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Review of the literature on benzene exposure and leukemia subtypes

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Abstract

The epidemiologic literature on benzene exposure and leukemia in the MEDLINE and TOXNET databases was examined through October 2004 using the keywords “benzene”, “leukemia” and “adverse health effects”. This search was complemented by reviewing the reference lists from extant literature reviews and criteria documents on benzene. Published studies were characterized according to the type of industry studied and design, exposure assessment, disease classification, and control for confounding variables. Study design consisted of either cohort studies or case-control studies, which were further categorized into population-based and nested case-control studies. Disease classification considered the source of diagnostic information, whether there was clinical confirmation from medical records or histopathological, morphological and/or cytogenetic reviews, and as to whether the International Classification of Diseases (ICD) or the French–American–British (FAB) schemes were used (no studies used the Revised European–American Lymphoma (REAL) classification scheme). Nine cohort and 13 case-control studies met inclusion criteria for this review. High and significant acute myeloid leukemia risks with positive dose response relationships were identified across study designs, particularly in the “well-conducted” cohort studies and especially in more highly exposed workers in rubber, shoe, and paint industries. Risks for chronic lymphocytic leukemia (CLL) tended to show elevations in nested case-control studies, with possible dose response relationships in at least two of the three studies. However, cohort studies on CLL show no such risks. Data for chronic myeloid leukemia and acute lymphocytic leukemia are sparse and inconclusive.
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1. Introduction

The first confirmed case of leukemia reportedly linked to benzene exposure was in 1928 [1]. Over the next few decades, benzene was still primarily regarded as a hematotoxin, although case reports of

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leukemia continued to be reported. For example, literature reviews by Panati [2], Saita [3], Browning [4] and Vigliani [5] cited 10, 23, 61, and >150 cases of leukaemia, respectively, linked to benzene exposure. Case series reports by Goguel [6], Girard and Revol [7] and Aksoy [8] cited a predominance of acute leukemia, and a predominance of myeloblastic and erythroleukemia. However, these subtypes were not mentioned exclusively, and the absence of phenotypic, molecular and/or cytogenetic analyses at the time prevented a definitive diagnosis in many cases, especially for acute leukemias.

By the 1970s, the first attempts to quantify the risk of leukemia due to benzene were made [9,10]. While these studies were rather crude by contemporary standards, they strongly suggested that the risk of leukemia was increased in workers exposed to high concentrations of benzene. Shortly thereafter, more robust methods of cohort enumeration and exposure estimation allowed refined estimates of the dose response relationship between benzene and aggregate leukemias [11,12]. More recently, several case-control studies, cohort studies and updates have been reported, some of which contain quantified benzene exposure estimates and more robust diagnostic procedures for leukemia subtypes.

Previous reviews of the leukemic subtypes associated with benzene have yielded disparate conclusions. Lamm et al. [13] concluded that the evidence strongly supported a causal connection between acute myelocytic leukemia (AML) and benzene, but that evidence linking acute lymphocytic leukemia (ALL), chronic myelogenous leukemia (CML) and chronic lymphocytic leukemia (CLL) to benzene was lacking. Savitz and Andrews [14] concluded that the overall pattern did not indicate an association limited to AML, and concluded that evidence linking lymphocytic leukemia to benzene was similar to that for myeloid leukemia. Discrepancies in the conclusions between these two reviews are based on the information available at the time of the review, as well as the study inclusion criteria employed.

Since the latest review, several new studies have appeared in the literature, including cohort updates [15,16], as well as nested case-control studies [17,18]. In addition, a large cohort study has been reported in Chinese workers [19,20]. Thus, an updated review of the literature relating benzene to specific leukemia subtypes is motivated by the availability of new relevant research as well as the use of refined diagnostic methods for leukemia subtypes.

2. Methods

2.1. Search and inclusion criteria

We searched the epidemiologic literature on benzene exposure and leukemia in the MEDLINE and TOXNET databases through October 2004 using the keywords “benzene”, “leukemia” and “adverse health effects”. We complemented this search by reviewing the reference lists from extant literature reviews and criteria documents on benzene. Over 1000 abstracts were reviewed to identify studies that possibly met criteria described below.

The selection of studies for inclusion in this report was based on several criteria. First, only peer-reviewed published studies were included. Second, studies were evaluated as to whether some attempt to measure benzene exposure per se was made. Studies that measured total hydrocarbons or total aromatics, for example, were not included, although benzene exposure may have been present. However, studies that measured benzene along with several other solvents or substances were included. Third, studies were required to have reported risks on at least one of the four major leukemia subtypes: acute myelocytic leukemia, acute lymphocytic leukemia, chronic myelocytic leukemia or chronic lymphocytic leukemia. Fourth, proportionate mortality studies and geographic-based studies involving aggregate rates (i.e., “ecologic” epidemiologic studies) were excluded due to the methodological deficiencies of these designs. In addition, case and case series reports did not qualify if no attempt to estimate a denominator (required for risk computation) was made. In those studies with an overlap in population, the most recently published study was selected unless the previous study contained more specificity regarding risks for leukemia subtypes. Coverage of non-English language studies may not be complete, although we did include such studies when appropriate documentation and translation could be obtained.

After reviewing abstracts, a full-text review was conducted on more than 400 possibly relevant publications. For studies possibly satisfying the above criteria, we abstracted all data on relative risk (RR) measures

(e.g., odds ratios (ORs); standardized mortality ratios (SMRs)), with corresponding confidence intervals, standard errors and *p*-values when available. If confidence intervals were not given, estimates were obtained using the methods of Cornfield [21] for case-control studies and Breslow and Day [22] for cohort studies. In some cases, standard errors or confidence intervals were estimated using methods outlined in Greenland [23]. In studies not reporting the full complement of subtype results, we used case listings to obtain cell-type specific counts, when available. Background mortality or incidence rates for leukemia subtypes were obtained from information supplied by the study or externally from published reports of comparable populations with respect to age, sex, time period, and geographical area. The Appendix provides further details of the estimation and selection procedures used for each study.

