The Fire Fighting Environment

Risk for

Breast Cancer, Gynecologic Malignancies and Lymphoma

A Report prepared for the International Association of Fire Fighters

by

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Appendix A Chemicals Present in Fire Fighter Environment

OVERVIEW OF WOMEN AND CANCER

The most common causes of death for U.S. women for many years has been cancer and heart disease with cancer being the leading cause of premature deaths under age 54 and heart disease rates higher in older women. In 1993, however, cancer became the leading cause of death for women of all ages (US DHHS, 1995). Breast cancer is the second most common cause of cancer deaths (after lung cancer) in women (if skin cancers are excluded) with the American Cancer Society estimating that about one in eight women will be diagnosed with breast cancer over a 95-year life span. Its incidence rate (number of new cases diagnosed in a year) is 113.2 per 100,000 white women and less common (99 per 100,000) among black women. (Landis et al. 1999)

Figure 1 displays the age-adjusted cancer incidence in white and black women using 1987 to 1991 data for the ten most common cancer sites. As illustrated in the figure, the second and third most common cancer types in both white and black women are colon/rectum and lung cancer. Following this, cancer of the body of the uterus (corpus) is the fourth most common cancer in both groups and then cancer of the ovary in white women and cervix in black women is the fifth most common cancer type diagnosed.

These cancer types are displayed by incidence rate in Figure 2. Racial differences are seen to be more common as the incidence of the cancers decreases. Figure 3 displays the expected new cases and cancer deaths for female cancers of the breast and reproductive organs in 1999, according to the American Cancer Society.

The variability in cancer incidence seen over time and across geographic and racial groups can be partially explained by two broad areas of influence on cancer risk: genetic components and environmental components.

Genetic Components of Cancer Risk

The understanding of the genetic basis for cancer risk has grown dramatically in recent years. This area of research grew out of observations that some types of cancer were more prevalent in certain families. Indeed, the recognition that daughters of mothers who developed breast cancer are also at increased risk of breast cancer development is an example of such observations of familial cancer risk. While breast cancer is a disease that has many factors influencing the likelihood of its development, research is focusing on genetic variation in genes influencing the susceptibility of developing breast cancer and ovarian cancers in some women. These genes called BRCA-1 (Miki et al. 1994) and BRCA-2 (Lancaster et al. 1996) have been studied in mice and may be useful in human risk assessment.

Other research on the genetic influence on cancer development involves examining genetic differences in enzymes that interact with or metabolize environmental cancer-causing agents. Genetic or familial differences in how the body chemically "handles" an environmental carcinogen may either enhance (by rapidly metabolizing the substance to a toxic form) or eliminate (by detoxifying the substance) the likelihood of cancer development. Research is focusing on a number of these carcinogen-metabolizing enzymes at present that may confer different susceptibility to environmentally-caused cancer. One example is a recent study of cigarette smoking associated with increased breast cancer risk in postmenopausal women who possess a metabolizing enzyme, N - acetyltransferase 2 that only "slowly acetylates" (detoxifies) carcinogens (Ambrosone et al. 1996). The genetically different forms of metabolizing enzymes obviously may have profound influence on the development of, or protection from, environmental cancer development.

Another area of genetic research involves genetic variation in genes that are responsible for correcting mistakes during the replication of DNA (the genetic material in a cell's nucleus). If an individual's DNA repair capacity is altered, they may presumably incur an increased risk of cancer development.

Environmental Risk Factors

There is a considerable body of evidence that a substantial portion of the cancer burden is environmentally caused or influenced by environmental agents. "Environmental agents include synthetic and naturally occurring chemicals, foods and nutrients, physical agents such as heat and ionizing radiation and non-ionizing radiation, social and economic factors that affect our health and behavior, lifestyle choices and substance abuse." (Varmus et al. 1997)

Among the most active research areas of environmentally influenced cancer risk is the study of chlorinated hydrocarbons and related compounds such as DDT, polychlorinated biphenyls (PCBs) and dioxins which are both

widespread and persistent in the environment. These agents possess estrogenic activity; that is, they mimic the biologic effects of estrogen. Unopposed estrogenic exposure is a risk factor for most of the gynecologic malignancies, suggesting a possible roll for environmental estrogens in the development of these cancers.

In the following sections of the document, the known personal and environmental risk factors for breast cancer, gynecologic malignancies and lymphoma will be discussed.

BREAST CANCER

Epidemiology

Breast cancer, the most common form of cancer in both black and white women in the U.S., is also the leading cause of cancer death in U.S. women (Ries, 1994). Breast cancer rates vary dramatically across geographic areas with rates in the U.S. among the highest in the world. Incidence rates increase with high socioeconomic status and with age. Between 1973 and 1991, invasive breast cancer incidence in this country increased by more than 25% in white women and 30% in black women (Ries, 1994). While the increase is not fully understood, it is partially attributed to the increased use of mammography in that time period (MMWR, 1990) with much of the increase in tumors identified occurring in the lowest stage tumors.

Both genetic and environmental factors are believed to play a role in breast cancer risk. Breast cancer risk increases with age and with a family history of breast cancer. However, inheritance accounts for less than 10% of breast cancers. Research has been focusing on host susceptibility genes, BRCA-1 and BRCA-2, which, when functioning normally suppress tumor growth but are often mutated in high risk for breast cancer families (Welp et al. 1998).

Risk Factors

Environment

Most of the risk factors for breast cancer development relate to the woman's lifetime burden of estrogen exposure (Welp et al. 1998). The early onset of menstruation (menarche) and late menopause, for example, increase the duration of lifetime estrogen exposure, raising the risk of breast cancer. Menopause after the age of 45 carried a 2.5 fold greater risk for breast cancer development in women compared to those with menopause before 45 in one U.S. study (Madigan et al. 1995). Hormone replacement therapy is another source of estrogen exposure and has accounted for moderate risk increases, about 35%, in a pooled study of data from 21 countries (ColGroupHorFact, 1997). This effect increases with duration of use and declines after five years from discontinuing treatment.

Oral contraceptive use may cause a slight risk shortly after discontinuation of use but the excess is not seen after ten years (ColGroupHorFact, 1996). A moderate risk, again in the 30% range, has been attributed to later age at birth of the first child (again allowing a longer duration of estrogen exposure to the woman) and for women who have no children (Madigan et al. 1995).

Interestingly, Bernadino Ramazzini, the founder of occupational medicine, described the breast cancer prone experience of nuns in 18th Century Italy, who would have had a prolonged duration of estrogen exposure, having never been pregnant.

