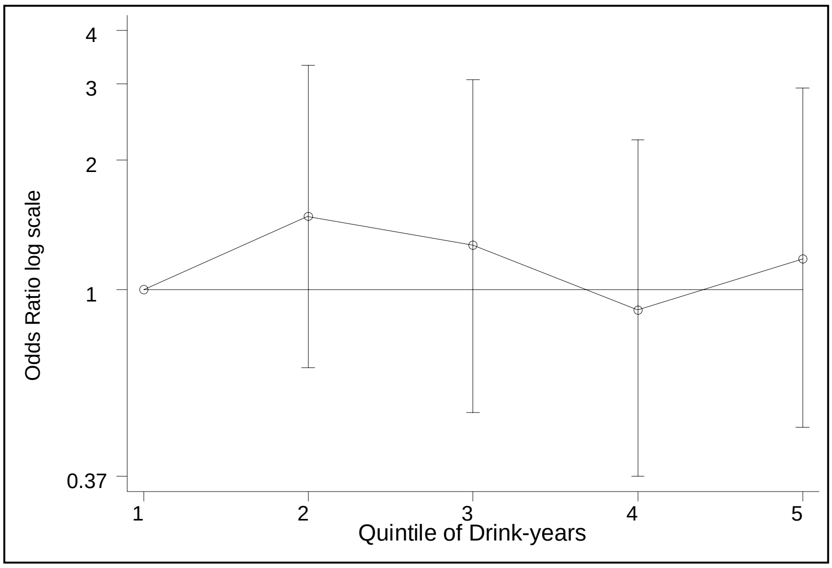


Figure 65: Alcohol and its Lack of Effect of on LH Cancer
(Drink-years have been grouped into quintiles according to numbers of subjects)
(ORs are relative to Quintile 1)

Interaction of Alcohol and Cumulative Exposure

Conditional (fixed-effects) logistic regression was carried out to examine the risk associated with drinking alcohol and exposure to benzene, see tables below. The results show that drinking did not confound or change the effect of cumulative exposure on risk of LH cancer or leukaemia. Consequently drinking was not considered to confound the analyses. The lack of effect on LH cancer suggested that analysis for lymphatic cancer alone was unnecessary.

Table 112: Alcohol and LH Cancer Odds Ratios by Cumulative Exposure Group

Conditional (fixed-effects) logistic regression		Number of obs = 473		
Cumulative Exposure Group	Odds Ratio	P>|z|	95% Conf.	Interval
Never Drinker, Cumexp Group 1	1.00			
Previous Drinker	0.90	0.75	0.48	1.71
Current Drinker	1.00	1.00	0.20	5.04
2	2.33	0.11	0.83	6.54
3	2.10	0.11	0.85	5.15
4	**2.47**	**0.04**	**1.05**	**5.81**
5	2.01	0.13	0.81	5.01
6	**3.14**	**0.01**	**1.36**	**7.21**

Odds Ratios relative to Never Drinker and Cumulative Exposure Group 1

Table 113: Alcohol and Leukaemia by Cumulative Exposure

Conditional (fixed-effects) logistic regression		Number of obs = 198		
Cumulative Exposure Group	Odds Ratio	P>|z|	95% Conf.	Interval
Never Drinker, Cumexp Group 1	1.00			
Previous Drinker	1.02	0.98	0.33	3.12
Current Drinker	1.46	0.76	0.14	15.59
2	9.23	0.09	0.71	120.0
3	**9.01**	**0.05**	**1.02**	**79.97**
4	**14.42**	**0.02**	**1.64**	**126.6**
5	6.26	0.14	0.56	70.00
6	**28.70**	**0.002**	**3.34**	**246.4**

Odds Ratios relative to Never Drinker and Cumulative Exposure Group 1

5. Summary and Discussion

5.1. Study Design and Methods

This study of lympho-haematopoietic cancer and benzene exposure was of a matched case-control design and was nested within the Health Watch cohort. Health Watch is a prospective cohort study of all-cause mortality and cancer incidence in the Australian petroleum industry that commenced in 1980 (Section 1.1). Eighty cases of lympho-haematopoietic cancer (ICD 9 200, 202-208: leukaemia, multiple myeloma and non-Hodgkin's lymphoma) were identified up to mid 2000 in the cohort of up to 15,732 male workers and retirees. To satisfy the criteria for inclusion in the study (Section 2.1), cases had to have first diagnosis of LH cancer after entering the Health Watch cohort and the diagnosis had to be confirmed by pathology report, cancer registration, letter from medical practitioner, or death certificate. In addition, the cases themselves, or a family member, had to report the cancer to Health Watch. This latter requirement was relaxed for individual cases who were lost to contact or were deceased. One case, thought to be neither lost to follow up nor dead did not self report so was not included in the study. The total number of cases included was therefore 79.

Five male controls were selected for each case, matched by year of birth and chosen randomly from a list of all eligible cohort members at the time of diagnosis. Subjects could be chosen as controls for more than one case and could at some future time become cases without being excluded as controls for previous cases.

5.1.1. Number and Types of Cancer Cases

The 79 cases of LH cancer satisfying the criteria for inclusion in the study included 33 leukaemias, 31 non-Hodgkin's lymphomas and 15 multiple myelomas (Section 3.1). After a histopathologist had reviewed the information on nine indeterminate leukaemias, the 33 leukaemia cases were classified as 9 AML, 6 CML, 2 ALL, 11 CLL and 5 "other" leukaemias consisting of 2 AUL, 2 unspecified lymphocytic leukaemias and a single case of hairy cell leukaemia. In part of the analysis, the AUL cases were included with the AMLs as ANLLs (acute non-lymphocytic leukaemia) in the cell type analysis.

5.1.2. Exposure Assessment

The exposure to benzene of cases and controls was estimated on an individual basis using a deterministic algorithm (Section 2.6 and Appendix 10). Subjects' job histories were obtained from company records and by interview of subjects or colleagues, and their tasks with exposure to benzene were identified (Section 2.4). Base Estimates of exposure to benzene for individual tasks were derived from company occupational hygiene exposure monitoring data (Section 2.7). These Base Estimates were multiplied by modifying factors to take account of differences in technology, products handled, era and site factors (Section 2.8). The resultant task exposure estimate was multiplied by the time per week on that task, summed and normalised to a standard working week to derive a daily average exposure for that job. The job exposure was multiplied by its duration in years and the exposure estimates for each job were summed to derive a cumulative exposure in ppm-years. This value was also divided by the duration of employment to derive the average exposure intensity in ppm.

5.1.3. "Peak" Exposures

As a result of pharmacokinetic modelling it was concluded that short-term variations in benzene exposures, within a day, did not markedly affect the metabolite dose to the target tissue, which was found to be averaged over several hours (Section 2.9). It was decided to consider only high daily doses and to ignore short periods of high exposure except to the extent that they contributed to the 8 hour TWA exposure.

Three approaches were taken to assess the extent of high exposures (Section 2.9). The first approach, involved identifying those individual subjects who had or hadn't handled concentrated benzene (CB) or benzene/toluene/xylene (BTX) and analysing the association with LH cancer on this dichotomous basis. Twelve subjects were identified who had handled CB/BTX and were thus considered to have a potential for high exposures.

The second approach used exposure estimates based on the existing algorithm but with tasks allocated on a daily basis rather than averaged over a week. The estimates of the frequency of the different mean daily exposures for individuals was based on the combination of tasks they performed (Section 2.10.1). The exposure situations that were considered were identified from reports collected during site visits.

The third approach considered infrequent high exposure events (HEE) in terms of equivalent 8-hour TWA exposures (Section 2.10.2). Some high exposures were simulated in the laboratory and new data were gathered by personal sampling at relevant industry sites. The estimated high exposures were added to the BEs for the appropriate number of days. The frequency of the various HEEs could not be assessed with accuracy and they could not be assigned to specific individuals with any certainty. Instead plausible frequency estimates were obtained from the company hygienists so that possible contributions from HEEs to groups of workers e.g. all mechanics pre 1975, could be examined in the analysis.

5.1.4. Statistical Analysis

Statistical analysis was performed using the statistical package Stata (Stata Corporation, Texas, USA). The principle test employed was matched case-control modelling using Conditional Logistic Regression (Section 2.14). Both dichotomous dependent variables (e.g. smoking/non-smoking) and explanatory variables (for example cumulative exposure, intensity of exposure, years of employment etc.) were used to calculate maximum likelihood estimates of odds ratios. The explanatory variables were first stratified into ranges (Section 3.6.5).

5.2. Demographics

In order to examine the adequacy of matching, cases and controls were compared and were found to be similar in most respects (Section 3.1). There was a similar proportion of subjects who had never smoked in each group but more current and fewer ex-smokers among the controls; these differences were not statistically significant. No difference in alcohol consumption was found between cases and controls. Most subjects were born in Australia and the second largest group was born in the UK. There were no significant differences between the cases and controls in this respect.

Overall, the cases and controls had similar years of employment and era of starting work in the industry. The leukaemia cases were slightly more likely to have started before 1975 than the lymphatic cancer cases, but this difference was not statistically significant. Less than 30% of subjects started work in the industry before 1960, and less than 5% before 1950. The subjects started work in the industry more recently than those in other comparable studies e.g. the UK Institute of Petroleum study [108].

On the basis of this demographic analysis it was concluded that the cases and controls were adequately matched.

5.3. Exposure Results

5.3.1. Cumulative Exposures

Lifetime cumulative exposures were low for the majority of the subjects, ranging from 0.005 to 57.3 ppm-years with a mean of 4.9 ppm-years. Nearly 85 percent of subjects had cumulative exposures of less than or equal to 10 ppm-years and only 0.6% had cumulative exposures greater than or equal to 40 ppm-years (Section 3.6.2).

5.3.2. Exposure Intensities

Estimates of average benzene exposure intensity (cumulative benzene exposure estimate divided by duration of employment) ranged from 0.001 to 2.07 ppm, with a mean of 0.20 ppm (Section 3.6.3). Average exposure intensity was estimated to be less than or equal to 1.0 ppm for 98 percent and less than or equal to 0.5 ppm for 90 percent of subjects. The highest exposures were for Drum Filling (approximately 1.8 ppm) and Rail Car Loading (approximately 1.6 ppm).

5.4. Risk Analyses

The association between benzene exposure and LH cancer was examined using a battery of statistical approaches. Direct comparison of the exposures for cases and controls was carried out using 2 x 2 contingency tests on unmatched data. The data was then analysed using conditional logistic regression with both quintiles of exposure and geometric (exponential) groups (in the ratio of 1:2:4:8:16 etc). This analysis was applied to LH cancer, and wherever there were sufficient numbers of cases, to leukaemia and lymphatic cancer (NHL and MM) and the leukaemia sub-groups. Analysis was also performed to examine, the effects of latency, duration of employment, period of first employment, industry site type, high exposures and smoking and alcohol.

5.4.1. <u>Lympho-haematopoietic Cancer</u>

Simple unmatched analysis suggested strongly that LH cancer as a whole was associated with benzene exposure (Section 4.1.1). When the exposure was grouped into quintiles (dividing the 474 subjects into five groups of approximately equal size) the odds ratio increased across the quintiles, reaching 3.32 (CI 1.40 - 7.91) for the fifth quintile (≥ 8 ppm-years). A similar result was obtained when the exposure grouping was by geometric steps in powers of two. The odds ratio for the highest exposure group (>16 ppm-years) was 4.51 (CI 1.79 - 11.35). Unmatched analysis by continuous cumulative exposure suggested that the risk of LH cancer increased with cumulative exposure by about 5% on average for each additional ppm-year, (P = 0.002). This assumes a log-linear (exponential) relationship because the increase in risk from n ppm-years is given by $(1.05)^n$. Thus a cumulative exposure of 20 ppm-year would increase the risk by $(1.05)^{20} = 2.65$. However because of the wide confidence intervals in this estimate, other exposure-risk relationships are possible.

Matched analysis was carried out by Conditional Logistic Regression (CLR). This showed a significant association between benzene exposure and LH cancer. Using quintiles to categorise exposure, the highest quintile (≥ 8 ppm-years) showed an odds ratio of 3.3 (CI 1.4 - 8.0) relative to the lowest quintile. The exposure-risk relationship (assumed to be log-linear for the purpose of this analysis) suggested that LH cancer increased by about 28% for each additional quintile of exposure.

For cumulative exposure measured in geometric steps, a similar increase in risk was observed: the odds ratio for the highest benzene exposure group examined (≥ 16 ppm-years) was found to be 4.86 (CI 1.86 - 12.72) relative to the lowest exposure group. In this case the exposure-response relationship implied that LH cancer increased by 4% for each doubling of benzene cumulative lifetime exposure (again assuming a log-linear exposure-risk relationship).

<u>*LH Cancer and Latency*</u>

The results of analysis using unmatched data by conditional logistic regression showed similar trends when stratified by periods of latency (Section 4.2.1). Exposures between 5 and 15 years prior to diagnosis had the strongest association with LH cancer and exposures within five years of diagnosis appeared to make a small contribution. Exposures more than 15 years before diagnosis appeared to make very little contribution if any, to the risk of LH cancer. The results were consistent with a mean latency of around 10 years prior to diagnosis (Section 4.2.2).

<u>*LH Cancer and Duration of Employment*</u>

The results provided no evidence of any association between duration of employment and the incidence of LH cancer. Although the highest quintile of duration (>29 years) showed a slightly elevated odds ratio of 1.23, this was not statistically significant (Section 4.3).

<u>*LH Cancer and Period of Employment*</u>

The effect of period of first employment on LH cancer and leukaemia was examined by separating the subjects into three groups by their start date in the industry (Section 4.4.1): pre 1965 (n = 147), 1965 -1975 (n = 161) and post 1975 (n = 87). The crude odds ratios for LH cancer compared to pre 1965 start dates, were found to be 0.73 for post 1965 and 0.89 for post 1975 start dates. Conditional logistic regression showed no association between period of start date and LH cancer as a whole. In addition, no association was found between LH cancers and cumulative exposure in different eras.

These results do not provide any evidence that the risk of LH cancer was significantly different in the three eras investigated (pre 1965, 1965 -1975 and post 1975).

LH Cancer and Industry Site Category

The odds ratio for LH cancer in the highest exposure group examined (>8 ppm-years) was significantly raised at Terminals but not at other industry sites including refineries (Section 4.5). This result probably simply reflects the fact that exposures were highest at terminals and any differences between various types of petroleum industry sites in terms of LH cancer incidence rates is best explained in terms of past differences in benzene exposure. The risk of LH cancer for subjects whose longest held job was at upstream sites, was significantly reduced.

5.4.2. Leukaemia

The results of unmatched analysis suggested a dramatic effect of cumulative benzene exposure on leukaemia risk (Section 4.1.4). When analysed by geometric exposure groups the odds ratio was found to be elevated for all groups above the lowest, reaching to about 40 (CI 6.77 - 189.4) for the highest exposure group. Conditional logistic regression gave an odds ratio about 100 (CI 8.84 - 1090) for the highest geometric exposure group, although the confidence interval was again very wide. Similar results were obtained for quintiles of exposure. The log-linear (exponential) exposure risk relationship implied that leukaemia increased by 78% for each additional quintile of benzene exposure (CI 28% - 154%) or 65% for each doubling of exposure (CI 25% - 1171%).

Leukaemia and Latency

Exposures more than 15 years prior to diagnosis of leukaemia were found to have much less effect than exposures less than 15 years before diagnosis (Section 4.2.2). The increase in odds ratio for LH cancer about 10 years after exposure would appear to be mostly a result of an increased risk of leukaemia. This is shown in the differences in the odds ratios for the most highly exposed workers: lymphatic cancer OR 5.09 (CI 1.0 - 26.0) compared to a leukaemia OR of 34.12, (CI 4.1 - 285).

Leukaemia and Duration of Employment

There was no detectable association between leukaemia and duration of employment (Section 4.3). The highest quintile of duration (29 - 43 years) showed a statistically insignificant increase in the odds ratio (OR 1.59 CI 0.37 - 6.85). Over the range of quintiles of duration of employment examined there was no consistent pattern, and no significant increases in odds ratio.

Leukaemia and Period of Employment

There was no significant difference in leukaemia rates when the results were analysed by period of first employment (pre 1965, 1965 - 1975 and >1975) (Section 4.4.1). Similarly, there was no detectable effect on leukaemia when analysed by cumulative exposures in these different eras (Section 4.4.2).

Leukaemia and Industry Site Category

A large and significant excess of leukaemia was found to be associated with exposure in terminals compared to other sites. The odds ratio for leukaemia in the highest exposure group examined for terminals (>8 ppm-years) was significantly raised (OR 7.05, CI 2.52 - 19.75). There was also an excess for Airports, based on four cases, but this was not statistically significant (Section 4.5).

When analysed according to site of longest held job, odds ratios for leukaemia were found to considerably lower in offices (no cases), in refineries and in upstream operations, than in terminals.

Leukaemia Sub-Types

There were relatively small numbers of cases of different types of leukaemia hence analysis of their individual associations with benzene exposure was compromised by low statistical power. Because of the small numbers of cases for particular leukaemia types, confidence intervals for the odds ratios would be expected to be very wide. As stated previously, there were 9 AML, 6 CML, 2 ALL, 11 CLL, 2 AUL and 3 other leukaemias. Analysis was performed separately for AML, CML and CLL.. In addition the two AULs were grouped with the AMLs as ANLLs. There were no cases of AML or CLL in the lowest quintile of exposure so that crude odds ratios could not be calculated. No analysis was possible for acute lymphocytic leukaemia for which there were only 2 cases. Analysis was performed for the other leukaemia types by exposure quintile. The odds ratios for the exposure group 5 relative to quintiles 1-3 were: AML OR 4.79 (CI 1.05 - 21.80), ANLL OR 5.71, (95% CI 1.22 -26.88), CLL OR 5.39 (CI 1.26 - 23.02) and CML OR 1.02 (CI 0.13 - 7.79).

The results of conditional logistic regression also suggested an association with benzene exposure for AML and CLL. In the highest exposure quintile the results were: AML OR 8.89 (CI 0.95 - 82.84), ANLL (AML and AUL) OR 8.29, (95% CI 1.31 - 52.3), CLL OR 7.15 (CI 1.29 - 39.70). Once again there was no apparent effect for CML OR 0.78 (CI 0.07 - 9.06).

The results suggest an association with benzene exposure only for AML, ANLL and CLL.

5.4.3. Lymphatic Cancer

The cases of lymphatic cancer (non-Hodgkin's lymphoma and multiple myeloma) were identified from the broad category of LH cancer. Simple (unmatched) analysis showed no clear association between lymphatic cancer and cumulative benzene exposure, either by quintile or geometric exposure group (Section 4.1). These results were confirmed by conditional logistic regression, which showed no significant increases in odds ratios in any exposure category. For example in the highest geometric exposure group (> 16 ppm-years, range 16.77- 57.31 ppm-years) the stabilised odds ratio was 1.25 (CI 0.35 - 4.54).

Analysis was performed to investigate the possibility of an association between benzene exposure and multiple myeloma alone (Section 4.1.6). The unmatched odds ratio for multiple myeloma in various quintiles of cumulative exposure were not significantly elevated. Conditional logistic regression showed no significant effect. Similarly negative results were obtained when exposures were put into geometric groups. The highest exposure group examined (>16 ppm-years) had an odds ratio for MM of 1.10 (CI 0.11 - 11.47). These results do not provide evidence of an association between exposure to benzene and the overall risk of multiple myeloma in the Australian petroleum industry.

Lymphatic Cancer and Latency

The effect of latency on lymphatic cancer was examined. Although there was no overall excess of lymphatic cancer associated with benzene exposure, the odds ratios for the exposure period less than 15 years prior to diagnosis were significantly elevated (OR 5.09, CI 1.00 - 25.96 for exposures > 8 ppm-years) compared with the lowest exposure group (<0.5 ppm-years). In contrast, the lymphatic cancer odds ratios for the exposure period more than 15 years prior to diagnosis were reduced (OR 0.15, CI 0.03 - 0.72 for exposures >8 ppm-years) compared with the lowest exposure group. This apparent excess of lymphatic cancer up to 15 years after exposure, despite an overall lack of association with benzene exposure, might be explained by a chance deficit of lymphatic cancers just in the lowest exposure group (the reference group for the odds ratios) in the period less than 15 years prior to diagnosis and a corresponding excess in the lowest exposure group in the period more than 15 years prior to diagnosis.

Lymphatic Cancer and Duration of Employment

Because there was no detectable association between lymphatic cancer and cumulative exposure it was unnecessary to examine a possible effect of duration of exposure (this being a major factor in cumulative exposure).

Lymphatic Cancer and Period of Employment

No significant association between lymphatic cancer rates and period of first employment (Section 4.4.1) or exposure era pre 1965, 1965 – 1975 and post 1975 (Section 4.4.2) was detected.

Lymphatic Cancer and Industry Site Category

The odds ratios for lymphatic cancer at terminals was higher than at other sites including airports, refineries, upstream sites and offices (where there were no cases) although none of these results were statistically significant (Section 4.5).

5.5. High Exposures

Analysis of the contribution of high exposures to LH cancer, leukaemia and lymphatic cancer were carried out on the basis of the following:

- subjects who had worked at some time with concentrated benzene or BTX;
- high day exposures;
- high day exposures and high exposure events
- exposure intensity (cumulative exposure divided by duration of exposure).

5.5.1. Exposure to Concentrated Benzene or BTX

All twelve subjects with exposure to CB/BTX had high cumulative exposures in excess of 16 ppm-years, and five were in excess of 32 ppm-years. This group also had a substantial excess of leukaemia (5 cases) but no lymphatic cancers (Section 4.6.1). Unmatched analysis indicated a strong association between CB/BTX exposure and LH cancer (OR 3.82, CI 1.24 - 11.81). The conditional logistic regression results suggested a similar effect (OR 3.57, CI 1.13 - 11.25). In the case of leukaemia, unmatched analysis indicated a strong association with CB/BTX (OR 12.6, CI 2.69 - 59.3) and CLR again gave a similar figure (OR 12.5, 95% CI 2.43 - 64.43).

Because the CB/BTX exposed subjects represent a special group with a potential for episodic high exposures, a further analysis was carried out after excluding these subjects (Section 4.6.2). For the remainder of the subjects, the leukaemia odds ratio for the highest exposure group (>32 ppm-years) was 39.0 (CI 3.04 - 501) compared to an odds ratio of 98.2 (CI 8.84 - 1090) when the CB/BTX exposed workers were included. The large difference in odds ratio, although not statistically significant, cannot be explained in terms of differential exposures; the estimated mean cumulative exposures for the CB/BTX exposed workers were almost identical to the other workers in the highest exposure group. This might suggest that other factor(s) such as episodes of very high exposure might have increased the risk of leukaemia for CB/BTX exposed workers.

5.5.2. High Day Exposures

By altering the algorithm used to calculate the cumulative exposure for individuals it was possible to calculate the daily average exposures for jobs or combinations of jobs, and for truncated cumulative exposures to be calculated as a surrogate peak exposure metric. Daily exposures in excess of a range of cut-offs were calculated and the truncated daily exposures were used to calculate the cumulative exposure. The cut-offs selected were 0.0, 0.1, 0.2, 0.4, 1.0 and 2.0 ppm. Conditional logistic regression was carried out for each of these six cut-off models (Section 4.6.3). The results did not show any increasing association between leukaemia and truncated cumulative exposure as the lower daily exposures were discounted. This suggests that job combinations with higher average daily exposures, up to 2 ppm, did not add disproportionately to the risk of leukaemia. This does not rule out the possibility that jobs with daily exposures in excess of 2 ppm could add disproportionately to the risk. The major shortcoming of this approach is that it ignores daily variations in exposure that are associated with all jobs, some of which can be much greater than the differences in average exposure between different jobs.

5.5.3. High Exposure Events

The probability of exposure to high exposure events was assessed on the basis of the job groups from reports obtained from sites and assessment by industry occupational hygienists. The odds ratios for LH cancer does not appear to alter when the high exposure events were added to the daily exposure estimates (Section 4.6.4). This suggests that they do not increase the risk of LH cancer substantially. On the other hand, leukaemia was found to be associated with high exposure events (OR 1.10, CI 1.04 - 1.16). This may be because those workers at risk of high exposure events were also those who were more highly exposed overall and therefore at increased risk of leukaemia, e.g. *Drum Fillers*. Conditional logistic regression analyses for cumulative exposure combined with high exposure events confirmed that the HEEs did not add disproportionately to the risk for the subjects in this study. The high exposure events were difficult to characterise with certainty, their frequency for any particular individual was not known and the exposures associated with them were not known with great certainty. For this reason, it is not possible to draw firm conclusions from this analysis.

5.5.4. Intensity of Exposure

Average intensity of benzene exposure is a major determinant of cumulative exposure and both have been shown to be associated with increased risk of leukaemia. Leukaemia risk is more closely associated with exposure intensity than with duration of employment (exposure) but does 10 ppm for 1 year result in a substantially greater risk than 1 ppm for 10 years? If so then this would indicate that the exposure intensity-risk relationship is non-linear. Conditional logistic regression for mean intensity of career and intensity of highest job controlling for duration showed slightly lower odds ratios than for these intensity variables alone. This suggests that duration has some effect.

For the subjects in this study, exposure intensity and cumulative exposure were very closely related making it very difficult to estimate the effect of one of these variables while controlling for the other. An analysis was carried out to examine the association between LH cancer and the intensity of the highest exposed job that was held by each subject (Section 4.6.5). Unmatched analysis suggested an effect from exposure intensity for leukaemia, but not for lymphatic cancer. Conditional logistic regression confirmed these findings and showed a significant exposure intensity-response relationship for leukaemia, particularly for the highest exposure job. However, because exposure intensity and cumulative exposure were so highly correlated this might have been explained in terms of the effect of exposure intensity on cumulative exposure. Two approaches were taken to try to examine the contribution of these two variables to the leukaemia risk: “goodness-of-fit” and “stepwise regression”. The standard goodness-of-fit statistic for conditional logistic regression models was not able to distinguish between cumulative exposure and exposure intensity. The Hosmer-Lemeshow statistic for unmatched logistic regression resulted in non-significant goodness-of-fit for both exposure metrics. Stepwise regression analysis also provided non-significant results and did not produce clear evidence in favour of one exposure metric over the other.

