NON HODGKINS LYMPHOMA

CANCER

SUPPLEMENT 7

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Things you need to do to file your Cancer Presumptive Claim

1. Call your immediate supervisor, and your Local IAFF representative to let them know you're filing a claim. They will also assist you through this process. Fill out an Injury report. This form is a DWC-1, and available online. Fill it out according to the Power point attached.
2. Send in, to your Human resources or Workers Comp Carrier, the paperwork given. These should be the NAWCJ document, CHAPTER 607 , House Bill 1388," Lemaster's" Meta-Analysis Study, and also any IARC monographs that are relevant to prove your case.
3. Also send a pre-employment physical from your department or any physical that showed normal findings prior to your diagnosis. Preferable to supply the pre-employment physical.
4. Keep in mind that if you're denied, to follow the Chapter 607 Presumptive Power point and involve your association to assist with your claim.
5. All claims denied must be denied in writing, with that written denial sent to the Texas Dept. of Insurance Per HB 1388. If denial has PLN-1 at the bottom left corner of denial letter, there is no timetable limitation to file appeal, PLN-11 has 15 days.
6. Gather all receipts related to any out of pocket expense you may have incurred.
7. Download records or online calendars to show your leave usage, so it may be converted to Occupational from Sick time instead.
8. Remember Occupational time is Tax Free! You may need to amend a tax return to recover those funds.

Contact Robert Webb if you need any information or have any questions
817-999-0573

THE BIG 6

Six qualifying criteria are needed in order to qualify your cancer as a Workers Comp claim.

(1) The necessity that the firefighter suffers from the type of cancer listed. This list is the IARC monographs. The cancer will need to be identified within the monographs and that information submitted.

(2) The precise occupation of the public safety employee who has contracted cancer. Firefighters are universally covered, Texas legislatures have added EMTs and other similar employees.

(3) The firefighter's pre-claim physical exam failed to reveal pre-existing cancer. This can be a pre-hire physical, or an earlier physical given by the fire department or city which showed no cancer or illness present.

(4) The firefighter's current work status. Is he or she still working, laboring somewhere else, or even retired? As of 2016, there is no provision for retired firefighters unless the disease manifested during employment years.

(5) Time of manifestation of the disease. Most cancer presumption statutes will require that, before the presumption is available, the employee have labored in his or her position for a certain period of time, and/or that the disease have manifested itself within a certain period of time. In Texas that period of time is five years.

(6) Time of incurrence of the cancer.

IARC 45

Table 1 (contd)

Monograph	Agent	Evidence of carcinogenicity[a]		
		Human	Animal	Group
Gasoline (contd)	Lead and lead compounds			
	Inorganic	I	S	2B
	Organolead	I	I	3
	para-Phenylenediamine	ND	I	3
Jet fuel	Benzene	S	S	1
Diesel fuels	Benzene	S	S	1
	Polycyclic aromatic compounds	ND	varies	2A–3
Fuel oils (Heating oils)	Benzene	S	S	1
	Carbazole	ND	L	3
	Nickel and nickel compounds	S	S	1*
	Polycyclic aromatic compounds	ND	varies	2A–3

[a]From Supplement 7 (IARC, 1987e); I, inadequate evidence; L, limited evidence; ND, no adequate data; S, sufficient evidence; 1, Group 1 – the agent is carcinogenic to humans; 2A, Group 2A – the agent is probably carcinogenic to humans; 2B, Group 2B – the agent is possibly carcinogenic to humans; 3, Group 3 – the agent is not classifiable as to its carcinogenicity to humans

*This evaluation applies to the group of chemicals as a whole and not necessarily to all individual chemicals within the group

components. The experimental studies summarized in the monograph on occupational exposures in petroleum refining are those in which any sample from petroleum refining processes or effluents was tested; laboratory fractions of process streams (e.g., distillates, extracts) are included but not evaluated.

The monograph on crude oil includes experimental studies in which undiluted or diluted crude petroleum oils or their composite mixtures were tested for carcinogenicity, and hygiene and epidemiological studies on persons potentially exposed to crude oil or its volatile components. Analogously to the treatment of process streams in the monograph on occupational exposures in petroleum refining, tests of laboratory-derived fractions of crude oil were included in the monograph.

The monograph on gasoline includes automotive gasoline (leaded and unleaded) used in automotive vehicles, and aviation gasoline used in aeroplanes with reciprocating engines. Aviation gasoline (boiling range, 25–170°C) differs from jet fuels (boiling range, usually 150–300°C), which are used in aeroplanes equipped with turbine engines. Automotive gasoline is manufactured by blending several process streams and additives. The principal streams used are full-range reformed naphtha, catalytically cracked and light steam-cracked naphtha, light straight-run naphtha and *n*-butane. One or more additional components may be used. Aviation gasoline usually contains 50–70% alkylated naphtha, as compared to 0–5% in automotive gasoline.

The fourth monograph in the present volume covers jet fuels. The basic component of most commercial and military jet fuels is the straight-run kerosene fraction produced by the

Mortality from leukaemia was significantly elevated in two refinery cohorts; in one of these, mortality increased with duration employed and also with time since first employment. Nonsignificant excess mortality from leukaemia was reported among two additional cohorts; in one of these, the excess was significant for boiler makers and pipe fitters. Elevated mortality from unspecified lymphatic leukaemia, unspecified myeloid leukaemia and acute monocytic leukaemia, but not other cell types, was reported in a subset of workers in the British cohort whose exposures included benzene. A significantly elevated incidence of lymphocytic leukaemia was reported in a large cohort study which included many of the refineries in the USA. Excess mortality from 'cancer of other lymphatic tissues' (multiple myeloma, polycythaemia vera and non-Hodgkin's lymphoma, excluding lymphosarcoma and reticulum-cell sarcoma), which was not significant, was reported in five refinery cohorts. One report indicated significant excess mortality from leukaemia and 'cancer of other lymphatic tissues' combined.

Mortality from malignant neoplasms of the brain was elevated in six of the refinery cohorts, but this was significant in only one of the studies and only for workers with short duration of employment. The elevated mortality was seen in operators and in maintenance and laboratory workers. A case-control study of astrocytic brain tumours showed a decreasing trend in risk with duration employed among men who had ever worked in petroleum refining during their lifetime. Another case-control study showed a significantly elevated risk for malignant neoplasms of the brain among men employed in petroleum refining.

Stomach cancer mortality was elevated among six refinery cohorts, significantly so in only one, among labourers, riggers and fire and safety workers; it was associated with lubricating oil production in one refinery and with solvent dewaxing in another. Mortality increased with increasing duration of employment in one of the studies.

Kidney cancer mortality was elevated, but not significantly so, among three petroleum refinery cohorts, particularly among operators, labourers and maintenance workers. Kidney and bladder cancer mortality combined was elevated in one refinery cohort. Five case-control studies of bladder cancer showed excess risk associated with employment in petroleum refining; the results were significant in two of these.

Pancreatic cancer mortality was reported to be elevated in four petroleum refining cohorts, and was associated with employment in the petroleum refining industry in one case-control study; however, none of these results was significant.

Excess mortality from cancer of the prostate, which increased with duration of employment, was reported in two refinery cohorts, and an overall excess was reported in two others. The only result that attained significance was found for men employed for 20 years or more in one of the refineries.

Lung cancer mortality was elevated in two refinery cohorts but not significantly so. There was a significant excess of lung cancer among workers with daily exposure to petroleum and its products in one of these cohorts. In five cohort studies, significant deficits in mortality from lung cancer were seen. In a case-control study, refinery maintenance workers and operators had a significantly elevated risk for lung cancer.

IARC 100 F

Table 1.5 Benzene in breath, blood and urine samples in the general population without occupational or known exposure to benzene[a]

Country	Analyte	Median/Mean	Reference
People's Republic of China	Urine	120 ng/L	Kim *et al.* (2006a)
People's Republic of China	Urine	69 ng/L	Waidyanatha *et al.* (2001)
People's Republic of China and Malaysia	Urine	1.49 ng/L	Ong *et al.* (1995)
Estonia	Blood	12 nmol/L	Kivistö *et al.* (1997)
	Breath	7 nmol/L	
	Urine	0.1 nmol/L	
Italy	Blood	110 ng/L (NS) 219 ng/L (S)	Brugnone *et al.* (1998)
Italy	Urine	1155 ng/L	Gobba *et al.* (1997)
Mexico	Blood	0.63 µg/L (service attendants) 0.30 µg/L (street vendors) 0.17 µg/L (office workers)	Romieu *et al.* (1999)
Singapore	Blood	1.27 nmol/L	Ong *et al.* (1996)
	Urine	1.29 nmol/L	
Thailand	Blood	65.6 ppt	Navasumrit *et al.* (2005)

[a] Including control workers
NS, non-smoker; S, smoker
From Johnson *et al.* (2007)

range from 0–42 ppm (1–136 mg/m^3) (Patel *et al.*, 2004).