Personal Environment

While postmenopausal obesity is a risk factor, likely due to estrogen formation in fat cells (Hulka et al. 1995), the role of diet and breast cancer remains controversial. Alcoholic drink consumption probably does increase the risk if consuming over four drinks per day, possibly due to liver effects on estrogen detoxification (Howe et al. 1991).

The evidence that tobacco smoking is playing a role in breast cancer development is mixed. However, there are data suggesting smoking may be a cofactor along with familial genetics to enhance postmenopausal breast cancer risk in women who slowly metabolize (acetylate) certain carcinogens and who were heavy smokers 20 years prior as compared to women who rapidly metabolize carcinogens (Ambrosone et al. 1996). This topic will be discussed more extensively in the section on PAH exposure.

As mentioned, breast cancer is a disease of the higher socioeconomic class almost worldwide (Faggiano et al. 1997). It is postulated that the estrogen burden of a woman is influenced by the socioeconomic group to which she belongs indirectly by diet and alcohol consumption, use of hormone replacement or oral contraceptives and reproductive history. These competing effect modifiers therefore make identifying an occupational or an environmental risk factor difficult. For example, the higher breast cancer incidence among higher socioeconomic groups may dilute or mask an apparent excess among a lower working class group that is exposed to an occupational carcinogen (Faggiano et al. 1997).

Timing of Exposure

As stated earlier and is true for other cancers, the risk of breast cancer development has been described to be determined by a combination of external exposure and personal factors or susceptibility. In the case of breast cancer, susceptibility may be a function of both genetics and reproductive patterns influencing one's estrogen burden.

A critical variable of susceptibility appears to be the time of exposure. There is an apparent vulnerable window of exposure during puberty and pregnancy when breast tissue may be more sensitive to environmental carcinogen exposures. This may be due to increased cellular growth and development. Critical timing of exposures resulting in enhanced breast cancer risk has been observed for atomic bomb survivors (Tokunaga et al. 1987); heavy smokers (Palmer et al. 1991) and DES users who took this drug to prevent miscarriage during pregnancy (Greenberg et al. 1984).

Animal Studies

The National Toxicology Program (NTP) of the National Institutes for Environmental Health Sciences (NIEHS) has performed long-term animal studies for 140 chemicals causing cancer in animals. Table 3 displays 20 chemicals that caused mammary gland tumors in rats and mice and were found to be carcinogenic in a least one other site (Griesemer et al. 1994). Among them are several drugs including furosemide, procarbazine and reserpine. Of special interest, benzene and

1,3- butadiene, documented human carcinogens for other organ systems (bone marrow and lymphatics) are among this list. The study authors discuss the halogenated ethanes as needing further investigation regarding their role in human breast cancer development.

Human Studies of the Ambient Environment

A number of chemical contaminants of the wider environment including some pesticide and herbicide residues and other compounds possess estrogenic activity or other hormonal activity which have made them suspect risk factors for breast cancer.

Organochlorine Pesticides (DDT)

Although results are mixed, there is good evidence for an environmental chemical acting as a breast cancer risk factor in the case of the organochlorine pesticide DDT, or more specifically DDE, its active metabolite (Krieger et al. 1994; Wolff et al. 1993). DDT has also been associated with mammary gland tumor development in animals (Scribner et al. 1981). The persistence of these agents and other chlorinated hydrocarbons which are stored in body fat have also fueled interest in studying occupational groups in agriculture and industries using large volumes of chlorinated hydrocarbons, for potential clues to breast cancer risk. Several recent mortality studies of workers in solvent-using industries have failed to show a strong breast cancer excess (reviewed in Welp). However, these were studies of cancer deaths, not new cases of breast cancer.

General findings of breast cancer excesses in women's occupations have typically included professional woman including teachers. (Hall et al. 1991; Rubin et al. 1993) The excess risk for teachers was also documented in a Chinese study in Shanghai (Petralia et al. 1998) and an Italian study (Costantini et al. 1994) as were the general trends in excesses in professional women including science researchers and health care workers.

When analysis of breast cancer mortality from death certificates is made by type of occupational chemical exposure, using a job exposure matrix, suggestive associations were found for styrene, some organic solvents including methylene chloride, carbon tetrachloride and formaldehyde, some metals and metal oxides and acid mists (Cantor et al. 1995b). The most consistent evidence was for styrene with an excess observed among both white and black women. The Chinese study documented a significant elevation of risk for high probability of exposure to organic solvents (SIR = 1.4) and for benzene and pesticide exposures (Petralia et al. 1998).

Physical Hazards

Ionizing radiation in high-dose exposure scenarios such as the atomic bombing of Japan, therapeutic x-ray treatment for tuberculosis and other illnesses in the past, are well established risk factors for breast cancer development with increased relative risks up to six fold with consistently observed dose response effects (John et al. 1993; Boice et al. 1996). The age of exposure is also a factor with highest risk ascribed to exposure between ages 10 to 20 and little risk after age 40 (Tokunaga et al. 1987). There is little evidence of occupationally incurred radiation exposure causing excess breast cancer risk (Laden et al. 1998).

Electromagnetic Fields

Evidence for electromagnetic field exposure (EMF) as a breast cancer risk factor is somewhat mixed but on the whole demonstrates an effect. Studies of populations employed in electrical occupations or populations environmentally exposed either by proximity to power lines or electric blanket use have been performed. Several studies have reported an excess risk of male breast cancer in relation to presumed EMF exposure based on job title, although these studies were based on small numbers (reviewed in Laden). Other studies have not shown an excess. Loomis and others reported a statistically significant 40% excess risk of breast cancer mortality in women employed in electrical occupations (Loomis et al. 1994). Other studies have both corroborated this (Coogan et al. 1996) and failed to observe an association (Cantor et al. 1995a). The biological mechanism here is thought to be the decrease in the secretion of the hormone melatonin from exposure to visible range environmental lighting or low level EMF. The melatonin drop results in an increase in estrogen and prolactin secretion.

Smoking and Polycyclic Aromatic Hydrocarbons

The evidence that tobacco smoking is playing a role in breast cancer development is mixed. Polycyclic aromatic hydrocarbons (PAH) which are significant constituents of cigarette smoke and air pollution, are known to cause mammary gland tumors in animals (Snell et al. 1962; Huggins et al. 1962). Cigarette smoking, however, has not been strongly linked to breast cancer risks in humans. However epidemiological evidence for the role of environmental smoke through exposure from household or workplace contact has accrued in the last fifteen years suggesting that passive smoking and a critical timing of the exposure earlier in a woman's life is important (Lash et al. 1999; Horton, 1988; Horton, 1992).

