MYELOMA/LEUKEMIA 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.

MYELOMA

LEUKEMIA

IARC

SUPPLEMENT 7

PAGES 120, 121 AND 137

USED TO CORRELLATE WITH IARC 98 PAGE'S 399, 400, 406 AND 533
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

[1]*IARC Monographs*, *26*, 47-78, 1981

[2]Kinlen, L.J. (1985) Incidence of cancer in rheumatoid arthritis and other disorders after immunosuppressive treatment. *Am. J. Med.*, *78* (*Suppl. 1A*), 44-49

[3]Isomäki, H.A., Hakulinen, T. & Joutsenlahti, U. (1978) Excess risk of lymphomas, leukemia and myeloma in patients with rheumatoid arthritis. *J. chron. Dis.*, *31*, 691-696

[4]Fries, J.F., Bloch, D., Spitz, P. & Mitchell, D.M. (1985) Cancer in rheumatoid arthritis: a prospective long-term study of mortality. *Am. J. Med.*, *78* (*Suppl. 1A*), 56-59

[5]Cohen, S.M., Erturk, E., Skibba, J.L. & Bryan, G.T. (1983) Azathioprine induction of lymphomas and squamous cell carcinomas in rats. *Cancer Res.*, *43*, 2768-2772

[6]*IARC Monographs*, *Suppl. 6*, 86-88, 1987

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

[1]*IARC Monographs*, *39*, 155-179, 1986

[2]Matanoski, G.M. & Schwartz, L. (1987) Mortality of workers in styrene-butadiene polymer production. *J. occup. Med.*, *29*, 675-680

[3]*IARC Monographs*, *28*, 183-230, 1982

[4]Owen, P.E., Glaister, J.R., Gaunt, I.F. & Pullinger, D.H. (1987) Inhalation toxicity studies with 1,3-butadiene. 3. Two year toxicity/carcinogenicity study in rats. *Am. ind. Hyg. Assoc. J.*, *48*, 407-413

[5]*IARC Monographs*, *Suppl. 6*, 126-128, 1987

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 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	Benzene	S	S	1
(Heating oils)	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

In further analyses of the Exxon refineries and chemical plants in Baton Rouge, LA, Baytown, TX, and Bayway/Bayonne, NJ, mortality was examined by occupation and work site (Hanis et al., 1985b). Directly adjusted death rates for each subgroup of interest and for the total US population were calculated using the age, sex, race and calendar year distribution of the total cohort as a standard; thus, direct comparisons could be made between mortality rates in cohort subgroups and in the US population by calculating ratios of the directly adjusted rates. Workers were classified as having been 'potentially exposed' or 'unexposed' on the basis of their longest-held job. The 'exposed' category included those who had worked as process operators, mechanical workers and labourers (75% of the study population); while the 'unexposed' category included primarily white-collar office workers (22% of the population). Cause-specific cancer rates were higher among potentially exposed workers than among the unexposed for every cancer site except brain, but none of the site-specific rate ratios was significantly different from 1.0. Directly adjusted death rates were consistently greater than those for the total US population only for renal cancer in each of the three plants. The death rates for pancreatic cancer were higher than the US rates among employees at the Baton Rouge and Baytown plants only, and elevated rates of large intestinal cancer occurred at the Baytown and Bayway/Bayonne plants.

A series of investigations of mortality has been performed among members of the Oil, Chemical and Atomic Workers international union (OCAW) in Texas (Thomas et al., 1980, 1982a,b, 1984). In all of these reports, proportionate mortality among male members of the OCAW was compared with that among US men, adjusting for age, race and calendar period.

The first report concerned 3105 Union members in Texas whose deaths in 1947–77 while actively employed were reported to OCAW and whose death certificates could be located (90%; Thomas et al., 1980). Of the white OCAW members, 1722 had held blue-collar jobs in petroleum refineries and petrochemical plants, primarily in maintenance and production (Thomas et al., 1982a), and had significant excess frequencies of deaths from cancers of the digestive and respiratory systems, skin and brain (ICD8 191, 192).

