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Benzene, a multi-organ carcinogen

Benzene, un cancerogeno multipotente

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Summary

Benzene has been shown to be both an animal and a human carcinogen. It is a multipotential carcinogen that causes human cancers of the lympho-haematopoietic system, kidney, liver, stomach, colon, and lung. Lympho-haematoreticular neoplasias, caused by benzene exposure in humans, include leukaemias, lymphomas, multiple myeloma, reticulum cell sarcoma and more. The lowest observable effect levels for benzene for all lympho-haematopoietic cancers combined is 0.14 parts per million. This is seven times lower than the current OSHA standard and consistent with that recommended by NIOSH. Applying a safety factor of 10 gives a value of 0.014 parts per million or 14 parts per billion and indicates that a "safe" concentration of benzene is far below that currently recommended by OSHA and 10-fold lower than recommended by NIOSH. It is reasonable and prudent to conclude that there is no safe level of exposure to benzene above zero that can protect workers and the public from the carcinogenic effects of benzene. Eur. J. Oncol., 13 (1), 7-19, 2008

Key words: **benzene, benzol, carcinogenesis, leukaemia, benzene history**

Riassunto

Il benzene è stato dimostrato cancerogeno nell'animale e nell'uomo. È un cancerogeno multipotente che causa nell'uomo tumori del sistema linfoemopoietico, del rene, del fegato, dello stomaco, del colon e del polmone. I tumori linfoemoreticolari, causati da esposizione a benzene nell'uomo, comprendono leucemie, linfomi, mieloma multiplo, reticolosarcoma ed altri. Il più basso livello di benzene con effetti osservabili per tutti i tumori linfoemopoietici nel loro insieme è 0,14 parti per milione. Questo livello è 7 volte inferiore all'attuale standard OSHA e corrispondente a quello raccomandato dal NIOSH. L'applicazione di un fattore di sicurezza di 10 dà un valore di 0,014 parti per milione o 14 parti per miliardo, e indica che una concentrazione "sicura" di benzene è ben al di sotto di quella attualmente raccomandata dall'OSHA e 10 volte inferiore a quella raccomandata dal NIOSH. È ragionevole e prudente concludere che non c'è un livello sicuro di esposizione a benzene al di sopra di zero che possa proteggere i lavoratori e la popolazione dagli effetti cancerogeni del benzene. Eur. J. Oncol., 13 (1), 7-19, 2008

Parole chiave: **benzene, benzolo, cancerogenesi, leucemia, storia del benzene**

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Introduction

The early history of uses and toxicity of benzene goes back to the 17th Century following the introduction of a variety of solvents. The effects of benzene on the haematopoietic system of humans in the form of depression of white blood- and blood-forming cells was so well-known that benzene was used as a treatment for polycythaemia, a pathological excess of red blood cells. Later, the carcinogenic effects on the haematopoietic and lymphoreticular system and on many organ systems in animals and humans became widely known. As knowledge of the leukaemogenic effects of excess benzene exposure in the workplace became known by researchers on several continents, the occupational benzene standard was gradually reduced from 100 parts per million (ppm) in 1946 to one ppm in 1987. Since that time, increasing information has caused cries for further workplace reduction of benzene exposure to 0.1 ppm by the National Institute for Occupational Safety and Health (NIOSH)[1] in 1986 and to 0.04 ppm by the Collegium Ramazzini[2] in 2005. Industry representatives argued benzene was safe at each level.

Motor fuel is one of the better-known complex mixtures of petroleum chemicals containing benzene to which humans are exposed. Gasoline consists of more than 2,000 chemicals of which at least more than 150 chemicals have a boiling range of between 140°C and 180°C. The gasoline hydrocarbons are composed of about 50-70% alkanes (paraffins) that consist of straight-chain hydrocarbons of the C_4 to C_{12} range; isoparaffins, which are branched-chain hydrocarbons of about the same size; and alkenes (olefins), approximately 5% of which are unsaturated linear and branched-chain hydrocarbons; and naphthenics, which are saturated cyclics.