5.5.5. Summary of the Evidence for a High Exposure Effect

Positive evidence for a disproportionate risk of leukaemia associated with high exposures, hence a non-linear exposure intensity-risk relationship, was provided by the CB/BTX exposed workers. These workers had a substantially larger leukaemia risk than non-CB/BTX exposed workers with similar estimated cumulative exposure. Further evidence was provided by the lack of an association between leukaemia and duration of employment. This suggests that exposure intensity is the more important component of cumulative exposure. This is perhaps not surprising given that the range of duration of employment was relatively narrow compared to the range of exposure intensity.

Analysis according to high day exposures, high exposure events and lifetime average exposure intensity did not provide corroborating evidence for a disproportionate effect from high exposures. However, all of these approaches were compromised in some way (Table 114) and the results do not exclude the possibility of a non-linear exposure intensity – risk relationship for the subjects and exposures in this study.

Table 114: Summary of Evidence for a Disproportionately Greater Leukaemia Risk from High Exposures

Variable	Results	Evidence for an Effect (shortcomings)
CB/BTX exposure	CB/BTX exposed subjects have greater risk of leukaemia than non-CB/BTX subjects with similar cumulative exposure	Positive (high exposures estimated with uncertainty)
High day exposures	Jobs or job combinations with higher average daily exposures, up to 2 ppm, do not add disproportionately to the risk of leukaemia.	Negative up to 2 ppm (ignores day to day variations in exposure for each job)
High exposure events	High exposure events identified in this study are not associated with additional risk of leukaemia	Negative (high exposure events are poorly characterised)
Exposure intensity	Leukaemia risk is strongly associated with career average exposure intensity and exposure intensity in highest exposed job	Weak positive (high co-linearity between the different metrics)
Duration of employment	No association was found between leukaemia risk and duration of employment.	Weak positive (range of employment duration is much less than the range of exposure intensity)
Simultaneous consideration of cumulative exposure and exposure intensity	Goodness-of-fit and step-wise regression do not provide significant evidence in favour of either cumulative exposure or lifetime average exposure intensity	Non-significant (high co-linearity between the different metrics, Goodness of fit statistics are unconditional)

5.6. Smoking and Alcohol

The data were analysed for evidence of any association between tobacco smoking and LH cancer, lymphatic cancer (non-Hodgkin's lymphoma and multiple myeloma) or leukaemia (Section 4.7.1). No consistent pattern was found for smoking status (never, previous or current); previous smokers appeared to have a slightly lower incidence of both leukaemia and lymphatic cancer than never smokers. Similarly there was no significant association between a quantitative measure of smoking (pack-years) and LH cancer. This analysis demonstrated that any effect of smoking must be small and could not explain the observed association between leukaemia and benzene exposure.

The cases and controls were very similar in their alcohol drinking histories There was no relationship between alcohol and risk of LH cancer, lymphatic cancer or leukaemia (Section 4.7.2).

The analysis demonstrated that smoking and/or alcohol do not confound the relationship between leukaemia and cumulative exposure to benzene, in this study.

5.7. Advantages and Disadvantages of This Study

5.7.1. Advantages of This Study

This study has a number of advantages over other similar studies.

- All health data has been collected prospectively.
- Because the controls were drawn from the cohort and individually matched, the selection biases inherent in most case-control studies (e.g. the healthy worker effect [163]) were reduced.
- Health Watch cohort is relatively recent. The earliest subject in the nested case-control study started work in the petroleum industry in 1941. The majority of subjects started work after

1965. In the Canadian IOL study, some of the subjects started work before 1910 [103], in the UK IP study, 27% of subjects started work before 1930 [106]. This means that exposure could be identified by co-workers with more precision that is possible in the more historic studies.

- The cohort has been followed up in a rigorous manner for 20 years with serial identification of current jobs, smoking habits and health status.
- There have been relatively few subjects (6%) lost to follow up [1]. Not only were few subjects lost to follow up but live status was confirmed every 5 years and so it is possible to be confident that the control selection used the correct risk set.
- The subjects, cases and controls, were drawn from the Health Watch cohort a prospective cohort study. In order to enter the cohort workers had to have been in the industry for more than 5 years and have worked at some time at a non-office-only site. Many petroleum company cohorts have used greater than 6 months or greater than one year as the minimum period of work in the industry before entry to the cohort (for example see references [45, 65, 67, 84, 96]). A long qualifying period is important for 2 reasons, firstly the inclusion of trivial exposures from short term workers has been avoided. The biases that are caused by short term workers who tend to have different risks of disease than more stable workers are also avoided [164]. More than one fifth of the subjects were in the lowest quintile of exposure (less than 0.34 ppm-years cumulative benzene exposure) so exclusion of workers with a short qualifying period did not reduce the variability of the exposures in the analysis.
- The cohort study was one of cancer incidence rather than mortality and the case ascertainment rate is high. Cancer registration in Australia is legally binding on pathology laboratories, and hospitals.
- The diagnoses of the cases were well established. Those that had been uncertain were reviewed by a histopathologist.
- Only 10 of the 474 subjects (2%) had incomplete job histories. The recent nature of the cohort and serial identification of jobs results in a high degree of confidence in the job histories. Few jobs were recalled after a long period of time. This is known to give rise to inaccuracy [165-167]. The degree of agreement with the company records also lends support to the accuracy of the job histories.
- The subjects' job histories have been examined and exposure to benzene estimated on an individual basis. Those subjects who were likely to have had exposure to benzene were identified and their probable exposure described in detail, usually by contemporary work colleagues. Those subjects who were unlikely to have had exposure to benzene have been identified by the exposure assessment team and their lack of exposure to benzene was confirmed by company hygienists and local co-workers.
- The exposure assessments were carried out blind as to name and health status of the subjects to reduce observer bias. Some of the site interviewees may have been able to identify the subject but were asked not to let the interviewer know the name or health status of the subject. This may have given rise to bias since the connection between benzene exposure and LH cancer has been the subject of much discussion. Company doctors did not feel that the employees would distinguish between the risk of different LH cancers (leukaemia versus multiple myeloma or non-Hodgkin's lymphoma) from benzene exposure however (Hamilton, Balint personal communications). The clear separation of risk between the lymphatic cancer and leukaemias suggests that observer bias was low.
- The exposure assessments were carried out with the guidance of experienced occupational hygienists from Australian petroleum industry who provided exposure data and reviewed the assessment process and outcomes. One of the members of the team who carried out the exposure assessment for the first 390 subjects was a retired occupational hygienist who had been employed in the petroleum industry since the 1950s.
- The inputs to the exposure assessments, particularly the BEs were validated from the literature (Glass, Gray et al paper submitted for publication). The exposure assessment for the 390 original subjects was compared to a qualitative exposure ranking outcome and the exposure assessment results were comparable with the rankings [2].
- The analysis for latency suggested that exposures more that 15 years prior to diagnosis added little to the risk. The earliest case in this study was diagnosed in 1981 so probably only exposures after 1965 were likely to have been important for this case. Half of the cases were

diagnosed after 1990 so that only exposures after 1975 were likely to have been relevant for these cases. Recent exposures, after 1975 can be expected to be more certain than those before 1965.

- The outcome analysis shows little excess risk associated with the lower exposure groups. The risk concentrates in the highest exposure group and the risk for leukaemia was clearly separated from the risk for multiple myeloma or non-Hodgkin's lymphoma. If the exposure assessment had been inaccurate there would be likely to have been non-differential misclassification and stratification of the odds ratios between exposure groups and between the lymphatic cancers and leukaemia would be less clear (168).
- Smoking and alcohol can be excluded as confounding exposures based on the analysis here.
- It is considered unlikely that subjects in this study were occupationally exposed to other confounding exposures. A comprehensive review of risk factors for leukaemia concluded that the only confirmed risk factors were exposure to radiation, benzene, chemotherapeutic agents and some retroviruses. There is some inconsistent evidence for leukaemogenic potential from pesticides, styrene and butadiene manufacture, ethylene oxide, pesticides, cigarette smoking, hair dyes, alcohol and autoimmune diseases (169).

5.7.2. Limitations of This Study

This study was based on relatively small numbers of cases. There were only 33 leukaemias of which 9 were AMLs. This limits the power of the study to detect excess risks for cancer sub-groups, particularly when the subjects were stratified by one or other of the exposure metrics or by leukaemia type.

Even though great care was taken with the exposure assessment, there are always uncertainties and unknown sources of variation in retrospective exposure assessments. There will have been day to day variation in exposure for any one worker as a result of environmental changes such as wind direction. There will also have been between worker variation as a result of personal factors such as height, site to site variation or variations over time in the equipment or products. All of these factors will contribute to the variation in the data used for the BE. Neither of these types of variation were taken account of in the algorithm. It was possible that the exposure one or more of the subjects may over represented at one end of the distribution of the data in a BE, i.e. the mean of the distribution of the BE data, over or under represents the mean exposure of the individual (170).

There was uncertainty about some of the BEs for which there was little Australian data e.g. *Mechanics*. There was also uncertainty about exposure pre 1975. The available exposure data for the BEs post-dated this period. The changes that took place in technology and working practices may not be accurately reflected in the database. Many exposures pre-1975 were increased by 20% to take account of for example the probably higher rate of fugitive emissions before 1975. In addition, it was considered that fitters had been 50% more heavily exposed prior to this date as a result of different work practices such as working on unpurged lines. This factor was used for 18 terminal fitters. Neither of these factors were validated and they therefore add uncertainty to the exposure assessment.

5.7.3. Smoking as a Background Exposure

One source of exposure to benzene which was not considered in the exposure assessment was from environmental tobacco smoke.

Personal exposure to benzene was examined as part of the EPA Total Exposure Assessment methodology or TEAM study (171). Typical indoor 24 hour average personal exposures had a mean of 0.005 ppm (3). Typical averaged outdoor air had a mean of 0.002 ppm (3). Factors increasing exposure were smoking or the presence of a smoker in the house and filling cars. Indoor air was generally higher than outdoor air by a factor of 2 or more.

A typical smoker absorbs 400µg of benzene per day from smoking. This is an order of magnitude less than the exposure estimated for a tanker driver (172). Non-occupational exposure from driving, refuelling a car, dietary and environmental exposures amount to approximately 250µg benzene absorbed per day. Passive smokers exposed at work had significantly elevated levels of aromatics on their breath compared to those not exposed at work (171). Environmental tobacco smoke was evaluated simultaneously in a “smoky” tavern, 0.007-0.008 ppm, and in the ambient air outside the tavern, 0.002 ppm (173). Similar exposures were found in smoke filled bars, between 0.008 and 0.01 ppm (174).

The background exposure estimate used for offices in the Health Watch study was 0.005 ppm. This allows for some smoking although it was based on average urban air exposure. Some smoky offices might have reached 0.008 ppm of benzene. Aircraft amenity rooms were reported by some interviewees, as being smoky in the past. However, it is unlikely that including exposure to benzene from passive smoking would have significantly affected the exposure estimates. Active smoking would have significantly increased exposure to benzene but this effect was included in the control of confounders and was not regarded as occupational exposure.

5.7.4. Choice of Metric for Exposure

There are a number of metrics which can be used to describe exposure to benzene. The following metrics for exposure have been commonly used either directly or lagged by 10 years to allow for latency.

- Duration of exposure
- Cumulative exposure ppm-years.
- Intensity (average) exposure (ppm) of all jobs or of highest ever job.

In this study, the cumulative exposure metric shows a strong relationship between risk of leukaemia and cumulative exposure for the highest exposure group. There was no such association for multiple myeloma or non-Hodgkin's lymphoma. Duration of employment was used as a surrogate for duration of exposure, this is not predictive of increased risk of LH cancer or leukaemia. Cumulative exposure was strongly affected by duration but intensity did not appear to be important, except at very high exposures given the strong association with the handling of concentrated benzene or BTX. The High day metric did not prove to identify risk except that associated with incidental/accidental high exposure events. This suggests that dose rate was important in the relationship between exposure and risk.

5.8. Risk of Leukaemia and Exposure to Benzene Identified from the Literature

The excess of leukaemia found in this study has been associated with lower exposure to benzene than was reported in other studies. There have been many mortality studies of benzene exposure and leukaemia most however did not carry out quantitative exposure assessments. Those that have been identified are presented below.

5.8.1. The Pliofilm™ Study

The Pliofilm™ rubber manufacturing process was carried out in two plants. A retrospective cohort was assembled which consisted of 748 white men who had been exposed to benzene between 1940 and 1949, the vital status of 75% of whom had been ascertained in 1975. There was a significant 5-fold excess of leukaemia. The exposure data were limited and required extrapolation, particularly in the second plant but were thought to be below the relevant exposure limit. This was reduced from 100 ppm in 1941 to 50 ppm in 1947 and then in stages to 10 ppm by 1969 (18).

Table 115: Table of SMRs (RR) reported for Pliofilm™ Cohort

Cause of Death	n	SMR	95% CI	Source
Lymphatic and Haematopoietic Cancer	21	2.21	1.37 - 3.38	(35)
Leukaemia	14	3.60	1.97 - 6.04	(35)
AML (ANLL)	8	5.0[39]	-	(33)
Multiple Myeloma	4	2.91	0.79- 7.45	(15)

[39] Relative risk rather than SMR

The LH cancer SMRs for the updated cohort that were reported in 1994/5 in shown Table 115. Criticism of the study has focussed on whether there had been underestimation of the exposure to benzene [175].

The Pliofilm™ exposure estimates have been reworked, increasing the exposure estimates [31, 33]. The main alternative exposure estimates are presented in Table 116 [35]. The original exposure estimations were defended as the best available at the time, they did not take into account episodic high exposures from spills or skin exposure, but these were rare. There had been some use of respiratory protection, which might have reduced exposure, but the high exposures cited [175] were measured in places where workers did not go. Unexposed workers had been excluded after company discussions [176]. The exposure data were re-evaluated and the cases individually discussed with reference to their work and likely exposures [19]. The exposure assessment was considered more likely to have been an over-estimate rather than an under-estimate [177, 178]. The original exposure estimates were later defended again by suggesting that the suggested revised exposures would have caused acute haematotoxicity which had not been identified [24, 179].

Table 116: Estimates of Benzene Exposure Intensity (ppm) for the Pliofilm™ Cohort

	Rinsky		Crump		Paustenbach	
	Site 1	Site 2	Site 1	Site 2	Site 1	Site 2
Median	1.0	4.7	7.2	10.9	14.8	46.0
AM	33.1	44.7	63.6	100.3	112.4	199.0
Maximum	728.0	815.2	1724.9	3185.5	3066.2	2321.6

5.8.2. Chinese Industry Exposure

A series of papers have been published examining benzene-exposed workers in China. Benzene was supplied as BTX (a mixture of benzene, toluene and xylene of unspecified purity) from petroleum refineries to a variety of industries where was it used primarily as a solvent [180].

30 deaths from leukaemia were identified in a cohort of 28,460 workers exposed to benzene and 28,257 workers not occupationally exposed to benzene [181]. The authors reported an SMR of 574 (P <0.01). In a later paper, the exposure of the cases was estimated to be between 2 - 153 ppm as an average exposure, giving between 10 - 5,000 ppm-years) cumulative exposure [182].

A cohort mortality study was described covering 672 factories with 75,000 male and female workers exposed to benzene and 40 control factories with 36,000 workers [183]. They found 95 lympho-haematopoietic cancers including 51 leukaemias. These cases were each matched with 4 controls and a nested case-control study was carried out [182].

Individual exposure estimates were made for the cases and controls, [184]. Benzene exposure estimates were presented for major industry groups between 1949 and 1987, usually in 5 year groups. Information was gathered from each site by local collaborators and this was used to construct a job exposure matrix. Exposures range from 47 ppm in the Rubber and Plastic industries in 1949-1959 to 2.1 ppm in Glass Products for 1985-1987. The study showed a relative risk of 2.3 (95% CI 1.1 - 5.0) for leukaemia. Another report on the study gave details of the haematopoietic cancer relative risk divided by cumulative exposure (Table 117) [185]. These studies suggest that leukaemia was associated with relatively low cumulative benzene exposures. The exposure response relationship was fairly flat however with increasing ppm-years of exposure.

Table 117: Relative Risk of Haematopoietic Cancers in Chinese Benzene Cohort (ppm-years)

	Not exposed	**<10**	**10-39**	**40-99**	**100-400**	**>400**
Relative Risk	1	2.5	2.1	2.9	3.1	2
Number of cases	12	9	8	10	18	9

A review of the Chinese cohort data criticised the exposure estimates suggesting that they were too low, citing 2 papers (38). The first paper suggested that at least 152 workers had been exposure to benzene with an AM of 49 ppm (186). The second paper (187) stated that the workers were heavily exposed but this was criticised by suggesting that evidence should have been provided that exposures in these workshops were not representative of other workplaces. They suggest that more exposure measurements were needed from more sites, 672 factories were not visited by NCI scientists (but were probably visited by local investigators who completed forms for the exposure assessment (184). They point out discrepancies in the benzene exposure estimates provided in the different papers produced by the group. Dosemeci's modelled data appears to be lower than that provided by Yin *et al* (181) for the cases.

They go on to compare the white blood cell (WBC) counts from the Pliofilm™ study Kipen *et al* (188) and the Crump and Allen (29) exposure estimates with the Yin *et al* (181) observations of reduced WBC counts compared to the Dosemeci *et al* (184) exposure estimates. They conclude that the Kipen study suggests that exposures over 150 ppm would be needed to result in WBC counts of 4000 observed in the Chinese-NCI studies. They suggest that the evidence suggests that there was a threshold of over 50-75 ppm necessary to induce a reduction in WBCs.

They suggest that the individuals with leukaemia may have been exposed to higher concentrations and have been misclassified as part of a larger group. In addition, specific monitoring data might have been available for the cases as reported in Yin et al 1987b but different exposures were attributed from the Dosemeci exposure assessments.

A further criticisms of the exposure estimates have been made (189). These focus on the discrepancies in the quantitative exposure estimates reported in the various papers, the heterogeneity in the exposure to benzene as the workers came from a number of industries and the fact that many of the workers have had other exposures.

5.8.3. Chemical/Petrochemical Industry

The mortality of 4602 men exposed to benzene for more than 6 months was compared to that of 3074 unexposed men from similar plants (190, 191). There was a non-significant excess of leukaemia compared to the general population. The non-exposed comparison group had no cases however so the excess was statistically significant compared to this group. Workers with a cumulative exposure of 60 ppm years had a relative risk of 3.93, but the confidence intervals were wide. Analysis by maximum peak exposure showed a trend for leukaemias but this was not statistically significant.

The Imperial Oil Limited case-control study of 14 leukaemia cases and their controls, found exposures for the subjects ranging from 0 to 220 ppm-years. The quartile ranges were 0 - 0.17, 0.18 - 0.49, 0.50 - 7.9, 8.0 - 219.8 ppm-years. The range of intensity of exposure was 0 - 6.16 ppm. The quartile ranges were 0 - 0.01, >0.01 - 0.19, 0.20 -0.49, 0.5 - 6.16 ppm. Job duration averaged 30.3 years for the cases and 28 years for the controls. The top exposure quartile, 8 - 219.8 ppm-years had an OR of 2.11 (95% CI 0.01 - 138) (96).

The Institute of Petroleum case-control study of 91 leukaemia cases and their controls, found exposures ranging from 0 to over 200 ppm-years. The quintile ranges were 0 - 0.26, 0.26 - 0.6, 0.6 - 1.65, 1.65 - 4.79, 4.79 - 200+ ppm-years. The job durations had a mean of 21.4 years. 25% of subjects had worked for less than 10 years and 10% for over 40 years. The top exposure quintile, >4.79 ppm-years had an OR of 2.13 (95% CI 0.09 - 5.03) (105).

5.8.4. Latency

The latent period for cancer development has been considered in several studies of leukaemia in the petroleum industry e.g. (46). In the current study the latent period between exposure and cancer diagnosis was 10 to 15 years. The current study is one of cancer incidence and the latent period for diagnosis might be expected to be less than the period to death which is the more usual use of latency in the studies considered below which is the period between exposure and death.

Generally speaking latency has been approached by examining the risk by time since first hire, e.g. [49, 70, 75, 78, 98]. In a cohort study of refinery workers the SMRs for leukaemia were found to rise with length of time since first employment, <20 years SMR 67, 20-39 years SMR 165, 40+ years SMR 148, [86]. This kind of increase and later decrease in the SMR was suggestive of a latent effect but was of course confused by the probable change in benzene exposure over the period. For example, another study showed a more complicated picture: <10 years SMR 91, 10-19 years SMR 110, 20-29 years SMR 80, 30-39 years SMR 127, 40+ years SMR 95, [60]. A similarly complex picture was seen in another refinery population [66].

The length of the latent period is uncertain, it may be as much as 20-30 years based mainly on ionising radiation studies [32, 75]. Aksoy reports the average duration of exposure to benzene among leukaemic patients as 9.93 years [192]. Vigliani reported latent periods (expressed as years since first exposed) of 3 to 24 years (mean 12 years) for 11 patients in Milan but between 1 and 46 for 8 patients in Pavia (there were 5 other patients for whom time since first exposure was unknown) [193]. In a benzene-exposed chemical industry cohort, the latency for 5 cases of myelogenous leukaemia was between 11 and 39 years [194].

Latency was more clearly examined by lagging estimated benzene exposures so that only the exposures within specific time frames referenced to the date of diagnosis were considered. In the Chinese benzene exposed cohort, the risk of non-Hodgkin's lymphoma was found to be most strongly associated with exposure to benzene more than 10 years prior to diagnosis. By contrast, the risk for acute non-lymphocytic leukaemia and related myelodysplastic syndromes was significantly associated with exposure within 10 years of diagnosis and the risk was not increased for those with more distant exposure [195]. The average latency for leukaemia was 11.4 years [180]. Another paper in the Chinese cohort study suggests that the latent period was 11 years from the start of exposure [182].

The mean latency (defined as length of time in years since first exposure until death) of 9 of the cases leukaemia in the Pliofilm™ cohort was 16 years. Seven men had 20 or less years latency but the range was from 3.5 to 37 years [21]. Another author suggested that a latency of less than 22 years was appropriate for the Pliofilm™ study [35]. Three of 12 cases died 9 or more years after they left the Pliofilm™ plant [26].

5.8.5. Exposure Comparison in Petroleum Industry Leukaemia Case-control Studies

The IOL [103] and IP studies [108] used the same or a very similar methodology to derive exposure estimates. The AIP study had more specific job histories than were available to the IP study. The data used to derive the Base Estimates were different however in the three studies. The studies each relied to a large extent on data from their own companies and country. The fact that most of the exposure estimates were similar adds to the confidence in their outcomes.

The job durations (where available) were compared in Figure 66 for the subjects in the AIP and IP studies. The AIP study subjects had a mean job duration of just over 20 years. The IP study has fewer workers with less than 20 years service than the AIP study and more with > 40 years of employment, (10% vs 2%)[106].

The cumulative exposures were compared in Figure 67 and Figure 68 for the subjects in the AIP, IP and IOL[40] studies. The lower quintiles and quartiles of cumulative exposure were similar, if anything they were higher for the AIP study. The range was much greater for the IOL [104] and IP [106] studies however. The IP and AIP studies report that the maximum cumulative exposure estimate was above 200 ppm-years but the maximum in this study was under 60 ppm-years.

[40] The API study reported exposure in total hydrocarbons and so was not easily comparable.