The carcinogenic potency of benzo (a) pyrene, a tobacco-related PAH, appears to be related to its ability to bind with (alter) DNA to form adducts (Arif et al. 1997). PAH - DNA adducts have been measured in human breast tissue (Perera et al. 1995) suggesting a role for PAH exposure in breast cancer development. As discussed earlier, women with a long smoking history and who possessed the slow type N - acetyltransferase 2 (NAT-2) enzyme which detoxifies smoke-related carcinogens slowly, rather than rapidly, were found to have a four to eight fold higher risk of breast cancer (Ambrosone et al. 1995). Several other studies of enzyme forms in smoking women have found some effect suggesting a role for tobacco smoking in breast cancer development in genetically susceptible women (Goldman et al. 1998). There are also some molecular similarities between the types and locations of mutations in the DNA of breast cancer patients compared to the mutations found in tobacco-exposed lung cancer patients, again implicating a role for constituents of tobacco smoke in breast cancer development (Goldman et al. 1998).

OVARIAN CANCER

The ovaries are a pair of small glands located on each side of the uterus. They store eggs and secret hormones that regulate pregnancy and menstruation. Ovarian cancer is the second most common gynecologic malignancy (endometrial cancer is first) and it accounts for 4% of all cancer in women. Over 25,000 new cases of ovarian cancer are expected to occur in 1999 (Landis et al. 1998). Ovarian cancer causes more deaths than any other gynecologic malignancy. The five-year (after diagnosis) survival rate is 47% for whites and 42% for African Americans (Landis et al. 1998).

Epidemiology

Ovarian cancer increases in age and reaches a peak in the seventh decade of life. Its incidence is highest in industrialized countries except for Japan. It is more common in white women in the U.S.-with an incidence rate of 13

per 100,000-than black women with an incidence rate of 7 per 100,000 (Ries, 1994). Like breast cancer, women who have never had children are more likely to develop ovarian cancer. Pregnancy and the use of oral contraceptives also reduce the risk. There is also an increased risk for women who have had breast cancer or are from a family with a breast cancer or ovarian cancer history. Mutations in the BRCA-1 and BRCA-2 genes (discussed in the breast cancer section) have been detected in these families. Another genetically-mediated syndrome usually related to colon cancer, hereditary nonpolyposis colon cancer, has also been linked to ovarian and endometrial cancer.

Animal Studies

Animal studies of the carcinogenicity of some occupational and environmentally encountered substances have been performed by the National Institute for Environmental Health Sciences (NIEHS) National Toxicology Program (NTP). They have reported eight chemicals found to cause ovarian cancers in mice including benzene displayed in Table 1.

Risk Factors

Considerable variation and incidence rates internationally as well as studies among migrants whose risk approaches that of the host country (Shen et al. 1998; Herrington, 1994; Parkin et al. 1997) suggest some environmental factors are influencing disease development. Dietary fat apparently plays a role associated with a slightly increased risk, as may protein and calorie intake (Parazzini et al. 1991). Smoking and alcohol, coffee and tea consumption apparently do not affect risk (Hartge et al. 1989; Parazzini et al. 1991).

Environmental

In a 1998 review of occupational and environmental risk factors for ovarian cancer, Shen and colleagues state: "Current evidence is characterized by poorly focused data for occupational and environmental agents, vulnerability to biases and an almost complete lack of quantitative exposure response data...Few high quality studies have been carried out and no chemical agents have been studied extensively with the exception of talc", which suggested a modest to moderate association.

In the Shen review of 48 epidemiologic studies of ovarian cancer, only hairdressers, beauticians and women working in the printing industry were found to have excess risk. For the hairdressers and beauticians, standardized incidence ratios (SIR) generally were under two (that is the risk was less than two times the expected rate). The printing industry risk ratios were higher but many were not statistically significant and based on few cases.

Study of ovarian cancer risk from specific classes of occupational and environmental agents have included examining solvents and related substances. These studies have involved a number of industries and exposure situations including chemical manufacturing, the rubber industry, painting and dry cleaning in a U.S. case - referent study of ovarian cancer. Years of occupational exposure to unspecified solvents were not associated with an excess cancer risk (Hartge et al. 1994). However, a Chinese case - referent study found a nonsignificant 40% excess risk from benzene exposure (Shu et al. 1989). Several other studies of various solvent-related occupations found no excess ovarian cancer risk but some studies were very small, limiting the likelihood of observing an effect (reviewed in Shen, 1998).

Pesticides/Herbicides

The carcinogenic chlorinated triazine herbicides were associated with a significantly elevated ovarian cancer risk of 2.7 in an Italian study (Donna et al. 1989). However, none of the doses could be quantified, but the association tracked both duration and likelihood of exposure. Atrazine exhibits hormonal effects on the hypothalamic - pituitary - gonadal axis and induces breast and reproductive cancers in rats (IARC, 1991).

Polycyclic Aromatic Hydrocarbons (PAH)

A U.S. case reference study examined data from 1978 to 1981 in ovarian cancer patients and other hospitalized comparison women matched for age and race. A blind exposure assessment was performed for each job/industry combination of the women looking at talc, ionizing radiation, PAH and solvent exposure. The only excess risk identified was for women exposed to PAHs for five to nine years (RR, relative risk = 1.8). However, this finding was not statistically significant, nor was there a trend with duration of exposure (Hartge et al. 1994).

Several studies have reported an increased risk of ovarian cancer in women occupationally exposed to asbestos (Newhouse et al. 1985; Keal, 1960). The Keal paper documents an excess of ovarian cancer or presumed ovarian-associated cancer in London women hospitalized for asbestosis. The women were exposed in asbestos grinding and spinning operations in asbestos textile manufacture among others. Most had greater than 15 years since exposure and 4-5 years of exposure duration. According to the author, this study was undertaken because "…an impression was formed at the London Hospital that women suffering from pulmonary asbestosis had ovarian neoplasms more often than other women."

The Newhouse paper examined the cause of death for 700 women factory workers from East London employed between 1936 and 1942 in the manufacture of asbestos textiles and products using crocedolite, amosite and chrysotile asbestos. Among the severely exposed there was and excess of deaths of carcinoma of the breast and ovary (five observed, 0.9 expected cases) which was highly significant at p<0.01. Newhouse makes the point that although the total number of tumors is low, the rate excesses were seen in persons with a longer exposure duration and greater exposure intensity, strengthening the finding.

The observation of a two to three fold ovarian cancer excess in asbestos textile gas mask filter makers, again in British workers before and during the Second World was reported by Acheson and colleagues (Shen et al. 1998; Acheson et al. 1982). Talc in provider for feminine hygiene use has also been studied, showing an increased risk of 1.92(p<.003) for ovarian cancers (Cramer et al. 1982). Prior to the Mid-1970s, talc may have contained some asbestos (Rohl et al. 1976; Cralley et al. 1968).

