



Health Watch exposure estimates: Do they underestimate benzene exposure?

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Abstract

A nested case-control study found that the excess of leukemia, identified among the male members of the Health Watch cohort, was associated with benzene exposure. Exposure had been retrospectively estimated for each individual occupational history using an algorithm in a relational database. Benzene exposure measurements, supplied by Australian petroleum companies, were used to estimate exposure for specific tasks. The tasks carried out within each job, the products handled, and the technology used, were identified from structured interviews with contemporary colleagues.

More than half of the subjects started work after 1965 and had an average exposure period of 20 years. Exposure was low; nearly 85% of the cumulative exposure estimates were at or below 10 ppm-years.

Matched analyses showed that leukemia risk increased with increasing cumulative benzene exposures and with increasing exposure intensity of the highest-exposed job. Non-Hodgkin lymphoma and multiple myeloma were not associated with benzene exposure.

A reanalysis reported here, showed that for the 7 leukemia case-sets with greater than 16 ppm-years cumulative exposure, the odds ratio was 51.9 (5.6–477) when compared to the 2 lowest exposed categories combined to form a new reference category.

The addition of occasional high exposures, e.g. as a result of spillages, increased exposure for 25% of subjects but for most, the increase was less than 5% of total exposure. The addition of these exposures reduced the odds ratios.

Cumulative exposures did not range as high as those in comparable studies; however, the recent nature of the cohort and local handling practices can explain these differences.

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1. Introduction

Benzene is present in crude oil, gasoline and at many stages in the refining process [1]. It has been designated a Group 1 carcinogen by IARC because of its

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leukemogenic properties [2]. The extent of the risk associated with benzene exposure below 10 ppm is a matter of debate however [3–10].

Health Watch is a prospective cohort study of about 18,000 employees who have worked for more than 5 years in the Australian petroleum industry. About 1300 of the cohort are women. The cohort commenced in 1981 with a face-to-face survey which was repeated in 1986, 1991 and 1996. Subjects provided demographic details, health status information and details of their work history. All Australian petroleum company employees were invited to participate except those employed at head offices and at sites with fewer than 10 employees. About 95% of eligible employees have participated [11]. The cohort thus consists of employees from offices, upstream extraction and processing sites, refineries, terminals and airports all over Australia. Subjects were followed by matching with the Australian national death and cancer registries. An excess incidence of lympho-hematopoietic cancer was identified among the male members of the cohort [12].

A nested case-control study was carried out in which exposure to benzene was quantitatively, estimated for individual cases and their matched controls [13]. Cases were defined as male members of the Health Watch cohort, who had:

- first diagnosis of LH cancer after entering the Health Watch cohort;
- 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, unless they were lost to contact by Health Watch, or were deceased.

There were 31 non-Hodgkin lymphoma, 15 multiple myeloma and 33 leukemia cases meeting these criteria identified in the cohort between 1981 and 1999. The leukemia subtypes were: 11 chronic lymphocytic, 6 chronic myeloid, 2 acute lymphocytic, 11 acute non-lymphocytic and 3 other leukemias. Leukemia, but neither non-Hodgkin lymphoma nor multiple myeloma was strongly associated with benzene exposure. Matched analyses showed that leukemia risk increased with increasing cumulative benzene exposures expressed in ppm-years and with increasing exposure intensity of the highest-exposed job in ppm. [12]. Cumulative exposure estimates were low in this

study compared to the Pliofilm study [6] and the Chinese cohort [10]. It has been suggested that there may be no increased risk of leukemia at cumulative benzene exposures below 200 ppm-years [8] or intensity of less than 20–60 ppm [9]. In our study the odds ratios for leukaemia were significantly raised unlike those reported from similar petroleum industry studies [14,15].

This paper re-evaluates the exposure-response relationship and investigates the factors behind the low exposure estimates.

2. Materials and method

The exposure assessment was described in a previous paper [13] but is briefly reviewed here. A job history was prepared for each subject, based on data which had been collected largely prospectively from the four cohort interviews that took place between 1980 and 1999 [12]. The job histories which were complete for 98% of subjects ($n = 494$) were then checked by the employing company against their records. We used each subject's job history to identify the range of products handled and tasks comprising each job by interviewing contemporary colleagues. This was carried out by interviewers blind as to the case status of each subject. The interviews were structured and used standard job-specific questionnaires.