We categorized studies according to characteristics including design, exposure assessment, disease classification, and control for confounding variables. We also classified studies with regard to the type of industry studied. Study design consisted of either cohort studies or case-control studies, which were further categorized into population-based and nested case-control studies. Exposure assessment considered the source of the underlying exposure data and the exposure metric(s) used. Studies using actual measurements or quantitative cumulative exposure estimates were distinguished from those using less informative surrogate measures including relative exposure intensity, employment duration, or ever/never classifications. Disease classification considered the source of diagnostic information and whether there was clinical confirmation from medical records or histopathological, morphological and/or cytogenetic reviews. We also classified studies as to whether the International Classification of Diseases (ICD) or the French–American–British (FAB) schemes were used (no studies used the Revised European–American Lymphoma (REAL) classification scheme). An evaluation of confounding included a determination of whether the study accounted for age, sex, and smoking, as well as other quantifiable aspects relating to case ascertainment, latency and follow-up completion. Finally, studies were classified by industry type to provide information on likely exposure intensity as well as the likelihood of other exposures in the work environment. These industrial sectors (according to approximate exposure intensity)

Table 1
Cohort studies on benzene and leukemia subtypes

Study (first author and year)	Country	Number of cases[a] (AML/CLL/CML/ALL)	Population at risk	Dose response analysis	Exposure metric	Disease classification	Control for: age/sex	Other exposures
Aksoy (1974) [10]	Turkey	19/0/0/3	Est.	No	Ever/never	Medical records	N	Few
Bloemen (2004) [15]	US	4/1/–/–	Yes	Yes	Cumulative	Death certificate/ICD	Y	Some
Collins (2003) [16]	US	5/2/–/–	Yes	Yes	Cumulative	Death certificate/ICD	Y	Some
Crump (1994) [24]	US	8/0/2/1	Yes	Yes	Cumulative	Death certificate/ICD	Y	Few
DeCoufle (1983) [25]	US	1/1/0/0	Yes	No	Ever/never	Medical records/ICD	Y	Some
Hayes (1997) [19]								
Li (1997) [20]	China	21/–/9/5	Yes	Yes	Cumulative	Medical records/FAB	Y	Multiple
Lynge (1997) [26]	Scandinavia	13/10/–/–	Yes	No	Ever/never	Cancer registry/ICD	Y	BTX[b]
Tsai (1983) [27]	US	0/0/0/0	Yes	No	Ever/never	Death certificate/ICD	Y	BTX[b]
Vigliani (1964) [9]	Italy	12/0/0/0	Est.	No	Ever/never	Medical records	N	Few

[a] Number of cases of AML, CLL, CML, and ALL exposed above benzene background level ("–" indicates no data).
[b] BTX, primarily benzene, toluene, and xylene.

included petroleum/gas; chemical; paint/multiple; and printing and rubber/shoe-manufacturing. Relative risk estimates and confidence intervals were plotted according to study design and industrial sector. Population-based studies were not plotted according to industry sector, but one workplace study involving multiple industrial sectors was classified under "paint/other" since a large percentage of study subjects were painters.

3. Results

The selection process identified 22 studies for inclusion. Nine of the 22 studies were cohort studies, which are summarized in Table 1.

Five of the nine cohort studies were performed in the US, no other country yielded more than one study. Seven of the nine cohort studies enumerated the total population at risk, while two provided only an estimate of this population. The latter two studies were thus unable to directly adjust for potential age differences in the exposed and comparison populations. These two studies are thus classified as "crude" cohort studies, as they have some unique methodologic weaknesses compared to the remaining seven. Four of the nine cohort studies yielded cumulative exposure estimates and examined dose response relationships. One of the cohort studies classified acute leukemias according to the FAB criteria, while four of the nine studies used only the death certificate diagnosis to classify leukemias. Three of the nine studies were done in an environment where benzene was the primary exposure, while only one of the nine studies was characterized by multiple agents other than benzene.

Table 2 summarizes the 13 case-control studies that met the study criteria. Four of the 13 were conducted in the US, with two each in Sweden, Italy and France. Only three of these thirteen studies were nested within larger cohorts, with attendant advantages in exposure assessment. On the other hand, the 10 population-based studies primarily used an ever/never exposure metric and thus, did not perform dose-response analyses. However, five of the 13 studies, all population-based, used the FAB nomenclature for classifying acute leukemias, usually with attendant cytogenetic analyses.

Fig. 1 shows characteristics of all 22 cohort and case-control studies. The studies were published between 1964 and 2004. Eleven studies consisted of multiple industries, five were in petroleum/gas workers, three in chemical workers, and three related to shoe, printing, and rubber industries. Regarding the highest quality exposure metric used, 6 had indices of cumulative exposure, 4 had information on relative intensity and/or duration of exposure, and 12 studies had

Table 2
Case-control studies on benzene and leukemia subtypes

Study (first author and year)	Country	Number of cases[a] (AML/CLL/CML/ALL)	Dose response analysis	Exposure metric	Disease classification	Other exposures
Population-based						
Adegoke (2003) [28]	China	26/–/15/9	Yes	Duration	Cancer registry/ICD	Multiple
Albin (2000) [29]	Sweden	39/–/–/–	Yes	Intensity	FAB	Multiple
Ciccone (1993) [30]	Italy	8/–/6/–	Yes	Ever/never	FAB	Multiple
Crane (1992) [31]	US	4/–/–/–	No	Ever/never	FAB	Multiple
Flodin (1986) [32]	Sweden	0/–/–/–	No	Ever/never	Medical records/ICD	Multiple
Linet (1987) [34]	US	–/36/–/–	No	Ever/never	Medical records/ICD	Multiple
Linos (1980) [35]	US	–/3/–/–	No	Ever/never	Medical records	Multiple
Malone (1989) [36]	US	–/13/–/–	No	Ever/never	Cancer registry/ICD	Multiple
Mele (1995) [37]	Italy	5/–/–/–	No	Ever/never	FAB	Multiple
Richardson (1992) [38]	France	15/–/–/0	No	Intensity	FAB	Multiple
Nested						
Glass (2003) [17]	Australia	6/7/1/–	Yes	Cumulative	Medical records/ICD	BTX[b]
Guenel (2002) [33]	France	6/4/6/3	Yes	Intensity	Cancer registry/ICD	Some
Rushton (1997) [18]	UK	25/30/8/2	Yes	Cumulative	Cancer registry/ICD	BTX[b]

[a] Number of cases of AML, CLL, CML, and ALL exposed above benzene background level ("–" indicates no data).
[b] BTX, primarily benzene, toluene, and xylene.