Women with asbestos exposure from other industries including Italian rock salt workers (Tarchi et al. 1994) and Norwegian pulp and paper manufacturing (Langseth et al. 1999) have also experienced ovarian cancer excesses.

Animal experiments have reported the inducibility of ovarian cancers in guinea pigs from asbestos exposure (Graham et al. 1967), and Heller has reported recovery of asbestos fibers from ovaries of women with a household asbestos exposure (9 of 13 women (69.2%)) and without obvious exposure (6 of 17 women (35%)). (Heller et al. 1996)

Occupational exposure to talc can occur in mining and milling but environmental talc exposure through the use of cosmetics and powder is thought to be a more common occurrence. Four large interview studies evaluating genital talc application from the U.S. and U.K. each found a 50 to 90% excess ovarian cancer risk (review in Shen).

Clearly these observations require further follow-up, but the evidence appears substantial that there is a relationship between asbestos exposure and ovarian cancer.

UTERINE ENDOMETRIAL CANCER

The spongy inner layer of the body of the uterus - the endometrium - is where most uterine cancers originate. Cancer of the endometrium is the most common gynecologic cancer in women and accounts for about 9% of the total cancers in U.S. women (Ries, 1994). The five-year survival rate is good at 83%. The disease is rare before the mid-40's but rises with later ages. In the U.S., rates for white women are almost twice that of black women. There is a significant geographic variation in incidence with the highest rate seen in North America and Northern Europe and low rates in Asia and Africa (from American Cancer society website).

Epidemiology

A dramatic increase in incidence occurred in the early to mid-1970's, but has since declined (Weiss et al. 1976) and was attributed to the use of estrogen (alone) replacement therapy in the 1960's and early 1970's, a practice which was significantly reduced in the late 1970's.

Animal Studies

Animal bioassay studies of potential carcinogenic chemicals performed by the National Toxicology Program at the NIEHS have identified 13 chemicals causing uterine cancers in rats or mice displayed in Table 2. Three of the agents

are chemotherapeutic drugs and one, ethylene oxide, is used widely in the health care industry as a sterilant. Two of the agents that are structurally related halogenated ethanes, bromo-ethane and chloro-ethane, produced tumors in a relatively high percentage of the animals, 56% at 400 parts per million and 86% at 1500 parts per million, respectively.

Risk Factors

Estrogen is the major risk factor for the most common type of endometrial cancer. Responding to the apparent adverse effect estrogen replacement had on endometrial tissue; it has become standard practice to use combination therapy of estrogen and progestogen for hormone replacement. In contrast to the cancer- promoting effect of unopposed estrogens during menopause, combined oral contraceptive preparations containing both estrogen and progestin have demonstrated a protective effect with lower endometrial cancer rates in several studies (Henderson et al. 1988; CancSterHormSt, 1987). The anti-estrogenic drug, Tamoxifen, used in breast cancer treatment may also increase endometrial cancer risk (Mignotte et al. 1998) although the evidence in conflicting (Katase et al. 1998).

Other risk factors for endometrial cancer are also common to breast cancer including high socioeconomic status, never having given birth or few children, early age of onset of menstruation and late age at menopause. Obesity, which is accompanied by increased levels of estrogen, is a recognized risk factor for ovarian cancer with the risk rising for very heavy women (Swanson et al. 1993).

UTERINE CERVICAL CANCER

Epidemiology

The uterine cervix is the neck or cuff of tissue at the bottom of the body of the uterus that protrudes into the vagina. Cervical cancer is the least common of the gynecologic malignancies with about 12,800 cases of invasive cervical cancer expected to be diagnosed this year. With the widespread practice of Pap smear screening, both the incidence of new cases and mortality from cervical cancer have declined in the past three decades. U.S. incidence rates are generally low compared to other rates worldwide. For example, 40 cases per 100,000 women in a high incidence locale such as South America versus 7 per 100,000 in U.S. white women and 14 per 100,000 in U.S. black women (Parkin et al. 1992).

Risk Factors

Sexual behavior has been identified as the major risk factor for both carcinoma in situ (cancer of the outer most layer of the cervix) and for invasive cervical cancer (Brinton et al. 1986). Early age for sexual activity and multiple sexual partners have also been implicated. There is also good laboratory and clinical evidence for the human papilloma viruses (HPV) - the agent causing genital warts in men and women - playing a role in cervical cancer development (Koutsky et al. 1988). Other factors including infectious agents, hormonal levels and diet may also be playing a role. Barrier contraceptive methods decrease the risk - likely by decreasing exposure to infectious agents.

There is recent evidence for nutritional factors playing some role including low intake of either vitamin C or beta carotene, possibly enhancing risk (Slattery et al. 1990; Brock et al. 1988). Although this has not always been found (Ziegler et al. 1990).

Cigarette smoking is a risk factor for cervical cancer development (Winkelstein, Jr. 1990) although the biologic mechanism is not well understood.

In central Europe, an increase in the incidence of carcinoma in situ was observed in the 1988 to 1989 time frame shortly after the Chernobyl incident. The increase in incidence was found in all age groups but the reaction appeared to be faster in younger women (Borovec, 1995).

LYMPHOMAS

Epidemiology

Lymphomas are cancers that affect certain white blood cells of the immune system. These white blood cells called lymphocytes have abnormal growth characteristics and altered infection-fighting ability when the disease occurs. Lymphomas are either classified as Hodgkin's disease or non-Hodgkin's lymphoma. The American Cancer Society estimates about 64,000 new lymphoma cases are expected in 1999, of which almost 90% (56,800) will be non-Hodgkin's lymphoma and the remainder (7200) will be the Hodgkin's type (American Cancer Society website). Incidence per 100,000 people is highest for white males at 18.6; followed by white females at 12.0; black males 12.8 and 8.1 among black females.

Risk Factors

Although there has been a decline in incidence for Hodgkin's disease between 1973 and 1991, there was a 73% increase in non-Hodgkin's lymphoma (Ries, 1994). Part of this dramatic observation has been due to the AIDS epidemic in that non-Hodgkin's lymphoma is about 60 times more common in AIDS patients than in the general U.S. population (Beral et al. 1991). However, the non-Hodgkin's lymphoma incidence rate began climbing years before the onset of the AIDS epidemic, implicating other factors.

Other immunodeficiency states, both generic and acquired through infection or medication use, have also been associated with an increased risk of non-Hodgkin's lymphoma. Kidney transplant patients, for example, on immunosuppressive medication to prevent kidney rejection, are at risk of developing non-Hodgkin's lymphoma 40 to 100 times more frequently than expected (Kinlen et al. 1979; Fraumeni, Jr. et al. 1977). Other viruses may also be implicated in some lymphoma developments (Mueller et al. 1992).