Aromatics, which are the most dangerous carcinogens in gasoline, are present at 30% to 40%, and consist mainly of benzene, toluene, ethylbenzene, and xylene. More than 1,000 other blending agents and additives are present in gasoline. As a result of phasing out of tetraethyl and tetramethyl lead, alcohols and methyl tert-butyl ether (MTBE) are being added at 5-20% to gasoline.

Total benzene usage today in the United States of America is approximately 17 billion gallons per year, and an estimated 238,000 people are occupationally exposed to benzene in petrochemical plants, petroleum refineries, and other operations. More than 90% of the benzene produced in the United States is manufactured from petroleum sources. Benzene has been shown to be a carcinogen in both animals and humans and is currently classified as a human carcinogen by the US Environmental Protection Agency (EPA), the National Toxicology Program (NTP) of the National Institute of Environmental Health Sciences (NIEHS) and the International Agency for Research on Cancer (IARC).

Benzene toxicity

The knowledge of benzene toxicity begins in the 19th and 20th Centuries (Tables 1, 2) and continues to the present. Regulatory agencies have addressed the safety of benzene as well as workplace concentrations (Table 3).

Of note is 1926 National Safety Council report on "Benzol"[33] that acknowledged the possibility of individual variation, susceptibility, and even hypersensitivity to damage to blood forming structures in man. The most characteristic pathological effect of benzol is its destructive influence upon cells in the bone

Table 1 - History of benzene toxicity in the 19th Century

Year	Item
1862	Lancet[3] reported *"A new domestic poison. Death due to inhalations of benzol vapours"*
1878	St. George's Hospital Report[4] recognized acute poisoning by "benzoline"
1889	Averill[5] reported a death from an accidental overdose
1897	Santesson[6] reported weakness, excess bleeding, and anaemia in 9 women using benzene cement; 4 of the women died within 1-4 months of onset of exposure
1897	Lenoir[7] reported weight loss, bleeding dyscrasias and fatalities in benzene-exposed workers

Table 2 - History of benzene toxicity in the 20th Century

Year	Item
1903	Simonen[8] reported accidental benzene poisoning
1903	Egli[9] wrote: "Ueber die Unrulle bei chemischen Arbeiten"
1905	Blumer[10] reported three cases of benzol poisoning
1907	Lewin[11] found that small quantities of benzol fumes produced a decrease in white blood cells (WBC)
1910	Selling[12] first reported benzene poisoning in the USA in 3 workers in a tin can plant in Baltimore, MD; two died
1913	Rambousek[13] reported 22 cases of acute benzol poisoning, 18 of which were fatal
1915-22	Schmitz[14], Hetzer[15] and Nick[16] reported cases of benzol poisoning
1916	Selling[17] established benzene as a bone marrow toxin in rabbit bioassays
1922	Hamilton[18] reported 14 cases of benzol poisoning with 7 fatalities
1928	Aksey[19], Delore and Borgomano[20] and Lignac[21] reported leukaemia following benzene poisoning in humans
1939	Greenburg[22] reported benzene poisoning in several hundred workers in the rotogravure printing industry
1939	Hunter[23] and Mallory *et al*[24] found 89 cases of benzene poisoning and several leukaemia deaths. Hunter observed: *"There is no level of benzene greater than zero that is safe over a long period of time"*
1960s	Vigliani and Saito[25] reported leukaemias in workers heavily exposed to benzene in Italy
1970s	Aksoy *et al*[26-32] reported leukaemias in workers (mainly shoemakers) heavily exposed to benzene in Turkey