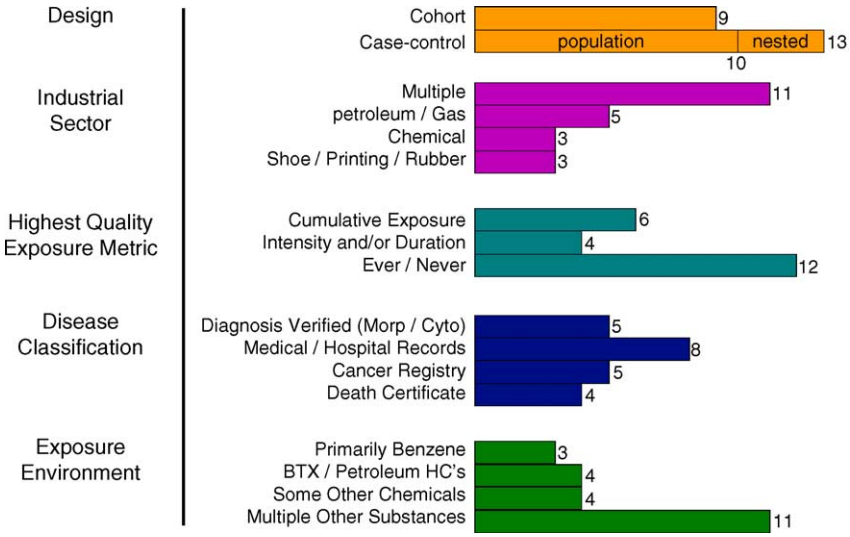

Fig. 1. Characteristics of 22 studies on benzene and leukemia subtypes.

an exposure characterization of ever versus never. Five of the studies employed FAB nomenclature, eight used hospital and/or medical records, while four used only death certificates to classify subtypes. The majority of studies ($n = 15$) had exposure environments characterized. by the presence of other chemicals or as having multiple substances; only three studies were in environments where primarily benzene was present.

Figs. 2 and 3 show relative risks and confidence intervals for AML by study design and industry sector, respectively. In Fig. 2, elevated risks are documented across cohort and case-control studies, and within the types of cohort and case-control studies. Risks are particularly high in the early crude cohort studies probably due to the higher exposures prevalent in these time frames, rather than design differences. Within the case-control studies, suggestive indications of dose response relationships are seen in all three nested studies, but only one of three population-based studies. This may be a result of relatively more precise exposure assessment in the nested studies. Fig. 3 shows particularly high and significant AML risks with positive dose response relationships especially in the more highly exposed rubber, shoe, and paint sectors. Risks are somewhat lower and often not statistically significant in the petroleum, gas and chemical sectors. These studies confirm that there is a well-documented relationship between AML and benzene, in which dose response relationships are seen across study designs.

Figs. 4 and 5 show results for CLL. An interesting pattern of results emerges by study design (Fig. 4), in that nested case-control studies tend to show elevated risks, with possible dose response relationships in at least two of the three studies. On the other hand, cohort studies show no such risks, while only one of three population-based case-control studies reports an elevated risk. When examined by industry sector (Fig. 5), there are few studies in more highly exposed sectors, but they do not suggest an excess risk of CLL. Most of the studies were conducted in relatively lower exposure

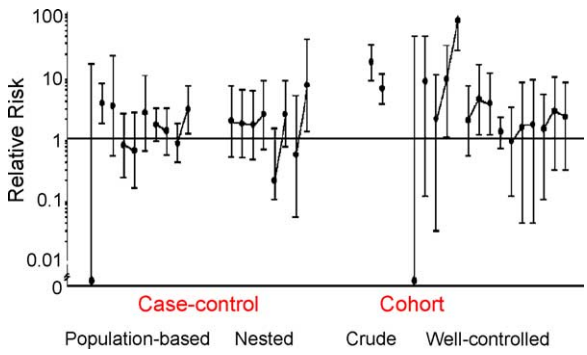

Fig. 2. AML results by study design.

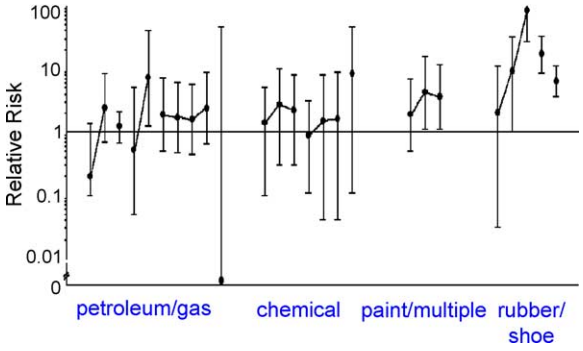

Fig. 3. AML results by industry sector.

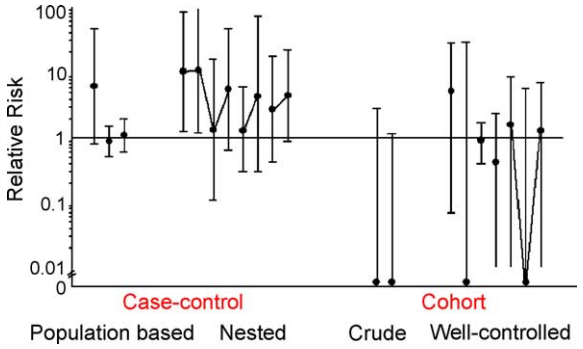

Fig. 4. CLL results by study design.

environments, with some suggestive dose response relationships within the studies.

Figs. 6 and 7 show risks for CML by study design and industry sector, respectively. Four of five cohort studies have not found CML in benzene-exposed workers. For case-control studies, the more suggestive evidence comes from population-based, rather than nested

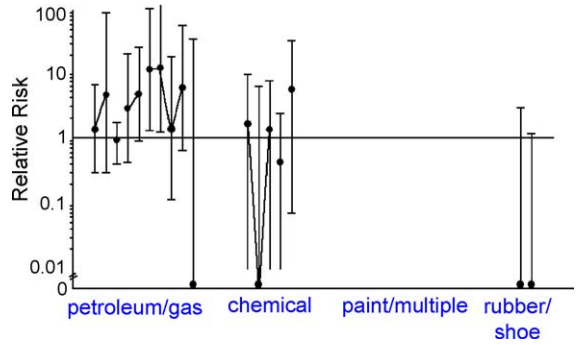

Fig. 5. CLL results by industry sector.