Subsequent analyses were limited to three petroleum refineries located in the Beaumont/Port Arthur area of the Texas Gulf Coast (Thomas et al., 1982a,b, 1984) and included 1194 retired workers as well as those who had died while actively employed between 1943 and 1979. Among 2509 deceased men who had been employed by the three refineries combined (Thomas et al., 1982a,b), the adjusted PMRs using national rates for all causes of death were significantly elevated for all cancers as well as for cancers of the stomach, pancreas, skin (ICD8 172, 173), prostate and brain (ICD8 191, 192) and for leukaemia. Nine deaths from multiple myeloma were observed and 4.6 were expected, but the PMR was not significant. When national cancer rates were used to calculate proportionate cancer mortality ratios (PCMRs), these ratios were also elevated but significantly so only for brain and leukaemia in whites. When county cancer mortality rates were used, none of the PCMRs was significantly raised. A detailed examination of brain tumour mortality in whites indicated that OCAW members had had elevated frequencies of mortality from benign and unspecified tumours of the brain as well as those specified on death certificates as malignant. [The Working Group noted that, of the 2509 deaths studied,

of benzene and methyl ethyl ketone was used in the dewaxing process until 1945, when toluene replaced the benzene. There was a significant excess of bone cancer (SMR, 10.3) based on three deaths; nonsignificant excesses were seen for cancers of the stomach, pancreas and prostate and for all lymphopoietic cancer. Mortality for cancer of the prostate increased with duration employed and was excessive only after 20 years of employment. Seven of the eight prostatic cancer deaths occurred among men who had worked in the lubricating oil department but had not been involved in the solvent dewaxing process.

Refinery C studied by Thomas et al. (1980, 1982a,b, 1984) was included in a report by Wong and Raabe (1989). A cohort of all individuals employed at the Mobil Beaumont, TX, petroleum refinery for at least one year between 1 January 1945 and 1 January 1979 was comprised of 6139 employees (1582 deaths; 123 354 person-years). Also included in this report were the Mobil refineries in Paulsboro, NJ (1946-79: number of employees, 4263; number of deaths, 1164) and Torrance, CA (1959-78: number of employees, 1621; number of deaths, 250). Observed mortality in the study cohorts was compared with that expected on the basis of rates for the general US population, adjusted for age, calendar period, sex and race. At the Beaumont, TX, refinery, SMRs were elevated for cancers of the pancreas, skin (ICD8 172, 173), prostate and brain, but were not significant; mortality from lymphatic and haematopoeitic cancer was significantly elevated, due to excess mortality from lymphosarcoma, reticulosarcoma, leukaemia and cancer of 'other lymphatic tissues' (ICD8 202—203, 208). Mortality from lymphatic and haematopoietic cancers increased with duration of employment at the Beaumont, TX, refinery. Mortality from leukaemia was significantly elevated among white men with 30 years' service or more and with 20—39 years' latency. A nonsignificant excess of prostatic cancer was reported at the Paulsboro refinery, and the SMR was significantly elevated among white male employees who had worked for at least 20 years (SMR, 1.6). The SMR for cancer of 'other lymphatic tissues' (ICD8 202—203, 208) was also slightly elevated at the Paulsboro refinery but was not significant. Slight excesses of mortality from stomach and brain cancer were reported at the Torrance refinery.

White male employees (blue-collar and white-collar) of the Shell Oil Wood River refinery in southern Illinois who had worked for at least one day during the period 1 January 1973 to 31 December 1982 and retirees who were alive on 1 January 1973 comprised a cohort of 3976 men, 8% of whom had left employment for reasons other than retirement and were lost to follow-up (McCraw et al., 1985). Using mortality rates for US white men as a comparison, the SMR for all causes of death was 0.76 (640 observed). SMRs were shown separately only for lymphatic and haematopoietic neoplasms; all other cancers were grouped. The SMR for leukaemia was significantly elevated. Mortality from cancer of 'other lymphatic tissues' (ICD8 202—203, 208) was slightly, but not significantly, elevated. There was no excess of other cancers combined. The expected number of deaths from acute myeloid leukaemia was estimated from data on cell-type-specific mortality from US cancer registries, and a significant excess was seen. The authors determined that none of the 14 men who had died from leukaemia were known to have worked in jobs with potentially high exposure to benzene; however, five of the men had been maintenance employees who had worked in numerous plant locations, and their potential exposure to benzene was unknown.