Table 3 - Agency and industry responses to benzene toxicity

Year	Item
1926	National Safety Council[33] on "Benzol" reported individual variation and susceptibility to damage to blood forming structures
1940	US Public Health Service[34] recognized toxicity and potential dangers of aliphatic and aromatic hydrocarbons and that prolonged benzene poisoning may become acute poisoning
1941	API[35] issued a report on toxicity of industrial organic solvents
1942	Shell Development Co. publication[36] on Benzene, Nitrobenzene, Aniline and Xylidine reported that: *"Benzene is considered toxic to humans in concentrations of 1:10,000"*
1948	API[37] in "Occupations, Tumors, and Allied Disease" concluded that *"Evidence shows causative interrelations between occupational exposure to benzol and leukemia"*. *"The evidence is not possible but probable in actuality"* (p. 598)
1948	Drinker[38] in API Toxicology Reviews: Benzene wrote that: "The only absolutely safe concentration for benzene is zero"
1958	ESSO[39]. Toxigram – Benzene. Esso Research & Engineering Company - Medical Research Division, Linden, NJ, concluded that: *"The hazard from benzene exposure is an insidious destructive effect of blood forming organs… Most authorities agree that the only level which can be considered safe is zero"*
1984	California Air Resources Board Report[40] to the Scientific Review Panel on Benzene stated that, *"Benzene should be treated as a carcinogen at all levels without threshold level"*

marrow. The typical result of benzol exposure is a decrease in the number of WBC followed by reduction in RBC. "*The hazard of benzol poisoning in American Industry is a serious one and constitutes one of the major problems of Industrial Hygiene*", at substantially higher exposure levels than currently in

place. Substitution by agents such as toluene, xylene, and naphtha for benzene was recommended.

Absence of evidence of effect is not equal to evidence of absence of effect

McMichael[41] reviewed studies that allegedly showed that exposure to benzene did not produce effects on the haematopoietic system in humans. McMichael's analysis showed that the large mortality study of Thorpe of 38,000 petroleum workers reportedly showed no excess benzene-related adverse effects. However, when exposed workers were compared to those not exposed to benzene, there was a 2-fold increased risk for leukaemia in the exposed group. This was also the case in the cohort study of eight oil refineries in Great Britain that showed no significant differences between benzene-exposed workers and the general population. Analyses that took account of variations in benzene exposure between categories of workers revealed the association between benzene exposure and leukaemia.

After a critical review of the industry-sponsored report by Paustenbach *et al*[42], Utterback and Rinsky[43] found that the authors "*have apparently overlooked important information in literature related to the use and testing of control ventilation in the rubber hydrochloride (RH) plants even though they extensively cite other information from the very same page of that source*" (p. 665). They used selected information, sometimes improperly cited, to adjust previously reported benzene exposure estimates for the RH worker cohort. Many cohort members were exposed to prolonged levels of benzene in excess of 100, 150, and even 200 ppm. Some of the highest benzene exposures supposedly lasted as long as a decade.

Infante[44] discussed biases in the following articles published by consultants and health professionals working on behalf of industry. He wrote that Wong[45] *"…concluded that benzene can only cause acute myelogenous leukemia, in contrast to other types of leukaemia, and that the threshold is between 370 and 530 ppm-years of exposure"*. In this publication, he failed to include data from his own benzene study whereby he reported a statistically significant dose response for benzene exposure and leukaemia among workers whose cumulative benzene exposures ranged from less than 15 ppm-years to more than 60 ppm-years[46-47]. Furthermore, in the latter study, none of the leukaemia deaths was from acute myelogenous leukaemia. Thus, the findings and conclusions he drew from his own study contradict his opinion that benzene causes only acute myelogenous leukaemia and that the cumulative exposure threshold is between 370 and 530 ppm-years".

Teitelbaum *et al*[48] questioned the validity of scientific evidence of Bergsagel *et al*[49] on the relationship between benzene and multiple myeloma, saying that: *"Clearly, the current paper was litigation driven"*.