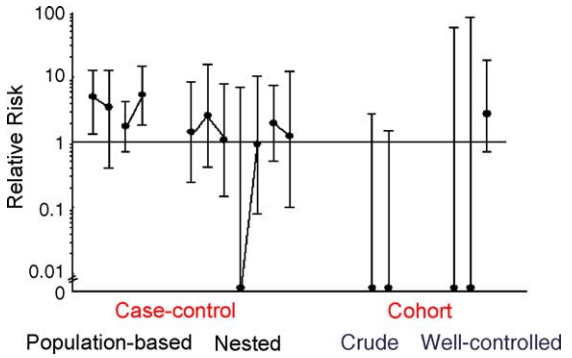

Fig. 6. CML results by study design.

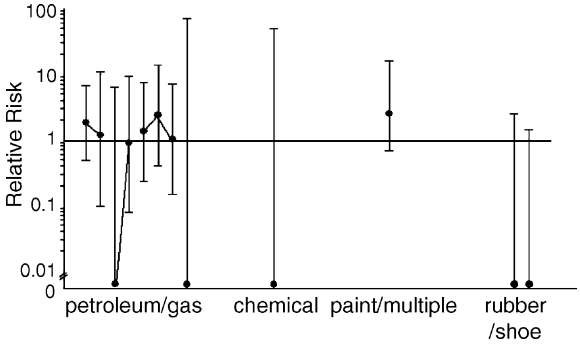

Fig. 7. CML results by industry sector.

case-control studies. However, the number of studies is small, and the width of confidence intervals often spans more than one order of magnitude, reflecting the relative rarity of CML.

Finally, Figs. 8 and 9 display risks for ALL, the rarest leukemia subtype in adults. In general, risk estimates in the cohort studies do not suggest elevated

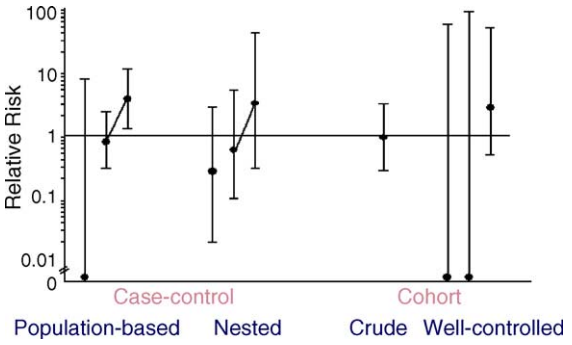

Fig. 8. ALL results by study design.

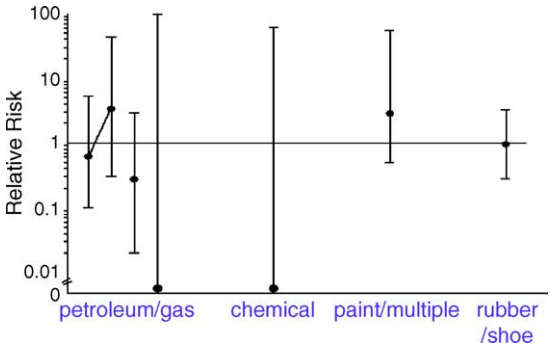

Fig. 9. ALL results by industry sector.

risks of ALL, but confidence intervals are extremely wide. The two case-control studies that have examined dose response both suggest a possible relationship, but two other case-control studies do not suggest an excess risk. Again, the paucity of studies on ALL and rarity of the tumor yields sparse information on the potential relationship with benzene.

4. Discussion

Although benzene is classified by many regulatory bodies as a proven human leukemogen, the precise relationship with different leukemia subtypes is still an open question. Most would agree that the relationship with AML is proven, but there is considerably more uncertainty regarding the other three major subtypes (as well as other LH cancers, which is not a focus of this paper). We surveyed the extant literature and used criteria that were focused on identifying studies which yielded information on exposure to benzene per se, the risk for specific leukemia subtypes, and the ability to estimate relative risks. We identified 22 studies conducted over 40 years that contained relevant information. The studies were classified according to various characteristics and results were presented by study design and industry sector with the aim of discerning whether the pattern of results differed by leukemia subtype.

Despite the considerable number of publications on benzene, it is surprising that this comprehensive search yielded only 22 relevant studies, even considering that we limited the search to the published literature. The paucity of studies probably derives from the fact that large populations are needed to detect increases in rare tumors, particularly CML and ALL, and the ability to subtype leukemias has evolved over the 40 years in which we identified studies. Several studies simply report on total leukemias with no further information. Yet etiologic factors between leukemia subtypes are marked [39].

Our results indicate that there are somewhat different patterns of risk between subtypes. The pattern of results may be influenced somewhat by the amount of information present for each subtype. Thus, it is easier to discern patterns for AML, and to some extent, CLL, because more studies report on these subtypes.

The AML results are, not surprisingly, consistent with a relationship with benzene. Dose response trends are seen across study designs, particularly in the "well-conducted" cohort studies. Higher risks are seen in the rubber, shoe, and paint industry sectors, where benzene exposures have been historically high. This pattern of the stronger designs and higher exposures showing higher risks is consistent with an AML/benzene relationship.

For CLL, a somewhat different pattern emerges. Most, but not all, of the suggestive results reside in the nested case-control studies, and not the cohort studies. Suggestive dose response relationships are present in two of three nested case-control studies [33,17]. The third nested case-control study shows somewhat elevated odds ratios in three of the four exposure categories, but not the penultimate category. This could be the result of small numbers within each category. The nested case-control studies have advantages in terms of benzene exposure assessment compared to the population-based case-control studies. Thus, the fact that these studies tend to show somewhat elevated risks, while two of the three population-based studies do not, can be thought of as consistent with a true relationship. Detracting from this, however, is the fact that none of the cohort studies suggests a risk. One cohort study, performed in Chinese workers, did not report CLL, consistent with the fact that this subtype is much less prevalent in the Chinese general population. The highly exposed shoe workers in both the Aksoy [10] and Vigliani [9] studies showed no CLLs.

