Environmental, Occupational Exposures to Benzene and Cancer: a Meta –analysis

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ABSTRACT

Background: *Many epidemiological studies have been able to address the relationships between benzene exposure in the environment and the level of risk. Incidence has risen in industrialized countries since the 1960s and is highly and rapidly fatal and represent the fifth leading cause of deaths from cancer and 50%-100% more common in men than women. To identify, appraising and synthesizing the risk of cancer from benzene exposure in environment or workplace, a meta analysis is conducted.*

Method: *Epidemiological studies were identified through a computerized Medline and search on follow up and case control studies. The risk were identified as Standardized Mortality Ratios (SMRs), Standardized Incidence Ratios (SIRs), Relative Risk (RR) and Odd Ratio (OR). Data extraction covered characteristic of the study (publication year, country, study type, case definition, sources of cases, reference population, follow up period, risk measures) and risk estimates. The extracted data were checked for consistency and entered into a database and checked for correctness. Summary of relative risk was calculated from log(RR) and log(upper and lower limit of 95% CI of log RR). SE and weight of all studies were estimated by fixed effect model.*

Results: *The identified studies were industrial-based (n=6), community-based (n=2), and multicentre hospital-based study (n=2). RR of each study were also show benzene exposure was favour to risk of malignancy. This findings indicated workers who were exposed to benzene have risk to get malignancy 2 times higher than person who were not exposed to benzene. The excess risk found for Benzene was based on 8 population that were exposed with benzene from oil or petroleum industry. The risk of soft tissue carcinoma due to benzene exposure was highest with RR=15,59 (95% CI= 1.74-139.3). The lowest risk was stomach carcinoma RR 2,51 (95% CI= 1,60-2,94) and hemopoetic malignancy in general with RR 2,63 (95% CI= 0,90-7,69).*

Conclusions:*This meta-analysis suggest that environmental or occupational exposures of benzene may increase the risk of cancer, with the highest case of soft tissue carcinoma and the lowest case of stomach cancer. The excess may be pronounced in men who works in petroleum industry for more than 10 years and exposed to moderate and even level of benzene.*

Keywords: *benzene, malignancy, industry, petroleum*

INTRODUCTION

Benzene has been widely used as multipurpose organic solvent and has long been recognized for its carcinogenicity and toxicity effects. It is used as a raw material in the synthesis of styrene, phenol, cyclohexane, aniline and in the manufacture of detergents and various plastics. In the past, benzene was widely used as a solvent, mainly in industry, paint removers, adhesives and rubber cements. It is also emitted in the process of the petroleum industry and has been associated with the high incidences of many types of cancer on workers and also for the community near oil fields. [1-4] Many epidemiological study has been able to address the relationships between benzene exposure in the environment and the level of risk. Exposures to high level and long term with low exposures of benzene increases the risk of cancer, especially chronic lymphocytic leukemia (CLL) and acute non- lymphocytic leukemia (ANL), lymphoma, multiple myeloma, kidney cancer, exocrine pancreatic cancer and nasal cancer. The International Agency for Research on Cancer has classified the evidence of carcinogenicity to humans as sufficient for benzene and limited for several aliphatic solvents. Although the level of exposure in most modern workplace is far below the limit recommended by OSHA, many research have begun to suggest that the very low level of occupational exposure to benzene has the risk of cancer in workers or community nearby. Incidence has risen in industrialized countries since the 1960s and is highly and rapidly fatal and represent the fifth leading cause of deaths from cancer and 50%-100% more common in men than women [5-18].To identify, appraising and synthesizing the risk of cancer from benzene exposure in environment or workplace, a meta analysis was conducted.

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METHODS

Epidemiological studies were identified through a computerized Medline and search on follow up and case control studies. All studies on morbidity or mortality of all type of malignancy related to benzene exposure were searched from Medline database. The search of the articles start on database start from January 1950 to April 2006. The searching terms were:

(1) (environmental OR occupational) AND benzene AND cancer
(2) benzene AND (mortality OR morbidity)
(3) cancer AND environmental AND occupational

A total of 22 studies were identified and were extensively reviewed. The inclusion criteria for the studies were describe subject's work type, studies reported on cancer, reported sufficient data for meta-analysis, reported job and occupational or environmental agent, benzene exposure, study setting and design, sample size and number observed, reported original results (reviews). The risk were identified as Standardized Mortality Ratios (SMRs), Standardized Incidence Ratios (SIRs), Relative Risk (RR) and Odd Ratio (OR). Data extraction covered characteristic of the study (publication year, country, study type, case definition, sources of cases, reference population, follow up period, risk measures) and risk estimates. The data extracted should be relevant, unbiased estimates of relative risk, measures of relative risks associated with specific exposure, estimates adjusted for at least known risk factors for cancer (age, sex and tobacco smoking).