Infante[50] reviewed the report of Wong and Raabe[51] and concluded that: *"Wong and Raabe from the Mobil Oil Corporation have recently said that benzene exposure causes acute myelocytic leukemia only… It is difficult to reconcile Wong's opinion in light of his own study results reported in the British Journal of Industrial Medicine in 1987"*. Infante added that: *"Wong and Raabe have recently concluded that a range of 400-500 ppm-years of benzene exposure is the threshold for leukemia. The data in the Dow study (Ott et al*[52]*; Bond et al*[53]*) and Wong's own study*[51] *clearly contradict this statement"*.

Bailar[54] summarizes as follows: *"Science is often conducted by manufacturers, and this puts a premium on doing bad science that is guaranteed to produce negative results due to a) small sample size, b) poor protocols, c) fuzzy statistics"…. "Thus, absence of evidence of effect is not equal to evidence of absence of effect"*.

The 1994 study[55] conducted by Mobil Oil Corporation's Gerhard K. Raabe and consultant Otto Wong is done not to identify greatly increased risk to workers but to support Mobil's position during litigation. Specific flaws in methodology include: absence of monitoring data, use of quantifiable exposure data, inclusion of office workers and others not exposed to benzene in the analysis, exclusion of non-white males, questionable collection of diagnoses and the predominance of deaths due to "old age or senility", and use of questionable statistical methods. These deficits were stipulated in a United States District Court opinion concerning Gerhard Raabe's affidavit on the Beaumont, Texas refinery

epidemiology study court opinion denying appeal of an adverse decision by Mobil Oil Corporation.

Michaels[56] describes the strategy of fabrication by manufacturers of dangerous or polluting chemicals by questioning the validity of independent scientific evidence. In the same way as the tobacco industry has met with some success, according to Michaels, the manufacturers and producers of substances such as asbestos, benzene, beryllium, chromium, diesel exhausts, lead, plastics, and many other dangerous chemicals such as solvents, TCE, PCE, vinyl chloride, methyl chloride, fluorocarbons and others utilize similar techniques to pollute and harm both environment and general populations as well as individuals in the workplace.

Michaels[56] and von Saal and Hughes[57] demonstrate, in their Table 1, the effect of funding on research and the outcome of research. Of the 104 studies sponsored by government, 94 studies showed dangerous effects. Of the eleven studies sponsored by industry, none showed harmful effects, and all eleven showed that BPA is not harmful. These findings do not need to be tested for statistical significance: the outcome is indisputably obvious.

Shanghai study

In 2006, the American Petroleum Institute (API), representing over 300 oil, chemical, and petrochemical corporations, launched a major study of benzene known as the "Shanghai Study". This "study" was to be funded by British Petroleum, Chevron-Texaco, Conoco-Phillips, Shell, and Exxon-Mobil Corporations. The study outcome was portrayed and advertised as a foregone conclusion. The study was said to show that adherence to the current occupational exposure limits (in the range of 1-5 ppm) does not create a significant risk to workers exposed to benzene. It was advertised as refuting allegations that non-Hodgkin's lymphoma can be caused by benzene.

As was the case of the tobacco industry executives who testified before the House Committee on Energy and Commerce Subcommittee on Health and the Environment on April 14, 1994 that cigarette smoking posed no health hazard and that nicotine was not addicting, the American Petroleum Industry (Shanghai) Health Study appears to be designed to allow the Industry to state that benzene produces no adverse health effects. In my opinion, this is a superb example of an attempt to negate scientific findings published during the last 200 years that show the harmful effects of benzene on humans.

Epidemiology

Table 4 lists types of haemolymphoreticular neoplasms known to be frequently associated with exposure to benzene. In China, Yin[75-79] reported similar increases in human cancers in Chinese workers exposed to benzene.

In addition to haemolymphoreticular cancers, benzene causes cancers of the lung, liver, gastrointestinal system and nasopharynx. Epidemiological studies by investigators describing these cancers are presented in Table 5.