Smaller numbers hinder a definitive assessment for the remaining two subtypes. For CML, there are only 10 studies (five case-control and five cohort) where relative risks are reported. The five case-control studies included at least crude assessments of dose response,

but only one [28] found a suggestive trend for CML. Similarly, only one of five cohort studies [20] found a somewhat elevated risk of CML. Categorizing results and searching for suggestive patterns was generally uninformative because there were relatively few studies, and of the ones conducted, few suggested an increase in risk for CML. While these results for CML seem the least persuasive in terms of a potential benzene/subtype risk, definitive conclusions are hindered by relatively few studies and wide confidence intervals.

Finally, for ALL, the paucity of studies is particularly apparent. Only eight studies have been conducted, (four cohort, four case-control) while only two of the case-control studies have reported at least crude dose response analyses. Both of these studies showed at least suggestive relationships [28,33]. Five of the other seven studies, however, report risks at or below unity, including three of four cohort studies. This pattern is not persuasive in demonstrating a benzene/ALL link, but as for CML, it is difficult to evaluate such patterns due to the sparse data.

We have shown that the risk for AML is consistent across study designs and somewhat higher in the more strongly designed studies and more highly exposed industry sectors. This pattern is not seen for the other three subtypes, although fewer studies have reported results for these subtypes. Particularly for ALL, results are sparse and difficult to evaluate. Thus, while the evidence to date confirms the link between AML and benzene, further work is necessary to allow more definitive conclusions for the other three subtypes.

It is instructive to compare our results with previous reviews. Lamm et al. [13], who concluded that benzene is related to AML and not to other subtypes, reviewed six studies with 126 total cases of leukemia. These authors showed that five of the six studies reported that more than two thirds of the cases in the six studies were AML. At the time of Lamm et al.'s review [13], there was nearly no information on background expected numbers of AML in the studies. Thus, the authors reported on the percentage of total leukemia cases that were AML. While this method provides insights, it does not provide information on the relative risks of subtypes. The present review contains information on two of the six studies reviewed in [13]. In addition, each of the other four studies used by Lamm were updated over the past 15 years, thus this report used the updated information for these four studies. In addition, this review added information from 16 new studies not included in [13]. Thus, this review differs from the Lamm report in that we concentrated on relative risk estimates rather than the proportion of cases, and new information was added for 20 studies.

Savitz and Andrews [14] also reviewed the literature on benzene and leukemia subtypes as well as other lymphohematopoietic cancers. Based on 14 studies applicable to leukemia subtypes, these authors concluded that the evidence linking benzene to subtypes other than AML is no less persuasive than that for AML alone.

In some cases, these authors applied inclusion criteria similar to ours, but there are also some important differences. Like the present report, Savitz and Andrews included only studies that measured benzene per se, and only included studies that generated relative risks based on appropriate numerator and denominator data. The major difference in inclusion criteria was that we required a study to report on at least one of the four major subtypes, while Savitz and Andrews also included studies that classified leukemias as "acute", "lymphocytic", and/or "myeloid", not otherwise specified. The present report included seven of the 14 studies in the Savitz and Andrews review pertaining to leukemia subtypes. In addition, we included either updated or more specific subtype information from two of the 14 studies, while the remaining five did not meet our study criteria. In addition, our review included 13 other studies, the majority of which were published after the Savitz and Andrews review [14].

Our results differ somewhat from those of Savitz and Andrews, who did not detect a difference in risks by leukemia subtypes. Part of this difference is simply due to the inclusion of more studies in the present review. Another reason for the difference is that Savitz and Andrews evaluated somewhat different entities. While we restricted evaluation to AML, ALL, CML, and CLL, Savitz and Andrews examined AML, CLL, "lymphocytic", "myeloid", and "acute leukemia". By comparing AML, "myeloid", and "acute" leukemia, Savitz and Andrews were comparing overlapping categories; that is, "acute" leukemia and "myeloid" leukemia would consist of many cases of AML. In fact, five of the six statistically significant results reported in the Savitz and Andrew review are from the three classifications that consist of presumably many or all cases of AML.

We are aware that the use of the REAL classification scheme will affect how leukemias and lymphomas are

reported in the future. In particular, acute lymphocytic leukemia is grouped with lymphoblastic lymphoma to form a new entity called "precursor lymphoblastic leukemia/lymphoma". This change is not a marked one, since ALL will probably predominate in this new category [40]. The new scheme has a much larger impact on CLL, as this will be one of three entities under "chronic lymphocytic leukemia/lymphoma". Small cell lymphocytic lymphoma and prolymphocytic leukemia will also be part of the new category. While we did not locate any benzene studies that employed the REAL scheme, we would expect that this new entity will ultimately provide a clearer picture of potential benzene-related risks, especially for B versus T-cell entities.

Other than the lack of data on rarer subtypes, there are other shortcomings of this review. Except for displaying the basis for disease classification in Tables 1 and 2, this review does not account for the quality of that classification directly. It is likely that earlier studies used cruder methods (many based on morphology only) to subtype leukemias. Rarer subtypes such as erythroleukemia and ALL may have been particularly prone to error in early studies, both in terms of specificity (misdiagnosis) and sensitivity (i.e., under-reporting). In addition, in some cases, we needed to estimate populations at risk, background rates of leukemia subtypes, standard errors, and/or confidence intervals. This source of uncertainty likely applies more frequently to risks of ALL and CML, since results for the other two subtypes were reported more frequently. We also did not examine the effect of including possibly different AML subtypes in the risk estimates; when there was a choice, we extracted the more inclusive results for AML. The studies that did not use the FAB scheme mostly included only the M1 and M2 subtypes of AML, although there were a few exceptions. To the extent that the risk of benzene-induced AML varies by subtype, we may have misestimated the risk of AML by including the widest definition of AML.