Duarte-Davidson *et al.* (2001) assessed human exposure to benzene in the general population of the United Kingdom. It was estimated that infants (< 1 year old), the average child (11 years old), and non-occupationally exposed adults receive average daily doses of benzene in the range of 15–26 µg, 29–50 µg, and 75–522 µg, respectively. These values correspond to average airborne benzene concentrations in the range of 3.40–5.76 µg/m^3, 3.37–5.67 µg/m^3, and 3.7–41 µg/m^3 for these three groups, respectively.

Benzene concentrations in breath, blood and urine samples collected among the general populations (without occupational or known exposure to benzene) in Asia, Europe and North America are presented in Table 1.5 (Johnson *et al.*, 2007).

2. Cancer in Humans

In *IARC Monographs* Volume 29 (IARC, 1982) the Working Group concluded there was *sufficient evidence* in humans for the carcinogenicity of benzene, noting that a series of cohort and case–control studies showed statistically significant associations between occupational exposure to benzene and benzene-containing solvents and leukaemia (predominantly myelogenous leukaemia). In *IARC Monographs* Supplement 7 (IARC, 1987) benzene was classified as a Group-1 carcinogen, citing additional evidence of an increased incidence of acute nonlymphocytic leukaemia (ANLL) in workers exposed to benzene in three cohort studies, including an update of a cohort cited in Volume 29 (IARC, 1982). Since 1987, there have been numerous reports from cohort studies in populations exposed to benzene, including updates of earlier reports, and new case–control studies of leukaemia or its subtypes, non-Hodgkin lymphoma (NHL), multiple myeloma, and to a

lesser extent other tumours in adults. There have also been several case–control studies of childhood leukaemia with data on benzene, solvents, gasoline, and other related exposures. In addition, several meta-analyses have been published of one or more tumour sites.

[The Working Group decided to restrict its review to those case–control studies of paediatric cancers that included estimates of environmental benzene exposure, rather than surrogate exposures such as proximity to petrol stations or traffic. Also, the Working Group weighed more heavily the findings from studies with estimates of occupational exposure to benzene rather than broader measures (e.g. to solvents) in case–control studies. It was also decided not to rely in general on case–control studies where exposure assessment was limited to asking study subjects directly if they had been exposed to particular chemicals. Furthermore, the Working Group did not consider cohort studies of workers in synthetic rubber-manufacturing due to the difficulty of separating out effects from benzene *vs* those of other chemicals that may cause haematological malignancies. The Working Group decided not to take into consideration a series of meta-analyses of studies of petroleum workers (Wong & Raabe, 1995, 1997, 2000a, b). There were methodological concerns about the expansion from paper to paper of additional studies, cohorts, and countries, and the overall approach may dilute out the risks associated with relatively highly exposed subgroups of these populations that in general were not identified. In addition, an increased risk of ANLL – or the alternative classification, Acute Myelogenous Leukaemia (AML), which is more restrictive but still constitutes most of ANLL – was not detected in the initial meta-analysis by Wong & Raabe (1995), this body of work was not considered relevant for assessing what additional cancers may be associated with exposure to benzene beyond ANLL/AML. Abd finally, the Working Group noted that some meta-analyses of the same tumour came to opposite conclusions, which could be due to different inclusion/exclusion criteria, focusing on different subgroups of the study populations, or to different approaches to selecting risk estimates for inclusion (e.g. Lamm *et al.*, 2005; Steinmaus *et al.*, 2008), thus complicating the overall assessment of the literature. The Working Group therefore decided not to rely in general on results of meta-analyses in its evaluations.]

2.1 Leukemias and lymphomas

2.1.1 Acute non-lymphocytic leukaemia/ acute myelogenous leukaemia

Since 1987, additional analyses of previously published cohort studies (e.g. results in Crump (1994) and Wong (1995), based on the cohort study described in Infante *et al.* (1977) and Rinsky *et al.* (1981, 1987), which reported an excess risk for combined (mostly acute) myelogenous and monocytic leukaemia) and new cohort studies with quantitative data on benzene exposure have shown evidence of a dose–response relationship between exposure to benzene and risk for ANLL/AML in various industries and in several countries (Hayes *et al.*, 1997; Rushton & Romaniuk, 1997; Divine *et al.*, 1999b; Guénel *et al.*, 2002; Collins *et al.*, 2003; Glass *et al.*, 2003; Bloemen *et al.*, 2004; Gun *et al.*, 2006; Kirkeleit *et al.*, 2008; see Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.1.pdf). It was also noted that the NCI-CAPM cohort study found evidence of an increased risk for the combined category of ANLL and myelodysplastic syndromes (Hayes *et al.*, 1997). Case–control studies do not add substantively to these conclusions (see Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.2.pdf). In one case–control study an increased risk for childhood ANLL was found for maternal self-reported occupational exposure to benzene (Shu *et al.*, 1988; see Table 2.1 online). One case–control

and of benign and malignant ovarian tumours, mammary gland carcinomas and carcinosarcomas, and Harderian gland carcinomas in female mice (NTP, 1986; Stoner *et al.*, 1986; Maronpot, 1987; Maltoni *et al.*, 1988, 1989; Huff *et al.*, 1989; Mehlman, 2002).

Increased multiplicity of lung adenomas was observed in male mice after intraperitoneal injection of benzene (Stoner *et al.*, 1986).

Exposure of genetically altered, tumour-prone mice to benzene by oral administration, skin application, or inhalation resulted in increased incidences of skin tumours (Blanchard *et al.* 1998; Holden *et al.*, 1998; French & Saulnier, 2000) and lymphohaematopoietic malignancies (French & Saulnier, 2000; NTP, 2007; Kawasaki *et al.*, 2009).

4. Other Relevant Data

4.1 Genetic and related effects

Benzene induced chromosomal aberrations, micronuclei and sister chromatid exchange in bone-marrow cells of mice, chromosomal aberrations in bone-marrow cells of rats and Chinese hamsters and sperm-head anomalies in mice treated *in vivo*. It induced chromosomal aberrations and mutation in human cells *in vitro* but did not induce sister chromatid exchange in cultured human lymphocytes, except in one study in which high concentrations of an exogenous metabolic system were used. In some test systems, benzene induced cell transformation. It did not induce sister chromatid exchange in rodent cells *in vitro*, but it did induce aneuploidy and, in some studies, chromosomal aberrations in cultured Chinese hamster ovary cells. Benzene induced mutation and DNA damage in some studies in rodent cells *in vitro*. In *Drosophila*, benzene was reported to be weakly positive in assays for somatic mutation and for crossing-over in spermatogonia; in single studies, it did not induce sex-linked recessive lethal mutations or translocations. It induced aneuploidy, mutation and gene conversion in fungi. Benzene was not mutagenic to bacteria (IARC, 1982, 1987). Chromosomal aberrations in human peripheral lymphocytes have been associated with occupational exposure to benzene for decades (Forni, 1979; IARC, 1982; Eastmond, 1993; Zhang *et al.*, 2002; Holecková *et al.*, 2004).

4.2 Leukaemogenic potential of benzene

Benzene is carcinogenic to the bone marrow causing leukaemia and myelodysplastic syndromes (MDS) and probably also to the lymphatic system causing non-Hodgkin lymphoma. Its carcinogenic mechanism of action is likely to be different for these two target tissues and probably multifactorial in nature. The metabolism of benzene will be summarized below and a review is presented of the current state of knowledge on the mechanisms of leukaemia and lymphoma induction by benzene. With regard to leukaemia, probable mechanisms of leukaemogenesis in the myeloid series, mainly acute myeloid leukaemia (AML) and MDS are discussed. Then, potential mechanisms by which benzene could cause acute lymphocytic leukaemia (ALL) in both adults and children are reviewed. Finally, mechanisms for the benzene-induced development of non-Hodgkin lymphoma are summarized, including that of chronic lymphocytic leukaemia (CLL), as it is now classified as a form of lymphoma.

4.2.1 Metabolism of benzene and its relevance to carcinogenicity

Benzene must be metabolized to become carcinogenic (Ross, 2000; Snyder, 2004). Its metabolism is summarized in Fig. 4.1. The initial metabolic step involves cytochrome P450 (CYP)-dependent oxidation to benzene oxide,

and mutations that are on the causal pathway to these malignancies. For childhood ALL and AML it has been shown that the disease is usually initiated *in utero*, since leukaemic translocations and other genetic changes have been detected in blood spots collected at birth (Wiemels *et al.*, 1999; Wiemels *et al.*, 2002; Greaves & Wiemels, 2003; McHale *et al.*, 2003). Thus, exposure of the mother, and perhaps even the father, to benzene could be just as important as exposure of the child in producing childhood AML and ALL, as has been suggested in several epidemiological studies (van Steensel-Moll *et al.*, 1985; McKinney *et al.*, 1991; Shu *et al.*, 1999; Scélo *et al.*, 2009). Supporting this hypothesis is an animal study demonstrating that *in utero* exposure to benzene increases the frequency of micronuclei and DNA recombination events in haematopoietic tissue of fetal and post-natal mice (Lau *et al.*, 2009). Another study showed that oxygen radicals play a key role in the development of *in utero*-initiated benzene toxicity through disruption of haematopoietic cell-signalling pathways (Badham & Winn, 2010). These studies support the idea that genotoxic and non-genotoxic events following exposure to benzene may be initiators of childhood leukaemia *in utero*.