Decouflé *et al.* (1983). During the period that the plant was a petroleum refinery, the products were gasolines, light oils, bunker oils, lubricating oils and wax. After conversion to a petrochemical plant, the primary products were alkyl benzene compounds. The study cohort included 259 men (blue-collar and white-collar) employed between 1 January 1947 and 31 December 1960. The cohort was followed for vital status through 31 December 1977, and observed mortality was compared with the expected rates of US white men, adjusting for age and calendar period. Mortality from lymphatic and haematopoietic cancers among the 194 subjects who had been employed for at least one year at the plant was significantly elevated; one of the cases had multiple myeloma, one had acute monocytic leukaemia, one had chronic lymphocytic leukaemia, and the fourth had multiple myeloma (treated with radiotherapy and melphalan) followed by acute myelomonocytic leukaemia two years later. The first three cases had begun their employment at the plant prior to 1947, and, thus, had worked there during both the refinery and petrochemical phases.

A cohort of 19 991 male workers who had worked for at least one year between 1 January 1962 and 1 December 1980 in one of 17 US refineries (Wong & Raabe, 1988), 51.3% of whom had been hired between 1940 and 1954 and 17.2% before 1940, was followed for vital status through 31 December 1980, and the mortality experience of the cohort was compared with that of US men, adjusting for race, age and calendar period (Kaplan, 1986). Altogether, 3349 deaths were observed; 707 (3.5%) persons were lost to follow-up. The only site-specific cancer for which excess mortality was noted was that of 'other lymphatic tissues' (ICD 202–203, 208), but this was not significant; 16 of the 30 deaths in this category were due to multiple myeloma. [The Working Group noted that no analysis was shown by duration of employment or latency.]

A prospective cohort study conducted by Schottenfeld *et al.* (1981) gave morbidity and mortality among men who had been petroleum industry employees in 19 US companies. A total of 55 007 white male petroleum refinery workers who had been working at any time between 1 January 1977 and 31 December 1979 were included in the analyses; 30 769 were first employed in 1960 or after. Mortality rates during the study period were compared with those of US white men in 1977. Standardized incidence ratios (SIRs) for cancer were calculated using rates for US white men obtained from cancer registry data. Among refinery workers, the SMR for all causes of death was significantly less than 1, and significant deficits were noted for many individual causes of death. There was a slight, nonsignificant excess of mortality from brain tumours. There was a significantly elevated incidence of lymphocytic leukaemia, and incidence was slightly elevated for cancers of the larynx and brain and for melanoma. The authors noted that there was underreporting of deaths. [The Working Group noted the short follow-up period (average, 1.6 years), which can result in either higher or lower figures. No analysis by duration of employment was shown.]

[The Working Group noted that the populations in many of the US studies overlapped (see footnote *c* to Table 11). The two industry-wide studies (Schottenfeld *et al.*, 1981; Kaplan, 1986) included many of the same refineries studied individually.]

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/m³) (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/m³, 3.37–5.67 µg/m³, and 3.7–41 µg/m³ 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

study of childhood cancer in Denmark did not find an association of estimates of environmental benzene exposure from air pollution with an increased risk for ANLL (Raaschou-Nielsen et al., 2001).

2.1.2 Acute lymphocytic leukaemia

Acute Lymphocytic Leukaemia (ALL) is now considered one subtype of NHL in the WHO-classification of lymphomas. In multiple cohorts there was a non-significantly increased risk for ALL, but the numbers of cases were small (Rushton, 1993; Wong et al., 1993; Satin et al., 1996; Divine et al., 1999b; Lewis et al., 2003; Kirkeleit et al., 2008; Yin et al., 1996; Guénel et al., 2002; Gun et al., 2006; see Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.3.pdf). [The Working Group noted that the magnitude of the risk-estimate in the NCI-CAPM cohort (Yin et al., 1996) was similar to the risk observed for ANLL in the same study, which was statistically significant. This approach has been suggested when attempting to interpret the association between occupational exposure to benzene and hematological subtypes that are less common than AML (Savitz & Andrews, 1997).]