Environmental

Occupational and environmental risk factors for lymphoma have focused on pesticide and herbicide use. There is abundant evidence that exposure to the herbicide 2,4-D is associated with a significant increased risk for non-Hodgkin's lymphoma which included an increase in risk with frequency of exposure (Zahm et al. 1990; Hoar et al. 1986). Organophosphate pesticide exposure may also affect non-Hodgkin's lymphoma risk (Zahm et al. 1990; Cantor et al. 1992).

Occupational Group Excesses

A recent meta analysis of non-Hodgkin's lymphoma in farming demonstrated that U.S. male farmers have a slightly elevated risk of developing non-Hodgkin's lymphoma with a relative risk of 1.1 (CI = 1.03 to 1.19). For female farmers, the relative risk equals 0.93 with a confidence interval (CI=0.82-1.06). These investigators discussed commonly experienced exposures to include infectious micro-organisms from livestock exposure, herbicides and insecticides (Khuder et al. 1998). The authors also discussed the extensive proposals for agricultural chemicals being potential risk factors for non-Hodgkin's lymphoma and the biologic plausibility for this due to the number of these agents that are known or suspect human carcinogens. Also discussed are the differing results found for male versus female farmers including the possibility of differing subsets of farming exposures related to different job tasks that may vary with gender.

In contrast to the previous meta-analysis, a number of studies have found non-Hodgkin's lymphoma and other lymphatic cancer excesses among female farmers or agriculture workers (Linet et al. 1993; Hansen et al. 1992).

Non-agricultural occupations have also been reported as a risk factor for non-Hodgkin's lymphoma development including working in the rubber industry (Monson et al. 1976); petroleum refining (Delzell et al. 1988); chemists (Olin et al. 1980) and dry cleaners (Blair et al. 1990). The proposed agent causing the risk is an exposure to organic solvents.

Hair dye use in some circumstances is also observed to increase risk in a number of recent studies (Zahm et al. 1992; Thun et al. 1994) and although the biologic plausibility is reasonable given the mutagenicity and carcinogenicity in animals with some of the hair dying agents, there are methodologic concerns about some of the studies that reported

these findings that do not allow a causal link to be made. They do suggest, however, the need for future studies to clarify these observations.

Of special interest, a recent large study of death certificates from 24 states examining the occupations of persons whose cause of death was non-Hodgkin's lymphoma found fire fighters to be among the significant associations made for occupation (Figgs et al. 1995). Based on 12 cases observed, an odds ratio of 5.6 was determined (CI=2.5-12.3). Other excesses were seen among engineers, chemists, medical professionals, farm managers, aircraft mechanics, electronic repairers and several others.

CHARACTERIZING EXPOSURE IN THE FIRE FIGHTING ENVIRONMENT

Health Studies of occupational groups classically examine the hazards encountered in the work environment. In the case of fire fighting, the products of combustion are the focus of investigation. Several undisputed human carcinogens have been measured in the fire environment and will be discussed below. Of interest, a recent paper examining DNA damage in several different occupational groups identified a higher frequency of DNA damage in fire fighters' peripheral white blood cells after a chemical plant fire (Oesch et al. 1995). However, of interest to us in this review is characterizing the more typical combustion products in the fire environment.

Combustion is a complex process, with the composition and amount of by-products produced a function of the source materials present and the conditions of combustion. These conditions include the amount of oxygen present, that is, the ventilation of the fire and the thermal energy transferred to the burning material (Lees, 1995; Hartzell et al. 1983).

Combustion products include thousands of chemical constituents that proceed from the simplest products of water and carbon dioxide derived from burning wood and natural materials, to the increasingly commonly encountered components of burning plastics, as these materials are being incorporated into furnishings, wall and floor coverings and home products. Industrial fires are even more complex; with the combustion products encountered a function of component materials used and processes performed at the site. Beyond structural fire fighting, the ubiquitous use of plastics and other synthetic materials enlarges the likelihood of hazardous material in fire smoke. This phenomenon has spawned the adage that a car fire is a "hazmat incident".

Environmental hazardous materials incidents present a mixed picture, in that the exposure is usually to only one or a few agents produced or spilled, but that agent could be released at very high concentrations or in an uncommonly encountered exposure scenario, likely exposing the fire fighter/responder to any of the 60-70,000 chemicals in commercial use.

Studies of the Fire Fighting Environment

As an industrial hygienist familiar with the fire fighting environment described in an article in 1995, "Despite the striking and often dramatic nature of these exposures, characterization of the exposures of fire fighters makes up a strikingly small body of literature". This is due to the limits on technically feasible methods to measure and analyze combustion-derived materials. Equipment and methods developed in industrial environments with comparatively lower exposure concentrations can be overwhelmed in a fire fighting environment. Other constraints on data gathering include the unplanned, emergent and life threatening nature of a fire scene, hampering information collection.

The data that are available come from the few studies where direct measures of exposure have been made and from indirect sources including area sampling at working fires and simulated test burns. These approaches have been reviewed in Lees, 1995 and McDiarmid et al., 1991.

Studies that have quantified concentrations of specific chemicals in the fire fighting environment through direct personal sampling of the fire fighter or area sampling of a working fire are presumed a better characterization of the exposure environment. These chemicals numbering 17, were summarized in the literature (McDiarmid et al., 1991) and a modified list of ten agents found more commonly or in higher concentrations, was discussed in a subsequent review (Lees, 1995).

In contrast to this short list, a very long list of over 90 chemicals can be compiled if qualitative only documentation of presence of a chemical in a fire is used as a criterion for inclusion, rather than actual concentration measured. Lees lists these agents documented qualitatively from three different studies (Lowry et al. 1985; Henriks-Eckerman et al. 1990; Atlas et al. 1985).

It is important to note that where concentrations are presented, they should not be construed as actual fire fighter exposures. Although they represent environmental measurements made within the breathing zone of the fire fighter, actual exposures are somewhat less when respiratory protective equipment is properly used. Assuming a nominal protection factor of 2,000 common for the positive pressure demand-type SCBA most commonly used by fire fighters, actual exposures 2,000 times less than the concentrations reported can be postulated (Lees, 1995). Short-term higher exposures, perhaps approaching the numbers presented, can be postulated as a result of temporary misfit of respirators, etc. During the overhaul phase, when respiratory protective equipment is less frequently used, however, air concentration of some chemicals may be as high or higher than those reported during the fire fighting phase (Burgess et al. 1979; Barnard et al. 1979).