We collated Australian personal benzene exposure monitoring data from participating companies and calculated the arithmetic mean exposure for each task represented. These were taken as base estimates (BE) of the exposure for the task. If more than one technology could have been used, e.g. top and bottom loading for road tankers, separate BEs were calculated for each technology. The BE was then allocated to individuals carrying out that task over the relevant period, in a relational database. No local data were available for some short-term tasks and data for these were sought from the literature.

The Australian BEs were derived from data largely collected since 1975, so there is uncertainty about how applicable they are to earlier time periods (Fig. 1). There was more available data associated with lower exposed jobs in refineries, e.g. reformer, crude distillation and catalytic cracker unit operators than with the more highly exposed jobs in terminals. Few data were available for short-term tasks, e.g. dipping and gauging.

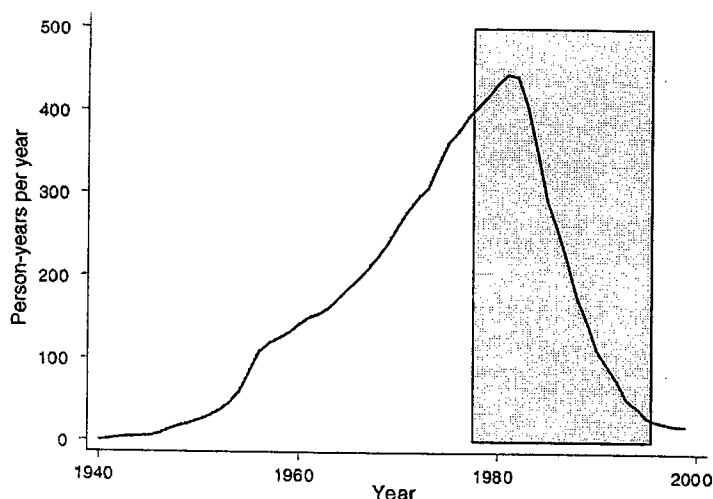


Fig. 1. Overlap between available Australian measured data (shaded) used for BEs and the distribution of person years in the case-control study.

The BEs were compared to relevant exposure data identified in the literature [16]. Literature data were not available for 12 of the 49 BEs. The literature data validated 19 BEs, and suggested that 4 other BEs should be adjusted. Fourteen other BEs were not confirmed by the literature data. However after comparing the quality and quantity of the literature data with the local data, we (in collaboration with the local occupational hygienists) judged that in these cases, the literature data were ill-defined, inadequate or the differences could be explained local work practices or by the lower benzene content of Australian crude oil. Thus we used the unadjusted local data BEs in these cases.

The basic tasks in refineries and terminals have not changed greatly since the 1950s, although the technology used and the frequency with which they are carried out, have changed. We collected information about the task frequency and technology change at the site visits and allowed for this in the exposure assessment. We did this by, for example, allocating a longer time on gauging in the 1950s because of more frequent excise checks.

We considered that general site exposures were higher before 1975 as a result of fugitive emissions. These were reduced in response to environmental regulations on hydrocarbon emissions, for example, the introduction of internal floating roofs in storage tanks which was thought to have more than halved storage

tank emissions around this time [17]. Although there were significant reductions in fugitive emissions at terminals and refineries, many of these were from tank tops and stacks remote from the worker's breathing zone. We increased the estimate of pre-1975 general site exposures (not resulting from specific tasks) by 20% to allow for this. This figure was chosen by the local collaborating occupational hygienists using their expert judgment. Terminal fitters were considered to have been exposed to more benzene before 1975 compared to the period after this date. More stringent 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, improved line purging procedures and more automated equipment. An arbitrary factor of 1.5 was applied to pre-1975 exposures by the collaborating expert hygienists in the absence of measured exposure data.