4.2.4 Mechanisms of lymphoma development

(a) General

Lymphoma is a cancer of the immune system that includes over 40 malignant diseases originating from B- and T-lymphocytes and natural killer (NK) cells (Swerdlow *et al.*, 2008). It is therefore not surprising that functional disorders of immune-system cells are associated with a risk for malignant transformation. Immune deficiency is one of the strongest known risk factors for non-Hodgkin lymphoma (NHL) (Hartge & Smith, 2007). The risk for NHL increases with the degree of immune deficiency, and there is no evidence of a threshold (Grulich *et al.*, 2007). Thus, even modest immunosuppression, especially at the local level, may increase the risk for lymphoma.

It is well recognized that lymphomas, like other tumours, develop according to a multistep pathogenic process (Smith *et al.*, 2004). Clonal progression of an initiated cell to a clone of highly malignant cells is well documented. Natural selection of clones already present within oligoclonal expansions gives rise to true monoclonal lymphomas. Thus, it is possible to make generalizations about the type of molecular mechanism responsible for each of the stages involved in lymphomagenesis. For example, a cell may become initiated and genetically unstable through errors in recombination and DNA repair, which could be spontaneous or induced by an exogenous chemical agent. Other early molecular events often inhibit apoptosis and lead to the expansion of an intrinsically genetically unstable population of cells, which is at risk for additional genetic events and tumour progression. An example is the t(14;18) chromosome translocation associated with B-cell lymphoma 2 gene *BCL2* dysregulation, which inhibits apoptosis (Cimmino *et al.*, 2005; Thomadaki & Scorilas, 2006). Normally, one of the key protectors against the selection and progression of malignant clones of cells into full-blown lymphoma is local immunosurveillance in which activated T-cells kill the mutated clones. It is generally accepted that if this immunosurveillance is no longer intact, e.g. in immuno-suppressed individuals, then the malignant cells divide and grow rapidly, collecting more mutations to become aggressive, rapidly growing tumours.

(b) Mechanisms of benzene-induced lymphoma development

From the discussion above, there are at least two probable mechanisms by which exposure to benzene could enhance the incidence of lymphoma, i.e. by inducing chromosome rearrangements associated with NHL, and through

immunosuppression leading to decreased immunosurveillance.

Benzene is well known to produce multiple cytogenetic abnormalities in lymphocytes (Tough & Brown, 1965; Forni, 1971, 1979; Picciano, 1979; Smith & Zhang, 1998; Zhang *et al.*, 2002). Further, benzene induces specific chromosomal changes associated with NHL in human lymphocytes (Zhang *et al.*, 2007). Fluorescence in situ hybridization (FISH) analysis showed increased levels of t(14;18) and del(6q) in benzene-exposed workers, but the higher levels of t(14;18) could not be confirmed in a follow-up study by use of real time-PCR (polymerase chain reaction) (McHale *et al.*, 2008). This may be because the PCR method only detected 50% of t(14;18) translocations or that the FISH method detects non-functional as well as functional translocations. Reduced immunosurveillance is another potential mechanism of NHL induction by benzene. The importance of T-cell immunosurveillance in preventing B-cell neoplasia is well established and is carried out by activated cytotoxic T lymphocytes. The toxic effects of benzene on T-cells is well documented and there appears to be a selective effect on $CD4^+$ T-lymphocytes resulting in a lowering of the $CD4^+/CD8^+$ ratio (Lan *et al.*, 2004). This immunosuppressive pattern is similar to the early onset of acquired immuno-deficiency syndrome (AIDS), and although it is not as severe it may be associated with an increased risk for NHL (Grulich *et al.*, 2007). Thus, benzene, like other leukaemogens including alkylating agents, topoisomerase inhibitors, and ionizing radiation, may cause NHL through a combination of immunosuppression and DNA double-strand break induction that leads to illegitimate recombination and chromosome rearrangements in lymphoid cells.

Thus, the biological plausibility of benzene as a cause of lymphoproliferative disorders has been strengthened in recent years. There are additional studies demonstrating that benzene produces lymphomas in laboratory animals, and a recent study showing that it does so simultaneously with AML in *Tp53*-deficient mice (Kawasaki *et al.*, 2009). Multiple studies show that it produces genotoxicity in the lymphocytes of exposed humans. Accordingly, there is considerable support for the notion that it is biologically plausible for benzene to cause human lymphatic tumours.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of benzene. Benzene causes acute myeloid leukaemia/acute non-lymphocytic leukaemia.

Also, a positive association has been observed between exposure to benzene and acute lymphocytic leukaemia, chronic lymphocytic leukaemia, multiple myeloma, and non-Hodgkin lymphoma.

There is *sufficient evidence* for the carcinogenicity of benzene in experimental animals.

There is strong evidence that benzene metabolites, acting alone or in concert, produce multiple genotoxic effects at the level of the pluripotent haematopoietic stem cell resulting in chromosomal changes in humans consistent with those seen in haematopoietic cancer. In multiple studies in different occupational populations in many countries over more than three decades a variety of genotoxic changes, including chromosomal abnormalities, have been found in the lymphocytes of workers exposed to benzene.

Benzene is *carcinogenic to humans (Group 1).*

References

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NHL

IARC

SUPPLEMENT 7

PAGES 120, 121 AND 137

USED TO CORRELLATE WITH IARC 98 AND IARC 100F

Chinese hamster bone-marrow cells. Azathioprine induced chromosomal aberrations but not sister chromatid exchanges in human lymphocytes *in vitro*. It induced chromosomal aberrations in *Drosophila*, was weakly mutagenic to fungi and was mutagenic to bacteria[6].

References

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BENZENE (Group 1)

A. Evidence for carcinogenicity to humans (*sufficient*)

Numerous case reports and series have suggested a relationship between exposure to benzene and the occurrence of various types of leukaemia[1]. Several case-control studies have also shown increased odds ratios for exposure to benzene, but mixed exposure patterns and poorly defined exposures render their interpretation difficult[1,2].

Three independent cohort studies have demonstrated an increased incidence of acute nonlymphocytic leukaemia in workers exposed to benzene[1,3]. An updating of a cohort study published earlier on benzene-exposed workers[1] confirmed the previous findings and added a further case of myelogenous leukaemia, giving a standardized mortality ratio (SMR) of 194 (95% confidence interval, 52-488), based on four cases; the difference was statistically significant when only myelogenous leukaemia was considered (4 observed, 0.9 expected; $p = 0.011$)[4]. A further cohort study found an excess of acute myeloid leukaemia (SMR, 394; 172-788) among refinery workers, based on eight cases; however, the patients had not worked in jobs identified as having the highest benzene exposure[5]. Another study of refinery workers showed no death from leukaemia (0.4 expected); however, the median exposure intensity for benzene was 0.14 ppm (0.45 mg/m^3), and only 16% of 1394 personal samples, taken between 1973 and 1982 inclusive, contained more than 1 ppm (3.19 mg/m^3). The median exposure intensity in 'benzene-related units' was 0.53 ppm (1.7 mg/m^3)[6].

In a Chinese retrospective cohort study, encompassing 28 460 workers exposed to benzene in 233 factories, 30 cases of leukaemia (23 acute, seven chronic) were found, as compared to four cases in a reference cohort of 28 257 workers in 83 machine production, textile and cloth factories. The mortality rate from leukaemia was 14/100 000 person-years among the exposed and 2/100 000 person-years among the unexposed (SMR, 574; $p < 0.01$). Mortality was especially high for workers engaged in organic synthesis, painting and rubber production. The mortality from leukaemia for cases that had previously had benzene poisoning was 701/100 000 person-years. 'Grab' samples of benzene in air were taken during the time of the survey in workplaces where cases of leukaemia were observed; the mean concentrations varied in a wide range, from 10 to 1000 mg/m^3, but the range 50-500 mg/m^3 covered most of them[7].

B. Evidence for carcinogenicity to animals (*sufficient*)

Benzene was tested for carcinogenicity in mice and rats by several routes of administration. Following its oral administration at several dose levels, it induced neoplasms at multiple sites in males and females of both species[1,8-11]. After mice were exposed to benzene by inhalation, a tendency towards induction of lymphoid neoplasms was observed[1,12,13]. Exposure of rats by inhalation increased the incidence of neoplasms, mainly carcinomas, at various sites[9,10,14-16]. Skin application or subcutaneous injection of benzene to mice did not produce evidence of carcinogenicity, but most of the experiments were inadequate for evaluation[1]. In a mouse-lung tumour bioassay by intraperitoneal injection, an increase in the incidence of lung adenomas was observed in males[17].