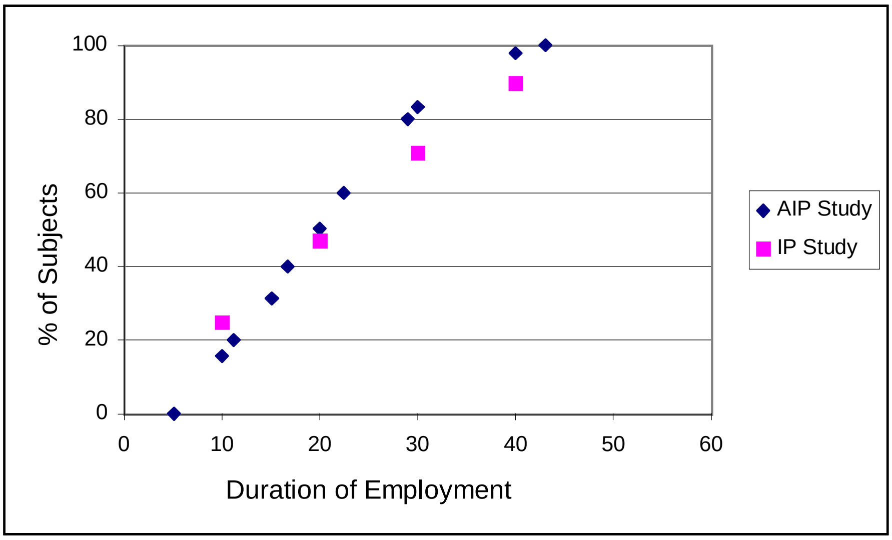


Figure 66: Inter-study Comparison of Subject Job Duration

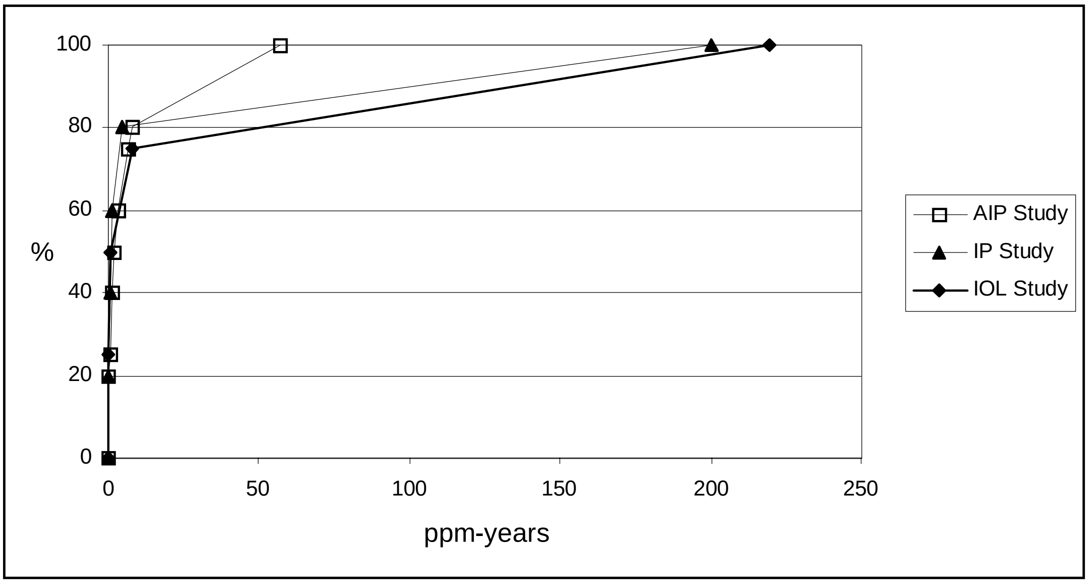


Figure 67: Inter-study Comparison of Cumulative Exposure Estimates

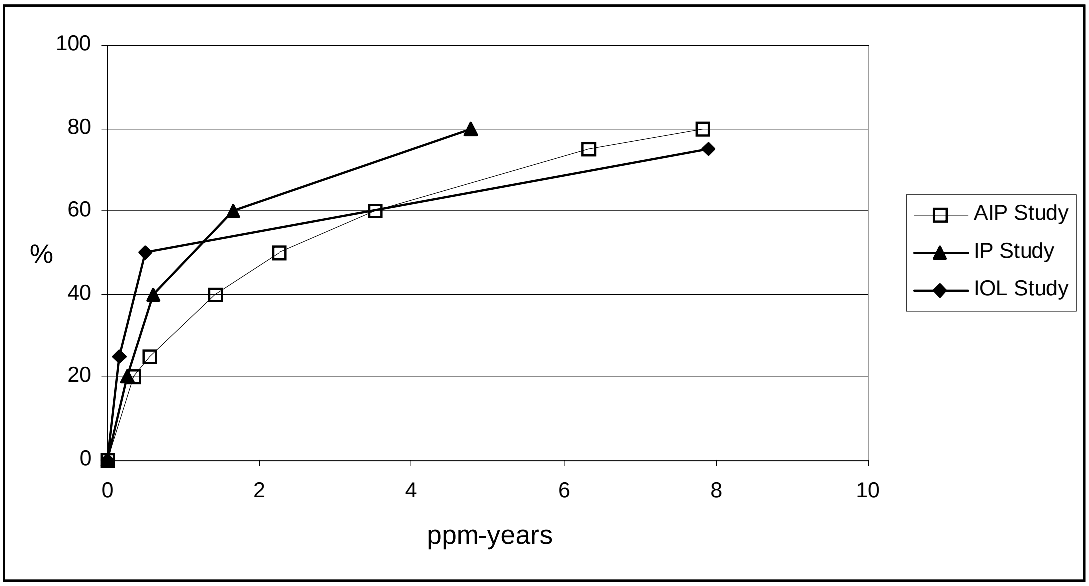


Figure 68: Inter-study Comparison of Cumulative Exposure Estimates (expanded scale)

Possible reasons for the lower exposure estimates in the current study than in comparable industry studies have been identified as follows:

1. More lower exposed workers in this study? This is probable, the IOL and IP studies were of distribution workers. Refinery, upstream and a high proportion of office workers were included in this case-control study. They will have had lower exposures than the distribution workers.

2. The cohort is more recent, so the use of older technologies resulting in higher exposure will be less frequent? This is likely. The other studies have subjects whose job histories go back to the early years of the century. There is, for example, only one top splash loader in this study. In addition, the IOL study recorded that between 1910 and 1940 benzol was added to gasoline increasing the benzene content to over 10% at times (103). This benzene boosting occurred in one Australian company too. However only 2 drivers in this study were involved in carrying this fuel for a short period before 1970. It was not clear what proportion of subjects in IOL or IP studies were top splash loaders or how many carried the benzene rich fuel, but given the period of time covered by these studies, some drivers probably did both. The IP study had benzol terminal operators whose average daily exposure between 1925 and 1945 was estimated to be over 7 ppm (108). This was higher than the exposures that were thought to have been experienced by the workers in the current study .

3. The BEs were too low in this study? This is not likely as the values have been largely validated. There were some differences specific to Australia compared to Canada e.g. Australia has always had open sided rather than fully enclosed drum sheds. The increased ventilation was likely to have resulted in lower exposure and hence a lower BE.

4. Operators have several tasks? The highest long term exposure was during drum filling without extraction in a comparatively enclosed area, BE 4.69 ppm when filling gasoline. Subjects in this study did not do this full time, over 40 years. Most drum fillers fill a mixture of products over the working week so that the final exposure estimate would normally be less than the BEs presented here. They filled diesel and other products containing no benzene and usually had other tasks such as *Rail Car Loading* and *Drum Laundry* that they rotate around which reduced average exposure over the week. The exposure of *Rail Car Loaders* would be less than 3.77 ppm on average for a similar reason.. There will have been a similar mix of tasks allocated to terminal operators in the IOL and IP studies. In the early years of the century operators at large terminal were thought to have been exposed to daily averages of 2.9 - 3.5 ppm benzene (108). By 1960 these values have fallen to 0.68 ppm which was closer to the exposures recorded in this study.

5. Shorter duration of employment per subject resulting in fewer ppm-years? This may be part of the explanation (Figure 66). Of course the workers with relatively high exposure may or may not be the ones with many years of duration. The mean intensity of exposure to benzene was also lower in this study than was reported in the IOL study. This may be as a result of 1. to 4. above.
6. Underestimation of background exposure? This would not be likely to explain the lack of very high exposures. The use of a background exposure value for office workers rather than their designation as zero exposure might explain the very slightly higher exposures at the low end the exposure distributions compared to those for the IOL and IP studies.

5.8.6. Exposure Response Ratios

In addition to uncertainty about the choice of metric and the extent of exposure, there is uncertainty about the model that should be used to describe the exposure response relationship. A number of papers used the Pliofilm™ cohort and one or more of the exposure estimations to estimate relative risk based different exposure response models, e.g. a one hit linear model, (26), a logistic regression model (21). It has been suggested that quadratic models gave a better fit to the data than linear models (33, 196). Calculated relative risks varied depending on the risk model and the exposure estimates employed. A linear model predicted that for 45 years at 1 ppm there would be an additional risk of leukaemia of between 4.4 and 15.2 per thousand (26). A quadratic model suggested that the additional risk was between 0.02 and 0.036 per thousand (33).

The Pliofilm™ was followed up until 1981, and the risk assessments were re-examined using the Rinsky and the Crump and Allen exposure assessments (29). Conditional logistic regression was used to estimate risk (Table 118). The exposure estimates were clearly crucial in determining whether there was an excess risk of leukaemia at an average exposure of 1 ppm over a working lifetime. Brett, Rodricks *et al*. Presented additional information that suggested that Rinsky underestimated cumulative exposure. They also referred to dermal uptake and exposure to benzene in other jobs, both of which would tend to have increased the likely dose. In summary they suggested that Rinsky probably over estimated the risk by a factor of between 3 and 24.

The haematological data from 459 Pliofilm™ workers was examined and they correlated better with the Crump and Allen exposure estimates than with Rinsky's (188). However, workers with a low blood count were removed from the area, resulting in a selection bias (23).

More recently toxicological evidence has suggested that there was a non-linear exposure response relationship for benzene exposure and risk of leukaemia, thus cumulative exposure was a poor estimate of risk (37). The Pliofilm™ cohort, was re-examined and the person years allocated on the basis of each person's maximally exposed job (using Rinsky's, Crump's and Paustenbach's exposure estimates). The likely maximally exposed job was associated with an excess risk of leukaemia between 20 and 60 ppm.

Table 118: Summary of Brett, Rodricks *et al*. Risk Assessments (29)

Exposure assumptions	**Additional lifetime leukaemia deaths per 1000 workers 45 ppm-years (95% CI)**
Rinsky	5.1 (0.83 - 11.7)
Crump and Allen I[41]	0.5 (0.13 - 1)
Crump and Allen ii[42]	1.3 (0.3 - 2.3)

Threshold

There is the question of whether a threshold of exposure to benzene exists, below which there is no risk of leukaemia. Cumulative exposure has been thought to be the appropriate measure and

[41] As presented to the EPA

[42] A ceiling of 131 ppm was applied to each job category

that exposure to peaks over 100 ppm were not necessary for cancer induction [177]. Others consider that there is no increased risk of AML below 200 ppm-years but the risk rises significantly at exposures above this [15].

An update of the Pliofilm™ cohort using the Rinsky, Crump and Allen, and Paustenbach exposure assessments derived risk assessments [34, 35]. The data were consistent with a 50 ppm-year threshold for an excess risk of leukaemia. The lack of cases in the population exposed after 1950 suggested that the cases were associated with the very high exposures that occurred in the early years of production.

The current study shows no evidence of a threshold expressed as cumulative dose. Excess risk was shown below 50 ppm-years. The high risk associated with handling concentrated benzene or BTX suggests that there may be a threshold effect in terms of a daily average exposure or intensity. In this study, such exposures added to cumulative dose but those subjects with CB/BTX exposure were at additional risk compared to others with similar cumulative dose. This suggests that the very much higher exposure on certain days carried additional risk.

5.9. Further Analysis

The findings support the need to maintain the Health Watch cohort in order to follow the trends in cancer rate as technological change reduces exposure in Australia and elsewhere in the world. This would also provide the basis for an improved exposure response relationship for low level benzene exposure relevant to both occupational and environmental risk assessment.

Addition of further cases would provide sufficient cases to carry out analysis by leukaemia sub-type. In particular, since the use of concentrated benzene and BTX was largely phased out of the industry by 1975, there should be a reduction in the number of cases. This reduction should have started in around 1990 and should be identifiable by 2000 if this type of exposure is causally associated with leukaemia. The cohort should be examined for any change in the SMR for leukaemia.

6. Conclusions

The findings of this study provide strong evidence for an association between previous benzene exposure in the Australian petroleum industry and an increased risk of leukaemia. There was evidence of an association with acute myeloid leukaemia and chronic lymphocytic leukaemia, but not chronic myeloid leukaemia. As there were only 2 cases of acute lymphocytic leukaemia no analysis was possible for this condition. No evidence was found of an association with other lymphatic cancers (non-Hodgkin's lymphoma and multiple myeloma).

The risk of leukaemia was found to be strongly associated with both cumulative exposure and exposure intensity. The analysis was not able to distinguish between the relative importance of these two exposure metrics. High exposure events identified in this study did not increase the risk of leukaemia. However, those workers who had exposure to concentrated benzene or benzene/toluene/xylene, even for relatively short periods of employment, were more likely to develop leukaemia than those who encountered the benzene in more dilute forms such as gasoline.

There was clear evidence that leukaemia was most strongly associated with benzene exposures in the period up to 15 years prior to diagnosis, and that exposures more than 15 years prior to diagnosis made little or no contribution to the risk. The risk was not significantly influenced by start date in the industry, duration of employment, or era of exposure.

The excess risk of leukaemia that has been observed in this cohort appears to be associated with lower cumulative exposures and exposure intensities than has been observed in other petroleum industry studies where an excess leukaemia risk has been found. The findings support the need to maintain the Health Watch cohort in order to collect further cases and to examine the trend in incidence, including the delayed effect of changes in technology.

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Appendices

Appendix 1 Health Watch

(Section extracted from Health Watch Report to ERDC 1998 [2])

The Health Watch program has a number of advantages over petroleum industry studies in other countries. The program is an industry-wide study, encompassing the production, refining and distribution sectors. The industry in Australia is highly integrated and interdependent between petroleum companies. Refining capacity is shared locally in a "borrow and loan" scheme and distribution terminal facilities are increasingly being shared between companies. The major petroleum companies have large share-holdings in some of the smaller exploration and production companies. Co-operation between companies in technical matters is co-ordinated through the AIP. From the outset of the program, Health Watch has had the co-operation of the trade unions, even though sensitive areas such as alcohol consumption and smoking habits were closely questioned as confounding variables.

Participation in Health Watch is voluntary and subjects are included only after obtaining full informed consent. The cohort consists of all employees except head office staff and those employed at sites with less than ten employees. The first survey was conducted from 1981 to 1983 and resulted in an original cohort of 10,979 men and 626 women. More subjects were recruited in the second and subsequent surveys. About 95 percent of eligible employees in the industry have participated in the surveys. An employee is taken into the cohort analysis after having served five years in the petroleum industry and remains in the Health Watch cohort for life. Currently, the cohort comprises 15,732 men and 1,178 women and over 180,000 person-years of observations have been amassed.

Employees in the industry are surveyed about every five years using a detailed job and health questionnaire administered by University of Melbourne research interviewers. This obtains information on jobs and tasks, on confounding variables including smoking and alcohol, and on health. Job descriptors are used as the main index of exposure. The employing companies maintain the flow of information on entrants, job changes and retirements. Contact with cohort members is maintained until death. Copies of death certificates are obtained and cancer incidence is validated through state cancer registries.

Results from the Health Watch program have been published in regular reports from the University and in several papers in scientific medical journals [115, 116].

Mortality in the male cohort is about 40 percent lower than the Australian national population rates and overall incidence of cancer is similar to the national rate. However, the incidence of the lympho-haematopoietic cancers (leukaemia, multiple myeloma and non-Hodgkin's lymphoma) is about twice that expected in the Australian male population and this excess is statistically significant.

In 1988 the Australian Institute of Petroleum commissioned a review of the Health Watch program [197]. Armstrong endorsed the view that a case-control study of lympho-haematopoietic cancers was warranted and that more information was needed on job histories, exposures to total hydrocarbons and specifically benzene.

Health Watch initiated a nested case-control study in 1988 to investigate the excess of lympho-haematopoietic cancers and the extent of exposure to benzene that had occurred while working in the petroleum industry. This case-control study compares the exposures of cases with that of controls, seeking to establish whether increased exposure has occurred in cases when compared to controls and whether there is a relationship between exposure and risk of developing lympho-haematopoietic cancers.

Lympho-haematopoietic cancers, as with all other cancers, appear only after an interval of time following any causative exposure. These intervals, known as the latency periods, vary greatly, both with the type of cancer concerned, and within any one type, between cases. Lympho-haematopoietic cancers probably have minimum and maximum latency periods, but these are not known with any certainty. In any assessment of exposure it is necessary to consider the probable extent of exposure some decades ago, as well as recent and current exposures. Although there is a general consensus that exposures in the petroleum industry were likely to have been higher in past decades, there are few benzene exposure data measurements to support this view. There is little consensus on how high exposure was in the 1950s.

The exposure assessment used to date has been qualitative and based on ranking the likely extent of exposure to benzene for the job titles concerned. A description of the ranking methodology was presented in Appendix 4 of the Health Watch Ninth Report [198]. The method of assessing exposure to benzene was similar to that described by [82] based on the company, the site, the job title, the likelihood of exposure and the percentage of benzene in streams. Univariate analyses indicated that there was increasing risk of lympho-haematopoietic cancers with some of the measures used. A similar qualitative study was carried out for the Health Watch Tenth Report and examined an enlarged group of subjects [1]. This assessment covered the original 28 cases of lympho-haematopoietic cancer and their controls and was extended to cover 35 new cases. Each of the 63 lympho-haematopoietic cancer cases was matched to five controls on year of birth and the total study group was 378 subjects. The 1997 results confirm that the lympho-haematopoietic cancer risk was higher among the more highly exposed subjects.

In 1995 a collaborative research grant was obtained from the Energy Research and Development Corporation, the Australian Institute of Petroleum and The University of Melbourne to assess the exposure to benzene of the subjects in the case-control study. This study, known as the Health Watch Retrospective Exposure Assessment project, examined on an individual subject basis, the likely extent of exposure to benzene over the years [2]. This will, in turn, contribute to the benzene risk assessment for current employees and current exposures. The methodology closely followed that developed and used by other petroleum industry studies in the USA, Canada and the UK, [102, 103, 108, 130].

Appendix 2 Background Information

(Section extracted from Health Watch Report to ERDC 1998 (2) and amended)

The Petroleum Industry in Australia - Developments over the Period 1940 to 1997

Refineries

During the period 1940 to 1945, all supplies of petroleum products for civilian use were rationed and centrally controlled. There were two main refineries operating, Clyde in NSW, and the small Commonwealth Oil Refinery at Laverton in Victoria. In 1948 a new refinery opened at Matraville, primarily for bitumen production. In 1953 a benzene/toluene/xylene (BTX) plant was opened at Matraville. This plant utilised crude BTX fractions from the coal gas industry and provided feedstock for the developing petrochemical industry. A new lubricating oil and bitumen refinery opened at Altona in June 1949. This had been converted to a fuels refinery by 1954. The 1950s and 1960s saw a rapid expansion in refining capacity with several new refineries coming on stream. Table 119 summarises the locations and start dates of refineries in Australia. The refineries at Matraville and Westernport closed in the early 1980s. The other refineries have undergone extensive modifications with new plants added and technologies upgraded.

Table 119: Refinery Locations and Start Dates

Refinery	Location	Year on Stream
Clyde	Sydney, New South Wales	1928
Matraville *	Sydney, New South Wales	1948
Altona #	Melbourne, Victoria	1954
Corio	Geelong, Victoria	1954
Kwinana	Perth, Western Australia	1955
Kurnell	Sydney, New South Wales	1956
Port Stanvac	Adelaide, South Australia	1963
Bulwer Island	Brisbane, Queensland	1965
Lytton	Brisbane, Queensland	1965
Westernport *	Crib Point, Victoria	1966

Altona Refinery was a lubricating oil and bitumen refinery from 1949 to 1954.
* Matraville Refinery closed in 1983 and Westernport Refinery in 1984

Lubricating oil production started in the 1950s at Corio and Kwinana Refineries, in 1964 at Kurnell Refinery and in 1976 at Port Stanvac Refinery. Table 120 summarises the locations and start dates of lubricating oil refineries in Australia.

In the 1940s supplies of finished products were imported from many sources which changed frequently because of wartime exigencies and post World War II shortages. After the war the Middle Eastern sources were re-established but Indonesia was supplying 32 percent of Australian crude imports by 1952, and at this time, Australian refineries could meet about 16 percent of local demand for petroleum. Over ninety percent of local demand for gasoline was met from Australian production by the 1960s.

Table 120: Lubricating Oil Refinery Locations and Start Dates

Refinery	Location	Year on Stream
Corio	Geelong, Victoria	1954
Kwinana	Perth, Western Australia	1955
Kurnell	Sydney, New South Wales	1964
Port Stanvac	Adelaide, South Australia	1976

Australian crude production started in 1964 from Barrow Island WA. In 1965 natural gas started flowing from Bass Strait. This marked the beginning of a decline in sales of domestic heating oils, diesel and furnace oils. In 1969 Bass Strait crude deliveries to refineries commenced and became the major crude supplier. Legislation made it compulsory for all petroleum companies with refineries to take a share of local crude, however transport logistics meant that most Australian crude was processed at refineries closest to the sources. A pipeline system was installed to carry crude from the Bass Strait to the three Victorian refiners, interstate refineries being supplied by tankers. Only one refinery ever received crude by barge (Clyde, NSW) and that ceased in 1966 when a pipeline was installed between Gore Bay and Clyde.

Bass Strait crude is relatively “light” and low in aromatic fractions, necessitating substantial changes in refinery plant and operation. Importation of Middle East crude continued throughout this time, firstly because local crude production never fully met Australian demand and secondly, because bitumen and lubricating oils could not be made from the lighter Australian crudes.

A four-fold increase in the price of Middle East crude in 1973 made the prevention of evaporative emissions cost effective and controls, such as floating roofs in tanks and fugitive emission controls on pumps and valve components, were rapidly installed. Secondly, increasing public demand for less environmental pollution resulted in regulations limiting emission of hydrocarbons to air from many sources, including refineries. These factors lead to a lowering of ground level emissions in refineries.

Unleaded gasoline became mandatory for new vehicles after 1986 (when catalytic converters became compulsory on new gasoline driven cars). This required refinery changes for production of low lead and unleaded gasoline.

Refinery operators carry out tasks involved in controlling plants which process hydrocarbon streams to produce gasoline components, e.g. distillation units, crackers and reformers. Tasks on the plant involving potential exposure to benzene include valve operation and sample collection. Part of the shift is normally spent in control rooms. Control rooms used to be located close to the units but from the late 1980s onwards the introduction of more sophisticated and remote technology for process control saw the construction of centralised control rooms at most refineries. These are pressurised and air-conditioned and therefore reduced the exposure to hydrocarbon vapours. The proportion of the operator’s time spent in control rooms will have varied between plants, the specific job responsibilities and the time period in which they were performed.

Operators who worked in lubricating oil and bitumen manufacture had less exposure to benzene. Toluene and MEK (but not benzene or BTX) have been used in Australian lubricating oil solvent dewaxing units. Bitumen has been made at most refineries but the solvents used for cutbacks did not contain benzene (jet fuel and kerosene were commonly used).

Marketing and Distribution Terminals

Bulk Products Receipt and Storage

In the 1940s most supplies of petroleum products for distribution terminals were imported from many different countries and sources changed frequently because of wartime exigencies and post World War II shortages. Products arrived from the Middle East, Italy, USA, Singapore, Indonesia, Venezuela and Chile, among other places. Until the pipelines from refineries were built in the mid-1950s almost all products arrived at the terminals by ship. Fuel products were pumped from ships at docksides by pipeline to terminals. Before product discharge commenced, all cargo tanks to be discharged were opened by fitters. Ullages (i.e. dip measurements using a weighted flexible steel measuring tape) were taken by a company representative, usually accompanied by a Customs officer, after which laboratory staff took samples of product for laboratory validation of quality. Personnel were instructed to stand upwind, but vapours were often encountered. Exposure time varied but commonly each process took about one hour. Some more modern tankers had vents from tank headspaces discharging at mastheads. When ullaging and sampling were completed, fitters connected flexible rubber hoses to the tanker manifolds. The hoses were usually clean and dry resulting in little exposure to hydrocarbons during connection.

At the receiving terminal, ullages were taken of receiving tanks and a "slops" tank, before pumping commenced. First a slug of water was pumped through to the slops tank, followed by product. As the interface between water and product approached, the duty chemist sampled the line product and determined visually when the hydrocarbon product arrived, the duty valve man then diverted the hydrocarbon product to its correct tank. As the sampling point had to be located in the pipeline set, usually in a trench, chemists were exposed to some hydrocarbons for perhaps fifteen minutes for each changeover. The valve man was not exposed. After the whole cargo was received the line was left full of water; then the flexible hoses were drained and disconnected by the fitters, usually without exposure unless gaskets and connections leaked. There were poor facilities on wharves for cleaning up and fitters often used rags wet with light hydrocarbons to clean themselves and their equipment.

After the storage tanks had settled, as verified by chemists taking samples from the tank top, the bottom water was drained off to a pre-set level by a tank farm operator. The drained off water flowed through the tank farm bunded area and with it small amounts of dissolved or dispersed hydrocarbons. Tank farm operators operated in pump houses that were often located in the bunded area so they may have had some exposure to hydrocarbons, including some skin contact. Improved handling facilities were gradually installed, the sequence varying from terminal to terminal. Major changes included the replacement of flexible hoses by Chiksan arms; discontinuance of water plugs between products and later the introduction of pigs between to separate products. Once products arrived by pipeline, separated by pigs, the use of a tank water table decreased and hence the sampling was reduced.

In the early years the tank farm operators took daily official Customs dips for determination of Customs duties payable and to check output. By the mid-1950s dipping was more usually weekly, and by the 1960s, permanent tape gauges were introduced. This reduced the skin exposure from handling the wet dip tape. Customs regulations required that a water table be present in the base of bulk tanks that received bonded products including petrol. After the levels were measured the tank was dewatered into the surrounding bund. The water stayed in the bund until the operator released it to the drainage system via a triple interceptor.

At one company's terminals, benzole or crude benzene, a by-product of coke oven operation at steel works was added to gasoline to boost the octane rating. Crude benzene from steel works was usually pumped by pipeline to a tank farm at a terminal with marine access. From there it was either drummed into 200 litre drums and despatched to other terminals or shipped out in bulk tankers to other marine terminals. At some sites, benzene from bulk tanks would be line blended into gasoline during receipt of a gasoline assignment into a storage tank. This was an intermittent practice and ceased in the mid-1970s.

Drummed Products Receipt

Special boiling point light hydrocarbons, heavier aromatic solvents, oxygenated chemical solvents, a wide range of lubricating oil base stocks, finished lubricating oils, solid bitumens and speciality products (e.g. extender oils and pesticides) all arrived in drums at terminals delivered from cargo vessels by tray trucks in the 1940s. The number of drums imported decreased dramatically in the 1960s, but the variety of product arriving increased.

There was virtually no exposure when handling intact closed drums, either by air or skin.