Given the multiplicity of chemicals potentially produced in combustion processes and the resulting variability of fire fighter exposures, one is faced with the problem of how to define fire fighter exposures for the purpose of assessing potential carcinogen exposure. The approach taken for the purposes of this review acknowledges that too few women fire fighters are currently present in the fire service, let alone an adequate number to survey for the incidence of specific reproductive cancers among them. We are therefore employing an approach used in the past to examine a similar question (McDiarmid et al. 1991) and will categorize combustion product chemicals documented in the peer-reviewed scientific literature, based on the availability, quality and applicability of fire fighter exposure data. We will then examine the evidence for the carcinogenicity of each of these constituents present in the fire fighting environment by specific cancer type.

Particulate and Smoke

Prior to discussing specific chemical constituents, the contribution that particulate makes to a fire fighter's potential exposure must be considered. In his review, Lees summarizes: "Smoke is the most obvious product of combustion and by far the most complex. A different set of products and product concentrations exists for every material burned and every set of combustion conditions. Smoke [may be] treated as a simple particulate aerosol. In addition to carbon particles, silica, fluoride, aluminum, lead, acids, bases and phenols have been identified in the particulate phase of smoke." (Large et al. 1990) (Large 1990; reviewed in Lees, 1995)

"Despite many papers on the respiratory effects of smoke inhalation, personal breathing zone measures of the particulate concentration in working fires have rarely been made. The earliest personal breathing zone measures date from the Harvard studies based on 20 samples, performed in the late 1970's. Results indicated a geometric mean particulate concentration of 21.5 mg/m^3 (GSD=4.7). In subsequent studies the geometric mean concentration increased only slightly." (Treitman et al. 1980; Gold et al. 1978; Burgess et al. 1977; Burgess et al. 1979) (reviewed in Lees; 1995)

A NIOSH study of 22 mostly residential fires determined the total particulate concentrations ranged from not detectable (ND)-560 mg/m^3 during the knockdown phase to ND-45 mg/m^3 during the overhaul phase. Mass median particle diameters were 10 μm during knockdown and 1 μm during overhaul at one fire. Some of the particulate was nonabestiform fibers; concentrations ranged from background (BG)-0.21 f/ml BG-0.36 f/ml for knockdown and overhaul respectively. (Jankovic et al. 1991) (summarized from Lees, 1995)

Diesel Exhaust

More recent work has focused on the exhaust of diesel engines typically used in fire apparatus, as a source of particulate smoke. From over 200 personal samples taken at 11 fire stations in 3 different parts of the country, total airborne particulate concentrations were found to range from 35-480 μg/m^3. The authors predicted an average concentration of 300 μg/m3, of which about 70% (225 μm/m3) was attributable to the diesel exhaust and the remainder to background and to cigarette smoking. Peak total particulate concentrations above 1 mg/m3 (1,000 μg/m3) were measured during departure of fire apparatus. (Froines et al. 1987) (in Lees, 1995)

Asbestos

Asbestos exposure during fire fighting has been described in the literature in the past 15 years related to demolition activities performed in the overhaul phase. The likelihood of exposure is a function of the age and type of structure involved - with commercial buildings constructed prior to the 1970s, being the most heavily contaminated with asbestos. The likelihood of encountering asbestos also depends on geographic location with certain large municipalities presenting all but certain exposure.

The strongest evidence for fire fighter asbestos exposure was presented by (Markowitz et al. 1991) and colleagues who evaluated New York City fire fighters whose employment began 25 years prior. Of 152 fire fighters without prior exposure to asbestos, twenty (13%) had pleural thickening or parenchymal opacities on chest x-ray consistent with asbestos exposure. The authors concluded that fire fighters with prolonged duration of fire service work may have an increased risk of asbestos exposure and consequently, asbestos-related diseases.

Polycyclic Aromatic Hydrocarbons (PAHs)

Polycyclic aromatic hydrocarbons are complex organic chemicals which have been implicated as the carcinogenic substances in soot and coal tar pitches and related materials (IARC, 1987). The first occupational cancer described in the last century in London chimney sweeps, the scrotal "soot wart," a skin cancer, was caused by this family of chemicals.

They have since been implicated in lung and bladder cancer and several others (IARC, 1987). These are also among the family of chemical constituents in tobacco smoke.

Jankovic and colleagues recently measured 14 PAHs in working fires (Jankovic et al. 1991). Of special interest, a recent study of fire fighter exposure to PAHs measured a small but significant (increase) difference in urinary 1-hydroxypyrene in samples obtained before, verses 6-7 hours after extinguishing a training school test burn of diesel fuel (Moen et al. 1997). The comparison of some of the PAH constituents of tobacco smoke, which has been much more comprehensively characterized than have fire fighting environments, allows the tobacco smoke data to be used as a potential "proxy" for fire fighter exposure.

Methods of Chemical Search

We searched the peer reviewed medical literature for recent articles on breast cancer, ovarian, cervical and endometrial cancer as well as lymphoma among women, looking for environmental or occupational exposures to suspected carcinogens, including pesticides, cigarette smoke, herbicides and volatile organic compounds. We were particularly interested in any articles on exposures of fire fighters, but were unable to find any that related to these malignancies in women.

Since there was so little in the literature that directly related to cancers of female reproductive organs among fire fighters, we turned attention towards agents reported in the fire fighting environment, in order to see what was known generally about their relationship to cancers of the female reproductive organs and lymphoma.

We found two articles summarizing components of smoke in the fire fighting environment (McDiarmid et al. 1991; Lees, 1995). There were 134 compounds qualitatively detected at in the fire fighting environment (Lees, 1995). Thirty two were quantitatively measured, and of these 9 were identified as well understood hazardous substances. See Appendix "Components of fire smoke: by groups of compounds and outcomes". These 9 include benzene and formaldehyde. We also decided to include two agents presumed to be common at fires. Asbestos is often an insulating material in older buildings, and fire fighters are exposed to asbestos fibers during the knockdown phase (Markowitz et al. 1991). The second chemical presumed present in fires was 1,3-butadiene, which is present as a softener in rubber products, and is present in tobacco smoke.

We searched the abstracts of eleven recent review articles (Table 4) for association of relevant cancers to each of the 134 chemicals documented as present in the fire fighting environment. The few direct matches we found are listed on Table 5. Most of the references were not to individual chemicals, but to groups of suspected carcinogens, such as tobacco smoke. The next phase of the evaluation was an electronic search of the peer reviewed medical literature, looking for the following:

Joint Appearance	
Combustion products listed in Table 5, asbestos, or 1,3-butadiene	Gynecological cancers, lymphomas or breast cancer

Five hundred and twelve contained references to smoking and breast cancer, 22 to asbestos and breast cancer, 26 to asbestos and ovarian cancers, and 460 to lymphoma and pesticides. Overall there were just under 3500 citations.