Cumulative exposure for each subject was estimated using a task-based algorithm, similar to that used in other petroleum industry exposure estimates [18,19]. The algorithm took into account: the percentage of benzene in the product handled, the proportion of time spent handling each product, the time spent on different tasks within a job, the technology used for the task and the years spent on each job [13]. Whenever a BE had to be applied to a task with different technology, a multiplier was used to scale the exposure, e.g. the BE

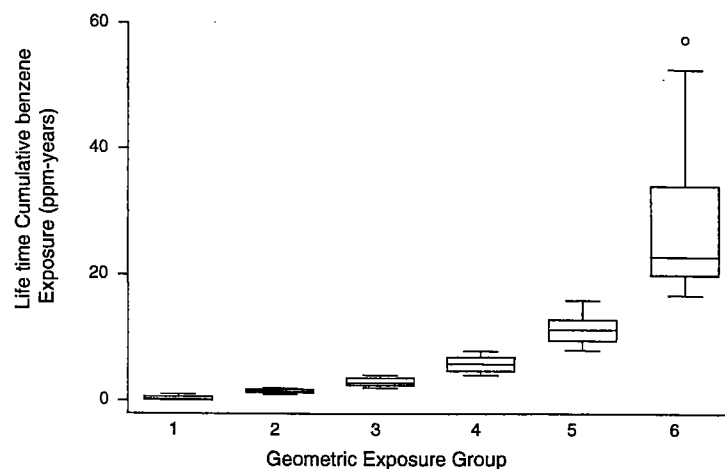


Fig. 2. Benzene exposure categories (lifetime cumulative exposure to benzene in ppm-years). (Vertical bars show range of exposures in each category except for outlier).

for top loading was attributed to a driver who used top splash loading and a factor of three was applied to increase the exposure estimate. Most of the multipliers were derived from exposure data; some were derived from the literature and a few were agreed by a panel of local Occupational Hygienists. These expert-derived multipliers were used for fewer than 160 tasks from a total of 3457 tasks assessed. The algorithm was used to estimate for each subject, the cumulative exposure to benzene in ppm-years and to identify the intensity of the most highly exposed job in ppm (cumulative exposure divided by years spent on that job). The subjects were categorized by cumulative exposure. Because the absolute difference between exposure for the two lowest exposure categories was small (Fig. 2), we decided for this reanalysis to combine them. This provided a larger reference category.

We also explored exposure that might not be represented in the BEs. Subjects may have experienced infrequent but potentially high exposures (high exposure events or HEEs) for example from spills or from tasks no longer performed, e.g. washing overalls in gasoline. This was considered important because these infrequent or historic exposures were unlikely to be represented in the BEs.

The HEEs that were considered were identified from the reports collected during the site visits. These were collected and allocated to a job category, e.g. a double fill for drum fillers with metered drum filling. The col-

laborating industry occupational hygienists were each sent the list of possible HEEs and their opinion of the likelihood of such exposures was individually canvassed in a telephone survey. The collated replies were examined by a panel of three industry hygienists and a consensus reached on:

- the probability of the exposure from each HEE, e.g. product spill during tanker loading;
- the group(s) of workers that might have been exposed, e.g. mechanics;
- the frequency for a particular exposure, e.g. once a year;
- the era over which the high exposures might have occurred, e.g. pre-1960;
- how long the exposure would have lasted on each occasion, e.g. 10 min washing overalls;
- the extent of skin exposure if any, e.g. hands wetted with product.

The HEEs were then allocated to groups of workers based on job activities and era considerations.

After due consideration some possible HEEs were not included for the following reasons:

- 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.
- Some activities occurred too infrequently to be included in the model, e.g. major spillages during

Table 1
Incidental high exposure events included in daily exposure assessment model

Job	High exposure event (HEE)	Frequency per person	Changes over time?	Site	Comments	Exposure (ppm) ^a
Drum fillers	Extensive splashes of overalls	1 per year	Stopped early 1990s	Drum sheds	From occasional drum overfills during metered delivery	3.43
Fitters	Extensive splashes of overalls	1 per year	Pre 1970	Terminals and refineries	Arms and top of legs	3.43
Fitters and mechanics	Washing hands in gasoline	2 per day	Pre 1950	Terminals and refineries	Practice widespread	0.35
		1 per day	1950–1980		A few individuals continue	0.17
	Washing tools in gasoline	4 min per day 15 min Friday	Pre 1975	Terminals and refineries	Used gasoline until about 1975, kerosene thereafter	0.20 0.76
	Washing components and equipment	15 min per day	Stops 1975	Terminals and refineries	Practice widespread. After 1975 used proprietary cleaners or kerosene	1.34
Mechanics	Washing overalls in gasoline	1 per week, 10 min exposure	Stops 1955	1 company	Friday left to soak for half an hour, pick out, drain, wear next Monday. After 1955 Clean overalls provided weekly	0.67
Lab technicians and samplers (not chemists)	Washing hands in LVN	2 min twice daily	Pre 1965	Terminals and refineries	LVN (1% benzene) at this time	0.11
	Washing fuel oil sample bottles in gasoline	15 min per day	Stops 1990	Refinery only	After 1990, only mineral turps used	1.34
	Washing hands in benzene	2 min once per week	Pre 1980	2 refineries		5.71
Rail car loader and road tanker filler	Tanker overflow	1 per year			Top dipped	1.88