In one case–control study in adults in Shanghai, a significant increased risk for ALL was found for the group with 15 or more years of self-reported occupational exposure to benzene (Adegoke et al., 2003); another study in the USA had only three exposed cases (Blair et al., 2001; Table 2.4 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.4.pdf). In a case–control study of childhood ALL no association was found with maternal self-reported occupational exposure to benzene, but a borderline significant association was noted with exposure to gasoline (Shu et al., 1988; see Table 2.4 online). No association with self-reported maternal exposure to benzene was found in a large study of childhood ALL in the

USA (Shu et al., 1999; see Table 2.4 online). A case–control study of childhood cancer in Denmark did not find an association of estimated environmental exposure to benzene from air pollution with ALL (Raaschou-Nielsen et al., 2001).

2.1.3 Chronic myelogenous leukaemia

Several studies in the petroleum industry and in other settings show non-significantly increased risks for CML, whereas other studies show no evidence of an association, including two that had quantitative estimates of exposure to benzene but no dose–response relationship (Rushton & Romaniuk, 1997; Guénel et al., 2002; see Table 2.5 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.5.pdf). Case–control studies have shown inconsistent results, with both increased risks (exposure for > 15 years was associated with an OR of 5.0 (1.8–13.9; Adegoke et al., 2003) and no increase in risk (Björk et al., 2001) reported (see Table 2.6 available at http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-19-Table2.6.pdf).

2.1.4 Chronic lymphocytic leukaemia

Chronic Lymphocytic Leukaemia (CLL) – also referred to as small lymphocytic lymphoma (SLL) – is now considered as a subtype of NHL in the WHO-classification of lymphomas. CLL can be an indolent disease of the elderly, which raises questions about cohorts that are not followed up until the study population is relatively old and about studies that use mortality instead of incident data. In addition, the diagnosis of CLL was less frequently made in the past, until complete blood counts were routinely obtained in recent decades.

Several cohort studies in the petroleum industry showed mixed results, with some non-significantly increased risks reported and other studies showing no association (see Table 2.7 available at http://monographs.iarc.fr/ENG/

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,

patients with essential trombocythemia (0.5–1%) and *polycythemia vera* (1–4%) (Abdulkarim *et al.*, 2009). Thus, benzene may first produce an MPD, which later transforms into AML.

An important role for epigenetic changes is also emerging in association with the development of leukaemia. Functional loss of the CCAAT/enhancer binding protein α (*C/EBPα*) (also known as CEBPA), a central regulatory transcription factor in the haematopoietic system, can result in a differentiation block in granulopoiesis and thus contribute to leukaemic transformation (Fröhling & Döhner, 2004). Recent work has shown that epigenetic alterations of *C/EBPα* occur frequently in AML and that *C/EBPα* mRNA is a target for miRNA-124a (Hackanson *et al.*, 2008). This miRNA is frequently silenced by epigenetic mechanisms in leukaemia cell lines. *C/EBPα* is also capable of controlling *miRNA-223* expression, which is vital in granulocytic differentiation (Fazi *et al.*, 2005). Altered expression of several miRNAs is also observed in some forms of AML (Dixon-McIver *et al.*, 2008; Marcucci *et al.*, 2008).

(b) Mechanisms of benzene-induced myeloid leukaemia development

There is strong evidence that benzene can induce AML via pathways I, II and IV, considerable supporting evidence for pathway V, some evidence for pathway III, but little information regarding pathways VI–VIII (see Fig. 4.2). Exposure to benzene has been associated with higher levels of the chromosomal changes commonly observed in AML, including 5q–/–5 or 7q–/–7, +8, and t(8;21) in the blood cells of highly exposed workers (Smith *et al.*, 1998; Zhang *et al.*, 1999, 2002). The benzene metabolite hydroquinone produces these same changes in cultured human cells, including cultures of CD34+ progenitor cells (Smith *et al.*, 2000; Stillman *et al.*, 2000). This provides strong evidence for the induction by benzene of AML via pathways I, II and IV (see Fig. 4.2).