Experimental evidence in animals is consistent with that in humans. Maltoni *et al*[99-108] found that rats and mice exposed to benzene developed significant excesses in tumours of the oral cavity, lung, forestomach, Harderian gland, Zymbal gland, mammary gland, ovary, uterus as well as lymphomas, leukaemias and other types of haemolymphoreticular cancers. Huff *et al*[109] expanded these studies using a broader dose range of

Table 4 - Types of leukaemias and lymphomas from benzene exposure in humans

Acute myelogenous leukaemia
Acute lymphocytic leukaemia
Acute erythroleukaemic leukaemia
Acute myelomonocytic leukaemia
Acute promyelocytic leukaemia
Acute undifferentiated leukaemia
Chronic myelogenous leukaemia
Chronic lymphocytic leukaemia
Hairy cell leukaemia
Hodgkin's lymphoma
Non-Hodgkin's lymphoma
Lymphosarcoma
Multiple myeloma
Reticulum cell sarcoma

From: Aksoy[58]; Bond *et al*[53]; Decouflé *et al*[59]; Delore *et al*[20]; Goguel *et al*[60]; Goldstein[61]; lnfante *et al*[50, 62]; McMichael *et al*[63-67]; Rinsky *et al*[68]; Schwartz[69]; Travis *et al*[70];Vianna and Polan[71]; Vigliani *et al*[72-73]; Wong[74]; Yin *et al*[75-79]

Table 5 - Excess human cancers in benzene workers

Leukaemia	Stomach	Kidney
Lung	Oesophagus	Urothelium
Liver	Nasopharynx	
Lymphosarcoma	Intestine (colon)	

From: Adelstein[80]; Berger and Manz[81]; Bond *et al*[82]; Brown *et al*[83]; Brownson *et al*[84]; Creppi *et al*[85]; Delahunt *et al*[86]; Goldberg *et al*[87]; Greene *et al*[88]; Hanis *et al*[89-92]; Lagorio *et al*[93]; Lundberg and Milatou-Smith[94]; Miller *et al*[95]; Partenen *et al*[96]; Schnatter *et al*[97]; Thomas *et al*[98]; Yin *et al*[75]

benzene and reported numerous cancers at a lower dosage in organs and tissues previously reported by Maltoni.

The distribution of leukaemias by cell type in Chinese workers exposed to benzene was summarized (Table 6) by Infante[50] using the Yin[75] study.

Hayes[110] evaluated a cohort of 74,828 benzene-exposed workers and 35,805 non-exposed workers employed from 1972 through 1987 in twelve cities in China to determine the incidence of haematological neoplasms and related disorders. Benzene exposure was associated with a wide spectrum of haematological neoplasms. Results are shown in Table 7 by cumulative exposure (ppm-years). For all haematological neoplasms, the relative risk (RR) using a 95% Confidence Interval (CI) was statistically significant at p<0.01. Relative risk for non-Hodgkin's lymphoma and leukaemia were significantly increased at p<0.02 and p<0.04 respectively.

Other studies showing significant increases in haemolymphopoietic cancers have been reported by Decouflé *et al*[59], Travis *et al*[70], Girard and Revol[111], Rushton and Alderson[112], and Paxton *et al*[113].

Table 6 - Distribution of leukaemias in Chinese benzene workers

Type of leukaemia	Cell-specific SMR	*p* value
Acute lymphocytic (ALL)	1.94	
Acute myelogenous (AML)	4.96	<0.001
Acute monocytic (AMoL)	4.54	<0.05
Acute myelomonocytic (AMMoL)	5356	<0.05
Chronic myelogenous (CML)	4324	<0.01

From: Infante[50] and Yin *et al*[75]

Table 7 - Relative risk for various haematologic neoplasms and related conditions in workers exposed to benzene

Type of neoplasia	RR	95% CI	p<0.05
All haematologic cancers combined	2.2	1.1-4.2	Yes
Myelodysplastic syndromes	3.2	1.0-10.1	Yes
Acute nonlymphocytic leukaemia/ myelodysplastic syndrome	7.1	2.1-23.7	Yes
Non-Hodgkin's lymphoma	4.2	1.1-15.9	Yes

From: Hayes[110]

Increased risk from exposure to low levels of benzene

The Collegium Ramazzini[2] in 2004 called for reduction of exposure to benzene to the lowest possible levels.