^a This includes exposure by inhalation added to exposure through the skin calculated as an 8-h equivalent exposure.

gasoline delivery that probably occurred less than once every 20 years for any one driver.

- Activities which were already represented in the BE data, e.g. fitter breaking lines containing gasoline.
- Activities that were thought to result in low exposures, e.g. handling benzene as a reagent in a fume cupboard.

The likely exposure (including via skin and inhalation) resulting from the HEE was then estimated as an equivalent 8-h TWA (inhalation only exposure) from new monitoring data for road tanker and rail car spills and laboratory simulations for the remainder of the

HEEs (Table 1). The total exposure was added to the BE for the appropriate number of days.

We calculated odds ratios (ORs) for leukemia, using conditional logistic regression using StataTM, for subjects categorized by cumulative exposure and by the exposure intensity of their highest exposed job. We calculated the odds ratio associated with benzene in ppm-years when treated as a continuous variable. We then examined the effect of adding HEEs to the cumulative exposure and again calculating odds ratios.

We compared the Health Watch exposure assessment outcomes, cumulative exposure, intensity and duration of exposure to those reported for the two

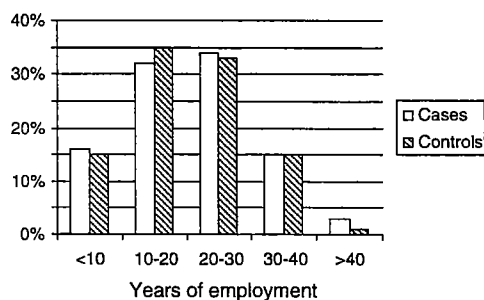


Fig. 3. Distribution of the years of employment of cases and controls.

comparable studies, the Canadian IOL study [14] and the UK IP study [15].

3. Results

Subjects had an average exposure period of 20 years (range 4–42) (Fig. 3). Exposure was relatively recent in this study, 63% of controls and 47% of cases started employment after 1965.

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% of subjects had estimated cumulative exposures less than or equal to 10 ppm-years and only 3.6% had greater than or equal to 40 ppm-years. The addition of HEEs increased exposure for 25% of subjects, notably fitters and vehicle mechanics, but for most of these subjects the increase was modest (less than 5%

of total exposure) (Fig. 4). The allocation of an HEE was not related to case-status (Pearson's χ^2 0.5).

The odds ratio for leukemia increased with cumulative exposure when exposure was treated as a continuous variable, OR 1.10 (1.04–1.16) per ppm-year. When the HEEs were added to the cumulative exposure the odds ratio was lower, OR 1.03 (1.01–1.05) per ppm-year.

Leukemia was strongly associated with cumulative benzene exposure of greater than 16 ppm-years with and without the addition of HEEs (Table 2) and was also associated with exposure of highest intensity job held greater than 0.8 ppm, controlling for exposure duration (Table 3).

The cumulative exposures were similar for the majority of the subjects in the three comparable petroleum industry case-control studies. Fig. 5 shows that there were only a few subjects in the IOL and IP studies with a much higher exposure than was estimated for any of the Australian subjects. The range of career intensities of exposure to benzene and the job durations were also similar in the three studies (Fig. 4; Table 4).

4. Discussion

These data provide evidence of an association between modest exposure to benzene (greater than 16 ppm-years cumulative exposure and greater than 0.8 ppm intensity of exposure) and increased risk of leukemia and provide some evidence of a dose-response relationship.