We began the task of winnowing through these by focusing on 10 recent review articles on cancers of the female reproductive organs, or cancers due to environmental or occupational exposures cancers (Table 5 lists the numbers of articles in initial search by cancer site and agent or class of agents). Next the large number of citation titles were reviewed, looking at the abstract if the title held promise. If the abstract was relevant, the article was copied from the journal and read. Relevant articles from bibliographies were pulled and read. This process resulted in 240 relevant citations.

Tobacco Smoke and Fire Smoke

While some articles focused on the carcinogenicity of the individual components of either fire or cigarette smoke, many (939) looked at cigarette smoke and cancers of the female reproductive organs and lymphoma. Not surprisingly, many of the components of residential fires are also found in cigarette smoke. We compared reviews of studies that identified products of tobacco (NAS, 1986), (Daisey et al. 1998; MMWR, 1986) with reviews of studies that identified components of residential fires (Lees, 1995; McDiarmid et al. 1991), and found 23 chemicals that overlapped. It is important to note that this overlap may not be an exhaustive list. Products of fire smoke are probably also more numerous than those reviewed, and may vary depending on the type and age of building, and of the materials used to build it and which it contains. Products of cigarette smoke number in the thousands, of which around 500 have had been qualitatively identified as being in both environmental and mainstream smoke. Sixty-nine of these have been reviewed in studies of environmental smoke (NAS, 1986), (Daisey et al. 1998; MMWR, 1986), and 23 were also present in residential fire smoke (Table 6). We therefore treat cigarette smoke as a proxy for fire smoke.

For this review, we include overlapping fire/cigarette smoke chemicals that are notoriously carcinogenic, and those that have been associated with human or animal breast, uterine or ovarian cancer. N-Nitrosiamine is a notorious carcinogen (MMWR, 1986). Benzene has been designated a human carcinogen (Vainio et al. 1984), and has been found to cause ovarian and breast cancer in animals (Griesemer et al. 1994) 1,3-Butadiene also has been causes ovarian and breast cancer in animals. Table 6 also presents cancers, human or suspected human, or animal linked with each chemical.

Some of the articles also grouped polycyclic aromatic hydrocarbons. See Appendix A "Components of Fire Smoke: By Groups of Compounds and Outcomes".

SUMMARY OF FINDINGS

In this project, we have attempted first to catalogue the chemical and particulate constituents of combustion previously documented in the fire fighting environment (numbering > 100). We have examined the peer-reviewed scientific literature for evidence that any of these chemicals were associated with an excess cancer risk in animals or humans, at the organ sites of interest. This collapsed the list to a number of 30 agents. Table 7 (6 substances) and the following discussion summarizes our findings of the chemicals or substances found in the fire fighting environment that may be associated with the cancers of interest. We have erred on the side of not listing an association if the findings are inconsistent or extremely controversial, but have raised these controversies in the text. Some of the categorizations in the Table appear with a question mark, representing evidence that, although not definitive, is still stronger and more consistent than those examples considered only hypothetical (controversial). We have taken added credence for a role in the causation of cancers of interest in this project, if the substances are recognized human carcinogens for another organ site (e.g. Benzene, 1-3, butadiene and asbestos). We also caution that this process is not necessarily inclusive, and there may be other chemicals – even appearing on the first pass list which are carcinogenic, but have not yet been shown to be so in the literature. With this proviso, we believe that the substances identified in Table 7 are the best candidates to be explored for potential association with breast cancer, the gynecologic malignancies and lymphomas in women fire fighters.

Benzene

Benzene is an undisputed human carcinogen causing leukemias. It is present in structural fire smoke (Brandt-Ralf; in MCDIARMID1991). It is a documented constituent of environmental tobacco smoke (Daisey et al. 1998). It was found to cause mammary and ovarian cancers in mice in the National Toxicology Program Studies (Griesemer et al. 1994).

1,3-Butadiene

1,3 – Butadiene is an animal carcinogen and a suspected human carcinogen. It was recently regulated by OSHA for its association with lymphatic cancer risk in exposed workers. Butadiene has been measured in fire smoke and is a constituent of cigarette smoke (Daisey et al. 1998). It causes ovarian and mammary gland cancers in animals tested in the National Toxicology Program, likely via a mutagenic mechanism (Griesemer et al. 1994).

Asbestos

Asbestos is also an undisputed cancer-causing agent is humans, responsible for lung cancer and gastro-intestinal excesses. Fire fighter exposure has been documented by asbestos-related x-ray findings in the lungs of New York City fire fighters (Markowitz et al. 1991). Asbestos exposure may contribute to ovarian cancer risk and there is some evidence (though less so) of a role in breast cancer risk (Newhouse et al. 1985; Keal, 1960).

PAHs

Fire fighter exposure to PAHs is documented by industrial hygiene measures (Jankovic et al. 1991). Disease risk is suggested secondarily by proxy through analogy with tobacco smoke. There is good evidence for cervical cancer risk from tobacco smoke (Winkelstein, Jr. 1990) and very recently for a possible role for environmental second-hand smoke and breast cancer development (Horton, 1992).

Diesel Exhaust

The National Toxicology Program (NTP) of the National Institute for Environmental Health Sciences (NIEHS) has examined evidence for the carcinogenicity of diesel exhaust (DE). They have summarized findings including documentation of lung cancer in some DE-exposed rodent studies. They report that the weight of the human epidemiologic evidence is that DE exposure causes an excess risk of lung cancer in the 1.2 to 2.0 fold range. The evidence for a bladder cancer risk is not as clear.

The composition of DE is complex and includes a large number of constituents, some in a chemical vapor phase and some in a particulate phase. The carcinogenic activity appears to reside in the particulate phase. A number of polycyclic aromatic hydrocarbons (PAHs) are present in DE and so there is potential for an overlap of exposure constituents and concomitant health effects.

Estrogenic Agents (DDT)

Estrogenic chemicals such as some organochlorine compounds like DDT may expose fire fighters in hazmat incidents or through exposure to combustion products of burning synthetic materials. These exposures may play a role in breast cancer, ovarian cancer or endometrial cancer development, though the evidence is not yet definitive.

The organophosphate pesticides and phenoxy herbicides have been implicated in lymphoma development. Exposure to fire fighters would be from hazmat incidents or unique fires when these substances are present.