Pathways III, IV and V are related to the inhibition of the DNA-related enzyme topoisomerase II, which is essential for the maintenance of proper chromosome structure and segregation; it removes knots and tangles from the genetic material by passing an intact double helix through a transient double-stranded break that it creates in a separate segment of DNA (McClendon & Osheroff, 2007; Bandele & Osheroff, 2009). To maintain genomic integrity during its catalytic cycle, topoisomerase II forms covalent bonds between active-site tyrosyl residues and the 5'-DNA termini created by cleavage of the double helix (Bandele & Osheroff, 2009). Normally, these covalent topoisomerase II-cleaved DNA complexes (known as cleavable complexes) are fleeting intermediates and are tolerated by the cell. However, when the concentration or longevity of cleavage complexes increases significantly, DNA double-strand breaks occur (Lindsey *et al.*, 2004). If topoisomerase II–induced double-strand breaks are incorrectly repaired, two unrelated (nonhomologous) chromosomes are fused together to produce translocations or inversions (Deweese & Osheroff, 2009).

There are different types of topoisomerase-II inhibitors. Epidophyllotoxins, such as etoposide, cause chromosome damage and kill cells by increasing physiological levels of topoisomerase II-DNA cleavage complexes (Baker *et al.*, 2001; Felix, 2001; Deweese & Osheroff, 2009). These drugs are referred to as topoisomerase-II poisons to distinguish them from catalytic inhibitors of the enzyme because they convert this essential enzyme to a potent cellular toxin. Other drugs, such as merbarone, act as inhibitors of topo-II activity but, in contrast to etoposide they do not stabilize topoisomerase II-DNA cleavable complexes. Nevertheless, they are potent clastogens both in vitro and in vivo (Wang *et al.*, 2007).

Several studies have shown that benzene in vivo, and its reactive metabolites hydroquinone

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 immuno-surveillance 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 immuno-suppressive 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 lympho-cytic 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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IARC 98

2. Studies of Cancer in Humans

2.1 Cohort, record linkage and proportionate mortality studies

2.1.1 Background

In 1989, the International Agency for Research on Cancer (IARC) classified painting as an occupation as *carcinogenic to humans* (Group 1) (IARC, 1989, Volume 47). At the time, the epidemiological evidence for the evaluation was primarily based on a total of eight studies (five record linkage and three cohort studies), listed in Table 23 of that volume. The primary findings in these data were relatively consistent excesses for all cancers (standardized mortality ratio [SMR] 1.21, 9100 cases), and for cancer of the lung (SMR 1.41, 468 cases). The lung cancer excess was noted to be above what could reasonably be expected to be due to confounding by smoking. Other findings which drew comment in Volume 47 were excesses for cancers of the oesophagus, stomach, and bladder, although these excesses were smaller than for cancer of the lung and were less consistent across studies. It was noted that results from a few studies showed excesses of leukaemia, and cancers of the buccal cavity, and of the larynx.

Cohort studies generally represent a stronger study design than record linkage studies. In the latter, the exposure is often taken from census employment data, is typically less accurate than the employment records upon which cohort studies are usually based, and does not usually take into account duration of employment. However, in the case of the cohort and record linkage studies listed in Table 23 by IARC in 1989, findings from both types of studies were reasonably consistent.

2.1.2 Cohort studies since IARC Monograph Volume 47 (Table 2.1)

Yin *et al.* (1987) studied workers who were employed at least 6 months within different factories in the People's Republic of China. They compared 13 604 benzene-exposed painters to 28 257 production workers without occupational benzene exposure with a similar sex and age distribution. Mortality follow-up occurred from 1972–1981, and the authors presented the leukaemia mortality rates separately for painters (15.9/100 000 person–years) and the comparison cohort (2.01/100 000 person–years). [The painters, not including paint-production workers, had a mortality rate ratio of [7.9] (14 leukaemia deaths) compared to workers in other production jobs without benzene exposure (four leukaemia deaths). This high rate ratio is presumably due to the selection of these painters for specifically benzene exposure.] No other cancer outcomes were presented.