Distribution by Road Tanker

In the 1940s road tankers used for bulk product deliveries had up to five compartments, each compartment varying in capacity from about 1000 to 2000 litres. Gasoline has always been by far the major product delivered in bulk road tankers. They were normally filled via a removable loading spear reaching to the tank floor or through an integrated fill tube. Top splash loading of gasoline was not a widespread procedure at Australian terminals during the period of interest to this study. Most tankers delivered three loads daily, although some drivers worked a considerable amount of overtime. Measurement of quantity loaded was by dipstick. The loading gantries were usually open structures covered by a galvanised roof. Loaders would fill the compartments to the designated fill point by manual control of the discharge valve to the flexible hose connected on the loading spear or through a fixed fill tube. The tanker loader would be either a storeman loader (when early morning loading was done before drivers arrived) or a driver (for daytime loading). The loader usually stayed on the loading gantry until loading was completed. The process took from ten to twenty minutes depending on the tanker size and number of compartments to be filled. Exposure varied with the product, wind or lack of it, and the temperature. In summer, even though the Reid Vapour Pressure of gasoline was reduced, vapour concentrations could be significant. Skin contact also occurred occasionally. Minor spills occurred perhaps every two or three days per terminal and were simply washed away with water and drained into an interceptor pit.

Tanker capacity increased over the next twenty years to 30,000 litres in the 1990s, but pump rates also increased and fill times remained similar. Metered loading was introduced from the 1960s and later became computerised. Bottom loading of bulk gasoline trucks began in the 1980s, followed by the introduction of vapour capture and recovery systems.

Other products handled in bulk on the same gantry included power and lighting kerosenes, automotive diesel oil, white spirit and mineral turpentine infrequently. There was usually a division between black oil and white oil trucks (and drivers). White oil trucks could take gasoline, kerosene or diesel. Product switching involved draining the tanks. Fitters, storemen and drivers would be involved in this task. Some sites had dedicated gasoline and solvent trucks.

In the early years a bulk road wagon would make perhaps three to five deliveries (drops) before returning to the terminal empty. The introduction of single company service station or retail outlets in 1951 meant that a road tanker could make much larger drops. Today there is usually only one drop per load. At each delivery point, the underground receiving tank would be opened and dipped with its own permanent dipstick, and a similar reading taken of the compartment from which fuel would be discharged. Then the hose and bonding cables were connected and the drop effected. Drivers were required to stay by their wagons during discharge. Vapour lines carried displaced vapour from the tank to some relatively remote point from where atmospheric discharge occurred. Most drivers wore gloves (leather in the early years, later PVC) and did not experience much skin contact. Deliveries took from fifteen to thirty minutes to complete. Industrial deliveries were basically similar, but involved lesser quantities of product.

More recently with computer controlled loading quantities, computer controlled billing and single load drops the use of dipsticks has all but disappeared.

Distribution by Rail Tank Cars

Rail tank cars were used to deliver bulk products to country areas. These were filled at loading gantries by storemen on the rail siding using flexible hoses connected to loading spears or fill tubes similar to those used on the road wagon stand. The operation was usually conducted in the open and was suspended if it rained. Loaders stayed on top of the loading hatches until the spear tip was well covered and returned as the tank approached its capacity. It took from 30 to 40 minutes to fill a 45,000-litre rail car. Measurement was by dipstick.

Tank cars were cleaned before being sent for repair. Fitters did this in the early years and more recently, contractors.

Drumming Operations

Drum filling was done by storemen in large sheds, often open on two or more sides, with adjoining loading bays at truck tray height on either or both the open sides. In the early years they had red gum floors with gaps between the planks so that spilt product dropped through the floor quickly. There was usually a drain below. Later the floors were made of reinforced concrete.

The filling machines were equipped either with short stubs or with loading spears that reached close to the bottom of the drum. At some terminals, there was a device that clamped to the bunghole and made a reasonable seal around the stub or spear. The vapour displaced by incoming liquid was either vented into the work space or went into small pipes leading from the spear collar area which were vented above the roof of the filling room. However, even where this arrangement was used, a considerable proportion of the vapour would escape for various reasons. There were no general extractor fans to remove vapour that entered the working area. In the 1970s local exhaust ventilation was introduced at some sites. Drum fillers often did other tasks such as stacking drums or loading trucks with full drums. Packaged goods drivers delivered drums.

Cleaning of slops pits containing gasoline residues was hand done but rarely, usually after heavy rains or during construction or maintenance work. It might be carried out 4-5 times per year.

Over the years the amount of drum filling fell as farmers and other customers converted to bulk tanks and bulk delivery superseded drum deliveries. However the proportion of gasoline filled rose. Some terminals drummed benzene in small amounts for speciality markets (e.g. tobacco farmers) up to about 1980 and added it to racing fuel, which was also drummed in small quantities. By 1990, drum filling of gasoline and fuels ceased at most terminals.

Drum fillers also sprayed brands on drumheads. There were three methods for branding drum heads (and sometimes drum sides). Originally very carefully screened brands were done with paste paints. Later on brands were screened using stencil brushes and low volatility stencil paints, and in more recent times stencilled with spray gun paints. In the 1990s this changed to pre-labelled drums or ink rollers and stencils. Spray painting is now less common.

Shell, Mobil, BP and to a lesser extent Caltex marketed aviation fuels, avgas being supplied in drums. Small quantities of avgas were diverted for blending of exotic motor car racing fuels. This latter activity, often done by blending in 200 litre drums, was associated with fairly high exposures to hydrocarbons, including aromatics, although it was on a very small scale and intermittent.

Drum Laundering

Drums were reused after cleaning in the drum laundry. This was usually close to or part of the drum filling shed. Drums were visually inspected through the bunghole and if necessary, inverted over rose spray heads and the inside washed with (perhaps warm) kerosene. Very dirty or rusted drums were given a small slug of kerosene or distillate, then a chain welded to a large bung was screwed into the drum and placed on a rumbler which oscillated. After a second draining, drums that were acceptably clean were given the spray treatment. Drums would be knocked into shape and resprayed or, if in a really poor condition, sent to an outside contractor for full reconditioning. The major source of exposure for workers in drum laundries was to vapours encountered during bunghole inspection. Experienced workers could tell whether drums contained much free liquid as they moved them about without needing to closely look inside.

With some exceptions drum cleaning was phased out at the terminals by the mid-1980s as reconditioning and cleaning was entirely contracted out.

Blending and Packaging

A number of products were manufactured at terminals. No benzene-containing feedstock was used. Solvent products with some benzene concentration may have been used to clean lubricating oil blending and packaging areas on a weekly basis. These practices would have ceased in the 1970s.

Grease packers would not normally be exposed to benzene during normal operations. They probably used white spirit for cleaning - but may have used solvents containing aromatics in the 1950s.

Other Terminal Activities

Painters' duties included painting bulk tanks inside and out, pipelines etc., delivery vehicles (until the mid fifties), including rail tank cars. Later the use of painted vehicles diminished and in any case painting was relegated to contractors. Until the late 1950s they also prepared screens for branding drum tops and sometimes actually did the screening work. They also performed general maintenance painting around the terminal but contractors now do this.

Up to 1975 some paints used for general work may have contained benzene but the more usual solvents were mineral turpentine, white spirit, toluene, xylenes and heavy aromatic solvents. After 1970 nearly all architectural and vehicle paints used were alkyd resin based and did not contain benzene. Also major painting works was largely contracted out by that time.

Fitters carried out all maintenance work around the terminal and on pipelines to the wharf. They also connected all flexible hoses to ship's manifolds for discharge to shore tanks but this work decreased when refinery pipelines were installed. In the early years, activity was very labour intensive. Fitters did a lot of manual cutting of pipes; pipeline systems were patched up rather than replaced when leaks occurred. Many pipelines were patrolled on foot to watch for leaks. Fitters or labourers cleaned product storage tanks with a fire hose after they had been emptied, vented and gas tested to below the lower explosive limit (LEL) after which they entered the tank to complete the cleaning. Respirators were normally worn during this activity. Tank cleaning was an infrequent activity since tanks were only taken out of service for cleaning after ten or more years of use. By the 1960s contractors normally carried out tank cleaning at most sites. Fitters often used rags or oily waste soaked in available products for cleaning up themselves when contaminated for instance by fuel oil. In at least one company a Friday afternoon clean up was common in 1950s and the floor might be cleaned with LVN (1% benzene)

Mechanics maintained the company's fleet of trucks. Higher flammability hydrocarbon products, and sometimes gasoline, were often used to clean engine parts as well as mechanic's hands and on occasions, overalls. This practice was more actively discouraged by the 1970s. At the same time ventilation of garages was improved.

Chemists were often exposed to hydrocarbons by skin and inhalation, e.g. during sampling of tanker ship cargoes or drums, line clearances for product changes in pipeline receipt of product, vapour testing of tanks, quality control testing in blending operations, and of course laboratory operations themselves, which sometimes required the use of benzene or other aromatic hydrocarbons, chlorinated solvents, etc. Chemists carried out less sampling and more analytical work when products arrived by pipeline from the refinery. By the 1960s laboratories were more likely to have air conditioning and fume cupboards.

Carpenters may have used some benzene-containing varnishes and thinners in the 1950s. Storemen other than those identified above, for example, those working in tool stores or material stores, would be unlikely to have had significant benzene exposure.

Watchmen, shunters, yard workers, boiler house attendants had minimal exposure to benzene. Office cleaners, chauffeurs and canteen staff would be unlikely to have been exposed to benzene.

Airports

Avgas (aviation gasoline) containing up to about three percent benzene and having a higher lead content than motor gasoline was exclusively used to fuel piston-engine commercial aeroplanes until the jets of the early to mid-1960s gradually superseded them. It is still used for light aircraft. Before 1956 all avgas was imported from the Middle East, U.S. or the Mediterranean. From January 1956 to 1980 Altona Refinery was the only refinery in Australia that produced avgas and this did not contain benzene. Some avgas was still imported. Corio Refinery starting producing avgas in 1980 and Kwinana Refinery in 1987. The output from these three refineries now meets most of the Australian demand.

Although over-wing refuelling of avgas for light aircraft has continued at about the same rate it has fallen to a small proportion of the work of petroleum company refuellers as jet aeroplanes have increased in size, frequency and fuel consumption. Avgas usage in 1939 was around 22 megalitres, by 1949 this had risen to 138 megalitres and peaked at 205 megalitres in 1957. From 1960 usage has remained constant at around 110 megalitres (Tresider 1988). With the advent of the jet engine the use of jet fuel JP1 (kerosene containing no benzene) increased rapidly. By 1959 jet fuel usage equalled avgas usage, by 1960 had doubled it and in 1988 was over twenty times the avgas usage [(160)].

Avgas was delivered to the aerodrome's tank farm by road tankers from a local terminal. As demand for jet fuel increased, pipelines were built connecting refineries directly to airport tank farms, from which jet fuel was delivered by hydrant systems to aircraft refuelling points. The distribution system is referred to as a joint user hydrant installation or JUHI.

Refuelling of avgas is still done from road tankers and refuellers usually fill their own vehicles. During over-wing refuelling of light aircraft using an injection nozzle, exposure may occur from displaced vapour. To prevent overfilling the operator was often required to visually check the fuel level in the tank.

Production – Onshore and Offshore

The exploration and production operations of the petroleum industry are known collectively as "upstream" operations. Exploration may involve minor exposures to hydrocarbons when an exploration well is successful and an open flow test is required but normally exploration is not a benzene-exposed activity.

Production operations include the obtaining of gas and crude from the underground reservoir and providing preliminary treatment at the well-head to remove sand, grit and most of the free water, before pumping to the stabilisation plant. These stages may be executed onshore or on offshore platforms. Since the systems are fully enclosed, exposure to hydrocarbons is infrequent and usually only occurs during laboratory testing, pig loading (an operation which takes about eight minutes and is usually only done periodically), opening of lines or vessels for inspection or maintenance, wellhead tests, or emergencies. Most of these operations are undertaken only occasionally, rather than regularly. As local crudes also have low benzene content (about 0.1 percent) benzene exposures are usually below the level of detection.

The stabilisation plant separates gas from crude and condensable liquids, and then separates the range of hydrocarbons, physical processes being used to achieve these steps. Some concentration of hydrocarbons boiling in the benzene range may occur and exposure controls such as looped sample lines and closed sewer lines may be needed. However, airborne benzene concentrations remain very low, mostly below the levels of detection.

The main product leaving the stabilisation plant is stabilised crude, that is crude that has been dewatered, had its sediments removed and brought to a specified vapour pressure. It may leave by either pipeline or tanker. Natural gas (methane, almost 100 percent) also leaves by pipeline. Other products (light ends, including ethane through to about pentanes) often called 'gas liquids', also leave by either pipeline or refrigerated/ pressurised transport. At some plants LPG may be separated on site and delivered to market by dedicated road tankers, special bulk tankers or pipeline.

During all these processes, the chemical nature of the materials is unchanged, so the total amount of benzene remains constant, although it may be concentrated to some extent by selective distillation processes. Australian production of crude dates from the late 1960s and modern technology has been fully utilised, so that all exposure to hydrocarbons is minimised.

Health, Safety and Welfare

When the surge in refinery construction started in the early 1950s, the latest technology in use overseas was employed. Characteristically this technology was less labour intensive than the older pre-war technology that continued to be used in terminals and distribution systems. For instance, when refineries opened they used Chiksan arms instead of flexible hoses for unloading crude, but terminals persisted with flexible hoses for a long time and they are still in use at some sites. In the 1970s the major companies started closing down smaller rural depots (mini-terminals) with older technology, or leasing them to agents.

In the early years, cotton overalls were supplied to some people, e.g. mechanics and chemists, but expected to last a week unless excessively soiled. Before 1947 the supply of clean laundered overalls was not extensive. Leather aprons were supplied to drum handlers and leather gloves were available generally. By the 1960s PVC gloves had largely replaced leather. In the 1940s, half face respirators and air-supplied hand driven full-face respirators were available but used only for jobs such as tank cleaning or emergencies. Clean recycled rags were available and used for most cleaning-up including men’s hands. Shower facilities were usually available from about the 1940s onwards, but some employees left the job in the clothes they had worn all day.

Reflecting changing community standards, environmental matters and occupational hygiene issues were addressed more positively from the 1970s. Companies started appointing occupational hygienists to their staffs, with five companies doing so during this period. From 1968 the National Health and Medical Research Council adopted most of the Threshold Limit Values promulgated by the American Conference of Governmental Industrial Hygienists and these were generally observed and adopted by companies, although actual measurements of exposure were taken infrequently. The National Health and Medical Research Council Occupational Exposure Limits were adopted and published as WorkSafe Australia Exposure Standards from 1985 onwards.

Throughout the industry, training and awareness programs in occupational health and safety became common in the late 1970s and 1980s and as a result work practices improved considerably. The Australian Council of Trade Unions adopted its first policy on occupational health and safety in 1979.

Regular provision of clean work clothing, protective equipment and use of showers increased over the 1970s. Skin contact with benzene containing fluids virtually ceased by the early 1980s and fewer spills occurred. Sampling points were largely changed to looped systems, lowering the discharge of material to atmosphere, internal membranes or floating roofs were installed in cone roof tanks containing gasoline, tank cleaning and draining became more mechanised or was done by contractors and improvements were made to workplace ventilation such as the installation of LEV at drum filling. Benzene exposure became less common as it was removed as a feed stock and from products.

Appendix 3 Previous Exposure Assessment for ERDC

(Section extracted from Health Watch Report to ERDC 1998 [2])

The background work lead to an initial work plan being prepared by the project occupational hygienists, Deborah Glass and Richard Manuell, with advice from other team members.

The steps involved in the exposure assessment process were:

1. Establish for each of the subjects, identified as a case or control, the complete work history in the petroleum industry, including details of the company and site where each job was held and details of the tasks performed during each period of employment.
2. Identify the tasks where exposure to benzene could occur for each of the subject's work activities and the time taken to execute these tasks, the products handled and technology in use for these tasks at each of the sites where a subject was employed and establish any changes to these factors that would have affected exposure.
3. Identify over time, the relevant sources of various products at each of the sites where there was a subject and estimate the probable benzene concentration in the product.
4. Obtain exposure data from the participating companies and from the literature to characterise current and past exposures.
5. Develop a model to allow retrospective exposure to benzene to be extrapolated from current exposure where data were not available.
6. Develop a method to rate peak benzene exposures.
7. Calculate a cumulative exposure index, intensity and peak rating for each subject.
8. Validate the derived exposure measurements.

It is possible that the retrospective exposure assessment method could be applied in future to a different set of subjects, and certainly to an expanded set. The development of a method that could be applied in future was therefore a priority.
A Project Advisory Group was formed to oversee the assessment process. The group met regularly during the project and consisted of the Study Manager, the project occupational hygienists, the occupational hygienists from the participating petroleum companies, and Associate Professor C. Gray and G. Sinclair from the Occupational Hygiene Unit at Deakin University. Other members of the Health Watch program team also attended meetings.

Three Health Watch surveys had been conducted since 1981. The first in 1981 to 1983 and the second in 1986 to 1987 obtained information on the worker's current job and any other jobs held in the preceding five years. The third survey in 1991 to 1993 obtained a complete job history from those interviewed. In 1994 Health Watch endeavoured to obtain complete job histories from all members of the cohort who were no longer working in the petroleum industry and who had not been interviewed in the third survey. Some subjects in the case-control study had been interviewed in all three surveys. All jobs had been coded using a job code classification system developed for the API [199, 200] with modifications to suit the Australian petroleum industry. This classification allowed jobs to be categorised by the processes on which they worked and the tasks performed. The job titles used by the subjects were also available from the questionnaires.

Appendix 4 Job Titles Categorised by Activity Group

Group	Description
Aircraft Refuelling	Aerodrome Assistant
	Aerodrome Attendant
	Aircraft Refueller
	Aircraft Refueller Attendant
	Aircraft refuelller
	Airport Refueller
	Assistant Airport Supervisor
	Leading hand refueller
	Pump Assistant
	Refueller
	Senior Aerodrome attendant
Drum Filling	Depot Superintendent
	Dept superintendent
	Driver (Packaged), storeman
	Drum filler
	Drum filler, storeman
	Drum filler/Spray painter
	Gauger/Storeman
	Leading Hand Storeman
	Operations Trainee
	Relief Storeman
	Storeman
	Storeman & blender (drum filler)
	Storeman & packer
	Storeman Filler
	Storeman in charge
	Storeman/Drum filler
	Terminal Foreman
	Terminal Manager
	Terminal Superintendent
Drum Laundry and Preparation	Boiler attendant (drum cleaning)
	Drum cleaner
	Drum filler, storeman
	Leading Hand Storeman
	Operations Trainee
	Pumper Gauger / Clerk
	Spray painter
	Storeman
	Storeman & packer
	Storeman Filler
	Storeman/ Spray painter

Group	Description
Fitting	Apprentice fitter & machinist
	Apprentice Fitter & Turner
	Apprentice Fitter/ Fitter
	Fitter
	Fitter & Turner
	Fitter Machinist
	Fitter Welder
	Fitter's Assistant
	Fitter/supervisor field
	Foreman
	Iron worker /general hand
	Leading hand fitter
	Maintenance fitter
	Maintenance fitter & turner
	Maintenance foreman
	Maintenance Offsider
	Maintenance technician
	Mechanic
	Mechanic/Fitter
	Operator
	Plant helper
	Platform mechanic
	Rig Mechanic
	Storeman
	Terminal Foreman
	Trades Assistant
	Trades assistant (Fitter)
	Trades assistant - maintenance
	Tradesman's (welder's) assistant
	Tradesman's assistant
	Utilityman
Laboratory	Chemist
	Chief Chemist
	Chief chemist, refinery chemist
	Experimental Technician
	Lab assistant
	Lab Assistant/ Lab Tester
	Lab Technician
	Laboratory supervisor
	Laboratory technician
	Laboratory Tester
	Non technical staff
	Plant chemist
	Project chemist
	Pumper/ gauger
	Research chemist
	Sample collector
	Senior Chemist
	Storeman
	Supervisor - Technical Services
	Technical Assistant
	Technical services manager
	Trainee

Group	Description
Office	Accountant
	Accountant - Vic & Tas
	Accountant/clerk
	Accounting supervisor
	Accounts Assistant
	Accounts Clerk
	Accounts Stock Clerk
	Acting superintendent
	Acting terminal manager
	Administration
	Administration Assist/ Sales Manager
	Administration assistant
	Administration manager
	Administration/ finance/ office manager
	Administration Manager
	Administration Officer
	Adminstration Manager
	Advisory engineer
	Aerodrome attendant
	Aircraft Refueller
	Aircraft refuelller
	Airport refueller
	Analyst Engineer
	Apprentice Instrument mechanic
	Area manager
	Area Manager (sales)
	Area Operator
	Area Supervisor
	Assistant Inspection engineer
	Assistant Superintendent
	Assistant superintendent crafts
	Assistant Terminal Manager
	Assistant to chief tech officer
	Assistant to Planner/Trade assistant
	Auto spare parts supervisor
	Aviation assistant
	Aviation Manager SA & NT
	Aviation Supervisor
	Borrow & Loan Clerk
	Bulk Dispatch Clerk
	Bulk Supervisor
	Buyer
	Buyer/ Clerical Supervisor
	Canteen assistant
	Cashier
	Chauffeur
	Chef
	Chemist
	Chief clerk
	Chief engineer (inspection)
	Cleaner
	Clerical supervisor
	Clerk

Group	Description
c	Clerk - (finance & stock)
	Clerk - accounts
	Clerk - bunkering & supply
	Clerk - Engineering
	Clerk Dispatch Officer
	Clerk Foreman
	Clerk Supervisor
	Clerk/ Sales Assistant/ Trainee Representative
	Clerk/Senior clerk
	Commercial accountant
	Commercial Manager
	Company secretary
	Conservation Engineer
	Construction & Maintenance Manager
	Construction Engineer
	Consultant Engineer
	contract coordinator
	Contractors supervisor
	contracts coordinator-distilation
	Control operator
	Cook/Canteen Assistant
	Corrosion engineer
	Cost Control Officer
	Country territory manager
	Courier
	Crane operator
	Credit Card administration manager
	Credit Clerk/ Section Head / Supervisor
	Credit controller
	Depot Audit
	Depot Inspector - Stock
	Depot Superintendent
	Design Draftsman
	Design Engineer
	Development Engineer
	Director Finance & Administration
	Dispatch Clerk
	Dispatch Planner
	Dispatch stock clerk
	Dispatcher
	Distribution Assistant
	Distribution manager
	Distribution Officer
	Distributor systems manager
	Draftsman
	Draughtsman
	Drivers supervisor
	EDP Clerk
	Education leave
	Electrical draftsman
	Electrical supervisor
	Emergency and Systems Officer
	Energy & Conservation Engineer

Group	Description
Office continued	Engineer
	Engineer Designer
	Engineering assistant
	Engineering Clerk
	Engineering draftsman
	Engineering maintenance supervisor
	Engineering Manager
	Engineering Officer
	Environmental engineer
	Equipment Officer
	Export manager
	Field Clerk
	Field maintenance manager
	Field Maintenance Supervisor
	Field Rep (Country)
	Field Rep (Metro)
	Field supervisor
	Fire, Security & Occupational Health
	Fiscal Manager
	Fitter
	Fleet supervisor
	Fleet transport manager
	Foreman
	General Manager
	Group Manager Industrial Relations
	Head operator
	Industrial Engineering Superintendent
	Industrial Manager
	Industrial Relations Assistant
	Industrial Relations Officer
	Inspection engineer
	Inspector
	Installation manager
	Installation Superintendent
	Installation Superintendent - Packages
	Installation supervisor
	Instrument foreman
	Instrument Supervisor
	Instrument/electrical reliability engineer
	Inter Company Clerk
	Inventory clerk
	Junior Clerk
	Junior Clerk/ Clerk
	Junior pumps clerk
	Junior sales clerk
	Leading hand fitter
	Leading hand instrument technician
	Leading hand refueller
	Library clerk
	Loss Control Training Officer
	Lube plant manager
	Machine monitoring assistant technician
	Mail boy

Group	Description
Office continued	Mail run driver Newport to Head office
	Maintenance Control Engineer
	Maintenance controller
	Maintenance cost analyst
	Maintenance engineer
	Maintenance Engineering Superintendent
	Maintenance Foreman (Relief)
	Maintenance planner
	Maintenance superintendent
	Maintenance supervisor
	Maintenance/ Transport Manager
	Manager
	Manager - Operating Business Systems
	Manager SA/NT
	Manager Victoria Tasmania
	Marketing assistant
	Materials clerk
	Materials specialist
	Mechanic
	Mechanical consultant
	Mechanical Foreman
	Merchandise warehouse clerk
	Merchandise/wharehouse clerk
	Mobile supervisor
	Motor vehicle inspector
	NT Regional manager
	Office
	Office services supervisor
	Oil Audit
	Oil Cashier
	Operating Supervisor
	Operations assistant
	Operations Engineer
	Operations Foreman
	Operations supervisor
	Operator
	Operator Course leader
	Order/Stock Clerk
	Orders & Dispatch Supervisor
	Orders clerk
	Pack dispatcher/ clerk
	Panel control technician
	Permit Liaison Officer
	Personnel & Industrial Relations Manager
	Personnel Officer
	Personnel/ Payroll Officer
	Pipeline supervisor
	Planner Scheduler
	Planning engineer
	Plant supervisor
	Platform supervisor
	Process engineer
	Process foreman

Group	Description
Office continued	Production planning superintendent
	Production Supervisor
	Project electrical supervisor
	Project Engineer
	Project inspector
	Project manager
	Project supervisor
	Project work
	Public Affairs Assistant
	Public Affairs Officer
	Pumper Gauger / Clerk
	Purchasing Officer
	Radio Operator
	Receptionist
	Refinery accountant
	Refinery chemist
	Refinery Scheduler
	Refining
	Refueller
	Regional manager
	Relief Clerk
	Relief Superintendent
	Relieving Officer
	Resource Protection Officer
	Retail Manager
	Retail marketing officer
	Safety assistant
	Safety man
	Safety officer
	Safety supervisor
	Sales assistant
	Sales Clerk
	Sales manager
	Sales manager Tasmania
	Sales Rep
	Sales Representative
	Section Head Accounting
	Security watchman
	Senior account manager (transport)
	Senior Aerodrome attendant
	Senior bulk dispatcher
	Senior Buyer/ Administrator
	Senior Chemist
	Senior Dispatch Clerk
	Senior Engineer
	Senior Engineering Assistant
	Senior Inventory clerk
	Senior machinery engineer
	Senior maintenance supervisor
	Senior Maintenance Supervisor - Instrument Electri
	Senior Maintenance Supervisor - Maintenance Servic
	Senior marine supervisor