After reviewed only 10 studies were included for further analysis. The studies were divided into agent specific studies, cancer type, risk estimates with verified exposures to agents, study design and were analysis separately. The extracted data were checked for consistency and entered into a database and checked for correctness.

Only cohort study were selected for analysis. Data were entered to MS Excel for Windows ver.2003 (Microsoft, Inc, USA). Summary of relative risk was calculated from log(RR) and log(upper and lower limit of 95% CI of log RR). SE and weight of all studies were estimated by fixed effect model. Statistical analysis were performed by Stata for Windows v.6.0 (Stata Corp.,USA).

Since there was only a few study report the risk for specific type of malignancies, the data were shown as described on the original articles.

RESULT AND DISCUSSION

Twenty two studies were identified reporting follow up or case control studies on benzene exposure from the environment or workplace and cancer published between 1996-2004. Twelve studies were exclude because they did not provide sufficient information to estimate a summary OR. The remaining 10 studies described 8 cohort studies and 2 case control studies. Study characteristics of design and occupational/environmental exposure were shown on table 1.

Table 1. Characteristics of 11 studies on the risk of malignancy due to benzene exposure

Author	Country	Year	Design	Brief description of study type
Lynge R, et al	Denmark	1996	Cohort	Industrial -based study on service station workers
Jarvholm B, et al	Swedish	1997	Cohort	Industrial-based study on petroleum workers
Huebner WW, et al	USA	2000	Cohort	Industrial -based study on petrochemical workers
Sebastian MS,et al	Equador	2001	Cohort	Community- based study on population near oil field
Hurtig AK, et al	Equador	2002	Cohort	Community-based study on population near oil field
Collins JJ, et al	USA	2002	Retrospective Cohort	Industrial- base of chemical plant worker
Alguacil J, et al	Spain	2002	Case control	Multicentre hospital base study on exocrine pancreatic cancer patients
Gun RT, et al	Australia	2003	Cohort	Industrial base study on petroleum workers
Lewis RJ, et al	Canada	2003	Cohort	Industrial base study on petroleum workers
Steffen C. et al	French	2004	Case control	Multicentre hospital base study on acute leukaemia patients

Table 2. Cumulative analysis cohort studies on risk malignancy due to benzene exposure

Study name	n	OR	95% CI	Z-Value	p-Value	RR
Lynge R, et al	33048	1.06	0.97 to 1.16	1.32	0.19	1.06
Jarvholm, et al	8638	3.05	2.20 to 4.23	6.69	<0.001	2.98
Huebner WW, et al	17884	2.08	1.82 to 2.38	10.69	<0.001	2.00
Sebastian MS,et al	2000	7.09	1.61 to 31.26	2.59	0.01	7.00
Hurtig AK, et al	273974	1.22	1.07 to 1.38	3.08	<0.001	1.22
Gun RT, et al	22144	1.44	0.92 to 2.26	1.58	0.11	1.44
Lewis RJ, et al	33182	4.33	4.04 to 4.65	40.84	<0.001	3.46
Collins JJ, et al	109127	1.44	1.17 to 1.77	3.50	<0.001	1.44
Fixed Effect Model	33048	2.16	2.06 to 2.25	33.43	<0.001	1.94

The identified studies were industrial-based (n=6), community-based (n=2), and multicentre hospital-based study (n=2). Proportional studies (two) representing a multicentre based study were excluded from further analysis because of poor information for meta-analysis.

Cumulative analysis of cohort studies were shown on table 2. Data from table 2 show the range of malignancy risk due to benzene exposure were 1.06 to 7.09 in term of OR and 1.06 to 7.00 in term of RR. Cumulative OR was 2.16 (2.06 to 2.25) and cumulative RR was 1.94 (1.86 to 2.01). This findings indicated workers who were exposed to benzene have risk to get malignancy 2 times higher than person who were not exposed to benzene. The excess risk found for Benzene was based on 8 population that were exposed with benzene from oil or petroleum industry.. Heterogeneity of RRs was nearly significant and maybe explained by differences in the quality and exposure levels of benzene from environment and workplace.