The current OSHA standard for occupational exposure for benzene is based on the data available in 1977. In the United States, a time-weighted average (TWA) eight-hour exposure is one part per million (ppm). This level is not protective for human health (Federal Register, 1977)[114].

In 1997, Hayes *et al*[110] reported a significant dose-response relationship between benzene exposure and all lymphohaematopoietic cancers (LHP) combined as well as for leukaemia and non-Hodgkin's lymphoma examined separately. In this analysis, a cumulative benzene exposure of 4.5 ppm-years was associated with a statistically significant 2-fold increased risk for all LHP cancers. This corresponds to a time-weighted average exposure of 0.11 ppm per year over a 40-year working lifetime. They noted that a cumulative exposure of 6.7 ppm-years was associated with a statistically significant 3-fold elevation in the risk of acute non-lymphocytic leukaemia.

A study[115] of Australian petroleum workers occupationally exposed to benzene demonstrated a statistically significant 50% increase in the incidence of leukaemia. For this cohort, 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 0.2 ppm. Average exposure intensity was estimated to be less than or equal to 1.0 ppm for 98% of subjects and less than or equal to 0.5 ppm for 90% of subjects. The average cumulative benzene exposure for the group was only 4.9 ppm-years. Average exposure was 200 parts per billion (ppb). Workers were followed for 12.8 years, in contrast to OSHA's

setting of permissible exposure level (pel) based on 45 years of exposure. A 50% increase in risk equates to 3.5 extra leukaemia cases per 1,000 population over a lifetime, i.e., life background risk is seven deaths from leukaemia per 100,000 population. Because 200 ppb relates to 3.5 cancers per 1,000, a risk of 1.0 per thousand (OSHA's significant risk level) would be related to 57 ppb (200/3.5=57 ppb). Thus, Australian workers were followed for an average of 12.8 years *versus* 45 years exposure considered by OSHA's risk calculations - a difference of 3.5 times less. Dividing 57 ppb by 3.5 less time of exposure gives 16 ppb.

To provide adequate safety for the general population for a carcinogen like benzene, the "no observable effect" level is divided by 100- to 200-fold to allow for individual variability, because the number of 16 ppb has an effect, i.e., is not the "no observable effect" level, and the only safe level for benzene exposure has to be zero.

Cytogenetic studies in general

A large body of scientific data suggests that an increased rate of chromosomal aberrations is of serious concern since chromosomal abnormalities have been associated with at least one-half of all spontaneously aborted foetuses[116] and with several congenital syndromes that also show an increased risk of malignancy[117]. In addition, chromosomal breakage, whether of genetic or environmental origin, has been associated with leukaemia[117]. The US EPA[118] Health Effects Research Laboratory described chromosomal aberrations as *"a major cause of heritable human disease, and their occurrence is often associated with cancer"*.

As summarized by Fenech[119]:

– cancer is a disease of altered gene expression involving a complex array of epigenetic events, gene mutation, chromosomal rearrangements and altered chromosome numbers;
– DNA damage biomarkers may serve as a surrogate for cancer;
– Nordic and Italian prospective cohort studies have confirmed that elevated rates of chromosomal aberrations in lymphocytes are predictive of cancer risk;
– the biomarkers of exposure and effect and clinical disease may all be largely influenced by susceptibility factors that include polymorphisms that alter activity of relevant DNA repair, carcinogenic metabolism, and apoptotic pathway genes.