Group	Description
Office continued	Senior Metal Engineer
	Senior plant inspector
	Senior platform supervisor
	Senior process engineer
	Senior stocks clerk
	Senior technologist
	Service Craft Supervisor
	Services Manager
	Shift controller
	Shift dispatch clerk
	Shift foreman
	Shift Supervisor
	Shift supervisor - Transport
	Shipping Assistant
	Stationary mailing clerk
	Stock Clerk
	Stock clerk/Load balancing
	Stocks Clerk
	Storeman
	Stores Assistant
	Superintendent
	Superintendent Marine Personnel and Cargoes
	Supervising Engineer
	Supervisor
	Supervisor Marine Personnel
	Supply officer
	Supply Programmer
	Technical services assistant
	Technical services manager
	Technician
	Technician trainer
	Technologist
	Technologist - Conservation
	Technologist - Environmental Affairs
	Terminal accountant
	Terminal Clerk
	Terminal Foreman
	Terminal manager
	Terminal Superintendent
	Territory manager
	Territory Manager
	Territory Marketing Manager
	Trade training supervisor
	Trades assistant
	Trainee
	Trainee chemical engineer
	Trainee manager
	Training co-ordinator
	Training Co-ordinator Manufacture and Supply
	Training development officer
	Training supervisor
	Transport clerk
	Transport dispatcher

Group	Description
Office continued	Transport maintenance clerk
	Transport maintenance supervisor
	Transport Supervisor
	TUSA Engineer
	Utilities Technologist
	Vic/Tas Operations Manager
	WA country sales manager
	Watchman
	Works Engineer
	Works supervisor
	Workshop foreman
	Workshop supervisor
	Zone engineer
	Zone supervisor
Other Refinery	Advisory engineer
	Area A Assessor
	Area Supervisor
	Assistant boiler operator
	Assistant Charge Engineer
	Assistant Construction Manager
	Assistant Inspection engineer
	Assistant Instrument Foreman
	Assistant Operator
	Assistant to Planner
	Boardman
	Boiler Attendant
	Building Trades Foreman
	Buyer
	Carpenter
	Charge Engineer
	Chemicals process engineer
	Chief engineer (inspection)
	Chief Mechanical Engineer
	Clerk
	Commissioning supervisor
	Conservation Engineer
	Construction & Maintenance Manager
	contracts coordinator-distilation
	Controller
	Corrosion Engineer
	Design Draftsman
	Development Engineer
	Draftsman
	Electrical draftsman
	Electrical Fitter
	Electrical mechanic
	Electrician
	Electrician maintenance
	Energy & Conservation Engineer
	Engine driver
	Engineer
	Engineer 'B'

Group	Description
Other Refinery continued	Engineer supervisor
	Engineering draftsman
	Environmental engineer
	Field maintenance manager
	Firefighter
	Fireman (firefighter)
	Foreman
	Fork lift driver
	General hand
	Head Inspector
	Head operator
	HSE Advisor
	Inspection engineer
	Inspector
	Inspector - Construction
	Instrument fitter
	Instrument Foreman
	Instrument Mechanic
	Instrument mechanic/ technician
	Instrument Technician
	Instrument/electrical reliability engineer
	Labourer
	Leading hand instrument technician
	Maintenance cost analyst
	Maintenance Engineering Superintendent
	Maintenance Foreman (Relief)
	Maintenance technician
	mechanical engineer
	Mechanical Foreman
	Messenger
	Operator
	Operator/ Panelman
	Panel control technician
	Panel Operator
	Panelman
	Permit Liaison Officer
	Plant helper
	Plant inspector
	Process Operator
	Process technician
	Production operator
	Project Engineer
	Project inspector
	Project manager
	Public Affairs Officer
	Refinery Engineer
	Rigger
	Rigger/ Plant helper
	Safety assistant
	Safety man
	Safety officer
	Senior Head operator
	Senior machinery engineer

Group	Description
Other Refinery continued	Senior mechanical engineer
	Senior Mechanical Technician
	Senior Operator
	Senior Operator/ Panelman
	Senior plant inspector
	Senior process engineer
	Senior storeman
	Senior technologist
	Shift controller
	Storeman
	Storeman & Packer
	Stores Assistant
	Supervisor
	Tech support co-ordinator
	Technologist
	Technologist - Conservation
	Technologist - Environmental Affairs
	Trades assistant
	Trainee chemical engineer
	Trainee inspector
	Trainee Instrument Supervisor
	Trainee operator
	Training Manager
	Unit operator
	Utilities Operator
	Various Operations
	Watchman
	Weighbridge operator
	Workshop assessor
	Zone Engineer
Other Terminal	Accountant/clerk
	Administration Assist/ Sales Manager
	Assistant Installation Superintendent
	Assistant Superintendent
	Auto spare parts supervisor
	Aviation quality control officer
	Barge filler
	Bitumen & Grease Blender
	Bitumen operator
	Bitumen sprayer/driver
	Blender
	Blender (leading hand)
	Blender and filler
	Blender Storeman
	Boiler Attendant
	Boiler attendant (drum cleaning)
	Boiler attendant, plant helper
	Boiler operator
	Builder's Labourer
	Chief clerk
	Clerk
	Clerk stocks & dispatch

Group	Description
Other Terminal continued	Courier
	Depot Superintendent
	Dispatch clerk
	Dispatcher
	Draftsman
	Driver (Packaged)
	DRO Manager
	Drum filler/Spray painter
	EDP Clerk
	Engineering assistant
	Engineering maintenance supervisor
	Engineering Manager
	Engineering Officer
	Filler
	Foreman
	Foreman - Yard
	Fork Lift Driver
	Fork Lift Driver (Leading Hand)
	Fork lift driver, storeman
	Forklift driver
	Gardener
	Gate check clerk
	Gate staff
	Gatekeeper
	Grease filling
	Installation manager
	Installation Superintendent
	Installation Superintendent - Packages
	Installation supervisor
	Leading hand storeman
	Lube plant manager
	Lube Works Foreman
	Maintenance Foreman
	Material Issues Storeman (Leading Hand)
	Oil blender
	Operations Trainee
	Operator
	Packaged goods driver
	Painter/ signwriter
	Plant helper
	Process foreman
	Production control officer
	Programmer Scheduler
	Pumper Gauger
	Relief Clerk
	Relief installation officer
	Relief Storeman
	Relieving Officer
	Security watchman
	Senior Dispatch Clerk
	Senior Inventory clerk
	Shift supervisor
	Shipping manager

Group	Description
Other Terminal continued	Spray painter/Stenciller
	Stationary mailing clerk
	Stenciller
	Stocks supervisor
	Storeman
	Storeman & Packer
	Storeman Blender
	Storeman filler
	Stores Operative
	Superintendent CBP
	Supervisor
	Technical control officer
	Terminal Foreman
	Terminal manager
	Terminal Operator
	Tradesman's assistant
	Transport clerk
	Vic/Tas Operations Manager
	Warehouse supervisor
	Works supervisor
	Workshop foreman
	Yard foreman
	Yardman
Other Upstream	Apprentice Instrument Mechanic
	Camp Attendant
	Crane Operator
	Electrical technician
	Electrician
	Emergency and Systems Officer
	Emergency services electrician
	Fork lift driver
	Helicopter pilot
	Hot work supervisor
	Instrument Mechanic
	Instrument technician
	Materials clerk
	Mechanical consultant
	Painter
	Pipeline supervisor
	Plant operator
	Platform supervisor
	Process instrument mechanic
	Radio Operator
	Radio operator /first aid
	Radio operator/First Aid officer
	refueller/utilityman
	Safety supervisor
	Security Guard
	Shift foreman
	Storeman
	Technician
	Technician trainer

Group	Description
Other Upstream continued	Terminal Clerk
	Tradesman's (welder's) assistant
	Trainee Operator/ Utilityman
	Unit Controller
	utility maintenance
	Utility man
	Warehouse Clerk
	Wireline Assistant
Rail Car Loading	Bulk Supervisor
	Filler
	Gauger/storeman
	Gauger/storemen
	Leading Hand Storeman
	Operations Trainee
	Operator/Rail loader
	Pumper gauger
	Relief Storeman
	Storeman
	Storeman & packer
	Storeman filler
	Terminal Superintendent
Refinery Operations	Assistant Operator
	Control operator
	Electrician
	Head operator
	Labourer
	Operator
	Plant Attendant/ Control Operator
	process
	Process Operator
	Process technician
	Production operator
	refinery technician
	Relief Operator
	Rigger
	Senior Assistant Operator
	Senior Head Operator
	Senior operator
	Watchman
Road Tanker Driving	Depot Superintendent
	Driver
	Driver (all bulk products)
	Driver (Country) & yard foreman
	Driver (Diesel/Petrol/Avtur/Oil)
	Driver (Heating Oil)
	Driver (Motor Spirit)
	Driver (packaged)
	Driver (Packaged), storeman
	Driver - Coast
	Driver - Country
	Driver - fuel
	Driver - gas

Group	Description
Road Tanker Driving continued	Driver - LPG
	Driver - Lube Oil Tanker
	Driver - Petrol Tanker
	Driver - product
	Driver - white products
	Driver Transport
	Heating oil deliveries
	Operator
	Relief driver
	Relief driver & superintendent
	Tanker Driver
	Terminal Superintendent
Road Tanker Loading	Bulk Fuel Loader (Leading Hand)
	Clerk
	Filler
	Filler/Checker
	Gauger/Storeman
	Operations Trainee
	Operator
	Pumper Gauger
	Storeman
	Storeman/Drum filler
	Terminal Foreman
	Truck Filler
Supervision	Acting Controller
	Acting superintendent
	Area Supervisor
	Assistant Engineer
	Assistant Maintenance Engineer
	Assistant shift controller
	Assistant superintendent crafts
	Assistant terminal superintendent
	Aviation Supervisor
	Building Trades Supervisor
	Bulk movements supervisor
	Bulk Supervisor
	Chemicals process engineer
	Commissioning supervisor
	Construction Supervisor
	Controller
	Corrosion assistant
	Corrosion engineer
	Dept Superintendent
	Distribution manager
	Drivers supervisor
	Electrical supervisor
	Engineering Manager
	Field Maintenance Supervisor
	Field supervisor
	Fleet supervisor
	Fleet transport manager
	Instrument foreman

Group	Description
Supervision continued	Instrument Supervisor
	Maintenance and bulk operations superintendent
	Maintenance controller
	Maintenance engineer
	Maintenance superintendent
	Maintenance supervisor
	Maintenance/ Transport Manager
	Manager
	Operating Supervisor
	Operations Engineer
	Operations supervisor
	Orders & dispatch supervisor
	Planner Scheduler
	Plant supervisor
	Process engineer
	Production Supervisor
	Project electrical supervisor
	Project engineer (manufacturing)
	Project engineer supervisor
	Project Supervisor
	Relief supervisor
	Relief terminal officer
	Senior maintenance supervisor
	Senior Maintenance Supervisor - Instrument Electri
	Senior Maintenance Supervisor- Maintenance Service
	Senior Mechanical Technician
	Service Craft Supervisor
	Shift controller
	Shift foreman
	Shift supervisor
	Shift supervisor - Transport
	Superintendent
	Superintendent CBP
	Superintendent Marine Personnel and Cargoes
	Supervisor
	Supervisor Bulk Dispatch
	Supervisor Marine Personnel
	Terminal manager
	Terminal Superintendent
	Training supervisor
	Transport maintenance supervisor
	Transport Supervisor
	Workshop supervisor
	Zone engineer
	Zone supervisor

Group	Description
Tank Farm Operations	Assistant Installation Superintendent
	Assistant operator
	Assistant Superintendent
	Boiler attendant, plant helper
	Chief clerk
	Foreman
	Foreman - Bulk operations
	Gauger/Storeman
	Head operator
	Operations Trainee
	Operator
	Pipeline Attendant/ Dipper
	Pipeline operator
	Plant Helper
	Plant technician
	Process Operator
	Pumper Gauger
	Pumper Gauger / Clerk
	Pumpman
	Pumpman/ operator
	Relief Storeman
	Relief Superintendent
	Senior Operator
	Stock Clerk
	Storeman
	Storeman & packer
	Storeman – Bulk operations
	Storeman/Drum filler
	Supervisor
	Terminal Foreman
	Terminal manager
	Terminal operator
	Terminal Superintendent
	Trainee Operator
Upstream Operations	Drilling crewman
	Machine monitoring assistant technician
	Operator
	Pipeline technician
	Plant assistant
	Platform assistant
	Process Operator
	Production operator
	Production Supervisor
	Senior platform supervisor
Vehicle Maintenance	Apprentice Motor Mechanic
	Garage mechanic
	Mechanic
	Motor Mechanic
	Motor mechanic/fitter
	Motor vehicle inspector
	Trades assistant
	Truck mechanic

Group	Description
Wharf and Jetty Operations	Barge Master
	Bunkering Attendant
	Leading Hand Storeman
	Loading master
	Operations Trainee
	Operator
	Pumpman
	Relief Storeman
	Rigger(wharf)
	Storeman
	Storeman & packer
	Storeman/Drum filler
	Terminal manager
	Terminal operator
	Terminal Superintendent
	Trainee assistant operator
	Wharf operator

Appendix 5 Activity Groups

(Section extracted from Health Watch Report to ERDC 1998 [2])

This appendix gives details of the tasks carried out by workers in each of the activity groups. The tasks were identified as those where there was the possibility of exposure to benzene. The tasks about which information was sought at the relevant sites are underlined.

- **Aircraft Refuelling**

These workers refuelled aircraft at airports. In the 1950s, road tankers (<u>Tanker loading</u>) were filled with either avgas (aviation gasoline) or jet fuel (which contains no benzene) at bulk terminals, usually near the airports, and then fuelled aircraft from a position near the wing tanks. As the demand for jet fuel rose, hydrant systems were installed for delivery of jet fuel (but not avgas) and pipeline connections completed from either refineries or major terminals to airport bulk storage units. Most avgas deliveries were made by "over-wing" procedures. Refuellers have to be available when aircraft need their services, so they spend a significant portion of their time waiting in the terminal, perhaps doing paperwork. They also perform four other tasks: <u>Refuelling</u> (with avgas) itself; <u>Gauging</u>, checking bulk tank contents; <u>Sampling</u> i.e. drawing samples of fuel for various check tests and <u>Other</u> which includes waiting time, paperwork, filter changing and minor mechanical duties. Supervisors would have spent much more time on paperwork than refuellers.

- **Drum Filling**

This activity was usually executed at terminals, rarely at refineries or depots, and consisted mainly of the filling of 205 litre (44 gallon) drums with principally gasoline, diesel or other fuels and less often with minor quantities of solvents, including benzene at some terminals. At large terminals it was often a full-time activity, but as the size of the terminal fell and the distance from major cities rose, the activity became more part-time. The usual job title for workers doing filling was *Storeman and Packer*. At very small sites in country areas the terminal manager may have spent time filling drums. Millions of drums were filled in the 1950s, but the demand for heating and lighting kerosene has fallen and most fuels are delivered in bulk these days. <u>Filling</u> was carried out mainly by stub filling, with metered delivery and no vapour capture, with the filler standing at the fill-point. The second task (<u>Other</u>), involved assembly of drums for filling, spray painting (or other branding means) of drum head brands, loading of tray trucks for delivery. There was considerable overlap of staff with the next activity, particularly in non-metropolitan sites.

- **Drum Laundry and Preparation**

Post World War II steel shortages obliged petroleum companies to charge deposits on drums and to then clean and re-use them many times over. Returned drums were first inspected by eye at the open large bung-hole and either passed for draining and cleaning on the premises, or sent for restoration by external contractors. The other activities included stacking the drums before and after cleaning and also the actual cleaning operation, usually performed by inverting the drum over a spray head and spraying (usually) cold kerosene inside the drum, although some terminals used rumbling devices. The cleaning fluid was re-circulated for a considerable period before being disposed of by various means. After cleaning, drums were usually re-sprayed or touched up. There was considerable overlap of staff with Drum Filling and the operation often took place in the Drum Filling shed. The common job title for a worker in this area was also *Storeman and Packer*.

- **Fitting**

The main task of fitters, <u>Other</u>, is broadly working on all sorts of site equipment installation, maintenance and repair, opening and closing of pipes for turnarounds or shutdowns in refineries, blanking of product lines for both refineries and terminals, digging ditches for access to underground pipes, sewers etc. There were six specific tasks identified and assessed in the study. Ship loading or unloading (as distinct from barge operations) involving the connection of hoses between tanker ship manifolds and wharf pipelines and the subsequent opening and draining of the hoses particularly in the 1950s and 1960s. Chiksan arms, which did not require open draining, were introduced in the 1970s. The frequency and time spent on this task declined as pipelines were installed from refineries to major terminals. Barge Loading where fitters connected and disconnected hose pipes from bulk shore tanks to barges. With the exception of bunker fuel, which contains no benzene, barge loading was only carried out at Gore Bay. Products handled were crude, gasoline, other fuels and, rarely, solvents, including benzene. Gauging of bulk tanks, either onshore or in marine vessels, by checking the content levels with usually hand-held dip-tapes. Line Pigging, i.e., loading and unloading pigs (product separation, cleaning or scraping devices) into or out of product pipelines, usually by hand or with small mechanical assists. Rail Tank Car Cleaning involving minor repair work to valves etc., but not normally requiring confined space entry; this was a regular task at terminals until the early 1970s. Bulk Tank Cleaning involving opening and blanking of product lines and tank hatches and manhole covers, and actual tank cleaning on occasions (although contractors usually did this task after the mid-1960s). This might have been followed by repairs to tank floors etc., internal painting (usually done by specialist contractors), and then closing up after repairs and other works were completed. Although broadly carrying out the same activities, upstream, refinery and terminal fitters come into contact with a different mix of products.

- **Laboratory**

The tasks of these people varied extensively but four specific tasks were identified. Bench work where the main exposure to benzene arose in carrying out quality control test on products such as gasoline that contain benzene, for example, physical tests such as distillation, octane rating determinations (at refinery laboratories), analysis of reformate and specific tests on detergents etc. at a Detergent Alkylate Plant (DAP). Several analytical procedures in the 1950s and 1960s involved the use of benzene, but mainly as a reagent used in small amounts and handled in fume cupboards. There do not appear to have been many tests conducted on coal-derived crude benzene (BTX, approximately 70 percent benzene) except perhaps checking of the BTX used for tobacco spraying mainly in NSW, Queensland and northern Victoria, or as a gasoline additive, used occasionally by one company from the 1940s into the 1970s, and by another for the manufacture of refined grades of benzene, toluene and mixed xylenes. Sampling was often done by laboratory personnel. Before refineries were built in the early 1950s laboratory workers usually sampled gasoline from incoming tankers as well as routine tank farm sampling. Refinery laboratory workers sampled benzene containing product streams, originally from open lines, but after the 1970s, mostly from looped or closed lines, of which the latter involved lower exposure to vapours. Washing glassware may have utilised reformate (containing up to 12 percent benzene) into the 1950s and solvents such as light virgin naphtha (with approximately 1 percent of benzene) were in wide use after that time. The Other task included laboratory duties that did not normally result in exposure to benzene, e.g. paperwork, analysis of lubricating oils, research and development work.

- **Office**

This group covered a variety of office-based or off-site tasks held by subjects. Time spent on-site was allocated to the appropriate activity group. Activities done by workers at the Kwinana Nitrogen Company site or at Castrol sites were also included in this group.

- **Other Refinery**

This group included all refinery operators on units where no benzene was expected (Table 121). It also included workers who were not covered in other groups, for example, Electricians, Electrical Fitters, Electrical Technicians, Instrument Mechanics, Instrument Technicians, Assistant Instrument Foremen, Builder's Labourers, Trades Assistants and Riggers. White-collar workers, such as engineers, who spent some time on-site, had that portion of their work allocated to this activity group. Employees in this group attended to various in-line devices and processors, remote gauges, control room monitors and general electrical work. They were not usually exposed to more than refinery background vapour concentrations, because either lines were drained and purged before these workers were involved, or the lines were narrow gauge, releasing very small amounts of fluids. No specific tasks were identified.

- **Other Terminal**

This group included all terminal workers who were not covered in other groups, for example, lubricating oil blenders and fillers, packaged store operators, forklift drivers and carpenters. They were not normally in contact with benzene containing materials.

- **Other Upstream**

This group included all upstream workers who were not covered in other groups, for example, helicopter pilots, radio operators, instrument mechanics. They were not normally in contact with benzene containing materials.

- **Rail Car Loading**

This activity included the specific task of Loading of rail tank cars, usually of 45,500 litre (10,000 gallon) capacity, but with some smaller cars. The products loaded were usually gasoline and diesel, the proportion of gasoline being higher in southern states, but ranging from about 40 to 70 percent of total volume loaded. Rail tank cars were used more extensively in the 1950s to 1970s than later, when they were widely replaced by road tankers. Rail tank cars were usually loaded by spear or built-in tube fill, without any vapour capture and with volumes validated by dipstick. More recently, meter filling has been used at some sites. At a few sites, splash filling was used until about the 1960s, but none are currently loaded this way. Loaders usually stood either on the rail tank car or close by on gantries during the loading process, which was seldom automated to any extent. Loaders usually had other duties as well, such as drum filling, marshalling rail tank cars for hand over to railway employees, or general yard duties. No evidence was discovered of benzene being handled by rail. These workers may also be called *Storeman and Packer*.

- **Refinery Operations**

All operators on refinery units where benzene was found (Table 122) were categorised into Refinery Operations but allocated a base estimate specific to the unit. Dewatering, the first task is a minor one in terms of probable exposure and time, includes the discharging of water accumulated in vessels or tanks containing crude oil or product into open or closed drains. Gauging, the second task, meant the measurement of product in tanks by use of hand held dip tapes inserted through hatches on top of tanks, side gauges permanently mounted in tanks and read from the side of the tank in closed systems, or remote gauges, usually read from control rooms. Operators were involved in the Sampling of benzene containing product streams originally from open lines, but after the 1970s mostly from looped or closed lines, of which the latter involved lower exposure to vapours. Line Pigging has been in use since the mid-1950s and is used to keep lines clear of deposits or to separate different products during transfers from ships to storage tanks (so that a single line can be a multiple carrier). Pigs are mainly used on crude lines but may also be used on wharf lines from tankers to terminals. The Other task includes the remaining time on the refinery unit, in the control room, adjusting flows, operating pumps and lines, cleaning etc. For most operators the majority of the time will be spent on this task.

- **Road Tanker Driving**

The main task performed by Drivers which involved exposure was Tanker Loading. From the late 1940s, road tankers were almost always filled via a removable loading spear reaching to the tank floor or through an integrated fill tube. Bottom filling of tankers had been introduced at most terminals by the early 1980s. Vapour capture started with bottom loading and vapour recovery followed soon after. Manual operation of flow control valves was usual until the mid- to late-1950s when metered controls were gradually introduced. About the same time as bottom loading started, full computer operated metered delivery commenced. Until bottom loading, most drivers stood on a gantry at loading hatch level during loading and typically drivers stood upwind when possible. With bottom loading, drivers remained at ground level during loading. Work practices varied considerably from site to site. Some drivers carried gasoline only, others carried light fuels (white products, which could include solvents and benzene), others heavy fuels only, while at smaller terminals, they carried all fuels as required. Since the mid-1970s, the average number of loads per shift has risen from about 2-3 to 3-4 and hours of work have risen too. Tanker volumes have increased from 5,000 litres to 35,000 litres but pump capacity and hose diameters have increased so overall the time to load (and unload) have remained similar. Tanker Unloading was found to be fairly uniform in both practice and over time, with vapour from receiving vessels being diverted to remote release points. In the early years it was common to split loads of fuel, with road tankers delivering to multiple service stations. Load splitting decreased from the early 1950s when service stations became tied to a single company, and is now uncommon. The time to unload a tanker has thus fallen overall. The task Other did not normally lead to exposure and including driving, paper work, waiting time, wagon washing etc.

- **Road Tanker Loading**

Before 1975, dedicated loaders (*Storemen and Packers*) did all Tanker loading at some sites whilst at other sites *Drivers* have always loaded their own tankers. At a few sites a storemen and packer or a designated driver did the first loads for the day and then drivers loaded their own tankers for subsequent loads. After 1975, it was usual for all drivers to load their own tankers. The actual loading task was the same as in item 12, except that full-time loaders loaded many more tankers than did drivers. Loaders loaded all products, but gasoline predominated. Benzene was not usually loaded from main gantries. Other tasks of loaders usually included drum filling, tank farm tasks etc.

- **Supervision**

No specific tasks were identifiable, however, for most subjects a breakdown of time spent in the office and on-site was available. Supervisors did not usually work hands-on, except in rare emergencies. Where the hands-on time was not known (which was usually the case), they have been allocated the exposure corresponding to the workers being supervised for ten percent of the period when they were on site.

- **Tank Farm Operations**

The tasks here were Dewatering (item 11); Gauging (item 11); Line Pigging (item 11); Interceptor/Separator Cleaning in terminals usually involved the pumping out and /or digging out of residues from triple interceptor pits, while in refineries larger API separators received attention. Since about the 1960s, contractors have mainly performed this work. Sampling (item 11); before the Australian refineries came on stream in the mid-1950s, more sampling was done during discharge of imported gasoline etc. from tankers to terminal bulk tanks. Tank Cleaning, very similar to item 4. The Other task included pump and valve operations, pipe line operation, minor maintenance and general yard duties. At smaller locations these operators may also carry out drum filling but this activity was usually recorded separately for these workers. The term “off-sites” was used in several refineries to include the tank farm.

- **Upstream Operations**

This included production workers offshore and onshore workers in gas and crude plants. The tasks identified here are Dewatering (item 11), Gauging (item 11), Interceptor Cleaning (item 15), Line Pigging (item 11), Sampling (item 11), Tank Cleaning (item 15). The Other task included pump and valve operations, pipeline operation, minor maintenance, general yard duties.