C. Other relevant data

Chromosomal aberrations in human peripheral lymphocytes have been associated with occupational exposure to benzene, although many of the studies are very difficult to interpret[18].

Benzene induced chromosomal aberrations, micronuclei and sister chromatid exchanges in bone-marrow cells of mice, chromosomal aberrations in bone-marrow cells of rats and Chinese hamsters and sperm-head anomalies in mice treated *in vivo*. It induced chromosomal aberrations and mutation in human cells *in vitro* but did not induce sister chromatid exchanges in cultured human lymphocytes, except in one study in which high concentrations of an exogenous metabolic system were used. In some test systems, benzene induced cell transformation. It did not induce sister chromatid exchanges in rodent cells *in vitro*, but did induce aneuploidy and, in some studies, chromosomal aberrations in cultured Chinese hamster ovary cells. Benzene induced mutation and DNA damage in some studies in rodent cells *in vitro*[18].

In *Drosophila*, benzene was reported to be weakly positive in assays for somatic mutation and for crossing-over in spermatogonia; in single studies, it did not induce sex-linked recessive lethal mutations or translocations. It induced aneuploidy, mutation and gene conversion in fungi. Benzene was not mutagenic to bacteria[18].

Several studies have shown elevated standardized mortality ratios for cancers at various sites among workers in the rubber industry (see p. 332), where there is potential exposure to 1,3-butadiene, among other chemicals[3].

B. Evidence for carcinogenicity to animals (*sufficient*)

1,3-Butadiene was tested for carcinogenicity in mice by inhalation. It was carcinogenic to animals of each sex, producing haemangiosarcomas of the heart, malignant lymphomas, alveolar/bronchiolar adenomas and carcinomas, papillomas and carcinomas of the stomach, hepatocellular adenomas and carcinomas, mammary-gland carcinomas and granulosa-cell tumours of the ovary[1]. Exposure of rats to 1,3-butadiene by inhalation resulted in increased incidences of tumours of the mammary gland, thyroid and pancreas[4].

C. Other relevant data

No data were available on the genetic and related effects of 1,3-butadiene in humans. It induced micronuclei and sister chromatid exchanges in bone-marrow cells of mice but not of rats treated *in vivo*. It was mutagenic to bacteria[5].

References

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1,4-BUTANEDIOL DIMETHANESULPHONATE (MYLERAN) (Group 1)

A. Evidence for carcinogenicity to humans (*sufficient*)

Leukaemia patients who had been treated with Myleran developed many different cytological abnormalities, and some developed carcinomas[1-8]. A follow-up study of patients with bronchial carcinoma who were randomized to chemotherapy after pulmonary resection showed that of 69 who had been given Myleran and had survived five years, four developed acute nonlymphocytic leukaemia (three myelomonocytic leukaemias and one erythroleukaemia) and 15 others developed pancytopenia in the succeeding four years; among 148 other survivors at five years who had not been given Myleran, one case of pancytopenia appeared. Risk was not dose-related, although the cases were confined to those who had received no radiation and no other cytotoxic agent[9].

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Table 2.10. Case–control studies of exposure to benzene and non-Hodgkin lymphoma

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)*	Adjustment for potential confounders	Comments
Franceschi *et al.* (1989) Italy	232 NHL cases below the age of 80 with histologically confirmed NHL, diagnosed within two yr before the interview, at a cancer centre and all general hospitals in the area under surveillance. 208 interviewed.	401 patients below age 80 admitted as inpatients for a wide spectrum of acute Conditions (excluding haematological) to the same hospitals.	Patients were asked to indicate, in addition to an occupational history, whether they had ever been exposed to 20 potentially cancerogenic chemical or physical agents, including benzene.	NHL 200, 202	Benzene and solvents	15	1.1 (0.6–2.3)	Age and sex.	
Scherr *et al.* (1992) USA	379 cases of non-Hodgkin lymphoma newly diagnosed January 1, 1980, through May 31, 1982, among residents of the Boston Standard Metropolitan Statistical Area treated in any of nine participating hospitals. 303 (80%) participated.	For each case, a control of the same sex and age (within 1 yr), town, and precinct of residence was selected from town residency lists. Of 423 potential controls, 303 were interviewed.	Home interviews. Each subject was asked about his or her current or most recent job, the job held 15 yr ago, major occupation, second most major occupation, and up to two occupations in which he or she was exposed to any of several specific agents.	NHL 200, 202	Exposure to benzene		1.2 (0.5–2.6)		Numbers of cases exposed and referent not specified. Prevalence of benzene exposure in the population 4%.

Table 2.10. Case–control studies of exposure to benzene and non-Hodgkin lymphoma

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)*	Adjustment for potential confounders	Comments
Gérin *et al.* (1998) Canada	Between 1979 and 1986, 4576 eligible men cases of 19 cancer sites (215 NHL) ascertained from all the large hospitals in Montreal 3730 (82%) agreed to participate; 82% of responses were obtained from the subject and the rest from a next-of-kin.	Men selected from electoral lists of the Montreal area, age-stratified to the age distribution of cancer patients. Of 740 selected, 533 (71%) were interviewed. For each case series, a pooled control group was formed by the addition of an additional 533 cancer controls selected randomly from eligible cancer cases to the 533 population controls.	Interviewers obtain a detailed description of each job the subject had in his working lifetime; chemists noted their confidence that the exposure occurred (possible, probable, definite), the frequency of exposure (less than 5% of the time, 5–30%, more than 30%), and the concentration of the agent in the environment (low, medium, high). These were then combined into exposure categories.	NHL 200, 202	Benzene Unexposed Low Medium/high	 187 19 9	 1.0 0.6 (0.4–1.0) 0.8 (0.4–1.6)	Age, family income, ethnic group, cigarette smoking, and respondent status.	

Table 2.10. Case–control studies of exposure to benzene and non-Hodgkin lymphoma

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)*	Adjustment for potential confounders	Comments
Persson & Fredrikson (1999) Sweden	106 and 93 cases of NHL age 20–80, born in Sweden, included in two earlier studies identified from a Department of Oncology and a regional cancer registry respectively, response rates 96% and 90%.	479 controls randomly selected from the population registers of the same geographic areas as the cases..	Mailed questionnaire including information about occupational exposures.	NHL 200, 202	Occupational exposure to benzene	3	0.8 (0.1–3.8)	Age, sex	Referent not specified
Mao *et al.* (2000) Canada	1469 of 1955 newly diagnosed, histologically confirmed NHL cases (764 men and 705 women) between 1994 and 1997 in eight Canadian provinces ascertained through cancer registries.	5073 population controls, of 8 104 selected in 5 provinces from the Provincial Health Plan database, in one from the Ministry of Finance property assessment database and in two by random digit dialling.	Mailed questionnaires were used to obtain data on exposure at work (or home) to any of 17 chemicals for at least one yr including benzene.	NHL 200, 202	Occupational exposure to benzene: Men None Any Women None Any	 330 36 555 5	 1.0 1.2 (0.8–1.9) 1.0 0.6 (0.2–1.8)	10-yr age groups, province, body mass index (< 20, 20–27. and > 27), and consumption of milk for both sexes, and education for women.	

Table 2.10. Case–control studies of exposure to benzene and non-Hodgkin lymphoma

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)*	Adjustment for potential confounders	Comments
Fabbro-Peray *et al.* (2001) France	627 incident cases of histologically confirmed malignant lymphomas diagnosed between 1 January 1992 and 31 December 1995 were identified from hospitals serving the region. All cases were French, living in Languedoc-Roussillon at the time of diagnosis, 18 yr or older, man or woman. and had negative serology for human immunodeficiency virus. Response rate 82%. 445 cases were classified as NHL, 72 HD (exclude	Two controls per case were randomly selected from electoral lists, stratified by county and size of municipalities, but unmatched. All controls were French, living in Languedoc-Roussillon, at least 18 yr old, and man or woman. Of 1 249 controls identified, 1 025 (52%) were interviewed	Personal interviews initially, then by telephone. The questionnaire requested information on chemical exposures, including benzene.	NHL 200, 202	Self-reported exposure to benzene: No Yes Cumulative number of d exposed Never erratic ≤ 810 d > 810 d	 423 22 433 4 8	 1.0 2.0 (1.1–3.9) 1.0 1.7 (0.4–6.8) 5.7 (1.4–23.2)	Age, sex, urban setting. and education level.	