Based on the literature to date, we found a consistent link between benzene and AML across study designs and industry sectors. For AML, more highly exposed industry sectors showed higher risks. This pattern was not evident in the other three subtypes. There was a suggestion of CLL risk in nested case-control studies, but not population-based nor cohort studies. For CML, there was not consistent evidence of a risk due to benzene in the studies reported to date. For ALL, there was also little consistent evidence of a link to benzene, although this was based on few studies and very wide confidence intervals. Sparse data limit definitive conclusions, especially for ALL, and somewhat for CML.

Appendix A. Estimation and selection procedures according to study

In this appendix, table numbers refer to tables in the papers cited, not to tables in this review.

A.1. Aksoy et al. [10]

Another Aksoy publication (1980) provided a distribution of leukemia subtypes among a series of hospital patients (exposed and non-exposed) comparable with respect to the time period and mean age at diagnosis [41]. The present study cites an overall incidence of leukemia in the general population of 6 per 100,000. Cell-type specific incidence rates can be estimated by multiplying the general population rate times the percentage of subtype in the non-exposed group. This yields non-exposed or background rates (per 100,000) of 1.5, 1.62, 1.26, and 1.62 for ANLL, ALL, CML, and CLL, respectively. The present study cites 22 leukemia and four pre-leukemia among 28,500 exposed workers during 1967–1973. Person years at risk (PYAR) can be estimated at 199,500. The breakdown of subtypes given is 14 AML, 19 ANLL, and 3 ALL. The study also reports an incidence rate of 13 per 100,000 for the 26 cases. From this, an incidence rate of 11 per 100,000 can be estimated for overall leukemia after subtracting the 4 pre-leukemias. The corresponding rates among exposed workers are then estimated at 9.5 per 100,000 for ANLL and 1.5 per 100,000 for ALL. There were no cases of CML or CLL. The expected cases for each subtype were calculated by applying the background rates estimated above to the total number of person years at risk (199,500). Confidence intervals were estimated using the procedure of Breslow and Day [22].

A.2. Ciccone et al. [30]

Based on the AML and CML case distribution presented in Table 2, crude ORs for low and high exposure groups were calculated separately and combined using the referent group with no exposure. Confidence intervals were estimated using Cornfield's method [21].

A.3. Collins et al. [16]

SMRs for ANLL and CLL were calculated for the combined exposure group and the method of Breslow and Day [22] was used to estimate confidence intervals.

A.4. Crump [24]

Of 14 total deaths from leukemia, 8 were AML (including 2 monocytic). We used this study rather than the Wong, 1995 update [42], because Wong only included six AML's, and we could also estimate other subtype specific risks from the data presented. For, AML, results from Crump were used. In addition, according to Rinsky et al. [43] there were also two CML, one ALL and two unspecified (Appendix A) in the Crump population. Based on SEER US. male age-adjusted incidence rates for each subtype during 1973–1978, an average percentage distribution yielded: 13% ALL, 43% CLL, 28% AML, and 17% CML (Ries et al., 2000) [44]. Study findings indicated an overall expected number of 4.75 leukemia deaths. Expected deaths for CML, ALL, and CLL subtypes were estimated by multiplying the percentage of the subtype times the overall expected number of 4.75. Confidence intervals were estimated using the procedure of Breslow and Day [22].

A.5. DeCoufle et al. [25]

The study reported 3 leukemia deaths among 259 exposed males followed through 1977. The subtypes were one CLL, one acute monocytic, and one acute myelomonocytic. The study cited a total expected number of 0.44 for leukemia with a p-value < 0.01. Expected numbers of deaths for subtypes were estimated based on the proportional distribution of SEER rates as explained above for Crump. Confidence intervals were estimated using the method of Breslow and Day [22].

A.6. Flodin [32]

Table 3 provides the number of exposed cases ($n = 0$) and controls ($n = 3$) along with a crude rate ratio of 0. The confidence interval for the case-control logit estimate was obtained using the SAS FREQ procedure (SAS, 2003) [45].

A.7. Glass et al. [17]

Confidence intervals were not reported for the exposure categories of CML in Table 6. Another report of this study population by the investigators provided a distribution of cases (accessed 11/4/2004 at http://www.aip.com.au/pdf/case_study.pdf). Confidence intervals, when not provided, were calculated for the case-control logit estimate using the SAS FREQ procedure (SAS, 2003) [45].

A.8. Guenel et al. [33]

The two exposure groups in Table 6 were combined and compared to the referent category of never exposed. Confidence intervals were calculated using Cornfield's method [21].

A.9. Hayes et al. [19]

ANLL results were obtained from Hayes et al. [19] and the other subtype results were obtained from Li et al. [20] since they were not reported in Hayes et al. [19].

A.10. Linet et al. [34]

The ORs presented in Table 2 ranged from 0.58 to 1.5. We selected the "NOHS all subjects" OR of 0.89 which was approximately mid-range.

A.11. Linos et al. [35]

The study reported 138 total leukemia cases; 4 were exposed to benzene compared to 3 among 276 controls. Three of the four exposed cases were CLL. Table 1 provided a case distribution by subtype with 46 total CLL. This implies there were 43 unexposed CLL cases. From this, a crude OR for CLL was calculated and confidence limits were estimated using Cornfield's method [21].

A.12. Lynge et al. [26]

Results for males (Table 3) and females (Table 4) were combined and confidence intervals were estimated using the method of Breslow and Day [22].

A.13. Malone et al. [36]

While the OR and confidence interval given in Table 1 indicates "aromatic hydrocarbon" exposure, the text states that this result is specific for benzene exposure.

A.14. Mele et al. [37]

Table 2 gives separate findings for acute promyelocytic leukemia (APL) and other AML. ORs are reported for the occupation of shoemaking adjusted for age, sex, education, and residence. Adjusted OR's and confidence intervals were calculated for the combined groups of AML by weighting the individual adjusted ORs and confidence intervals by the proportion of cases in each AML sub-type.

A.15. Richardson et al. [38]

Table 5 reports adjusted ORs for "high or medium levels" of benzene exposure for ALL and AML. No confidence interval was given for ALL and it was estimated based on the control frequencies in Table 2 compared to the ALL case frequencies in Table 5 using the SAS FREQ procedure (SAS, 2003) [45].