- **Vehicle Maintenance**

A mechanic's work included work done on site vehicles, the engine and the tanker and pumps, mainly in a naturally ventilated workshop. Vehicles in the 1950s were roughly half gasoline driven and half diesel, but by the 1970s, truck fleets were almost all diesel, except for forklift trucks, which were either diesel or LPG powered. Traditionally, mechanics used gasoline for cleaning parts and on occasions, overalls, but this practice was gradually discouraged and by the early 1980s had practically ceased. The tasks here were Use of gasoline as a solvent and all Other work.

- **Wharf and Jetty Operations**

Barge Loading, other than of bunker fuel for ships, was carried out at Gore Bay for crude and gasoline, and at Matraville for receipt of crude BTX from non-petroleum sources. It was usually executed using hose and pipeline connections without vapour control. Dipping and Gauging Ships was very similar to those tasks described in item 11. Line Pigging (item 11). Product Load out/receipt involved principally the connection of hoses to ships' manifolds, draining of hoses after discharge was completed and general clean up after the ship had gone. The introduction of Chiksan arms (item 4) probably reduced wharf and jetty exposure. Sampling (item 11). Tank Inspection meant ensuring the ships' tanks were empty after discharge and clean before product loading. This occasionally required tank entry after appropriate air purging. Other tasks included time spent on the wharf or jetty other that that allocated to the above tasks e.g. paperwork, bunkering ships etc. For many workers this was a part time activity, carried out when ships arrived, and they spent the rest of their time in the terminal loading rail tank cars, drum filling etc.

- **Unclassified**

These activities were not identifiable from the information provided or obtained.

Appendix 6 Tasks Associated with each Activity Group

(Section extracted from Health Watch Report to ERDC 1998 [2])

Group	Task
Aircraft Refuelling	Gauging Refuelling Sampling Tanker loading Other
Drum Filling	Filling Other
Drum Laundry & Preparation	Other
Fitting	Barge loading Gauging Jetty work Line pigging Rail car cleaning Tank cleaning Other
Laboratory	Sampling Washing glassware Other
Office	Other Sampling
Other Refinery	Other
Other Terminal	Other
Other Upstream	Other
Rail Car Loading	Rail car loading
Refinery Operations	Dewatering Gauging Line pigging Sampling Separator cleaning Tank cleaning Other
Road Tanker Driving	Tanker loading Other
Road Tanker Loading	Tanker loading Other

Group	Task
Supervision	Gauging Mechanical work Product load out/receipt Rail car loading Sampling Tank inspection Tanker loading Other
Tank Farm Operations	Dewatering Gauging Interceptor cleaning Line pigging Sampling Tank cleaning Other
Unclassified	Other
Upstream Operations	Dewatering Gauging Interceptor cleaning Line pigging Sampling Tank cleaning Other
Vehicle Maintenance	Mechanical work Other
Wharf and Jetty Operations	Barge loading Dipping and gauging ships Line pigging Product load out/receipt Sampling Tank inspection Other

Appendix 7 Exposure Definitions

(Section extracted from Health Watch Report to ERDC 1998 [(2)])

Not Occupationally Exposed (NE)

In a modern community such as that virtually all members of the Health Watch cohort live and work in, everyone is exposed to benzene. It is present in urban and rural air, likely to be encountered by anyone that uses and fuels a motor car for private or commercial use and it is a constituent of tobacco smoke.

For the purpose of this exposure assessment the term “not exposed” will apply to the work task rather than to the person. Previous jobs, hobbies, smoking and other life style confounders therefore, will not be considered here.

Any task will be considered to be unexposed to benzene if any of the following conditions apply:

1. Takes place at a site remote from handling, e.g. an office in the city.
2. Takes place in a building which is remote from sources of exposure and the worker does not regularly enter an area where products with more than 0.1 percent benzene are handled, e.g. boiler houses, lubricating oil blending plants.
3. Takes place in a centralised control room with full air conditioning, including scrubbers.

Periods spent in small control rooms next to the plant will be considered to be exposed at a background level for the plant, unless specific measurements of exposure are available.

Background Exposure (B)

Tasks which incur only secondary or bystander (not hands-on) exposure to benzene will be classed as having background exposure. The actual concentration used in the exposure assessment will vary from site to site but will be set at a level recorded in environmental measurements. Background exposure concentrations will normally be higher than typical urban air concentrations.

Exposed (E)

Likely to have inhaled some benzene or had skin contact with benzene containing materials in normal day to day operations.

Total Hydrocarbon Measurement

There was no uniformity in carbon range or in analytical methods and therefore the total hydrocarbon measurements cannot be compared between companies. When occupational hygiene monitoring became more common, it was unlikely that total hydrocarbon measurements were made where no benzene exposure was anticipated. However where benzene exposure was anticipated specific benzene measurements were taken.

Appendix 8 Refinery Units categorised by Benzene Exposure

(Section extracted from Health Watch Report to ERDC 1998 (2))

Table 121: Refinery Units at which Subjects Worked with no Benzene Exposure Likely

Unit†	Site
Alkylation	Altona, Bulwer Island, Corio, Kwinana, Lytton
Bitumen (Cutbacks in kerosene or jet fuel only)	Altona, Bulwer Island, Clyde
Catalytic hydrogen desulphuriser (CHD)	Altona
Copper chloride	Kwinana
Cryogenic liquids recovery (CLR)	Altona
Diesel hydro treating unit (DHTU)	Kurnell
Ethylene production	Clyde
Fluid catalytic cracker gastail (FCCU gastail)	Lytton
Feed preparation (Feed prep)	Altona
Ferrofiner	Kwinana
Furfural solvent extraction (FRU)	Corio, Kurnell, Kwinana
Hydrodesulphuriser (HDS)	Clyde
Hydrex unit	Corio
Hydrofiner	Kwinana
Iso-siv (Aromatics Recovery)	Kurnell
Lubricating oil manufacturing plant	Corio, Kurnell, Kwinana
Movements and Storage	Bulwer Island
Polymerisation	Corio, Kurnell, Kwinana, Lytton
Polypropylene	Clyde, Corio,
Propane deasphalting (PDU)	Corio, Kurnell, Kwinana
Reduced crude unit (RCU)	Kwinana
Saturated gas plant (Altona)	Altona
Solvent dewax (MEK unit)	Corio, Kurnell, Kwinana
Sulphur recovery unit (SRU)	Altona, Kurnell, Kwinana
TCC heaters and structure	Altona
Treating splitting unit (TSU, propane/propylene separator)	Kurnell
Vacuum distillation unit, high vacuum unit (VDU)	Corio, Kwinana, Lytton

† Only refinery units where subjects had worked are listed

Table 122: Refinery Units at which Subjects Worked with Possible Exposure to Benzene

Type of Unit	Unit†	Site
Catalytic Crackers	Catalytic cracking unit (CCU)	Clyde, Corio, Kwinana
	Fluidised catalytic cracking unit (FCCU)	Kurnell, Lytton
	Thermofor catalytic cracker (TCC)	Altona*
Crude Units	Crude distillation unit (CDU)	Altona*, Bulwer Island, Clyde, Corio, Kurnell, Kwinana, Lytton, Matraville
Reformers	Ultraformer	Bulwer Island
	Platinum reformer (Platformer)	Clyde, Corio, Altona*
	Catalytic Reformer (Cat reformer)	Kwinana
	Rheniformer (Rhenium catalytic reforming unit)	Kurnell
Other	Detergent Alkylate plant (DAP)	Corio
	Mogas solutiser	Altona
	Mogas blending	Altona, Corio
	Rotating (around several units)	Bulwer Island, Kurnell, Port Stanvac, Westernport
	Solvents	Lytton, Clyde
	Sour Water	Kurnell

† Only refinery units where subjects had worked are listed

* Some subjects from Altona refinery indicated that they had worked in Area 2 or Area 3. Area 2 includes CDU and TCC units. Area 3 includes CDU, reformer and solutiser units

Appendix 9 Initial Site Assessment Form

Name of Site: ....

Name of Contact (to arrange a visit/contact for more information):

....

Position: ....

Telephone Number: ....

Date Site opened: ....

Current plan of the site available? Yes / No Past plans available? Yes / No

		Date Started	Date Stopped
Road Tanker loading	Top splash load, open hatch		
	Top splash load, Camlock fitting		
	Spear submerged filling		
	Bottom load without vapour capture		
	Bottom load with vapour capture		
	Bottom load with vapour capture & recovery		
Rail filling gantry	Top splash load, open hatch		
	Top splash load, Camlock fitting		
	Spear submerged filling		
Barge Filling	Any method		
Tanker loading	Any method		
Drum filling	Petrol		
	Benzene/BTX		
	Other solvent		
	Other (specify)		
	No vapour capture		
	Vapour capture with removal by displacement		
	Vapour capture with mechanical removal		
Manufacturing operations	Bitumen cutbacks with solvents		
	Benzene in agricultural or similar products		
	Benzene in solvents or degreasers		
Tank Farm	Please indicate proportion of main products.		
	Mogas		
	Avgas		
	BTX or other aromatics		
	Solvents		
	Kerosenes		
	Crude Oil		
	Refinery Intermediates (e.g. topped crude or reformates)		

Appendix 10 Algorithm for Exposure Assessment

(Section extracted and edited from Health Watch Report to ERDC 1998 [2])

The Task Estimate (TE) is the average benzene concentration (in ppm) that a subject would be exposed to while doing that task and was given by:

$$TE_{ijk} = BE \times K_l \times \ldots\ldots \times K_s, \qquad \text{(Equation 1)}$$

where:

TE_{ijk} =	Task Estimate for task *i* of activity *j* of job *k* (in ppm)
BE =	Base Estimate for the task. This was the average benzene exposure (in ppm) for the period that the task was carried out.
K_l to K_s =	EMs for adjusting Base Estimate to exposure scenario for task *i* of activity *j* of job *k*`1

The Activity Estimate (AE) is the average benzene concentration (in ppm) that a subject would be exposed to while doing that activity. It was calculated as a time-weighted average of the Task Estimates and was given by:

$$AE_{jk} = \sum_{i=1}^{n_{jk}} TE_{ijk} \times (T_{ijk} / A_{jk}), \qquad \text{(Equation 2)}$$

where

AE_{jk} =	Activity Estimate for the activity *j* of job *k* (in ppm)
T_{ijk} =	Average time in hours per week on task *i* where there were n_{jk} tasks for activity *j* of job *k*
A_{jk} =	Average time in hours per week on activity *j* of job *k*

A similar calculation was done for the Workplace Estimate (WE) of exposure. This was the average benzene concentration (in ppm) that a subject would be exposed to during the course of his job. The Workplace Estimate was normalised to a 35-hour week. It was calculated as a time-weighted average of the individual Activity Estimates.

The WE for the job *k* was given by:

$$WE_k = \sum_{j=1}^{n_k} AE_{jk} \times (A_{jk}/35) = \sum_{j=1}^{n_k}\sum_{i=1}^{n_{jk}} TE_{ijk} \times (T_{ijk}/35), \qquad \text{(Equation 3)}$$

where

WE_k =	Workplace Estimate of exposure for the job *k* (in ppm)
n_k =	Number of activities for job *k*

A new job starts when the mix of activities or tasks changes or when an EM changes. Where an activity could not easily be split into activities and tasks, e.g. the job title *Fitter*, the job was considered to have only one activity and one task and the Workplace Estimate was the Task Estimate normalised to 35 hours. For each subject an individual Cumulative Estimate was then constructed showing the exposure associated with each of the job titles held by the subject as recorded in the job history.

The Cumulative Estimate (CE) of benzene exposure for a subject was given by

$$CE = \sum_{k=1}^{n} (WE_k \times Y_k) \text{,} \qquad \text{(Equation 4)}$$

where

$CE =$	Cumulative Estimate of a subject's benzene exposure (in ppm-years)
$WE_k =$	Workplace Estimate of exposure during the job *k* performed by the subject.
$Y_k =$	Years spent in job *k*
$n =$	Total number of jobs for this subject

This model averages all exposures making it appear that all days have the same exposure. It can be used to generate, on an individual basis, cumulative exposure in ppm-years, average intensity of exposure by dividing the summed ppm-years by the period of work in the industry. Intensity of maximally exposed or longest held job. It does not identify individuals with occasional high exposures which would not raise their average exposure.

A Worked Example of the Estimation Process

This example is taken from [(2)] was prepared by Adams and amended by Glass.

As an example of how the estimation process works consider a subject who was a driver for ten years and then became a supervisor at a terminal for a further two years. When working as a driver he spent on average 5 hours loading and 40 hours waiting, driving and unloading per 45 hour week. The terminal information indicated that the benzene content of the gasoline carried was 2.5 percent and 75 percent of loads were gasoline.

This job comprised of one activity *Road Tanker Driving* and two tasks *Tanker Loading* and *Driving and Unloading*. The Base Estimate for the *Tanker Loading* task was 1.76 ppm when the benzene content of the gasoline was 3.0 percent and 100 percent of loads were gasoline. The Base Estimate for *Driving and Unloading was* 0.16 ppm. The Task Estimates were therefore, (using Equation 1):

$$TE_{Tanker\ Loading} = 1.76 \times (2.5/3) \times (75/100) = 1.1\ ppm$$

and

$$TE_{Driving\ and\ Unloading} = 0.16\ ppm$$

From Equation 2 the Activity Estimate for this activity was:

$$AE_{Road\ Tanker\ Driving} = 1.1 \times (5/45) + 0.16 \times (40/45) = 0.26\ ppm$$

Since there was only one activity, the Workplace Estimate for the driver job was the Activity Estimate normalised to 35 hours per week (Equation 3):

$$WE_{Driver} = 0.26 \times (45/35) = 1.1 \times (5/35) + 0.16 \times (40/35) = 0.33ppm$$

Once he became a supervisor he spent 25 hours a week in the office and 20 hours out on site supervising the loading of rail cars. No breakdown was given of the time he spent out on site with hands-on involvement in rail car loading. Where the amount of time spent hands-on was not known, the arbitrary figure of ten percent of the time for that activity was allocated to the hands-on task.

This job was considered to have two activities *Office* and *Supervision*. The *Office* activity had just one task *Other*. Since the activity out on site involved supervising the loading of rail cars then the

Supervision activity comprised of two tasks *Rail Car Loading* and *Other*. The proportion of time spent hands-on was attributed to the *Rail Car Loading* task and the rest to the *Other* task.

The BE for the *Other* task in the *Office* activity was the urban background BE of 0.005 ppm. The BE for the *Rail Car Loading* task was estimated as 3.52 ppm where the benzene content of the gasoline carried was 3.0 percent and 100 percent of loads were gasoline. Since no breakdown of the time out on site was given it was assumed that there was 2 hours (10 percent of 20 hours) of hands-on involvement. The appropriate BE for the *Other* task in the *Supervision* activity was the *Terminal Background* BE. This was 0.14 ppm. Thus, from Equation 2,

$$AE_{Office} = TE_{Office} = 0.005\ ppm$$

and

$$AE_{Supervision} = 0.14 \times (18/20) + 3.52 \times (2/20) = 0.48\ ppm$$

The Workplace Estimate for the supervisor job was (from Equation 3):

$$WE_{Supervisor} = 0.005 \times (25/35) + 0.48 \times (20/35) = 0.28\ ppm$$

For this subject who spent ten years as a driver and then two years as a supervisor, the Cumulative Estimate of benzene exposure was obtained from Equation 4:

$$CE = (10 \times 0.23) + (2 \times 0.28) = 2.9\ ppm\text{–}years$$

Appendix 11 Criteria for Measurement Data to be Used for a Base Estimate

(Section extracted from Health Watch Report to ERDC 1998 [(2)])

The monitoring data used to generate the base estimates had been gathered from a number of sources, by a number of methods and by a number of different people and companies. No data had been collected solely for epidemiological purposes. For this reason the data quality was critically examined and compared to criteria for acceptability of data.

The data was classed as acceptable if it contained the following information:

The job title of worker monitored.

The tasks performed during monitoring, including materials handled.

Job site/location during monitoring including inside/outside if appropriate.

Control technology in use, e.g. local exhaust ventilation (LEV) or personal protective equipment (PPE).

Date to within one year.

Duration of monitoring and relationship to whole period of work.

Monitoring methods.

Results, including units and limits of detection, for benzene and whether this was for a specific period or a time-weighted average (TWA) normalised to eight hours.

An indication of whether the results were typical for that job or task or covered abnormal situations e.g. spills, i.e. reason for the sampling, routine, special case etc.

A sample identifier in case follow up was needed.

The following information was also of interest but its absence did not preclude the use of the data:

Worker identification to show where there have been repeated samples on the same person.

Sample times to identify where samples have been taken sequentially.

The data was classed as unacceptable if it did not contain adequate information on the monitoring method used; no units were given for the measurements; the year in which the measurements were made was not stated; there was little or no detail of the tasks monitored; or there was no information on whether the exposure was typical for the work or why the measurements were made.

Data that fell between these criteria was used where there was no other available for that task.

Incomplete data were checked against records or with the company occupational hygienist that provided the data, or in some cases with the site information gathered during the site interviews e.g. technology in use. The following information was not always provided with the data but was identified by contact with the company occupational hygienist for some companies: the limit of detection; the technology in use (e.g. spear filling); the products being handled; and whether the results were typical for the site. Missing information was identified where possible and inserted into the data. If the information could not be established, the data were discarded.

Appendix 12 Additional Exposure Data

Methods

A series of occupational hygiene surveys were carried out for benzene exposure and environmental air concentrations in various terminals and refinery sites. Personal and environmental sampling was performed using thermally desorbable adsorbent tubes packed with graphitised Tenax® and carbon molecular sieve. Short term benzene exposures were monitored with the thermally desorbable tubes and a MicroTIP® photoionisation detector was used to investigate patterns of short term hydrocarbon exposure.

Sampling

Sampling was carried out using SKC multi-range sampling pumps at calibrated flow rates of about 50 mL per minute. The pumps and sampling trains were calibrated at the beginning and end of each sampling period using an electronic soap bubble flow meter (Gilson Gilibrator).

Analysis

The samples were analysed by gas chromatography - flame ionisation detector after two stage thermal desorption with a Perkin-Elmer ATD 50®. The first stage of desorption occurred at 250ºC for 20 minutes (box (valve and transfer line) 150C) and the cold trap was held at minus 30ºC. After first stage desorption the trap was heated to 230ºC and flushed via a heated transfer line to the gas chromatograph (Perkin Elmer PE 8500). Twin chromatographic columns were connected to the inlet via an input splitter. A polar column (SGE BPX5 25m, 0.22mm ID 0.25µm film thickness) was used in parallel with a non polar column (SGE BPX70 25m, 0.22mm ID 0.25µm film thickness) at a head pressure 100 KPa Helium. The chromatographic temperature profile was: initial 33ºC for 0.5 min, ramp at 30ºC / min to 200ºC, hold at 200ºC for 15 min. The detectors were two flame ionisation detectors held at 260ºC. The detection limits for benzene were as follows:

- Personal samples (split ratio 160 : 1) 1.2 microgram per tube.
- Environmental (no split) 0.006 microgram per tube. The lower limit of quantitation on a typical 20 Litre air sample was better than 0.001 ppm.

The MicroTIP intrinsically safe photoionisation detector was provide by Shell Services International. The instrument was calibrated against a standard atmosphere hydrocarbon mix prepared in a Teflon bag by micro syringe injection and a calibration curve was produced.

Results

The results of the additional monitoring, including some that was carried out in 1998, are summarised in Table 123.

In most cases the results provided reasonable validation for the existing BE values. In some cases there were differences that could be explained by technology changes, for example the rail car loading that was investigated involved bottom loading with vapour recovery and exposures were minimal, whereas previous values from which the BEs were derived were for older technology without vapour recovery.

Table 123: Results of Exposure Monitoring for Validation Data

	Product	Technology	n[43]	BE ppm	Newly acquired data			
					mean	range	n	Comments
Office	-	-	-	0.001	<0.001	<0.001	4	Original BE based on urban air
Canteen rooms	-	-	-	NA	0.002	<0.001 - 0.007	3	Work clothes, non smoking.
Refinery Background	-	-	277	0.07	0.025	0.008 - 0.059	3	Most of the original data was below detection limits
Barge Loading	Gasoline	Flexible hose barge loading	20	2.21	NA	NA	-	No additional data was obtained
Dewatering	Gasoline	Open drain dewatering	1 (4)	0.63	0.6	0.01 - 1.05	4	Occurred along with other duties, variable
Separator Skimming		Separator cleaning	14	0.12	0.08	0.0 - 0.16	4	Highly variable
Interceptor Cleaning		Interceptor cleaning	-	0.12	0.3	0.15-1.3	12	Gully suction -Interceptors, pits and oil catchers
Drum Fill: Stub, Open	Gasoline	Stub/spear no LEV open fill	106	3.52	-	-	8	Based on simulation with MEK, stub increases concentrations by about 50%
Drum: Stub, Enclosed	Gasoline	Stub no LEV enclosed fill	18	4.69	-	-	-	No example found
Drum Filling: Stub, LEV	Gasoline	Stub, LEV	24	1.55	1.4	0.6 - 1.5	10	Mostly gasoline and avgas
Drum Preparation		No technology	8	0.14	0.11	0.1 - 0.6	4	General area samples
Drum Laundry		No technology	4	0.39	0.2	0.1 - 0.6	4	General area samples
Mogas Blending		No technology	11	0.42	-	-	-	No additional data
Gauging	Gasoline	Dip tape gauging	1	4.20	0.3	0.1 - 1.0	4	8 hour - side gauge mostly mixed duties inc sampling
Sampling	Gasoline	Open sampling	2 (?)	0.67	0.4	0.04 - 1.1	29	Products included avgas, Optimax and unleaded
Lab Washing Glassware	X55	Solvent washing	2	0.40	-	-	-	Pending
Mechanic		Non-gasoline solvent	7 (100)	0.33	-	-	-	No additional data collected
Ship Dip/Gauge	Gasoline	Dip tape, hatch	4 (10)	5.41	3.9	0.0 - 4.5	4	Ship loading, gauging etc.

[43] Numbers in brackets indicate data from the literature

Table 123 continued

	Product	Technology	n[44]	BE ppm	Newly acquired data			
					mean	range	n	Comments
Tank Cleaning Crude	Crude	Gas test, scrape & hose	2	2.01	0.3	0.0 - 1.0	4	Crude tank cleaning etc.
Tank Test Crude	Crude	Gas test	12	0.30	0.0	0.0 - 0.07	4	Stand-by person and area samples
Tank Cleaning Gasoline	Gasoline	Gas test, scrape & hose	46	0.15	-	-	4	Results pending
Terminal Fitter		No technology	10	0.67	-	-	-	No additional data
Refinery Fitter		No technology		0.38	0.05	0 - 0.1	7	Variable job
Rail Car Loading	Gasoline	Fill tube/spear	179	3.77	-	-	-	No data available to separate fill tube/spear and dipstick/metered
Rail Car Loading	Gasoline	Bottom loading with vapour recovery	179	-	0.0	0.0 - 0.01	4	Outdoor work
Refuelling with Avgas	Avgas	Over-wing refuelling	9	1.65	-	-	-	No additional data collected
Road Tanker Load Bottom	Gasoline	Bottom loading,	31	0.55	-	-	-	Data pending
Road Tanker Load Top	Gasoline	Fill tube/spear	68	1.76	-	-	-	Data pending

[44] Numbers in brackets indicate data from the literature

Appendix 13 Exposure Modifying Factors Considered for Inclusion in this Study

(Section extracted and edited from Health Watch Report to ERDC 1998 (2))

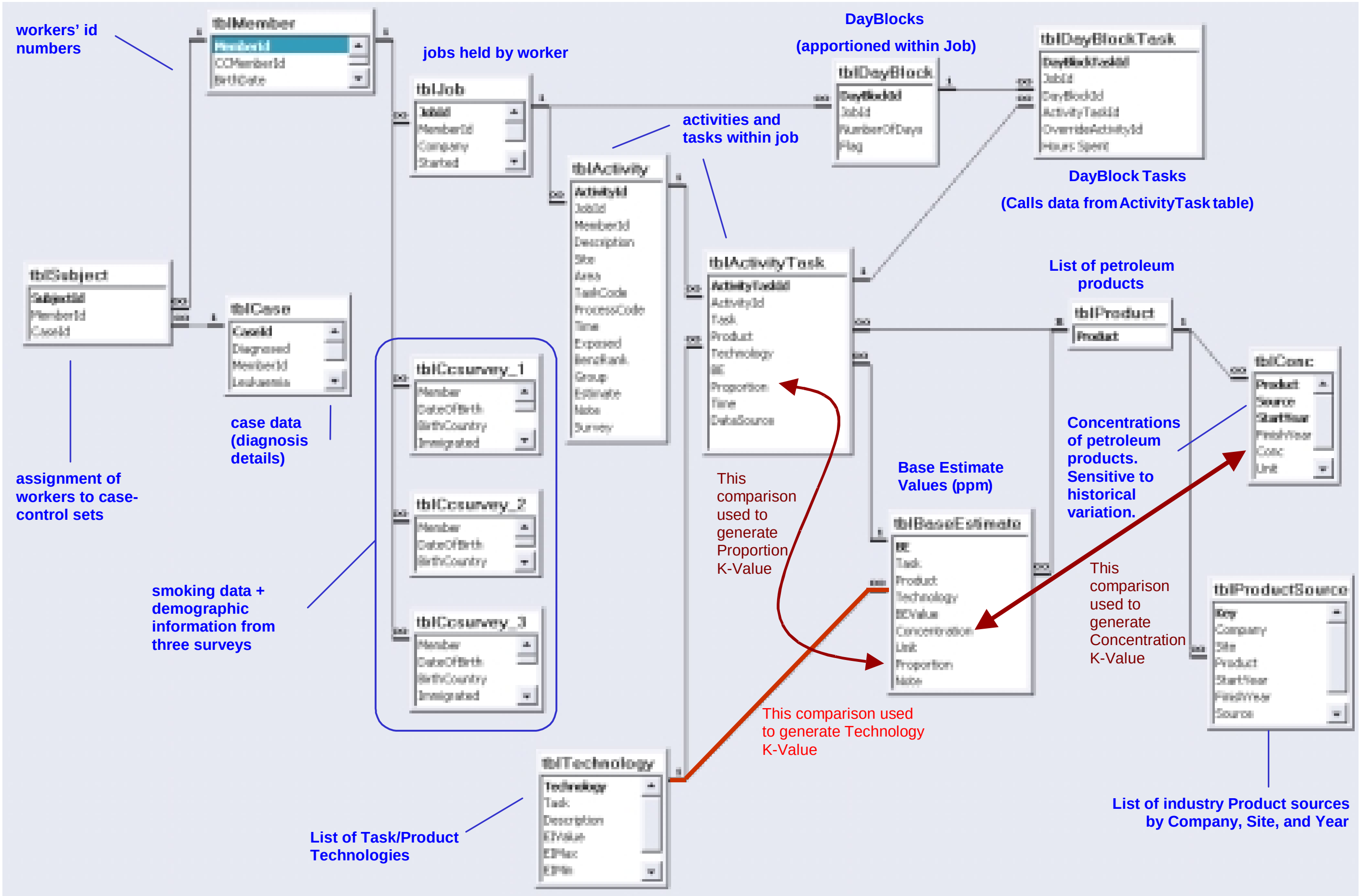
Modifier Category	Exposure Modifiers Considered
Workplace	Production and emission control technology, other than ventilation Extent of the system's enclosure, types of handling systems e.g. bottom loading, vapour recovery, degree of automation # Reliability, whether controls were in place and in use and effective Incident frequency and extent
	Volumes (rate and quantity) of material handled and percentage losses as fugitive emissions rather than spills #
	Task layout, distance to source of exposure # [45]
	Other site emission sources and geometry with respect to specific k
	Regulations affecting exposure #
Task	Length of time spent on the task * # [46] Task frequency (may be less than once a day.) Task duration. Other tasks carried out. Significant periods of overtime or normal working days longer than 8 hours.
	Materials handled * #
	Type of work clothing, RPE and gloves worn
	Work practices specific to that site including attitude to health and safety issues
	Cleaning methods and materials used on self, plant and tools # [47]
Environment	<u>Outside jobs</u> Wind direction and variability Wind strength and variability Temperature and variability * Background i.e. urban/rural Seasonal changes e.g. to clothing, PPE
	<u>Inside jobs</u> Ventilation type and efficacy * # Temperature and variability. Seasonal changes e.g. to ventilation, clothing, PPE.
Materials	Volatility of materials (Reid Vapour Pressure for gasoline) *
	Benzene content of materials * #
	Composition changes, time, season, region #

* Indicates EMs that proved practicable for use in the IOL study model

# Indicates EMs used in this study

[45] EM used for laboratory, drum filling and drum laundry workers only
[46] This was considered separately from the EMs in the algorithm but it was included for the sake of completeness.
[47] EM used for laboratory workers, mechanics and fitters only

Appendix 14 Diagram of the Relationships in the Database



Appendix 15 Specific Comments on the Base Estimate Calculation

Airport Background BE 0.08 ppm

A Base Estimate of 0.08 ppm was used for work on the tarmac not involving avgas. The samples used in the calculation were from refuelling aircraft with jet fuel or with avgas containing no benzene. The samples from Airport D showed significantly higher benzene exposure levels than those observed at the other sites. Exposures at most of the other sites were below the limits of detection.