Table 2.10. Case–control studies of exposure to benzene and non-Hodgkin lymphoma

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)*	Adjustment for potential confounders	Comments
Blair *et al.* (2003) USA	All cases of non-Hodgkins lymphoma in the cancer registry of Iowa between March 1981 and October 1983, and from a surveillance network of hospitals in Minnesota from October 1980 to September 1992. 622 of 715 man cases age 30 or more participated.	Population-based controls frequency-matched to cases by 5-yr age group, vital status at the time of the interview, and state of residence. Controls for cases less than 65 yr of age were selected by random digit dialing, controls for cases 65 yr or older were selected from listings provided by the Health Care Financing Administration, and controls for deceased cases were selected from state death certificate files. Response rates 77–79%	Personal interviews of 438 cases and 184 next of kin of cases and 1 245 controls (425 with next of kin). Detailed occupational history, with job exposure matrix for specific exposures.	NHL 200, 202	Benzene Low High Follicular lymphoma Benzene Low High Diffuse lymphoma Benzene Low High Other lymphoma Benzene Low High	 141 12 53 5 45 4 43 3	 1.1 (0.8–1.4) 1.5 (0.7–3.1) 1.3 (0.9–1.9) 1.9 (0.7–5.3) 1.2 (0.8–1.8) 1.8 (0.6–5.4) 0.8 (0.5–1.2) 0.9 (0.3–3.1)	Age, state, smoking, family history of malignant lymphoproliferative diseases, agricultural exposure to pesticides, use of hair dyes, direct or surrogate respondent.	Referent for OR not specified.

Table 2.10. Case–control studies of exposure to benzene and non-Hodgkin lymphoma

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)*	Adjustment for potential confounders	Comments
Dryver *et al.* (2004) Sweden	1414 consecutive cases of pathology-confirmed NHL patients over 18 yr of age at diagnosis were identified in the south Swedish regional tumour registry between 1990 and 1998, 1249 were contacted and 925 participated. After exclusions 859 remained in the analysis.	2820 age, sex and parish-matched individuals were concurrently identified using the Swedish unique person identification number and sent the same questionnaires., 1943 (69%) returned completed questionnaires. After exclusions 1 310 remained in the analysis.	Self-administered questionnaire including information regarding occupations and exposures to gasoline and solvents. Using a job-exposure matrix, additional information on exposures (including to benzene) was derived.	NHL 200, 202	Self-reported exposure to: Gasoline Gasoline exposure ≥ 5 yr versus < 5 yr	 78 45	 1.5 (1.0–2.0) 1.9 (1.2–3.1)		Referent not stated No analysis of specific exposure to benzene.

Table 2.10. Case–control studies of exposure to benzene and non-Hodgkin lymphoma

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)*	Adjustment for potential confounders	Comments
Fritschi *et al.* (2005) Australia	1230 cases age 20–74 notified to the Central Cancer Registry of New South Wales (NSW) with incident NHL first diagnosed between 1 January 2000 and 31 August 2001 and resident in NSW or the Australian Capital Territory (ACT). Of potentially eligible cases 144 were deceased; 842 were approached for interview, 717 responded.	1687 potential controls were randomly selected from the NSW and ACT Electoral Rolls to approximately match the expected distributions of cases with respect to age, sex and region of residence. After exclusions 1 136 who could be contacted were approached, 694 agreed.	Self-administered questionnaire mailed to each subject including a detailed lifetime occupational history. 28 jobs and 16 industries were identified, an occupational hygienist, who was blind to case status of the subject, allocated modules to jobs considered likely to have significant exposures. The modules were completed by a computer assisted telephone interview, with exposures allocated by an occupational hygienist.	NHL 200, 202	Benzene Unexposed Exposed Non-substantial Substantial p for trend	 626 68 66 2	 1.0 1.1 (0.8–1.6) 1.2 (0.8–1.7) 0.3 (0.0–1.5) 1.0	Age, sex, state and ethnic origin.	

Table 2.10. Case–control studies of exposure to benzene and non-Hodgkin lymphoma

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)*	Adjustment for potential confounders	Comments
Kato *et al.* (2005) USA	722 women newly diagnosed with NHL between 1 October 1995 and 30 September 1998 identified through a rapid case ascertainment system coordinated with the NYS Cancer Registry. Participation rate after informed consent 56% (376 cases)	Population-based controls frequency-matched to the projected age distribution of the cases and selected from an age-stratified random sample from the NYS Department of Motor Vehicles driver's license files for those under age 65 (248, 30% participation), and from the Health Care Financing Administration beneficiary files for those age 65 yr or older (215, 67% participation).	Telephone interviews included occupational exposure to benzene.	NHL 200, 202	No solvent exposure Benzene exposed	285 7	1.0 1.5 (0.4–5.7)	Age at index date, family history of hematologic cancer, college education, surrogate status, yr of interview, body mass index 10 yr before interview, average frequency of use of pain-relieving drugs, total number of episodes of systemic antibiotic use, total number of uses of household pesticide products and duration of work involving pesticide exposures.	Next-of-kin were interviewed for 20.5% of the cases and 3.2% of the controls.

Table 2.10. Case–control studies of exposure to benzene and non-Hodgkin lymphoma

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)*	Adjustment for potential confounders	Comments
Miligi *et al.* (2006) Italy	1428 newly diagnosed cases of malignant lymphoma (of 1 719 ascertained) in men and women age 20 to 74 yr in 1991–1993 were identified in 8 areas in Italy, identified through periodic surveys of hospital and pathology departments as well as in some specialized haematology centres	1530 controls (of 2086 identified) formed by a random sample of the general population in the areas under study stratified by sex and 5-yr age groups.	In-person interviews primarily at the interviewee's home. The questionnaire included a detailed occupational history (including collection of detailed data on specific jobs) and extraoccupational exposure to solvents. Industrial hygiene experts assessed a level of probability and intensity of exposure to groups or classes of solvents and certain individual substances.	NHL 200, 202, 204.1	Benzene: Unexposed (to any solvent) Very low/low Medium/high p for trend Duration of exposure for medium/high: ≤ 15 yr > 15 yr p for trend	 820 49 58 39 14 	 1.0 0.6 (0.4–0.9) 1.6 (1.0–2.4) 0.44 1.2 (0.7–2.0) 2.9 (0.9–9.0) 0.09	Age, sex, education, and area.	Cases of CLL were included with NHL. For the 20 cases assessed as diffuse follicular NHL the OR for medium/high level benzene exposure was 2.4 (95% CI: 1.3–4.5).

Table 2.10. Case–control studies of exposure to benzene and non-Hodgkin lymphoma

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)*	Adjustment for potential confounders	Comments
Seidler *et al.* (2007) Germany	710 patients with lymphoma (participation rate 87%), identified in six participating areas. 115 had Hodgkins lymphoma, 554 B NHL and 35 T NHL.	710 sex, region and age-matched (± 1 yr of birth) population control drawn from the population registration office (44% participation rate).	Personal interview including job title, industry, and specific job tasks. A trained industrial physician subsequently assessed the intensity and frequency of exposure to specific chlorinated and aromatic hydrocarbons (including benzene).	NHL 200, 202	B-NHL Benzene ppm/yr 0 0- ≤ 8.6 8.6- ≤ 130 > 130 T-NHL Benzene ppm/yr 0 0- ≤ 8.6 8.6- ≤ 130 > 130	 459 41 39 11 26 3 3 1	 1.0 0.9 (0.6–1.4) 1.0 (0.6–1.5) 1.0 (0.4–2.3) 1.0 1.2 (0.3–4.4) 1.7 (0.5–6.1) 1.7 (0.2–15.0)	Age, sex, region, smoking and alcohol consumption	German component of the Epilymph study (See Cocco *et al.*, 2010)

Table 2.10. Case–control studies of exposure to benzene and non-Hodgkin lymphoma

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)*	Adjustment for potential confounders	Comments
Wang *et al.* (2009) USA	832 cases of Non-Hodgkins lymphoma in women age 21–84 diagnosed in Connecticut, 1996–2000, 601 (72%) interviewed.	Women with Connecticut addresses frequency matched by age to cases and recruited by random digit dialing from among women aged less than 65 yr (69% participation) or by random selection from centres for Medicare and Medicaid Service files for women aged 65 yr or older (47% participation). 717 controls interviewed.	In person interviews collected lifetime occupational histories on jobs held for at least a yr. Exposure to organic solvents and formaldehyde associated with each job assessed by linking the coded occupational data with a job-exposure matrix by industrial hygienists.	NHL 200, 202	Diffuse Large B-Cell Lymphoma: Benzene exposure			Age, family history of haematopoietic cancers, alcohol consumption, and race.	For all NHL (which included CLL – see Table 2.8) the OR for medium to high intensity of benzene exposure was 1.5 (95% CI: 0.9–2.4), based on 34 cases.
					Never	149	1.0		
					Ever	40	1.2 (0.8–1.8)		
					Average intensity:				
					Low	25	1.0 (0.6–1.7)		
					Medium-high	15	1.8 (0.9–3.4)		
					p for trend		0.04		
					Follicular Lymphoma: Benzene exposure				
					Never	107	1.0		
					Ever	29	1.3 (0.8–2.0)		
					Average intensity:				
					Low	18	1.1 (0.6–1.8)		
					Medium-high	11	1.8 (0.9–3.7)		
					p for trend		0.18		