Cytogenetic studies in animals

In animal studies, Gad-El-Karim *et al*[120] reported that the myeloclastogenic effect of benzene appears to be the earliest benzene-induced cellular damage in which chromosomal DNA is a primary critical target, is readily identifiable (scorable), and antedates changes in peripheral blood counts (leukocytes, platelet counts, etc). Benzene's myeloclastogenicity is a function of its metabolism. Modification of benzene metabolism by an appropriate mixed function oxidase (MFO) inducer as 3-methylchanthrene (3MC) or beta-naphthoflavone (BNF) or the co-administration of toluene is reflected in the extent of chromosomal damage, being increased or decreased, respectively. Benzene myeloclastogenicity is greater with the oral than with the intraperitoneal route of administration. The authors further stated that: *"The following points may be significant in interpreting the mechanism of benzene myeloclastogenicity: a) enhancement of chromosomal damage by P-448 rather than P-450 enzyme inducers; b) hydroquinone (HQ), catecholamines (CA), or phenols (PH) do not possess any of the potent myeloclastogenicity of the parent compound, benzene. HQ, in fact, shows a mild clastogenic response at a toxic dose (200 mg/kg b.w.); c) the unique presence of trans, trans-muconic acid in the urine of benzene-treated mice and not of those animals treated with HQ, CA, or PH"*.

Huff[121], Kari *et al*[122] and Tsutsui *et al*[123] also found a variety of chromosomal aberrations, gene mutations and carcinogenicity of benzene metabolites in animals including hamsters, F344/N rats and B6C3F1 mice. Eriksson and Karisson[124] reported mouse peripheral blood lymphocytes (PBL) showed a significant increase in the sister chromatid exchanges (SCEs) after inhalation exposure to benzene at levels as low as 1 ppm for 6 hours. Rat PBLs showed significant decreases in mitotic activity after inhalation exposure to benzene levels

as low as 3 ppm for 6 hours. The authors concluded that: *"Benzene can induce statistically significant cytogenetic effects in PBLs of both mice and rats after a 6-hour inhalation of benzene at low concentrations"*.

Cytogenetic studies in humans

Chromosomal changes in workers exposed to atmospheric benzene were reported in the 1960s and early 1970s[125, 126]. In a study of peripheral blood lymphocytes in subjects exposed to benzene, Forni *et al*[127] confirmed increased rates of chromosomal changes.

The mechanism by which benzene causes cancers has been shown to be cytogenetic. Picciano[128] studied peripheral lymphocytes from 52 workers exposed to low levels of benzene (less than 10 ppm) and found an increase in aberration rates as compared to that of a 44-person group seen for pre-employment examination. Statistically significant differences were found in the distribution of specific types of chromosomal aberrations. These induced aberration levels were not related to the age of the workers. Based on these studies, continued monitoring of benzene-exposed workers (as well as industrial populations exposed to any clastogenic agent) with medical cytogenetic surveillance, environmental monitoring, and lifetime epidemiologic investigation was recommended.

White *et al*[129] wrote: *"In the 1977 OSHA benzene hearing record, Kilian and Daniel of Dow Chemical Company's Bio-Medical Research Laboratory released the results of a cytogenetic study of Dow employees exposed to benzene (Holder[130]). This study, discussed in the section on effects from low-level exposure to benzene, clearly demonstrated a significant increase in structural chromosomal aberrations resulting from average benzene exposures below atmosphere concentrations of 10 ppm"*.

Nise *et al*[131] reported that earlier benzene exposure was significantly ($p < 0.01$) associated with benzene exposure and a clastogenic effect on B-lymphocytes. Santos-Mello and Cavalcante[132] found a significantly higher frequency of chromosome deletions among gas station attendants than a control group and considered these workers form a risk group. Nilsson *et al*[133] found a significant ($p<0.04$) increase in single strand breaks in DNA of workers exposed to gasoline with average concentration of 0.13 ppm of benzene.