The values for Airport D and two from Airport B were from short-term samples (80 to 95 minutes) and were from monitoring only during peak refuelling time. Consequently they were not included in the BE. The other samples were all over five hours in duration. The BE was based on relatively small number of data points, n=40. The measured exposure to benzene during refuelling with jet fuel may have resulted from jet engine exhaust gases or from vehicle emissions.

Barge Loading BE 2.21 ppm

All the data, n=20, used in the BE of 2.21 ppm were from 1982 and came from the one site – the only place where gasoline or crude was loaded onto barges in Australia. The exposures were relatively high and had a log-normal distribution. The data included exposures for the men on the barge and on the wharf. Barge exposure was generally much higher than wharf exposure but the men could do either job, so a single BE was generated using all the data.

Catalytic Cracking Unit (CCU) BE 0.16 ppm

The *CCU Operator* BE was 0.16 ppm. Data of less than 180 minutes duration were excluded from the calculation of this BE. The majority (287 of 295) of the exposure data came from one refinery. The exposure data for the CCU operators at Refinery F were significantly higher than that of CCU operators from other sites. These data were gathered during a shut down and steam out and so were not typical of normal exposure. There were only seven samples from Refinery F and the high mean exposure value is mainly driven by one very high value. Hence the Refinery F data were excluded from the analysis. There are only two types of catalytic cracking units used in Australia and their operations are very similar so that it was reasonable to assume that an operator's exposure would be similar between sites (Ward personal communication). The data were heavily censored, and probably have a log-normal distribution above 0.1 ppm (exp. -2.3 observed value), where the half limit of detection (0.05 ppm) has been substituted (-3 observed value).

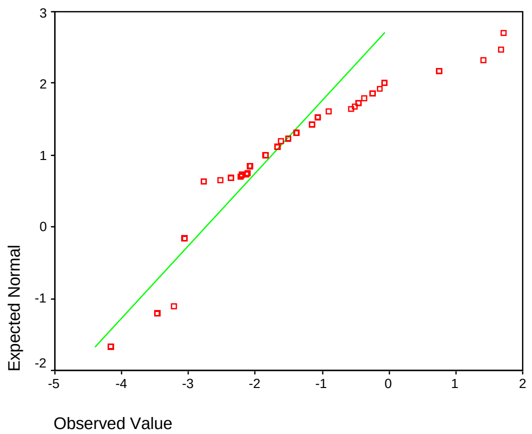


Figure 69: *CCU Operator* BE Data
Normal Q-Q plot log Benzene Concentration for all Refineries Combined [48]

[48] In a normalised Q-Q plot, data are ordered and the expected value of each point calculated from its quantile position, assuming the mean and standard deviation of the data set. If the distribution is normal, the data fall on a straight diagonal line.

Crude Distillation Unit (CDU) *BE 0.11 ppm*

The data were pooled from all sites to generate this BE of 0.11 ppm, n=404. Data of less than 180 minutes duration were excluded. Statistical analysis showed that there was no reason to believe that the exposures were different between sites. Analysis by year for the sites with the majority of the data showed that exposure did not appear to have changed significantly. Without the half limit of detection values (below Observed Value -3, on the Q-Q plot) the exposure distribution would probably have been log-normal.

The job grades were not supplied with some of the data and the job titles varied between sites, so development of separate BEs for operator and head operator was not possible. For Area 2 at Refinery A, where the refinery operators dealt with a number of units, a mean of the *CCU Operator* and *CDU Operator* BEs was used.

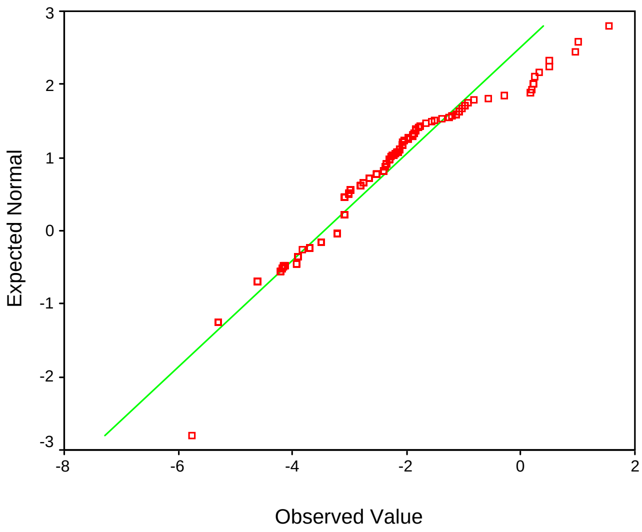


Figure 70: *CDU Operator* BE Data
Normal Q-Q plot log benzene concentration data all refineries combined

Detergent Alkylate Plant (DAP)

BEs: Op. pre 1989 1.86 ppm; Head Op. pre 1989 0.74 ppm; Maintenance 1.02 ppm.

The DAP was commissioned at Refinery D in 1961, it is the only Australian unit of this kind. From 1981 onwards there was extensive monitoring of operators and head operators in the DAP. Some monitoring of maintenance workers in the DAP was also carried out.

There were 354 data points for the job title *DAP Operator* and 125 data points for the job title *DAP Head Operator* that were sufficiently well characterised for BE calculation purposes. Measurements of less than 180 minutes duration were excluded and an outlier of 174 ppm was also excluded on the basis that this was probably a contaminated sample. Twenty data points were excluded because there was no job title associated with them. Remedial work to reduce exposures was carried out on the DAP in 1989. This included the introduction of a pipeline to bring the benzene directly from the jetty to the unit. Analysis of the data grouped into pre and post 1989, showed that exposures were lower for both operators and head operators after 1989 when the upgrade occurred. There were also significant differences in exposures between operators and head operators. The exposure data were log-normally distributed.

Significant work was put in to ensure that the data were correctly ascribed to a specific job title. Early in the examination of the data it was clear that some data with the job title “maintenance” were samples taken on men who at other times were described as operators or head operators. The jobs and names were checked with personnel and only the data that were definitely associated with a job title in normal operation, were used to generate the BE. In discussion with the hygienists it was decided that the workers had described the plant conditions rather than the job. The term maintenance meant that during the survey the plant had been undergoing maintenance and the men were not carrying out normal duties but maintenance type duties.

The data for operators before 1989 were used to generate a time-specific BE of 1.86 ppm for *DAP Operators*. This BE was used in the calculation of exposure estimates for a supervisor in the control room and for a subject who worked in an office close to the unit for a considerable period. A separate BE was generated for the *DAP Maintenance* workers 1.02 ppm. This was based on 27 data points.

A BE of 0.74 ppm was derived for the job title *DAP Head Operator* for the period pre-1989. This was calculated using the data points for head operator from 1981 to 1989.

These BEs do not take into account the use of respiratory protective equipment. The information supplied was that operators wore full respiratory protection when handling the HF catalyst. During normal operations, respiratory protective equipment was less likely to have been worn by many workers, particularly by the head operators before 1985, the period of interest to the retrospective exposure assessment study.

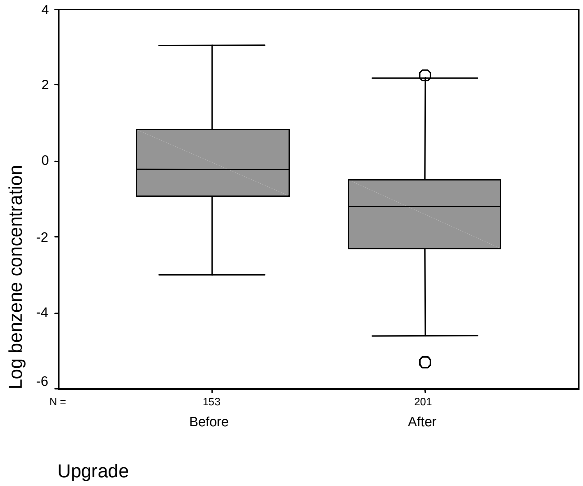


Figure 71: *DAP Operators pre and post 1989*[49] BE Data
Box plot log benzene concentration

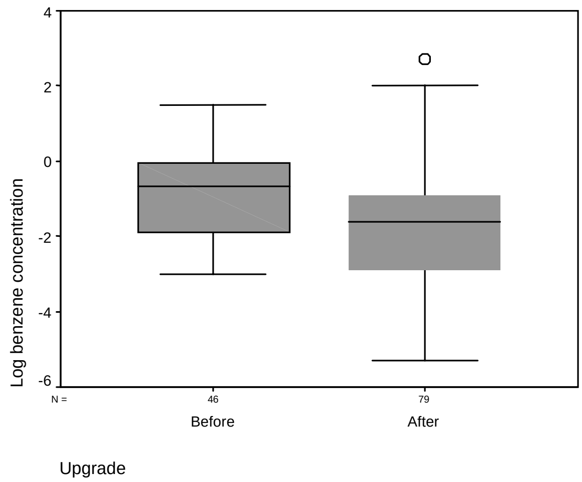


Figure 72: *DAP Head Operators* pre and post 1989 BE Data
Box plot of log benzene concentration

[49] Box plots show the median, interquartile range and outliers as open circles.

Dewatering BE 0.63 ppm

Few Australian data were available. There was only one Australian data point from Refinery J provided by the New South Wales Work Cover Authority. The technology associated with that sample was assumed to be open drains as the sample was taken in 1979. Some data on dewatering were found in the literature, n=4, and these were included in the BE. This is an uncertain BE of 0.63 ppm. No further data were found to validate this BE.

Driving and Unloading BE 0.16 ppm

No Australian data were available on exposure during driving and unloading tasks. One petroleum company occupational hygienist had measured the actual loading task and the whole day's exposure in paired tests. Exposure for the driving and unloading component of the activity was calculated from the paired tests. The results showed that the contribution to the day's exposure from the driving and unloading tasks was very small. The value of 0.16 ppm used for *Driving and Unloading* BE was obtained from the literature.

Unloading occurs primarily at service stations where there is remote venting. This practice had not changed over the years so exposure was taken to be low during this task over the period of interest. In the early years, deliveries of gasoline to farmers and small businesses were in sealed drums and in later years, delivered in bulk. However use of gasoline on farms has declined in favour of diesel which contains no benzene.

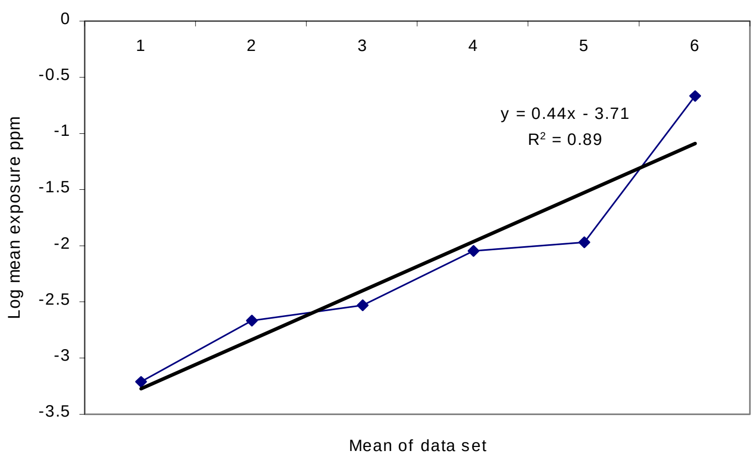


Figure 73: Log of Exposure Mean Data used in the *Driving and Unloading* BE

Drum Filling

BEs: Stub LEV 1.55 ppm; Enclosed 4.69 ppm; Open 3.52 ppm

Although exposures differed by site, the differences between technology accounted for much of this. The exposures were significantly lower when local exhaust ventilation was used, compared to when no local exhaust ventilation was used. The exposures during filling with local exhaust ventilation *(Drum Filling Stub* LEV) were log-normally distributed with an AM of 1.55 ppm, n=24. The stub and spear filling data were very similar at open drum platforms so the data were pooled. Those drum platforms considered to be enclosed[50] gave a slightly higher exposure *(Drum Filling Enclosed)* (4.69 ppm), n=18, than the open ones (*Drum Filling Open)* (3.52 ppm), n=106. There were no data points for drum filling with displaced vapour removal.

[50] All drum filling sheds in Australia were open on one side, the term "enclosed" was a comparative term to describe some fill areas which were more compact than others.

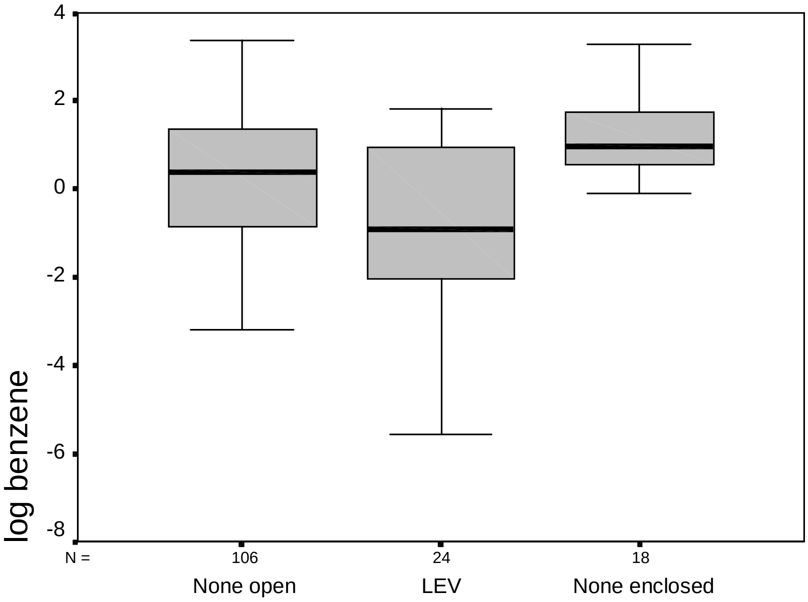


Figure 74: *Drum Filling* Operations Box plot of log Benzene Concentration BE Data

<u>Drum Laundry and Preparation</u> BEs: Laundry 0.39 ppm; Preparation 0.14 ppm

The 12 data points for these BEs came from one company. Four samples were of drum cleaning activities and the other eight samples were from the preparation area. The mean for the drum cleaning data 0.39 ppm, was nearly three times the mean of the drum preparation data 0.14 ppm. However, because of the small numbers in each group and the larger variability in the drum-cleaning data, the analysis of variance showed no significant difference between the two activities. After consideration of the potential exposure sources involved in the two activities it was decided to calculate separate BEs. The *Drum Laundry* BE was applied to workers who carried out cleaning tasks, while workers in preparation, e.g., spray painters, drum stackers were given the *Drum Preparation* BE. In one or two cases the worker carried out both tasks and they were given the *Drum Laundry* BE. The small number of data points makes these BEs uncertain.

Drum laundries were classified into low, medium and high exposure classes depending on the period, ventilation and proximity to the filling station. The sites whose measured data were used for calculation of these BEs were assumed to be in the low range because the measurements were all made in the 1980s.

<u>Gauging and Pigging</u> BE 4.20 ppm

There were very little data on gauging either from the Australian petroleum companies or in the literature. The available literature data were not well characterised, in particular the data had very little information on the product being gauged [142]. The Australian data were for open gauging and it was assumed that the remaining literature data were too. This is a BE with high uncertainty, as it is based on just the one Australian data point of 4.20 ppm for gasoline.

There were no data available for pigging operations. This was a minor short-term task but may be significant for some subjects particularly those that pigged lines containing benzene. There was also a potential for skin contact if workers did not wear protective gear. The value for gauging has been used as a substitute.

Instrument Fitter *BE 0.48 ppm*

Only data of more than 180 minutes duration were used in the calculation of this BE. Most of the data came from one site (40 of 42 data points) and were below the detection limit (30 of 42 data points). There were however two large outliers: 7.2 ppm and 10.6 ppm. These were included in the BE calculation as no valid reason was found to exclude them. Such values might be expected when there were occasional high exposures from particular jobs perhaps on unpurged lines. If the two high values are omitted the mean would be reduced from 0.48 to 0.06 ppm.

The value for this BE lies between the BEs for *Refinery Fitter* and *Refinery Operator Not Exposed* which is as expected. This is a BE with some uncertainty, because of the outliers, the number of data points below the limit of detection and the fact that it was mainly drawn from one site.

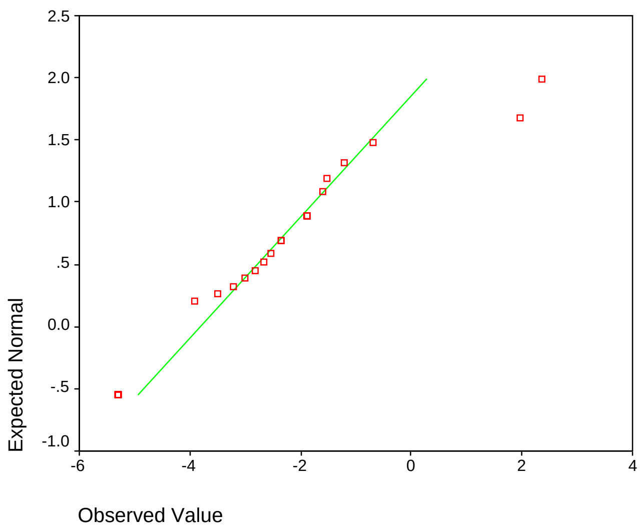


Figure 75: *Instrument Fitter* BE Data
normal Q-Q plot of log benzene concentration data for all refineries combined

Laboratory *BEs: BH 0.75 ppm; BL 0.15 ppm, O 0.09 ppm*

Laboratories were classified primarily by whether they were quality control laboratories, carrying out regular checks on products containing benzene (*B*), or other laboratories (*O*), such as research and development laboratories or lubricating oil laboratories. For some data, the type of laboratory could not be identified and the data were excluded. Data from operators, supervisors and work experience people were also excluded. The data were then categorised on whether there was good general ventilation (*L*) or poor ventilation (*H*) in the laboratory. At one site a major upgrade took place and the laboratory changed category from *Laboratory Bench High* to *Low* in 1994.

The *Other High* and *Other L*ow labs were based on smaller amounts of data. The benzene exposure was low in both tpes of laboratory and it was decided to pool the data giving a *Lab Other* BE of 0.09 ppm, n=127. There were significant differences in exposures between quality control labs with poor ventilation, *Laboratory Bench High* BE 0.74 ppm, n=534, quality control labs with good ventilation *Laboratory Bench Low* 0.15 ppm, n=65, and the other labs. Data sets for the three types of laboratories each had an approximately log-normal distribution. Since this BE is used for exposure estimates at both the activity and task level, all data, including the short-term measurements, were used in its calculation.

Laboratory Washing Glassware *BE 0.40 ppm*
The *Laboratory Washing Glassware* BE was used for time spent washing lab glassware in solvent. This BE is uncertain. It was based on two measurements during glassware washing with X55 solvent (LVN) (0.3% benzene at the time).

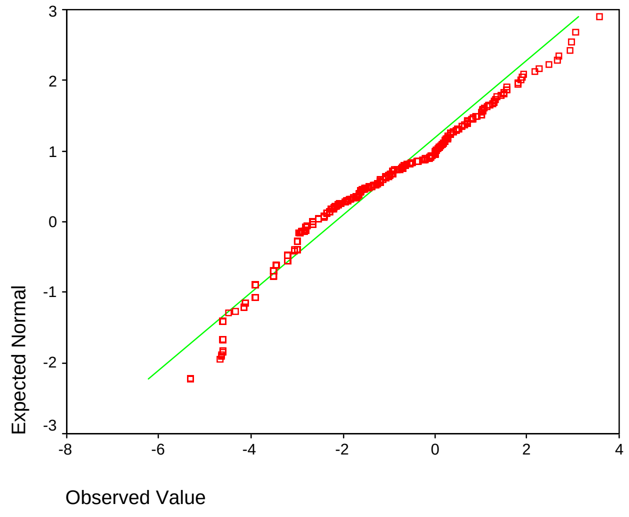


Figure 76: *Bench High Laboratory* BE
Normal Q-Q plot of log benzene concentration data

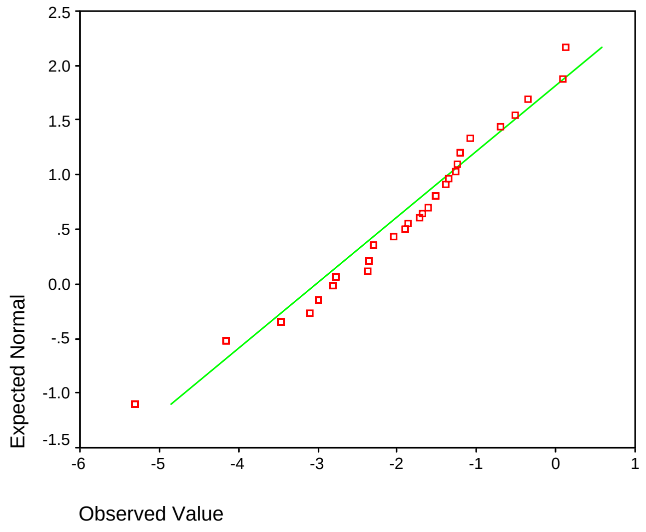


Figure 77: *Bench Low Laboratory* BE
Normal Q-Q plot of log benzene concentration data

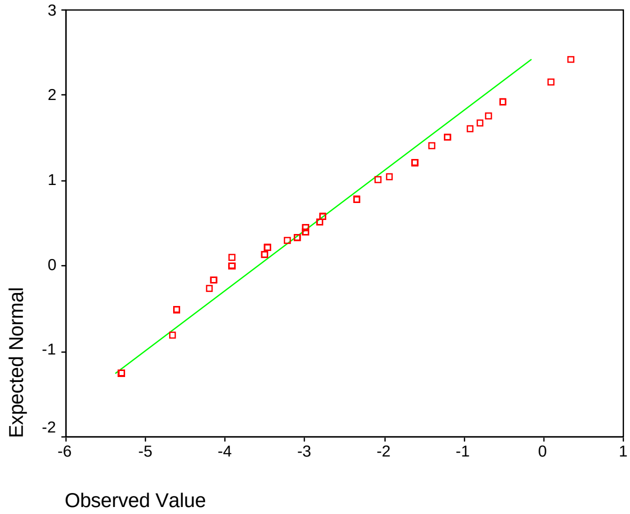


Figure 78: *Other Laboratory* BE
Normal Q-Q plot of log benzene concentration data

<u>Mechanic</u> BE 0.33 ppm

This BE drew on literature data and data from one company, n=7, but the measurements were all for car mechanics in retail garages. No data were available for truck mechanics. The exact number of samples in the literature data was not clear so the mean of means was used, weighting the data sources equally [108, 138, 141, 142, 201-206]. It is not certain that all the mechanics were exposed to gasoline, the references suggested that the primary source of exposure was benzene from exhaust gas. The Australian data were lower than that from the literature but not significantly so and the ranges overlapped so all data were included in the BE calculation giving a BE of 0.33 ppm. This is an uncertain BE because of the absence of Australian data on truck mechanics.