Table 2.10. Case–control studies of exposure to benzene and non-Hodgkin lymphoma

Reference, study location and period	Characteristics of cases	Characteristics of controls	Exposure assessment	Organ site (ICD code)	Exposure categories	No. of exposed cases	Odds ratio (95% CI)*	Adjustment for potential confounders	Comments
Cocco *et al.* (2010) (Epilymph study – 6 European countries)	All consecutive adult patients first diagnosed with lymphoma 1998–2004 resident in the referral area of the participating centres. 2 348 cases provided informed consent, overall participation 88%	Controls from Germany and Italy were selected by random sampling from the general population, and matched to cases by sex, 5-yr age group, and residence area. The other 4 centres used matched hospital controls, with eligibility criteria limited to diagnoses other than cancer, infectious diseases and immuno-deficient diseases. 2 462 controls provided informed consent, participation rate 52% for population controls and 81% for hospital.	Trained interviewers conducted in-person interviews with cases and controls, using the same structured questionnaire translated to the local language. Questions included information on a list of all fulltime jobs held for 1 yr or longer. Industrial hygienists in each participating centre coded the occupations and industries.	NHL 200, 202	B-cell lymphoma: Benzene			Age, sex, education and centre.	Only subjects whose exposure was assessed with high degree of confidence were included in the analysis.
					Unexposed	1061	1.0		
					All exposed	118	1.1 (0.8–1.4)		
					Low	34	0.9		
					Medium	29	1.1		
					High	55	1.3		
					p for trend		0.34		
					DLBCL: Benzene				
					Unexposed	325	1.0		
					All exposed	28	0.9 (0.6–1.4)		
					Low	9	0.8		
					Medium	8	1.0		
					High	11	0.9		
					p for trend		–0.67		
					Follicular lymphoma: Benzene				
					Unexposed	140	1.0		
					All exposed	17	1.6 (0.9–2.9)		
					Low	5	1.3		
					Medium	8	3.0		
					High	4	1.0		
					p for trend		0.10		

NHL, non-Hodgkin lymphoma; ppm, parts per million; yr, year or years

1.2 Composition of fire smoke

1.2.1 *Fire chemistry*

Smoke from fires comprises suspended liquid and solid particulate matter, gases and vapours that result from the combustion or pyrolysis of material. There is a very large number of toxic components in smoke (for reviews, see Tuve, 1985; Meyer, 1989; DiNenno *et al.*, 2002; Côté, 2003). The basic form of the overall combustion reaction of organic (carbon-containing) compounds is illustrated by the burning of methane:

$$CH_4 + 2O_2 + \text{Energy of activation} \rightarrow CO_2 + 2H_2O + \text{Heat of combustion} + \text{Light}$$

Given the appropriate ratio of fuel (wood, solvent, plastic, rubber), oxygen, and combustion temperature, the products of combustion should be only water and carbon dioxide (CO_2).

Complete combustion is approached only under carefully controlled conditions. Uncontrolled or unintentional combustion tends to be "fuel rich" and therefore incomplete. The combustion of methane (CH_4) illustrates the formation of free radicals in an 11-step chain reaction, the first two of which are:

$CH_4 \rightarrow CH_3^{\bullet} + H^{\bullet}$

$H^{\bullet} + O_2 \rightarrow OH^{\bullet} + O^{\bullet}$

The free radicals formed during combustion are very reactive and side reactions are propagated to yield hundreds of chemical products, and smoke.

Most polymers found in buildings will burn or thermally degrade to simpler monomers. Thermal degradation products include methane, ethane, ethylene, benzene, toluene, and ethylbenzene in addition to the following monomers: ethylene, vinyl chloride, acrylonitrile, tetrafluoroethylene, styrene, methyl methacrylate, ethylene glycol, terephthalic acid, phenol, formaldehyde, hexamethylenediamine, adipic acid, propene, vinyl chloride, vinyl acetate, vinylidene chloride, chloroprene, 1,3-butadiene, ethyl acrylate, ethylene oxide, methylacrylate, urea, phenol, and isoprene.

The burning of plastics typically produces voluminous amounts of soot, together with higher levels of hydrogen cyanide (HCN), hydrochloric acid (HCl) and acrolein (CH_2=CHCHO) than the burning of materials such as wood, and fossil fuels. More smoke evolves from fires involving aromatic polymers, such as polystyrene, compared to aliphatic polymers, such as polyethylene.

In addition to the chemical agents described above, particulate matter is produced under conditions of incomplete combustion. The particulate matter is an aerosol consisting of condensed phase components of the products of combustion and finely divided carbon particulates that have not undergone combustion but remain suspended in the air. Although the particles themselves are microscopic in size (0.3–1.6 μm), they

rapidly coalesce and thereby become visible. These particles are also adsorbents (similar to activated charcoal) and are an additional vehicle for the transport and inhalation of toxic combustion products. Smouldering yields a substantially higher conversion of fuel to toxic compounds than does flaming, although it occurs more slowly (Ohlemiller, 2002).

1.2.2 *Modern versus pre-modern fires*

All types of fire release toxic and carcinogenic substances, including benzene, 1,3-butadiene, and formaldehyde. The focus has generally been on substances having short-term acute effects: carbon monoxide (CO), carbon dioxide, hydrogen cyanide, nitrogen oxides (NO_x), sulfur dioxide (SO_2) and hydrogen chloride. With the increasing use of polymers in building construction and furnishings, there is concern that the burning of these new materials might release large quantities of other highly toxic substances (Austin *et al.*, 2001b).

Combustion and pyrolysis products from newer building materials and furnishings were believed to be more toxic than smoke from fires in buildings built before these materials became commonplace, and more toxic than smoke from wildland fires (Betol *et al.*, 1983; Alarie, 1985). However, many of the carcinogenic products of combustion identified are volatile organic compounds and are common to most burning materials. In a more recent study, no new or unusual non-polar volatile organic compounds (VOCs) were observed in current structural fires compared to the combustion of wood (Austin *et al.*, 2001b, 2001c). Adding polyvinyl chloride (PVC) to the fire load at simulated apartment fires was observed to significantly increase levels of polychlorinated phenols (IARC Group 2B), while polycyclic aromatic hydrocarbon (PAH) levels remained essentially unchanged (Ruokojärvi *et al.*, 2000). The increases in levels of polychlorinated biphenyls (PCBs, 0.021 to 0.031 mg/m^3), polychlorinated benzenes (0.002 to 0.010 mg/m^3) and I-TEQs [or PCDD/F] (3.5 to 5.4 ng/m^3) as products of combustion were not significant [possibly due to the small sample size]. In another study, proportionately higher levels of ethyl benzene (IARC Group 2B) were found at an electronics factory fire when compared to levels at residential and mixed occupancy fires (Austin *et al.*, 2001b).

The emission of combustion products (in mg per kg of material burned) for the same material varies greatly depending on combustion conditions such as ventilation (oxygen supply), temperature, and heating rate. Nonetheless, the relative amounts of the various non-polar VOCs found in smoke at municipal structural fires have been found to be remarkably similar from fire to fire, namely with the same 14 of 144 target compounds, dominated by benzene (IARC Group 1), toluene and naphthalene (IARC Group 2B) (Austin *et al.*, 2001b, 2001c).

1.2.3 *Carcinogens found in smoke at fires*

Table 1.1 lists the agents in Groups 1, 2A, and 2B that have been detected at fires in one or more studies, together with corresponding IARC evaluations, human and animal evidence of carcinogenicity, and for the agents in Group 1, the cancer sites in humans.