In benzene-exposed workers, increased chromosomal aberrations (hyperdiploidy) of chromosome 9 ($p<0.01$) was found, and there was a significant correlation ($p<0.003$) between hyperdiploidy and decreased absolute lymphocyte count, an indication of benzene haematotoxicity[134].

In 2002, Sul *et al*[135] studying lymphocytes from workers exposed to benzene showed clear DNA damage in B-lymphocytes and less prominent DNA damage in T-lymphocytes (Comet assay). Significant decreases of RBC and WBC were found in Chinese workers exposed to benzene and correlated with both personal benzene exposures and levels of urinary metabolites s-phenylmercapuric acid and t,t-muconic acid[136].

Lan *et al*[137] reported analysis of lymphocyte subsets among workers exposed to benzene in China stating: *"Benzene is toxic to various components of the hematopoietic system. To evaluate its effects on lymphocyte subset populations, we carried out a cross-sectional study of 31 unexposed controls, 20 workers exposed to mean concentration 1.8 ppm (median 1.7 ppm, range: 0.5-6.6 ppm) benzene, and 37 workers exposed to 21.9 ppm (range: 12.8 ppm, 2.2-84.6) in Tianjin, China. As expected, the absolute lymphocyte, granulocyte, platelet, and red blood count decreased with increasing benzene exposure and the red blood cell mean corpuscular volume increased"*. In follow-up studies Lan *et al*[138] demonstrated that benzene causes decreases in white blood cells and platelet counts at levels below 1 ppm for white cells ($p<0.0001$) and platelets ($p<0.023$) (Table 8). She also found evidence that a single nucleotide polymorphism (SNP) in five genes was associated with a statistically significant decrease in total WBC counts among exposed workers and one SNP was associated with an increase in WBC counts.

Chromosomal aberrations were found in workers exposed to low levels of benzene[140]. Human lymphocytes showed damage after exposure to low levels of benzene and benzene metabolites consisting of chromosomal aberrations and aneuploidy at concentrations of benzene in air from 0.014-0.743 ppm (mean = 0.557 ppm). Benzene also caused a significant increase in monosomy and

Table 8 - Peripheral blood cell counts and benzene exposure level

Subject category	Controls (140)	< 1 ppm (109)	*p* for <1 ppm *vs* controls
Benzene air level (ppm)	<0.004	0.57 (0.24)	<0.0001
White blood cells (WBC)	6,480	5,540	<0.0001
Granulocytes	4,410	3,360	<0.0014
Lymphocytes	2,130	2,130	<0.003
CD4+ T-cells	742	635	<0.003
B-cells	218	186	<0.003
Platelets	230,000	214,000	<0.023

From Lan *et al* [139]

trisomy of chromosomes 8 and 21. Translocations between chromosomes 8 and 21 [t(8:21)] were eight-fold more frequent in the high-level exposure group compared to the control group.

DNA damage was found to be highly elevated in gasoline service attendants, factory workers, and school children in Bangkok (p<0.001) exposed to benzene[141].

Conclusions

Studies on experimental animals and large numbers of epidemiology studies strongly and indisputably demonstrate that benzene is a powerful, multipotential carcinogen in humans. Its carcinogenicity is affirmed by numerous international agencies including IARC, the US EPA, NTP, OSHA, and many other authoritative organizations. Benzene exposure is associated with all known haematopoietic and lymphoreticular tumours including acute and chronic leukaemias, lymphoma, multiple myeloma, myelodysplastic syndrome, and aplastic anaemia. Benzene is also associated with a large variety of solid tumours such as those of kidney, lung, gastrointestinal system, and others. Based on available information, as early as 1990, this author[142] recommended occupational benzene exposure be reduced to between 0.004 ppm to 0.1 ppm. We now have sufficient evidence that exposure to very low levels of benzene can cause tumours in humans. Based on this information, it is prudent to recommend that environmental exposure be reduced to low parts per trillion and the occupational exposure be limited to 40 ppb[143].

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