Forest plot diagram of each study, cumulative OR and 95% CI and the weight of each study were shown on diagram 1. Overall OR summary was estimated by fixed effect models. The weight of each study were shown on the right side.

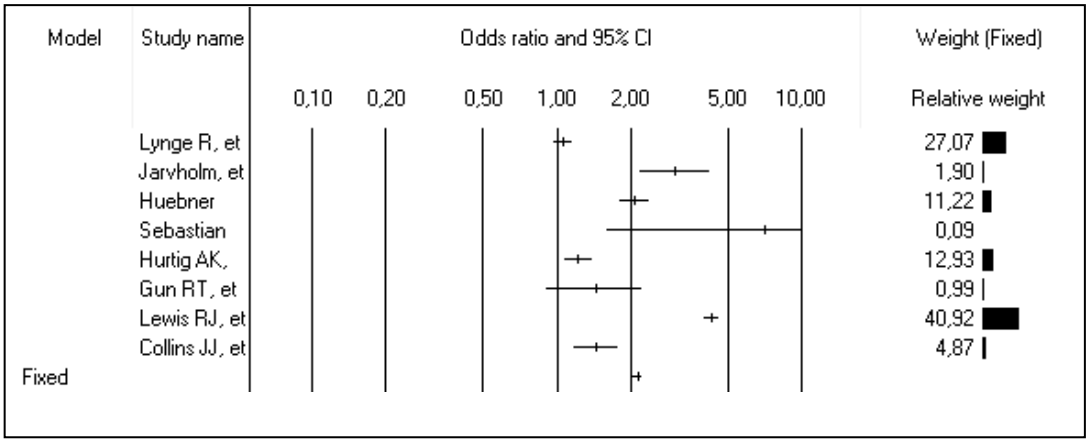

Diagram 1. Forest plot diagram of OR and 95% CI from all studies. Overall OR summary was estimated by fixed effect models. The weight of each study were shown on the right side.

The diagram show exposure of benzene was favour to risk of malignancy, however, 95 % confidence intervals of 2 studies [8,18] were include 1, therefore the risk of those 2 studies were inconclusive.

Similar to OR, RR of each study were also show benzene exposure was favour to risk of malignancy. Only 1 study [8] was inconclusive. Forest plot of RR cumulative RR were shown on diagram 2.

This results were consistent with other case-control study that benzene exposure is favour to the risk malignancy. See table 3. The risk of specific type of malignancy due to benzene exposure were shown in table 4.

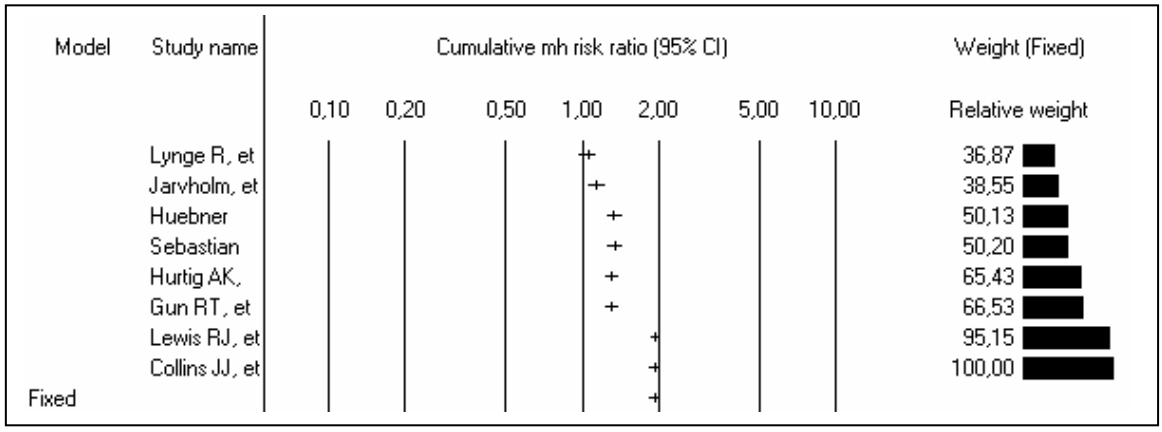

Diagram 2. Forest plot diagram of cumulative-MH RR and 95% CI from all studies. Overall RR summary was estimated by fixed effect models. The weight of each study were shown on the right side.