Hrubec *et al.* (1995) followed a cohort assembled from a roster of approximately 300 000 caucasian, male WWI and WWII veterans for mortality from 1954–1980. These men served in the US Armed Forces at some time during 1917–1940, and held active

The OR for employment as a painter was 13 (95% CI: 2.0–554; 13 cases and one control). Tobacco use was not associated with leukaemia.

Persson *et al.* (1989) assembled cases of lymphoma (Hodgkin disease and non-Hodgkin lymphoma) from the Orebro Medical Centre Hospital in Sweden during 1964–1986 for a study of occupational exposures. There were 54 Hodgkin disease cases (35 men and 19 women), and 106 non-Hodgkin lymphoma cases (66 men and 40 women), aged 20–79. A total of 275 controls (157 men and 118 women) who had originally been drawn from population registries for previous studies were included. A mailed questionnaire was used to gather information on chemical exposures on the job, and during leisure time. Two Hodgkin disease cases and two non-Hodgkin lymphoma cases reported jobs as painters, while no controls were painters.

La Vecchia *et al.* (1989) evaluated occupational exposure and risk of lymphoid neoplasms in a case–control study in Milan, Italy. Study subjects, aged 15–74 years, were assembled from hospitals in the area during 1983–1988. Results reported were 69 cases of Hodgkin disease (44 men and 25 women), 153 cases of non-Hodgkin lymphoma (93 men and 60 women), and 110 cases of multiple myelomas (56 men and 54 women). A total of 396 controls (269 men and 127 women) diagnosed with acute conditions were selected from hospitals providing cases. Trained interviewers obtained information on 16 occupations, 13 occupational exposures, and other potential risk factors. ORs were adjusted for age, sex, area of residence and smoking. Although ORs were not presented, the authors reported no significant association with painting.

Heineman *et al.* (1992) used the Danish Cancer Registry and the Danish Central Population Registry to evaluate occupational exposures and risk of multiple myeloma among men. A total of 1098 cases (diagnosed during 1970–1984) and 4169 age-matched population controls with occupational information were included in the analysis. Only the most recent occupation was available from recent pension records. Industries where the men were employed were available from 1964 to diagnosis. Possible exposures based on occupation and industry were assessed by Danish industrial hygienists. ORs were calculated adjusted for age. The OR for men employed in the paint industry was 2.3 (95% CI: 0.4–11.1; three cases), while occupational painters had an OR of 1.0 (95% CI: 0.5–2.1; 11 cases). Exposure to paints and lacquers classed as 'possible' had an OR of 1.0 (95% CI: 0.8–1.4; 69 cases), and exposure classed as 'probable' had an OR of 0.8 (95% CI: 0.6–1.2; 39 cases).

Cases diagnosed during 1975–1984 from the University Hospital in Linköping, Sweden were assembled for a case–control study of occupational exposures and malignant lymphoma among men (Persson *et al.*, 1993). A total of 31 cases of Hodgkin disease, 93 cases of non-Hodgkin lymphoma, and 204 controls were available for study. Controls were population-based and had been selected for other studies. A mailed questionnaire was used to gather information on occupational exposures, leisure time exposures, and other factors. The OR for Hodgkin disease among painters was 2.3 (90% CI: 0.4–11; two cases).

Persson & Fredrikson (1999) pooled data from two case–controls studies to evaluate the role of occupational exposures in the development of non-Hodgkin lymphoma. The data

0.4–2.5; six cases) for chronic myeloid leukaemia. ORs for all leukaemia from potential exposure to paints differed between men (OR, 0.9; 95% CI: 0.5–1.5; 32 cases) and women (OR, 1.7; 95% CI: 0.9–3.4; 25 cases).

2.2.5   Solid tumours

(a)   Multiple cancer sites

Case–control studies of solid tumours among persons potentially exposed to paints are listed in Table 2.5.