A.16. Rushton et al. [18]

No confidence interval was reported for the ALL OR for cumulative exposure as a continuous variable. The confidence interval 0.97–1.08 was obtained from Table 5 of the investigators' final report (Institute of Petroleum, June 1995) [46].

A.17. Tsai et al. [27]

There were no leukemia deaths compared to 0.29 expected among 454 workers followed between 1952 and 1978. Expected deaths for subtypes were estimated using the procedure outlined above for the Crump study. Confidence intervals were obtained using the method of Breslow and Day 1985 [22].

A.18. Vigliani et al. [9]

The study reported an incidence of 10 per 100,000 for all leukemia among the general population of Milan during 1959–1961. The percentage of subtypes was given as 46% acute, 28% CML and 26% CLL. Separate subtype data for Tuscany indicates that 16% of acute leukemia are ALL (personal communication, Constantini, 2004) [47]. Subtype incidence rates (per 100,000) for similar time periods were estimated based on this distribution: 3.86 for AML, 0.74 for ALL, 2.8 for CML, and 2.6 for CLL. Table 1 provides the number of acute leukemia cases by year from 1960 to 1963 for 5000 exposed workers in Pavia and Milan. The text states that no cases of CML or lymphatic leukemia (i.e., ALL or CLL) occurred among exposed workers. Therefore, all 12 acute leukemia in Table 1 are AML. All cases occurred during 1960-1963 among exposed workers with an estimated 20,000 PYAR. Expected numbers were derived by multiplying subtype background rates estimated above by 20,000 PYAR (expected = 0.15, 0.77, 0.56, and 0.52 for ALL, AML, CML, and CLL, respectively). Confidence limits were obtained by the method of Breslow and Day [22].

References

[1] P. Delore, C. Borgomano, Leucemie aigue au cours de l'intoxication benzenique. Sur l'origine toxique de certaines leucemies aigues et leurs relations avec les anemies graves, J. de Med. de Lyon 9 (1928) 227–233.
[2] F. Penati, E.C. Vigliani, Sul problema delle mielopathe aplastiche, pseudoaplastiche e leucemiche da benzolo, Rassegna. Med. Ind. 9 (1938) 345–361.
[3] G. Saita, Mielosi aplastica e successiva mielosi leucemica, leucipenica, provocata da benzolo, Med. Lav. 36 (1945) 143–158.
[4] E. Browning, Toxicity Metabolism of Industrial Solvents, Elsevier Publishing Co., New York, 1965.
[5] E.C. Vigliani, Leukemia associated with benzene exposure, Ann. N Y Acad. Sci. 27 (1976) 143–151.
[6] A. Goguel, A. Cavigneaux, J. Bernard, Les leucemies benzeniques de la region parisienne entre 1950 et 1967, Nouv. Rev. Fr. Hematol. 7 (1967) 465–480.
[7] P.R. Girard, L. Revol, La frequence d'une exposition benzenique au cours des hemopathies graves, Nouv, Rev. Fr. Hematol. 10 (1970) 477–484.
[8] M. Aksoy, K. Din Col, S. Erdem, G. Din Col, Acute leukemia due to chronic exposure to benzene, Am. J. Med. 52 (1972) 160–166.
[9] E.C. Vigliani, G. Saita, Benzene and leukemia, N. Engl. J. Med. 271 (1964) 872–876.
[10] M. Aksoy, S. Erdem, G. Din Col, Leukemia in shoe-workers exposed chronically to benzene, Blood 44 (1974) 837–841.
[11] P.F. Infante, J.K. Wagoner, R.A. Rinsky, R.J. Young, Leukaemia in benzene workers, Lancet (1977) 76–78.