Table 3. Case-control studies on the risk of malignancy of due to benzene exposure exposure

Author	Design	Sample size	Observed	Odd Ratio (95% CI's)
Alguacil J, et al	Case control	185	14	2.1 (0.5 to 15.3)
Steffen C. et al	Case control	565	31	4.0 (1.5 to 10.3)

Table 4. The risk of specific type of malignancy due to benzene exposure.

Type of malignancy	Relative Risk (95% CI)
Soft tissue carcinoma	15.59 (1.74 to 139.3)
Rectum carcinoma	10.40 (1.16 to 12.98)
Skin melanoma	10.15 (2.91 to 46.97)
Kidney carcinoma	9.20 (1.03 to 82.20)
Mesothelioma	8.68 (5.51 to 13.03)
Lymph node carcinoma	4.74 (1.89 to 11.88)
Cervix carcinoma	4.01 (2.97 to 5.41)
Nasal carcinoma	3.50 (1.18 to 6.10)
Stomach carcinoma	2.51 (1.60 to 2.94)
Hemopoietic malignancy in general	2.63 (0.90 to 7.69)
- Leukemia	0.73 (0.32 to 1.66)
- Acute Myeloblastic Leukemia	0.92 (0.22 to 3.89)
- Multiple Myeloma	2.08 (0.95 to 3.95)

The risk of each type of malignancy was also analyzed from the study. Table 4 show the risk of soft tissue carcinoma due to benzene exposure was highest with RR=15,59 (95% CI= 1.74-139.3). There is also a possibility of effect modification of environmental or occupational determinants by lifestyle (tobacco, alcohol and coffee consumption) or others dietary factors. Generic factors may also interact with environmental or occupational exposure. Only one study that consider the interaction of tobacco smoking and the effect of benzene in the body. Rectum carcinoma with RR 10,40 (95% CI= 1.16-12.98), skin melanoma with RR 10,15 (95% CI= 2,91-46,97), kidney carcinoma with RR 9,20 (95% CI= 1,03-82,20) and mesothelioma with RR 8,68 (95% CI= 5,51-13,03) were also reported high on workers exposed to benzene or community lived near the oil and petroleum industry. The lowest risk was stomach carcinoma RR 2,51 (95% CI= 1,60-2,94) and hemopoetic malignancy in general with

RR 2,63 (95% CI= 0,90-7,69). The strongest evidence that benzene causes acute non-lymphocytic leukaemia (ANLL) or the slightly narrower category acute myeloid leukaemia (AML) is based on one large study with high exposure to benzene. [5]. This may be contradicted with most of the studies about benzene exposure and cancer, which found that benzene was very toxic to hemopoietic system and cause cancer for community or workers to low level or high level of benzene from environmental or occupational exposure. [3,4,6-8,19-22] It was also consider that epidemiological meta-analyses have imperfect combinalibity of result associated with different study types, methods, population, exposure circumstances and diagnosis specificities. Differences in results from different study types were not consistent and populations were also poorly characterized. There were also studies that did not specify whether the cohort consisted of men or women. In all studies there were also a likelihood substantial heterogeneity across populations in the quantity of benzene exposed and intensity of exposure categories, route of toxic agents (respiratory, dermal or ingestion), time aspects of exposure (period, latency, duration), applied scales of exposure and the malignancy diagnosis. Publication bias was minimal or non existent in this study bas a very small studies expressly considered the benzene exposure and occupational determinants of cancer. Control of confounding was difficult as there maybe some determinant was not included in the study.

CONCLUSION

Results of this meta-analysis suggest that environmental or occupational exposures of benzene may increase the risk of cancer, with the highest case of soft tissue carcinoma and the lowest case of stomach cancer. The excess may be pronounced in men who works in petroleum industry for more than 10 years and exposed to moderate and even level of benzene. Future research should concentrate on refined assessment of concentration and time aspects of exposure, assessment of interactions between occupational and environmental factors, lifestyle, large studies and refined statistical methods.

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