Bethwaite *et al.* (1990) conducted a case–control study of multiple cancers using data from the New Zealand Cancer Registry. Age-adjusted ORs were calculated comparing painters with a particular cancer against painters without that cancer (and cancers that could be caused by the same exposures as that particular cancer). Occupational information (current or recent jobs) was obtained from the cancer registry. A total of 23 types of cancer were evaluated including buccal cavity, oesophagus, stomach, colon, rectum, liver, gallbladder, pancreas, larynx, lung, soft tissue sarcoma, malignant melanoma, prostate, testis, bladder, kidney, brain/nervous system, non-Hodgkin lymphoma, Hodgkin disease, leukaemia, and others. There were no significant increases in risk except for bladder cancer, and multiple myeloma.

In case–control study, Bouchardy *et al.* (2002) identified 58134 incident cancer cases in men from five cantonal Swiss Cancer Registries (Basel, Geneva, St Gall, Vaud, and Zurich) during 1980–1993. The overall proportion with histological or cytological confirmation of diagnosis was 95.1%. The study was restricted to cases aged 25 years or more at registration (and less than 65 years in St Gall and Vaud). The longest, current or most recent occupation at registration was recorded (the main or most accurately specified occupation was used in the Zurich Registry). Subjects with unknown occupation were not reported separately. The association between different cancer sites and work in a pre-defined set of industries and occupation was studied by estimating ORs adjusted for age, registry, civil status, period of diagnosis, nationality, urban/rural residence and socioeconomic status. For each neoplasm, registrants for the other cancer sites were used as the reference. The results for all sites with at least five exposed cases (excluding cancers of the lung, bladder and haematopoietic system because they are mentioned below) are reported in Table 2.5. There were no notable increases in risk except for cancers of the renal pelvis (OR, 2.2; 95% CI: 1.1–4.2; 14 cases) and liver (OR, 1.4; 95% CI: 1.0–2.0; 39 cases). [Use of patients with all other types of cancers as controls in this study could complicate the interpretation of the observed association since some of the cancer types may well be linked to exposure to paints, and use of patients with all other types of cancers as controls would cause an underestimation of the association between painting and bladder cancer risk.]

Ramanakumar *et al.* (2008) evaluated painting-related occupations and the risk of several different cancers including cancers of the oesophagus ($n = 97$), stomach ($n = 248$), colon and rectum ($n = 754$), prostate ($n = 438$), bladder ($n = 478$), and kidney ($n = 174$), in a re-analysis of data from a large case–control study from Montreal, Canada [Siemiatycki *et*

tar paints, 70 painters using general paints, and 27 on-site controls. Aromatic-DNA adduct levels (adducts/10^8 nucleotides) tended to be higher in coal-tar paint users (0.38 ± 0.23, $P = 0.07$) and general paint users (0.38 ± 0.24, $P = 0.06$) compared to on-site controls (0.26 ± 0.13). When both groups of painters were combined, they showed greater adduct levels than on-site controls ($P < 0.05$). Glycophorin A mutation frequencies measured in 55 individuals with MN heterozygote genotypes were not significantly different among the three job groups (Lee et al., 2003).

Several chromosomal abnormalities could be detected in the bone marrow of most patients with acute myeloid leukaemia. In a study by Crane et al. (1996), routine cytogenetic data from 213 patients (129 enrolled in the period 1976–1983, and 84 enrolled in the period 1986–1990) with acute myeloid leukaemia were correlated with environmental exposures to organic chemicals (eg., benzene), paints, pesticides, and other substances such as dyes, glues, or varnishes. A suggestive effect was found between exposure to paints and the –7/7q chromosomal abnormality (odds ratio, 7.50) but this was non-significant and only observed in the set of patients enrolled between 1986–1990.

In summary, most cytogenetic studies among painters measuring a variety of cytogenetic end-points and markers of genotoxicity showed elevated levels of genetic damage. These effects were by and large similar for smokers and non-smokers. In addition, several studies have shown a dose–gradient with years or weeks worked and the cytogenetic end-point. These studies support that painters have increased levels of DNA damage. However, the number and size of the studies is generally small. Furthermore, as no comprehensive exposure assessment has been done in any of these studies, it is difficult to relate the observed genotoxic effects to any specific component(s) of paint.