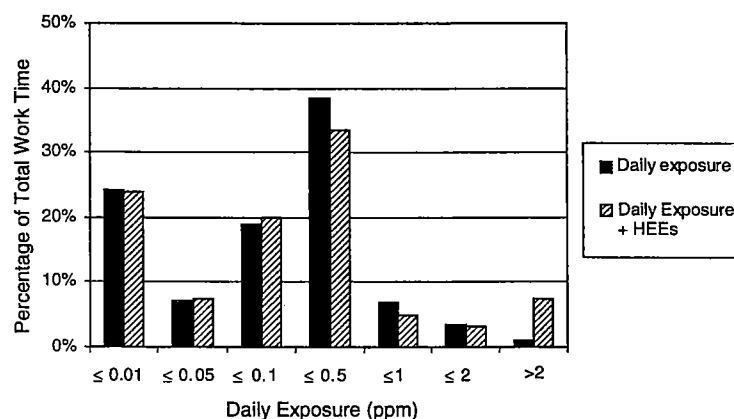


Fig. 4. Daily exposures by percentage of work time showing the effect of including the contribution of high exposure events (HEEs).

Table 2
Conditional (fixed-effects) logistic regression, leukemia by cumulative exposure to benzene (ppm-years)

Benzene exposure (ppm-years)	Number of controls	Number of cases	Cumulative exposure OR (95% CI)	Cumulative exposure including HEEs OR (95% CI)
≤2	84	9	1.00	1.00
>2–4	30	8	2.89 (0.97–8.52)	3.07 (1.02–9.28)
>4–8	27	3	1.17 (0.27–4.98)	1.22 (0.28–5.22)
>8–16	21	6	3.11 (0.91–10.56)	2.68 (0.71–10.08)
>16	3	7	51.88 (5.64–477)	7.79 (2.34–25.89)

Table 3
Conditional (fixed-effects) logistic regression, leukemia by intensity of highest exposed job (ppm) ever held controlling for career duration

Benzene exposure intensity (ppm)	Number of controls	Number of cases	OR (95% CI) ^a
≤0.1	65	5	1.00
>0.1–0.2	26	9	3.84 (1.16–12.69)
>0.2–0.4	25	4	2.16 (0.49–9.35)
>0.4–0.8	31	4	1.52 (0.34–6.70)
>0.8–1.6	11	6	6.34 (1.54–26.18)
>1.6–3.2	6	3	5.58 (1.00–31.04)
>3.2	1	2	19.56 (1.41–270.8)

^a Controlled for career duration.

Table 4
Comparison of AIP, IP and IOL benzene exposure intensities and duration of employment

	Range of mean career intensity (ppm)	Range highest job intensity (ppm)	Mean job duration (years)
AIP [23]	0.001 to 2.3	0.001 to 4.9	20.4
IP [15,19]	<0.02 to ≥0.4	<0.02 to 14.4	21.4
IOL [14] ^a	0 to 6.2	<0.5 to ≥6.2	30.3 cases, 28 controls

^a Data for leukemia cases and controls only.

The combination of the two lowest cumulative exposure categories reduced the odds ratios compared to those reported previously [12]. The association between increased risk of leukemia and benzene expo-

sure for the most highly exposed category remained strongly and significantly raised however. The study is a small one so that modest changes to the original reference category (which contained only three cases

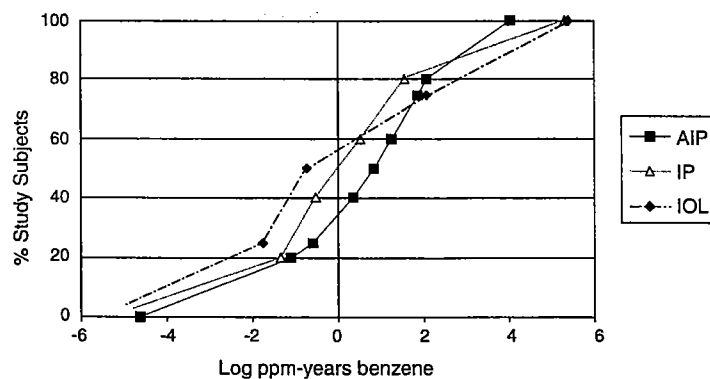


Fig. 5. Inter-study comparison of cumulative exposure estimates.

of leukemia) can have a large impact on the calculated odds ratios. The combination of the two lowest exposure categories (nine cases of leukaemia) provides a more stable reference category. This combination is probably warranted because the absolute difference in the two original exposure categories, (≤ 1 ppm-years and $1 \leq 2$ ppm-years) is very small and within the uncertainty of the exposure estimates.