Table 1.1. IARC evaluations and cancer sites in humans of chemicals measured at fires

Chemicals measured at fires	Overall evaluation	Human evidence	Animal evidence	Volume	Cancer sites in humans (For Group 1 agents only)
Acetaldehyde	2B	Inadequate	Sufficient	36, Suppl. 7, 71	
Arsenic	1	Sufficient	Limited	23, Suppl. 7	Skin, lung, liver (angiosarcoma)
Asbestos	1	Sufficient	Sufficient	14, Suppl. 7	Lung, mesothelioma, larynx, gastrointestinal tract
Benz[*a*]anthracene	2B	Inadequate	Sufficient	32, Suppl. 7, 92	
Benzene	1	Sufficient	Limited	29, Suppl. 7	Leukaemia
Benzo[*b*]fluoranthene	2B	No data	Sufficient	32, Suppl. 7, 92	
Benzo[*k*]fluoranthene	2B	No data	Sufficient	32, Suppl. 7, 92	
Benzofuran (coumarone)	2B	No data	Sufficient	63	
Benzo[*a*]pyrene	1	No data	Sufficient	32, Suppl. 7, 92	Lung, bladder, skin
1,3-Butadiene	1	Sufficient	Sufficient	71, 97	Lymphohaematopoietic system
Cadmium	1	Sufficient	Sufficient	58	Lung
Carbon black (total)	2B	Inadequate	Sufficient	65, 93	
Chrysene	2B	Inadequate	Sufficient	3, 32, Suppl. 7, 92	
Dibenz[*a*,*h*]anthracene	2A	Inadequate	Sufficient	32, Suppl. 7, 92	
Dichloromethane (methylene chloride)	2B	Indadequate	Sufficient	71	
Ethylbenzene	2B	Inadequate	Sufficient	77	
Formaldehyde	1	Sufficient	Sufficient	88	Nasopharynx; (nasal sinuses and leukaemia, suggested)
Furan	2B	Inadequate	Sufficient	63	

1.3.3 *Surrogates of exposure*

As a matter of practicality, epidemiologists have generally used years of employment or, in one case, years of active duty fighting fires (Demers *et al.*, 1994), as a surrogate for exposure to smoke. This does not take into account the reduction in exposures when respiratory protection was used, differences between exposure groups, the intermittent nature of exposures, differences in tasks, or the fact that not all firefighters actually combat fires. In a Montreal study, only 66% of fire department personnel were 1st line firefighters (Austin *et al.*, 2001a). Years of employment has not been found to correlate with exposure to combustion products or related adverse health effects (decline in pulmonary function or airway responsiveness) (Musk *et al.*, 1977; Takehito & Maeda, 1981; Sparrow *et al.*, 1982; Sherman *et al.*, 1989). The number of fires fought has, however, been correlated with the mean annual reduction in pulmonary function (Peters *et al.*, 1974). Among firefighters at the same fire, statistically significant differences in exposure to combustion products have been found between front-line firefighters and both squad leaders and ordinary firefighters (Takehito & Maeda, 1981). The same study found no significant difference between ordinary firefighters and the officers who accompanied them.

Two epidemiological studies used estimated cumulative runs as a surrogate for exposure (Austin *et al.*, 2001a; Baris *et al.*, 2001). In one study (Austin *et al.*, 2001a), a good correlation between the number of runs per firehall and time spent at fires was observed ($r = 0.88$). However, different crews could have similar numbers of runs yet spend significantly different lengths of time at fires. The study by Austin *et al.* (2001a) identified distinct firefighter exposure groups based on job title, fire hall assignment, and time spent at fires.

1.3.4 *Exposure to carcinogens found in smoke at fires*

Table 1.2 presents the results of the studies that have measured the substances listed in Table 1.1, and particulate matter (total, respirable, PM_{10}). Unless otherwise indicated, reported levels do not take into consideration the use of respiratory protection. Table 1.3 provides a summary of the results from Table 1.2 for each substance, according to the type of fire or exposure (i.e. wildland, municipal, training fire, or municipal fire scene (arson) investigation).

The carcinogens found in one or more studies include nine known human carcinogens (Group 1), four probable human carcinogens (Group 2A), and 21 possible human carcinogens (Group 2B) (for a review, see Bendix, 1979; Lees, 1995).

Many of the wildland and municipal firefighter studies result from opportunistic sampling with sometimes wide margins of error, and may not be representative of firefighter exposures.

Two studies reported extremely high levels of benzene, up to 165 and 250 ppm (Burgess *et al.*, 1979; Brandt-Rauf *et al.*, 1988, respectively) [the former study used an accurate and precise sampling and analytical methodology]. Benzene levels in the remaining studies ranged from not detected to 23 ppm.

mortality from cancer. Excesses of brain tumours (SMR, 2.1; 95% CI: 1.2–3.3) and lymphatic and haematopoietic cancers (SMR, 1.3; 95% CI: 0.9–1.8) were found. Younger firefighters (< 40 years of age) showed an excess risk of cancer (SMR, 1.45; 95% CI: 0.8–2.39), primarily due to brain cancer (SMR, 3.75; 95% CI: 1.2–8.7). The risk of lymphatic and haematopoietic cancers was greatest for men with at least 30 years of exposed employment (SMR, 2.1; 95% CI: 1.1–3.6), especially for leukaemia (SMR, 2.6; 95% CI: 1.0–5.4).

Demers *et al.* (1994) further examined the incidence of cancer in a subcohort of 2447 male firefighters who were employed for at least one year during 1945–1979 in Seattle and Tacoma, who were still alive on January 1st 1974. Incident cancer cases were ascertained through the Cancer Surveillance System of the Fred Hutchinson Cancer Research Center, a population-based tumour registry. The follow-up period was from 1974 to 1989. Cancer incidence in firefighters was compared with local rates and with the incidence among 1878 policemen from the same cities. The overall risk of cancer among firefighters was found to be similar to that of both the police (SIR, 1.0; 95% CI: 0.8–1.3) and the general male population (SIR, 1.1; 95% CI: 0.9–1.2). No excesses were observed for the most common organ sites. An elevated risk of prostate cancer was observed relative to the general population (SIR, 1.4; 95% CI: 1.1–1.7), but was less elevated compared with rates in policemen (incidence density ratio [IDR], 1.1; 95% CI: 0.7–1.8), and was not related to duration of exposure. The risk of colon cancer, although only slightly elevated relative to that of the general population (SIR, 1.1; 95% CI: 0.7–1.6) and the police (IDR, 1.3; 95% CI: 0.6–3.0), appeared to increase with duration of employment.

Giles *et al.* (1993) conducted a cancer incidence study of 2855 male firefighters employed by the fire brigade in Melbourne, Australia, during 1917–1988. All were operational personnel, who would more than likely have been called to combat fires. The follow-up period was from 1980 to 1989, and was estimated to have been 95% complete. To determine cancer incidence during the follow-up period, fire brigade employment records were linked to the Victorian Cancer Registry. SIRs were calculated by the direct method using the population of the State of Victoria as the reference group. The cohort accrued a total of 20 853 person–years, and 50 firefighters developed cancer during the period of observation. The SIR for all cancer sites and all ages combined was 1.13 (95% CI: 0.84–1.48). For firefighters under the age of 65 years, the all-site SIR was 0.84 (95% CI: 0.56–1.20); for those above 65 years of age, the all-site SIR was 2.14 (95% CI: 1.32–2.37). The only site-specific cancer that was elevated in the age group of 65 and older was colorectal cancer, with an SIR of 3.65 (95% CI: 1.13–7.94). The SIR for all other cancers in the age group 65 and above after removing colorectal cancer remained elevated, with a residual SIR of 1.83 (95% CI: 1.03–3.02).

Guidotti (1993) examined the mortality by cause of death for two cohorts totaling 3328 firefighters active during 1927–1987 in Edmonton and Calgary, Alberta, Canada. Associations were examined by cohort (before and after the 1950s) and by

years of service weighted by exposure opportunity. The study attained 96% follow-up of vital status and over 64 983 person–years of observation; 370 deaths were recorded. Excesses were observed for all malignant neoplasms (SMR, 1.3; 95% CI: 1.0–1.6), and for cancers of the lung (SMR, 1.4; 95% CI: 0.9–2.1), bladder (SMR, 3.2; 95% CI: 0.9–8.1), kidney and ureter (SMR, 4.1; 95% CI: 1.7–8.5), colon and rectum (SMR, 1.6; 95% CI: 0.9–2.7), pancreas (SMR, 1.6; 95% CI: 0.5–3.6), and leukaemia, lymphoma and myeloma (SMR, 1.3; 95% CI: 0.6–2.3). The lung cancer excess was confined to Edmonton; there was no consistent association with duration of employment, exposure opportunity, or decade of entry into the cohort (before or after the 1950s) except that the highest risk was observed among Edmonton firefighters with over 35 weighted years of service. Urinary tract cancer excess was observed mostly among firefighters entering service after 1950, and appeared to increase with the length of service and exposure opportunity, and was observed in both cities.

Aronson *et al.* (1994) conducted a retrospective cohort mortality study of all male employees of the six fire departments within metropolitan Toronto, Ontario, Canada ($n = 5995$). The study population consisted of all male firefighters who had worked for at least 6 full months in metropolitan Toronto at any time during 1950–1989. Mortality was ascertained through computerized record linkage and compared to that of the male Ontario population specific to cause, age, and calendar period during 1950–1989. The cohort accrued 114 008 person–years and the average duration of follow-up was 21 years. Mortality was examined by duration of exposure. The SMR for all malignant neoplasms was 105 (95% CI: 91–120), for brain tumours, 201 (95% CI: 110–337), and for "other" malignant neoplasms, 238 (95% CI: 145–367). Non-significant increases in risk were observed for some other sites, in particular rectum (SMR, 171), larynx (SMR, 140), and testis (SMR, 252).