4.2.2 Genotoxicity information for individual constituents of paints

It is not possible to provide information on the genotoxicity and mechanism of action of all known components of paint or exposures related to painting activities (for an overview of main substances to which workers may be exposed in painting trades, see Section 1.1). We therefore limit this overview to selected chemicals as described in section 4.1.

(a) Benzene

Chromosomal aberrations in human peripheral lymphocytes have been associated with occupational exposure to benzene and include hypo- and hyperdiploidy, deletions, breaks, and gaps (ATSDR, 2007a). SCE 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 SCEs 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 (IARC, 1987). It induced chromosomal aberrations and mutation in human cells in vitro. In-vitro studies strongly imply that benzene's genotoxicity is derived primarily from its metabolites hydroquinone and 1,4-benzoquinone through their ability to inhibit

among painters when compared to 79 unexposed male workers. In contrast, T-suppressor cell count was increased among exposed workers when compared to controls (Moszczyński *et al.*, 1996).

Kim *et al.* (1999) evaluated haematological effects among 57 shipyard painters exposed to ethylene glycol monoethyl ether acetate (EGEEA), a solvent widely used for paints. Painters were divided in two exposure groups (high/low). Mean EGEEA levels were 3.03 and 1.76 ppm, respectively. In addition, environmental monitoring revealed detectable levels of toluene, ethyl benzene, xylene, butanol, isopropanol, ethanol, ethyl acetate, butyl acetate, methyl isobutyl ketone, and nonane. No benzene or other glycol ethers could be detected in the bulk samples of some paints and thinners or air samples. Mean white blood cell counts in the high exposure group (6033 cells/µl ± 1433) were lower ($P < 0.05$) than in the control group of 41 unexposed workers in non-production areas of the same factory (7031 cells/µl ± 1400). Six (11%) of the 57 painters were leucopenic (leucocyte count < 4500 cells/µl) while none of the controls was affected ($P < 0.05$). Results indicate that EGEEA might be toxic to the bone marrow.

These studies on haematological effects among painters show consistently that peripheral blood cell counts and morphology of the cells are affected by the exposures encountered during the handling or making of paints. The relation between haematotoxicity and cancer are not directly clear except that in a study among subjects exposed to benzene, subjects with benzene poisoning (total white blood cell count < 4000/µl or white blood cell count between 4000 and 4500/µl and platelet count < 80 000/µl, with repeated confirmation of this count in a few months in a peripheral blood examination) had an increased risk for developing acute myeloid leukaemia (relative risk, 70.6; 95% CI: 11.4–439.3; Rothman *et al.*, 1997). However, it needs to be recognized that although this lends plausibility to a possible association between severe haematoxicity and acute myeloid leukaemia, it does not necessarily mean that the association is relevant for less severe, transient haematological effects.

(b)   Immunological effects

Hexamethylene diisocyanate (HDI) is an aliphatic diisocyanate that is used almost exclusively in the manufacture of paints and surface coatings. HDI can induce occupational asthma (Vandenplas *et al.*, 1993), and HDI-specific IgE and IgG have been detected in selected patients with diisocyanate asthma or small populations of exposed workers (Grammer *et al.*, 1988; Cartier *et al.*, 1989; Baur *et al.*, 1996; Tee *et al.*, 1998; Redlich *et al.*, 2001). Besides specific Ig responses, increased proliferation of HDI-specific lymphocytes has been observed upon in-vitro cell stimulation with HDI (Redlich *et al.*, 2001). These results indicate that HDI-containing paints can trigger specific systemic immunological responses.

4.3   Susceptible populations

A few studies have addressed the interplay between genetic factors and biological and clinical end-points. Gene–environment interactions related to specific exposures and
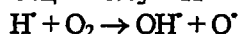
1.2   Composition of fire smoke

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:

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

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:

$$CH_4 \rightarrow CH_3^\cdot + H^\cdot$$
$$H^\cdot + O_2 \rightarrow OH^\cdot + O^\cdot$$

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	

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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 fireball 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.