[12] W.G. Ott, J.C. Townsend, W.A. Fishbeck, R.A. Langner, Mortality among individuals occupationally exposed to benzene, Arch. Environ. Health 33 (1978) 3–10.
[13] S.H. Lamm, A.S. Walters, R. Wilson, D.M. Byrd, H. Grunwald, Consistencies and inconsistencies underlying the quantitative assessment of leukemia risk from benzene exposure, Environ. Health Perspect. 82 (1989) 89–97.
[14] D.A. Savitz, K.W. Andrews, Review of epidemiologic evidence on benzene and lymphatic hematopoietic cancers, Am. J. Ind. Med. 31 (1997) 287–295.
[15] L.J. Bloemen, A. Youk, T.D. Bradley, K.M. Bodner, G. Marsh, Lymphohaematopoietic cancer risk among chemical workers exposed to benzene, Occup. Environ. Med. 61 (2004) 270–274.
[16] J.J. Collins, B. Ireland, C.F. Buckley, D. Shepperly, Lymphohaematopoietic cancer mortality among workers with benzene exposure, Occup. Environ. Med. 60 (2003) 676–679.
[17] D.C. Glass, C.N. Gray, D.J. Jolley, C. Gibbons, M.R. Sim, L. Fritschi, G.G. Adams, J.A. Bisby, R. Manuell, Leukaemia risk associated with low level benzene exposure, Epidemiology 14 (2003) 569–577.
[18] L. Rushton, H. Romaniuk, A case-control study to investigate the risk of leukaemia associated with exposure to benzene in petroleum marketing and distribution workers in the UK, Occup. Environ. Med. 54 (1997) 152–166.
[19] R.B. Hayes, S.N. Yin, M. Dosemeci, G.L. Li, S. Wacholder, L.B. Travis, C.Y. Li, N. Rothman, R.N. Hoover, M.S. Linet, Benzene and the dose-related incidence of hematologic neoplasms in China, J. Natl. Cancer Inst. 89 (1997) 1065–1071.
[20] G. Li, D. Tanrong, X. Zhang, A cohort study of cancer among workers exposed to benzene, Chin. J. Ind. Hyg. Occup. Dis. 15 (1997) 349–353.
[21] J. Cornfield, A statistical problem arising from retrospective studies, In: J., Neyman, (Ed.), Proceedings of the Third Berkeley Symposium on Mathematical Statistics and Probability, Berkeley, CA, University of California Press, 1956, pp. 135–148.
[22] N.E. Breslow, N.E. Day, The standardized mortality ratio, in: Bulletin of the International Statistical Institute: Proceedings of the 45th session invited papers, Amsterdam, 1985, pp. 55–74.
[23] S. Greenland, Quantitative methods in the review of epidemiologic literature, Epidemiol. Rev. 9 (1987) 1–30.
[24] K. Crump, Risk of benzene-induced leukemia: a sensitivity analysis of the pliofilm cohort with additional follow-up and new exposure estimates, J. Toxicol. Environ. Health 42 (1994) 219–242.
[25] P. Decoufle, W.A. Blattner, A. Blair, Mortality among chemical workers exposed to benzene and other agents, Environ. Res. 30 (1983) 16–25.
[26] E. Lynge, A. Andersen, R. Nilsson, L. Barlow, E. Pukkala, R. Norlinder, P. Boffetta, P. Grandjean, P. Heikkila, L.G. Horte, R. Jakobsson, B. Moen Lundberg, T. Partanen, T. Riise, Risk of cancer and exposure to gasoline vapors, Am. J. Epidemiol. 145 (1997) 449–458.
[27] S.P. Tsai, C.P. Wen, N.S. Weiss, O. Wong, W.A. McClellan, R.L. Gibson, Retrospective mortality and medical surveillance studies of workers in benzene areas of refineries, J. Occup. Med. 25 (1983) 685–692.
[28] O.J. Adegoke, A. Blair, X.O. Shu, M. Sanderson, F. Jin, M. Dosemeci, C.L. Addy, W. Zheng, Occupational history and exposure and the risk of adult leukemia in Shanghai, Ann Epidemiol. 13 (2003) 485–494.
[29] M. Albin, J. Bjork, H. Welinder, H. Tinnerberg, N. Mauritzson, B. Johannson, R. Billstrom, U. Stromberg, Z. Mikoczy, T. Ahlgren, P.-G. Nilsson, F. Mitelman, L. Hagmar, Acute myeloid leukemia and clonal chromosome aberrations in relation to past exposure to organic solvents, Scand. J. Work Environ. Health 26 (2000) 482–491.
[30] G. Ciccone, D. Mirabelli, A. Levis, P. Gavarotti, G. Rege-Cambrin, L. Davico, P. Vineis, Myeloid leukemias and myelodysplastic syndromes: chemical exposure, histologic subtype and cytogenetics in a case-control study, Cancer Genet. Cytogenet. 58 (1993) 135–139.
[31] M.M. Crane, J.E. Godwin, J.F. Annegers, M.J. Keating, Is histological subtype a marker for environmental exposures in acute myelogenous leukemia, Cancer Epidemiol. Biomarkers Prev. 1 (1992) 183–188.
[32] U. Flodin, M. Fredriksson, O. Axelson, B. Persson, L. Hardell, Background radiation, electrical work, and some other exposures associated with acute myeloid leukemia in a case-referent study, Arch. Environ. Health 41 (1986) 77–84.
[33] P. Guenel, E. Imbernon, A. Chevalier, A. Crinquand-Calastreng, M. Goldberg, Leukemia in relation to occupational exposures to benzene and other agents: a case-control study nested in a cohort of gas and electric utility workers, Am. J. Ind. Med. 42 (2002) 87–97.
[34] M.S. Linet, W.F. Stewart, M.L. Van Natta, L. McCaffrey, M. Szklo, Comparison of methods for determining occupational exposure in a case-control interview study of chronic lymphocytic leukemia, J. Occup. Med. 29 (1987) 136–141.
[35] A. Linos, R.A. Kyle, W.M. O'Fallon, L.T. Kurland, A case-control study of occupational exposures and leukaemia, Int. J. Epidemiol. 9 (1980) 131–135.
[36] K. Malone, T. Kowpsell, J. Daling, N. Weiss, P. Morris, J.W. Taylor, G.M. Swanson, J.L. Lyon, Chronic lymphocytic leukemia in relation to chemical exposures, Am. J. Epidemiol. 130 (1989) 1152–1158.
[37] A. Mele, M.A. Stazi, A. Pulsoni, G. Visani, B. Monarca, G. Castelli, L. Rocchi, G. Avvisati, F. Mandelli, Epidemiology of acute promyelocytic leukemia, Haematologica 80 (1995) 405–408.
[38] S. Richardson, R. Zittoun, S. Bastuji-Garin, V. Lasserre, C. Guihenneuc, M. Cadiou, F. Viguie, I. Laffont-Faust, Occupational risk factors for acute leukaemia: a case-control study, Int. J. Epidemiol. (1992) 1063–1073.
[39] M.S. Linet, R.A. Cartright, The Leukemias, in: D. Schottenfeld, J.F. Fraumeni Jr. (Eds.), Cancer Epidemiology and Prevention, Oxford University Press, New York, 1996, pp. 841–892.
[40] L.J. Herrinton, Epidemiology of the revised European–American lymphoma classification subtypes, Epidemiol. Rev. 20 (1998) 187–204.
[41] M. Aksoy, Different types of malignancies due to occupational exposure to benzene: a review of recent observations in Turkey, Environ. Res. 23 (1980) 181–190.

[42] O. Wong, Risk of acute myeloid leukemia and multiple myeloma in workers exposed to benzene, Occup. Environ. Med. 52 (1995) 380–384.
[43] R.A. Rinsky, R.W. Hornung, S.R. Silver, C.Y. Tseng, Benzene exposure and hematopoietic mortality: a long-term epidemiologic risk assessment, Am. J. Ind. Med. 42 (2002) 474–480.
[44] In: L.A.G., Ries, M.P., Eisner, C.L., Kosary, B.F., Hankey, B.A., Miller, L.X., Clegg, B.K., Edwards, (Eds.), SEER Cancer Statistics Review, 1973–1997, National Cancer Institute, NIH Pub no. 00-2789, Bethesda, MD, 2000.
[45] SAS Institute Inc., SAS/STAT_Users Guide, version 6, fourth ed., vol. 2, Cary, NC, SAS Institute Inc., 1989, pp. 846.
[46] L. Rushton, H. Romaniuk, The Institute of Petroleum Epidemiological Study: Results of a case-control study to investigate the risk of leukemia associated with exposure to benzene in petroleum marketing and distribution workers in the United Kingdom, University of Nottingham, June 1995.
[47] S. Constantini, personal communication regarding cell-specific leukemia rates for Tuscany, Italy.