The addition of HEEs to the exposure estimates decreased the odds ratio both when exposure was treated as a continuous measure and as a categorical variable. The majority of the HEEs were attributed to the more highly exposed workers so the odds ratio for the highest exposure category was considerably more affected than the ORs for the lower exposure categories. The reduction in ORs is probably because the leukemia risk is associated with higher exposures when the HEEs were added and hence the risk per ppm-year was reduced. An alternative explanation may be that non-differential misclassification has occurred and this is known to reduce observed odds ratios in most circumstances [20]. The accidental and historic high exposures may not have been experienced by the individuals in the study to whom they were applied; that is, the precision of the original exposure estimates was reduced.

The cases and controls were well matched [12] and the exposure estimates were detailed and based on verified job histories. The job history was checked against company records so the potential for recall bias was limited [12]. In addition, the lack of association between non-Hodgkin lymphoma and multiple myeloma suggest that recall bias was low. We reported in a previous paper [12] that we found no association between tobacco consumption and leukemia. We consider it unlikely that there were other confounding exposures, e.g. radiation or retroviruses [12].

There are differences in the industry sectors which were included in the three petroleum industry case-control studies. Refinery, upstream and a high proportion of office workers (more than 25% of subjects did office work for the majority of their career) were included in this case-control study. These workers would have had lower exposures than the distribution workers in the previous studies [14,15]. It has been suggested that we should reanalyse the data excluding the white-collar workers. However, this would remove three leukemia cases and a number of controls and thus reduce the power of the study.

Socioeconomic group was not suggested as a known risk factor for leukemia in recent reviews [21,22]. The proposed analysis would thus be using blue-collar work as a surrogate for exposure. Removal of the lower-exposed white-collar workers reduces the exposure contrast in the study population, and would probably decrease the odds ratios as a result of consequently different reference population. It would also make the study less generalisable to the non-petroleum industry population.

The cohort is more recent than the IOL and IP studies, which have subjects whose job histories go back to before 1920. Thus the use by subjects of older technologies resulting in higher exposure would have been less frequent in our study. There was, 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 [18]. The IP study included benzol terminal operators whose average daily exposure between 1925 and 1945 was estimated to be over 7 ppm [19]. This benzene boosting occurred in one Australian company too, however, we do not have any benzol terminal operators in this case-control study so this is not a plausible daily exposure for any subjects. We had two drivers who were involved in carrying this higher benzene fuel for a short period before 1970 but their exposure to fuel vapour would be comparatively brief each day during tanker loading and unloading. In the early 1900s, operators at large UK terminals were thought to have been exposed to daily averages of 2.9–3.5 ppm benzene [19]. By 1960 these values had fallen to 0.68 ppm which was closer to the exposures recorded in our study. In our study, leukemia risk was not found to be associated with era of exposure when cumulative exposure was taken into account, suggesting that earlier exposures had been estimated no less accurately than more recent exposures [12].

The highest common exposure was during drum filling with 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 drum filling BE. They also filled diesel and other products containing little or no benzene and usually had other tasks which gave rise to lower exposure to benzene.

Most of the BE values were derived from local exposure monitoring data and have been validated [16].

There were some known differences in work practice or circumstances between Australia, the UK and Canada, for example Australia has always had open sided rather than fully enclosed drum sheds. The increased ventilation is likely to have resulted in lower exposure, and hence, it is expected that an Australian study would have a lower drum filling BE than the Canadian study.

Between-worker variation in exposure measurements, resulting from personal factors such as individual work practice, was not included in the exposure assessment reported here. There was no unbiased way of retrospectively identifying the effect of such differences.

5. Conclusions

Our data demonstrate a strong association between leukemia and modest benzene exposure greater than 16 ppm-years, expressed as cumulative exposure or greater than 0.8 ppm intensity of highest exposed job. The addition of occasional high exposures to the exposure estimates results in lower observed odds ratios, when the exposure is treated as a continuous variable and as a categorical variable.

The exposure estimates were based on almost complete and verified job histories and were individually tailored and detailed. They drew primarily on Australian exposure data provided by the participating companies that we believe to be reasonably accurate estimates of exposure in the Australia petroleum industry over the relevant periods. They are similar to exposure estimates for the majority of individuals from other comparable studies although these other studies included some individuals with much higher exposure. These higher exposures are not thought to have occurred to members of the Health Watch case-control study.

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