<u>Mogas (Gasoline) Blending</u> BE 0.42 ppm

The Mogas blending data came from one site in 1996. There was a majority of low exposures but a few very high ones. The BE was 0.42 ppm, n=11.

<u>Rail Car Loading</u> BE 3.77 ppm

There were no significant differences between the exposure data for filling by spear and fill tube. The data varied by site but those sites with more measurements gave more apparent outliers. It was considered appropriate to group all the data rather than try to attribute site-specific values. The exposure data overall had a log-normal distribution. The *Rail Car Loading* BE was 3.77 ppm, n=179.

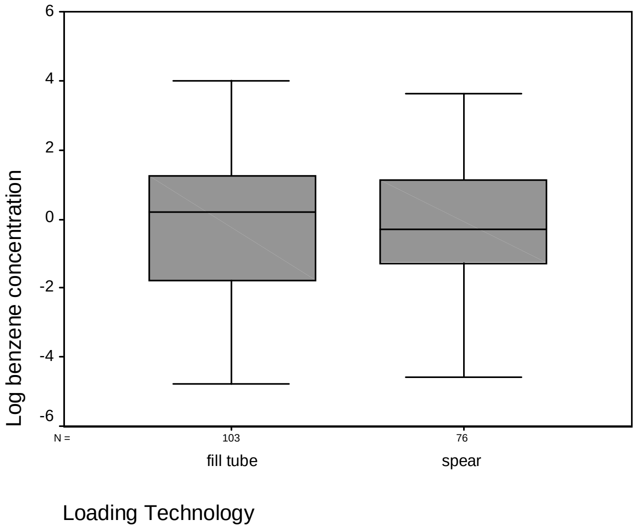


Figure 79: *Rail Car Loading* BE Box plot of data by Loading Technology

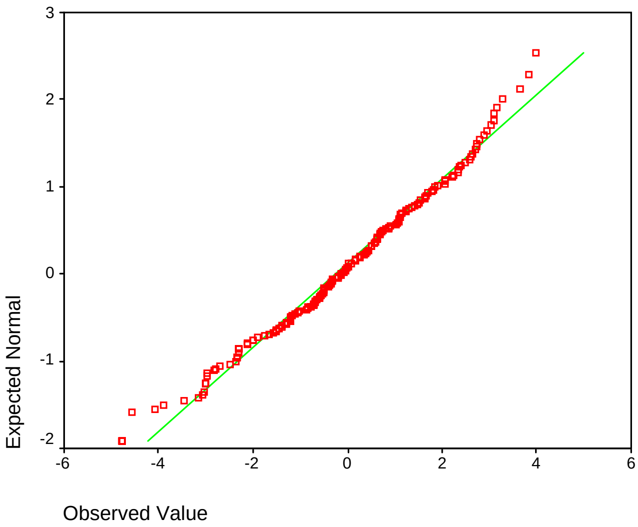


Figure 80: *Rail Car Loading* BE Normal Q-Q plot of log Benzene Concentration Data

Refinery Fitter BE 0.35 ppm

Refinery fitters usually work on any unit in the refinery. A range of units was represented in the data used for the BE, but the measurements may over-represent the more highly exposed units since exposure measurements were more likely to have been made during work on those units where benzene could be expected to be present. The data form an approximately log-normal relationship with a mean of 0.62 ppm (CI 0.36 - 0.88) n=369. At the two sites with large numbers of measurements, the data were log-normally distributed. If the measurements taken over less than 3 hours are removed from the BE data, the mean drops to 0.35 ppm (CI 0.22 - 0.48). This included removal of a data point of 39 ppm that is an outlier.

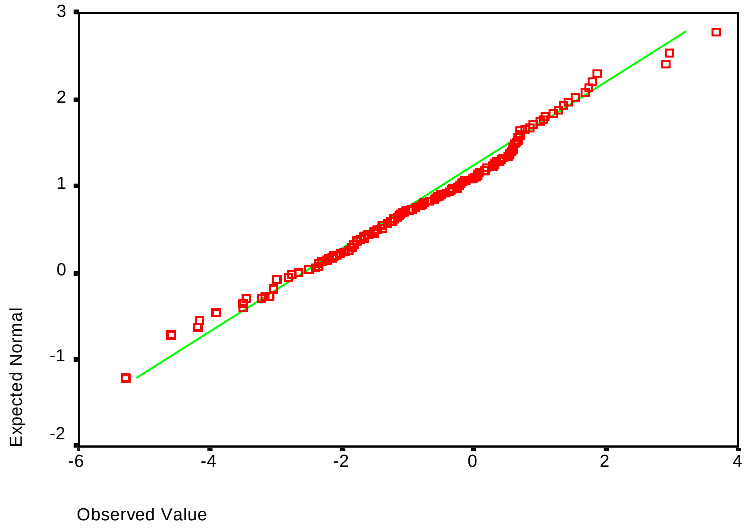


Figure 81: *Refinery Fitter* BE Data including outliers
Normal Q-Q plot of log benzene concentration data

<u>Refinery Operator Not Exposed (Background)</u> BE 0.07 ppm

The data used here came from a number of refineries and a number of different units. The decision to include the data was based on whether the unit had been classified as unexposed by the occupational hygienists (one with no benzene in the stream). One area that had not been so identified was the Chemical area of Refinery C. In the event these data appeared different to that from other areas and so they were excluded from the analysis. The remaining data, n=277, had an approximately log-normal distribution, (of which 174 data points were below the limit of detection) and had a mean of 0.07 ppm. The effect of varying limits of detection (0.01, 0.02, 0.03, 0.05, 0.07, 0.09, 0.1 and 0.2 ppm) were visible as steps in the plot of the data, as logs of half these values (-5.3, -4.6, -4.2, -3.7, -3.4, -3.1, -3.0, -1.9).

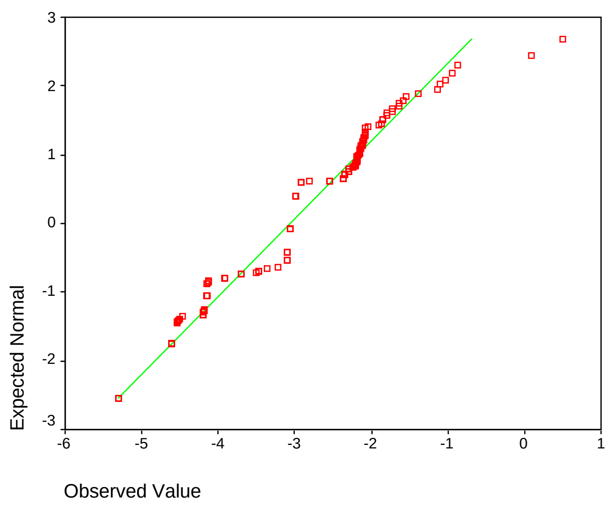


Figure 82: *Refinery Operator not Exposed* BE Data
Normal Q-Q plot of log benzene concentration data

Refinery Operator Plantwide *BE 0.08 ppm*

Only samples collected over longer than 180 minutes were included, n=25. The data from all sites were pooled for use at other sites with plantwide operatives and gave a BE of 0.08 ppm.

Reformer *BE 0.39 ppm*

Data of less than 180 minutes duration were excluded from the calculation of this Base Estimate. There were a number of values below their limit of detection (77 of 263 samples). For areas 3A and 3B of Refinery A, a mean of the *Reformer Operator* and the *Refinery Operator NE* BEs was used.

The reformer data from Refinery E contained two high values, 54 and 27 ppm, reflected in the wide confidence intervals associated with this BE. These high values were included in the original BE calculation because there was no evidence that they were not possible true exposures (Ward personal communication). There is no reason to suppose that the differences between reformers and how they were run should result in differences in long-term exposures for the operators. For this reason the data were pooled for the *Reformer Operators* giving a BE of be 0.39 ppm (CI 0.26 - 0.52) rather than use site specific ones which would have given one site a much greater figure than that for the remaining sites.

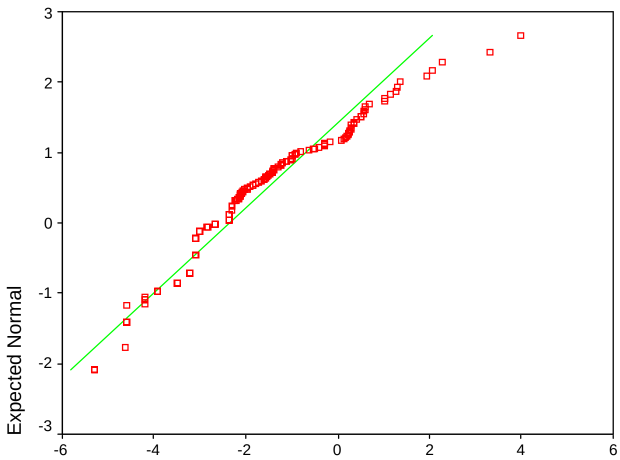


Figure 83: Original *Reformer Operator* BE Data (including outliers)
Normal Q-Q plot of log benzene concentration data

Table 124: Site Specific Reformer Mean Exposures

Refinery	Number of samples	Mean exposure (ppm)	Mean exposure (ppm) outliers removed
A	19	0.12	0.12
B	0	—	—
C	76	0.16	0.16
D	13	0.03	0.03
E	121 (119)	1.30	0.64
F	9	0.08	0.08
G	17	0.50	0.5
H	8	0.09	0.09
Mean		**0.33**	**0.23**

<u>Refuelling with Avgas</u> BE 1.65 ppm

The exposure measurements were carried out over periods of time on the tarmac, driving and in preparation, not just the task of refuelling with avgas. The proportion of non-refuelling work would be greater for the longer sample times. Since refuelling with avgas was a short-term task, generally taking less than an hour per ‘plane, only the 9 data points collected over less than one hour were used to generate the BE.

The mean from all 45 data points was 0.76 ppm, the mean from all data less than two hours sampling duration (15 data points) was 1.13 ppm and for less than one hour (9 data points). Figure 84 shows that the mean exposure drops as the sample time increases, plateauing at about 0.8 ppm.

This BE was used only when refuelling with avgas. The *Airport Background* BE, 0.08 ppm was used for refuelling with jet fuel, the time on the tarmac, driving and in preparation.

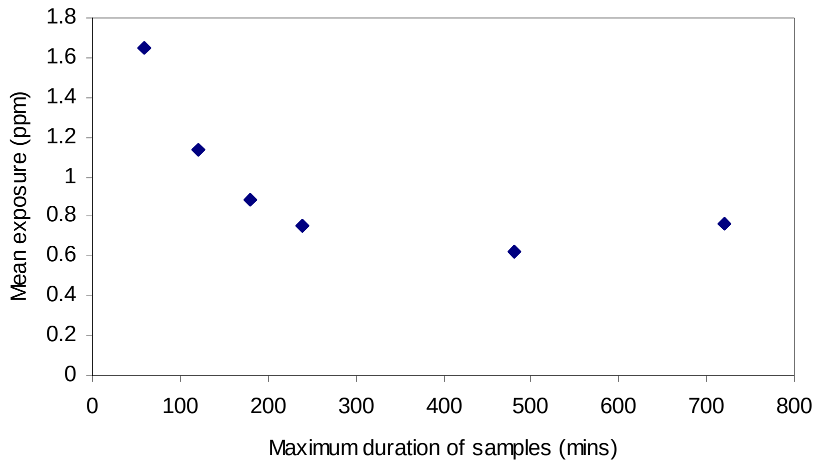


Figure 84: Comparison of Mean Exposure During Refuelling with Sample Duration

<u>Road Tanker Loading</u> BEs: Top 1.76 ppm; Bottom 0.55 ppm

Exposure varied by site. No significant differences in exposure were found between bottom filling with and without vapour recovery and between top filling with spear or fill tube. However there was a significant difference in exposures between top and bottom filling (Figure 85). Both the combined top-filling data, n=68, BE 1.76 ppm and the combined bottom filling data, n=31, BE 0.55 ppm, gave rise to log-normally distributed exposures. The histograms and normalised Q-Q plots of the data are presented in Figure 87 to Figure 89. The data points used for the BE calculation did not record whether the tankers were dipped or metered so analysis by this factor was not possible.

One study found that the ratio between exposures with and without vapour recovery was 24:31, i.e. the difference in the driver’s exposure is small compared to the overall variability [(207)]. Another study demonstrated an exposure ratio of 1 : 4 between bottom and top loading total hydrocarbons [(208)]. These values are comparable with the ratio observed in this study of 1:3.2 and 1:2.9 (2.8) for the literature data. Another study calculated a task-based ratio of 6:10:23 for exposure to benzene during bottom loading without vapour recovery, with vapour recovery and top loading [(209)]. This would give rise to a ratio of 1:2.3-3.8, similar to that described here.

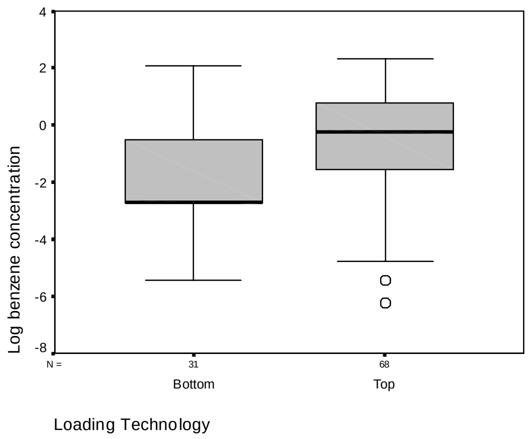


Figure 85: Box plot of *Top* and *Bottom Road Tanker Loading* BE Data

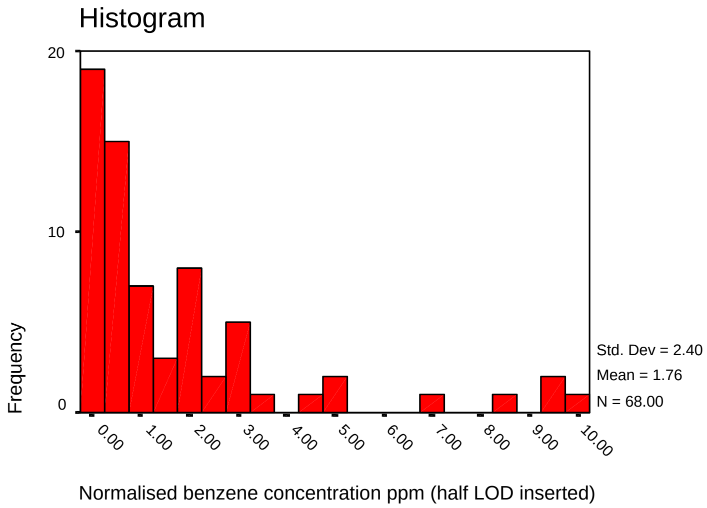


Figure 86: Distribution of Company Data for *Top Loading* used in BE (ppm)

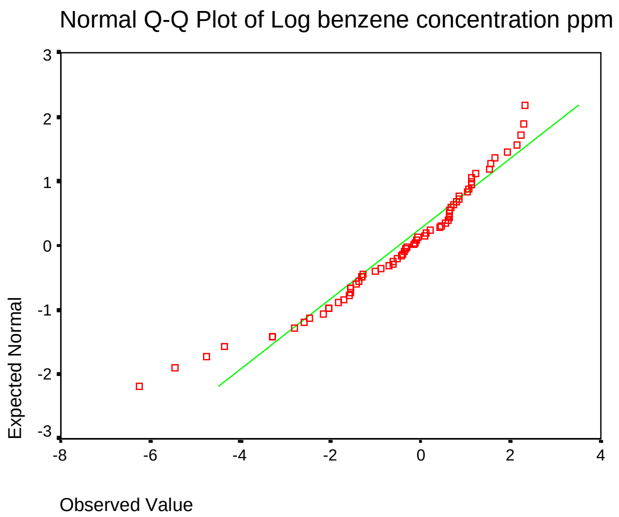


Figure 87: Plot of Normalised Data for *Top Loading* used in BE (ppm)

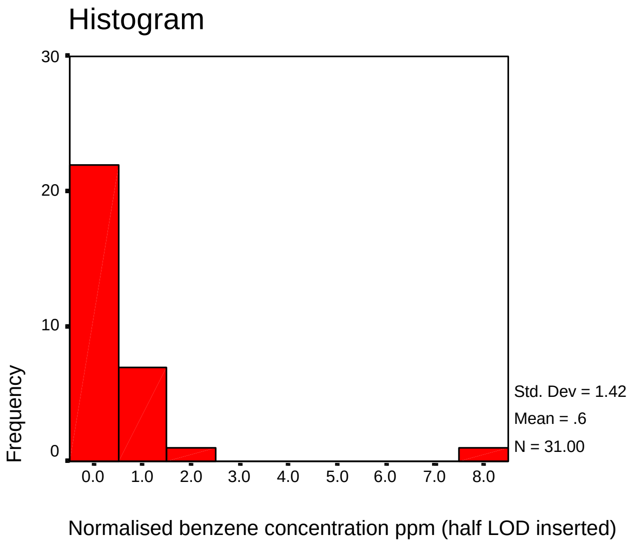


Figure 88: Distribution of Company Data for *Bottom Loading* used in BE (ppm)

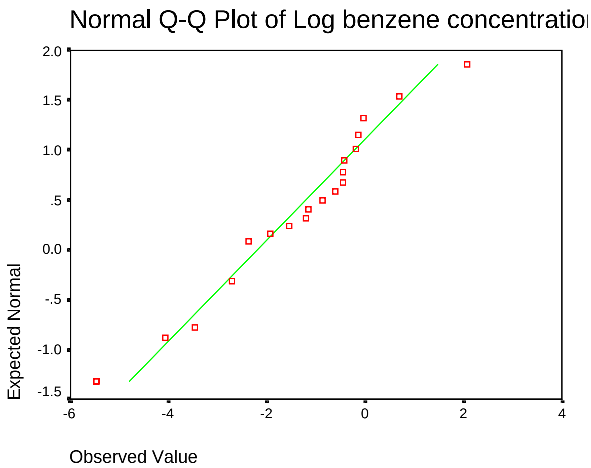


Figure 89: Plot of Normalised Data for *Bottom Loading* used in BE (ppm)

<u>Rural Background</u> BE 0.001 ppm

The BE value of 0.001 ppm, was taken from the literature based on recent New South Wales CSIRO and Victorian EPA measurements [144].

<u>Sampling</u> BE 0.67 ppm

There were few petroleum company data available for exposure during sampling. Two measurements were found, but both were below the limit of detection and one was only 12 minutes in duration, the other was for in line sampling. Data from the literature were used but the percentage of benzene in the streams sampled was not stated [134, 135]. It has been assumed that the data were associated with open sampling. This BE of 0.67 ppm is therefore particularly uncertain.

<u>Separator Skimming/Interceptor Cleaning</u> BE 0.12 ppm

There were few Australian data on this activity (14 data points) and exposure during sludge cleaning was included giving a BE of 0.12 ppm. It was assumed that the exposure at interceptors and separators was the same and was similar at refineries and at terminals.

Ship Dipping and Gauging *BE 5.41 ppm*

There were very few Australian data available (4 data points). Some additional measurements were taken from the literature. In one study the manual gauging of gasoline on ships, gave rise to exposures of 1.15 ppm based on a 10 minute sample, 0.21 ppm based on a 193 minute sample (140). In another study measuring exposure during manual gauging on a ship, the TWA was 33.54 ppm, range 5.96 to 114.42 ppm based on 8 samples (141). The percentage of benzene in the products handled had to be estimated for these literature values. This is an uncertain BE.

Ship Loading/Unloading *BE 0.11 ppm*

This BE is used for refinery and terminal staff only, not for ship's crew who were not included in the case-control study. Most of the data came from unloading benzene using flexible hoses, on the jetty at one site. Two outliers, 197 and 159 ppm, were excluded as probably contaminated samples. A small amount of data was collected during the unloading of gasoline at the same site using flexible hoses. There were three data points from another site where gasoline was unloaded using Chiksan arms; these data were not included in the BE of 0.11 ppm.

Sour Water *BE 0.06 ppm*

The data came from one site and 25 of the 28 data points were below the limit of detection.

Tank Cleaning *BEs: Gasoline 0.15 ppm; Crude 2.01 ppm; Crude Test 0.30 ppm*

There were 4 types of data; cleaning gasoline tanks (n=2), cleaning crude tanks (n=13), cleaning crude ballast or slops tanks (n=46), and gas testing but not cleaning crude tanks (n=12).

The job of cleaning a gasoline tank was rather different to that of cleaning a crude or slops tank, these would have contained more sludge, and required more time scraping and shovelling (Figure 90). The *Tank Cleaning Gasoline* BE of 0.15 ppm, was therefore generated for cleaning gasoline tanks as a mean of the two available values. This estimate was used for gasoline and benzene tank cleaning (normalised for the product benzene concentration).

The *Tank Cleaning Crude* BE, used for cleaning crude tanks was generated using the crude and slops storage data, n=59 normalised to 0.1 percent benzene. This BE of 2.01 ppm, was used for cleaning crude tanks only. The same percentage of benzene was used for the product in the ballast tanks as for the crude tanks since the partition coefficient of benzene into water is low and as the tanks would have been drained, it would be benzene from the remaining crude sludge that would be released.

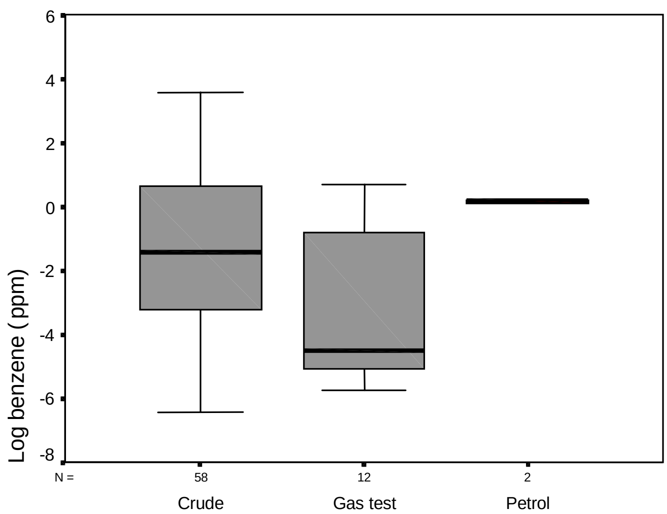


Figure 90: Box plot of *Tank Cleaning* Data by Product Stored

The Australian data included twelve samples taken on the operator outside the tank. These were used to generate a *Tank Cleaning Crude Test* BE of 0.30 ppm for operators carrying out a gas test on a crude tank and not doing the cleaning.

The majority of the tank cleaning done by subjects was carried out before 1970. After this date contractors did most tank cleaning. It was likely that some respiratory protection would have been used when cleaning but this was not considered in the BE. There is evidence that respirators are unlikely to be very effective in the long-term particularly when heavy physical work in a head down position, such as shovelling, takes place [210, 211]. This would be particularly relevant in the early years when the consensus is that respiratory protection was less likely to be worn or to have been kept in good condition.

<u>Tank Farm</u> BEs: Refinery 0.14 ppm; Terminal 0.36 ppm

The tank farm data were divided on the basis of the type of site (refinery or terminal). It was considered that there was a difference in the products stored between refineries and terminals that could result in differing exposures to benzene. The refinery tank farm BE of 0.14 ppm was based on 94 measurements. The terminal tank farm BE of 0.36 ppm was based on only 10 measurements. This is higher than the mean estimate for terminals from the literature of 0.17 ppm, but this did include some short-term tasks.

<u>Terminal Fitter</u> BE 0.67 ppm

The data on fitters' exposure at terminals (n=13) appeared to have been collected on the more exposed tasks that a fitter carries out and hence the BE of 0.67 ppm may overestimate long-term average exposure. The data were log-normally distributed. A data set from movements in a barge loading facility, hence not a normal terminal was excluded from the original BE calculation. The mean of this set was 0.2 ppm (CI 0.08 - 0.34).

<u>Terminal Operator not Exposed (Background)</u> BE 0.14 ppm

Data for this BE were measurements of benzene exposure for terminal operators carrying out tasks where no benzene is handled. The measurements were made at only four sites from one company. Six of the ten measurements were below the level of detection.

<u>Upstream Fitter</u> BE 0.04

The data for this BE came from one company, there were only twelve samples of which seven were below the limit of detection. The BE of 0.04 is somewhat uncertain therefore.

<u>Upstream Operator</u> BEs: Offshore Operators 0.02 ppm; Onshore Operators 0.06 ppm

The data were divided on the basis of whether they came from offshore (oil extraction) or onshore (oil stabilisation) operators. The data used for the offshore operators came from one company (6 data points) and gave a BE for Offshore Operators of 0.02 ppm. The data were taken during still conditions that occur infrequently, less than ten percent of the time, and from a platform with the highest benzene concentration in its crude (Hamilton personal communication). This BE probably over estimates exposure, however, it is still very low. The exposure data on onshore operators at Upstream Company C were higher than that from the other onshore production sites but there was no obvious reason for this. From one upstream production site there were exposure data on workers in the crude stabilisation plant and in the gas plant. There was no statistically significant difference between the data collected in the crude and gas plants. The BE for *Onshore Operators* is 0.06 ppm.

<u>Urban Background</u> BE 0.005 ppm

The *Urban Background* BE of 0.005 ppm was taken from the literature based on recent New South Wales CSIRO and Victorian EPA measurements.

Last page