Tornling *et al.* (1994) conducted a cohort mortality study of all male fire fighters employed for at least 1 year in the City of Stockholm, Sweden during 1931–1983 ($n = 1116$). The population was identified from annual employment records. Follow-up for mortality was from 1951 until 1986, and for cancer incidence from 1958 to 1986. Except for four persons who had emigrated from Sweden, follow-up was 100% complete. To assess the occupational exposure as a firefighter, an index of participation in number of fires was calculated for each individual based on the number of reports on all fires in Stockholm that had been maintained since the beginning of the twentieth century. The all-site cancer mortality in 1958–1986 was equal to the expected (SMR, 100; 95% CI: 83–119). An excess of stomach cancer incidence (SIR, 192; 95% CI: 114–304; 18 observed versus 9.37 expected) was observed. There was also a tendency for higher incidence and mortality in stomach and brain cancers with increasing number of fires. Four brain cancer cases were observed compared to 0.8 expected (SIR, 496; 95% CI: 135–1270) in the highest exposure category.

For acetaldehyde, inhalation exposure leads to degeneration of nasal epithelium followed by hyperplasia and proliferation in rats (IARC, 1999). For acrolein, repeated inhalation results in changes in bronchiolar epithelial cells and emphysema in dogs (IARC, 1995). Dermal absorption does not appear to be important for acetaldehyde and acrolein.

Formaldehyde exposure results in DNA–protein cross-links and chromosomal abberations. Cell proliferation, which appears to amplify the genotoxic effects of formaldehyde, is increased at concentrations of around 6 ppm. No clear mechanism has been identified for the induction of myeloid leukemia in humans (IARC, 2006). Acetaldehyde causes gene mutations in bacteria; gene mutations, sister chromatid exchanges, micronuclei and aneuploidy in cultured mammalian cells; DNA damage in cultured mammalian cells and in mice in vivo. Acetaldehyde–DNA adducts have been found in white blood cells from human alcohol abusers (IARC, 1999). Acrolein induces gene mutation, sister chromatid exchange and DNA damage in cultured mammalian cells, but reportedly does not induce DNA damage in rats or dominant lethal mutations in mice treated in vivo (IARC, 1995).

4.1.3 *Benzene*

Benzene is systemically absorbed following inhalation, and due to rapid evaporation, dermal exposure should not be a significant source of systemic dose for firefighters. Benzene is oxidized primarily by CYP2E1 to benzene oxide, which exists in equilibrium with its tautomer oxepin (Kim *et al.*, 2006; 2007). Spontaneous rearrangement of benzene oxide produces phenol that is either excreted or oxidized by CYPs to hydroquinone, which is excreted or oxidized by myeloperoxidase in the bone marrow to 1,4-benzoquinone. Conversely, NAD(P)H quinone oxidoreductase 1 transforms 1,4-benzoquinone to hydroquinone. Hydroquinone and 1,4-benzoquinone are thought to influence the toxic effects of benzene through their ability to inhibit topoisomerase II and microtubule function, induce oxidative stress, and damage DNA. Other major metabolites include catechol, representing the pathway involving the hydrolysis of benzene oxide by epoxide hydrolases, and *trans,trans*-muconic acid, representing the pathway involving oxidation of oxepin and ring opening. Reaction between benzene oxide and glutathione, possibly mediated by glutathione-*S*-transferases (GSTM1, GSTT1), can produce the minor metabolite *S*-phenylmercapturic acid (Kim *et al.*, 2006; 2007). Although it is widely accepted that benzene toxicity is dependent upon metabolism, no single benzene metabolite has been found to be the major source of benzene haematopoietic and leukemogenic effects (ATSDR 2005). At low exposure levels, benzene is rapidly metabolized and excreted predominantly as conjugated urinary metabolites. The metabolism of benzene in the bone marrow is consistent with the increase in haematopoietic cancers seen in humans (ATSDR, 2005).

Chromosomal aberrations in human peripheral lymphocytes have been associated with occupational exposure to benzene and include hypo- and hyperdiploidy, deletions, breaks, and gaps (ATSDR, 2005). Sister chromatid exchange was not found to be a significant effect of benzene exposure in humans. In-vivo animal studies provide convincing evidence of the genotoxicity of benzene. Benzene induced chromosomal aberrations, micronuclei and

5. Summary of Data Reported

5.1 Exposure data

Several types of firefighters exist, including municipal, wildland, industrial, aviation, and military firefighters. Municipal firefighters may be assigned to combat firefighting units only or to unexposed activities such as fire prevention or technical support. Firefighters may also be fire-scene investigators who are exposed during fires or shortly following a fire. Many firefighters work in shifts (see the monograph in this Volume).

Both municipal and wildland firefighting involve two phases: in an initial phase (knockdown and attack, respectively), the fire is extinguished; in a second phase (overhaul and mop-up, respectively), small fires and hot-spots are extinguished.

All fires generate an enormous number of toxic combustion products, including known and possible carcinogens, long-lived free radicals, and particulate matter. Smoke particles may serve as vehicles for adsorbed volatile organic compounds. Peak exposures to some carcinogens may be very high, notably for benzene, 1,3-butadiene, and formaldehyde. The concentrations of respirable particulate matter to which firefighters may be exposed during overhaul can reach 50 mg/m^3, or up to 1000 mg/m^3, and above in the case of coarser particles. Exposures of firefighters to volatile organic vapours have generally been in the low parts-per-million range.

Firefighters may be exposed at different levels depending on crew assignment, tasks and/or the time spent at fires. Wildland firefighters appear to spend more time at fires during a fire season than municipal firefighters spend during an entire year. In municipal firefighting, overhaul also involves pulling down ceilings and walls, which may entail exposures to substances other than combustion products. Both municipal and wildland firefighters engage in heavy work levels when combating fires, and the increased respiration rate results in an increase in absorbed dose. In recent decades, very effective respiratory protection equipment has been made available to municipal firefighters. In most jurisdictions, wildland firefighters generally do not use respiratory protection.

5.2 Human carcinogenicity data

The Working Group reviewed 42 studies of cancer in firefighters that included 19 cohorts, 11 case–control studies, and 14 studies that used other designs. The studies that were most relevant to the assessment of the risk for cancer among firefighters were the larger historical cohort studies.

Elevated relative risks for cancer at many different sites were identified by one or more studies, but few were observed consistently. A recent meta-analysis evaluated 32 studies and found that the risk for cancer in firefighters was significantly elevated for ten sites, four of which showed the strongest evidence of an association. Since that analysis, two more large epidemiological studies of cancer in firefighters have been

reported. Therefore, another meta-analysis that included these two studies was performed by the Working Group for the four primary cancer sites. Three types of cancer showed significant summary risk estimates: the incidence of testicular cancer was ~50% in excess based on six studies and approximately 150 cases, that of prostatic cancer was ~30% in excess based on 17 studies and approximately 1800 cases, and that of non-Hodgkin lymphoma was ~20% in excess based on seven studies and more than 300 cases.

Four cohort studies that investigated testicular cancer in firefighters yielded risk estimates that ranged from 1.2 to 2.5 and one case–control study gave odds ratios that ranged from 1.5 to 4.3. One of three studies found a positive trend between duration of exposure and the increased risk for testicular cancer.

Of 20 studies of prostatic cancer, 17 reported elevated risk estimates that ranged from 1.1 to 3.3; however, only two reached statistical significance and only one study showed a trend with duration of employment.

The studies that investigated non-Hodgkin lymphoma in firefighters used different definitions of this tumour. Five cohort and one case–control studies that evaluated non-Hodgkin lymphoma reported risk estimates that ranged from 0.9 to 2.0. Only one study evaluated exposure–response with duration and did not find a positive relationship.

Although firefighters are exposed concurrently to a multitude of chemical compounds that include numerous carcinogens, human epidemiological studies at best used indirect (poor) measurements of exposure to such agents. Also, exposures of firefighters vary considerably depending on their job activities, and only crude measures of exposure, such as duration of employment and number of runs, have been used in these studies. Despite these limitations, increased risks for some cancers were found for firefighters in the meta-analysis.

5.3 Animal carcinogenicity data

No data were available to the Working Group.

5.4 Other relevant data

Smoke is a complex mixture of suspended particulate matter, gas, and vapour. The lack of data on toxicokinetics and toxicity of the adsorption of chemical components onto particles prevents a full understanding of the effects of smoke on firefighters. The toxicokinetics of chemical mixtures are not well understood but are probably of significant importance because of the multiplicity of chemicals in smoke. For individual smoke components, inhalation was considered to be the major source of exposure; however, dermal absorption is also an important route of exposure for polycyclic aromatic hydrocarbons and polychlorinated biphenyls.

There are insufficient studies to evaluate genotoxic effects in firefighters.

There is clear evidence of chronic and acute inflammatory respiratory effects in firefighters, which provides a potential mechanism for carcinogenesis, although the major effect would be expected in the respiratory system.

No genotoxicity studies in animals were found that involved exposure to smoke from the combustion of structural materials. Smoke causes lipid peroxidation, which may be associated with cancer. Wood smoke suspensions has been shown to cause DNA strand breakage and lipid peroxidation in cell cultures.