Figure 1

SEER age adjusted incidence rates per 100,000, U.S. population for 1987-1991, 10 most common sites for White and Black females - 1998 (from American Cancer Society web address)

White		Black	
Cancer	Incidence rate	Cancer	Incidence rate
Breast	113.2	Breast	94.0
Lung & Bronchus	41.3	Colon/Rectum	46.7
Colon/Rectum	39.9	Lung & Bronchus	44.5
Corpus & Uterus NOS	22.2	Corpus & Uterus NOS	14.5
Ovary	15.6	Cervix	14.0
Lymphoma	14.7	Pancreas	12.7
Melanoma of Skin	10.9	Ovary	10.3
Cervix	7.8	Lymphomas	9.9
Leukemia	7.8	Stomach	7.9
Urinary Bladder	7.8	Multiple Myeloma	7.7

Figure 2

SEER age adjusted incidence rates per 100,000 U.S. population for 1987-1991 for selected sites, White & Black females

Cancer type	1987-91 in women	
	White	Black
Breast	113.2	94.0
Cervix	22.2	14.5
Corpus & Uterus NOS	15.6	10.3
Ovary	7.8	14.0

Figure 3

Expected new cases and cancer deaths for selected cancers in 1998

Cancer type	Expected in 1998 in women	
	New Cases	Deaths
Breast	178,700	43,500
Cervix	13,700	4,900
Endometrial	36,100	6,300
Ovary	25,400	14,500
Lymphoma		
Hodgkin's Disease	3,400	700
Non-Hodgkin's Lymphoma	24,300	11,900

Table 1

Chemicals Causing Ovarian Neoplasms in Mice and Carcinogenic at Other sites[1] in National Toxicity Program Studies

Chemical	NTO Tech Report No.	Mutagenicity[2]
Benzene	289	-
1,3 Butadiene	288	+
N-Methyloacrylamide	352	-
5-Nitroacenaphthene	133	+
Nitrofurantoin	341	+
Nitrofurazone	337	+
4-Vinylcyclohexene	303	-
4-Vinyl-1-cyclohexene diepoxide	362	+

[1]For male or female mice or rates
[2]Mutagenicity in Salmonella assay

From Griesemer & Eustis, J. Occup. Med. 36:847-8, 1994

Table 2

Chemicals Causing Uterine Neoplasms in Rats or Mice and Carcinogenic at Other sites[1] in National Toxicity Program Studies

Chemical	NTO Tech Report No.	Mutagenicity[2]	Rat	Mouse
3-Amino-9-ethylcarbazole	093	+	+	-
Bromoethane	239	+	-	+
Chloroethane	346	+	-	+
C.I. Direct Blue 15	397	-	+	NT[3]
3,3'- Dimethoxybenzidine	372		+	NT[3]
Ethylene oxide	326		NT[3]	+
Glycidol	374	+	-	+
ICRF-159	078[4]	+	-	
Isophosphamide	032[4]		+[5]	
Procarbazine hydrochloride	019[4]	-		+
4,4'- Thiodianiline	047	+	+	-
1,2,3-Trichloropropane	384	+	-	+
Trimethylphosphate	081	+	-	+

[1]For a least one gender or species
[2]Mutagenicity in Salmonella assay
[3] Not tested in this species
[4] Sprague-Dawley rats
[5] Leiomyosarcomas

From Griesemer & Eustis, J. Occup. Med. 36:847-8, 1994

Table 3

Chemicals Causing Mammary Gland Neoplasms in Rats or Mice and Carcinogenic at Other sites[1] in National Toxicity Program Studies

Chemical	NTO Tech Report No.	Mutagenicity[2]	Rat	Mouse
Acronycine	049[3]		+	-
Benzene	289	-	-	+
1,3 Butadiene	288	+	NT[4]	+
2,4 Diaminotoluene	162	+	+	-
1,3 Dibromo-3-chloropropane	028[5]	+	+	-
1,2 Dibromoethane	086[5]	+	+	+
2,3 Dibromo-1-propanol	400	+	+	
1,2-Dichloroethane	066[5]	+	+	+
3,3 Dimethoxybenzidine	372		+	NT[4]
3,3 Dimethylbenzidine	390	+	+	NT[4]
Ethylene oxide	326		NT	+
Furosemide	356	-	-	+
Glycidol	374	+	+	+
Hydrazobenzene	092	+	+	-
Nithiazide	146	+	+	-
Phenesterin	060[1]	-	+	-
Procarbazine	019[1]	-	+	-
Reserpine	193	-	-	+
Sulfallate	115[5]	+	+	-
1,2,3-Trichloropropane	384	+	+	-

[1]For a least one gender or species
[2]Mutagenicity in Salmonella assay
[3]Sprague-Dawley rats
[4]Not tested in this species
[5]Osborne-Mendel rats

From Griesemer & Eustis, J. Occup. Med. 36:847-8, 1994

Table 4

Review articles on women's reproductive cancers and environmental contaminants or occupational exposures

Article	Types of cancer
(Adami et al. 1995)	Endometrial cancer and breast cancer
(Dich et al. 1997)	Breast cancer and lymphoma
(Laden et al. 1998)	Breast cancer
(Lovejoy, 1994)	Cervical cancer,
(Lynge et al. 1997)	Cervical cancer, lymphohemopoietic cancers
(Persson, 1996)	Lymphoma
(Rego, 1998)	Lymphoma
(Welp et al. 1998)	Breast Cancer
(Wolff et al. 1996)	Breast cancer
(Wolff et al. 1995)	Breast cancer

Table 5

Numbers of articles in initial literature search by cancer site and agent

Cancer	Smoking	Pesticides	Asbestos	Benzene	Formaldehyde	Ammonia	Bisphenol-A	1,3-Betadiene	Benzo(a) pyrene Pyrene	Furan	Toluene	Total
Ovarian	88	416	26	4	14	3	0	7	8	0	1	
Breast	512	598	22	34	120	13	14	3	88	2	18	
Cervical	28	39	4	2	38	2	0	0	28	1	5	
Endometrial	75	15	0	0	4	0	0	0	0	4	0	
Lymphoma	236	460	58	111	157	67	157	31	57	7	44	
Total	**939**	**1,528**	**110**	**151**	**333**	**85**	**171**	**41**	**181**	**14**	**68**	**3,621**

Table 6

Overlapping components of fire and cigarette smoke and evidence of carcinogenicity in animals or humans

Overlapping components	Cancer			
	Any	**Breast**	**Ovarian**	**Endometrial/ Cervical ****
1,3-Butadiene	H? (Bulbulyan et al. 1999) (Bulbulyan et al. 1999) (Sathiakumar et al. 1998)	A (Griesemer et al. 1994)	A (Griesemer et al. 1994)	
2-Butanone				
Acetaldehyde				
Acetic acid				
Acrolein				
Ammonia				
Benzene	H (Vainio et al. 1985)	A (Griesemer et al. 1994)	A (Griesemer et al. 1994)	
Benzo(a)pyrene	H? (Vainio et al. 1985)	H? (Vainio et al. 1985)		
Benzo(e)pyrene				
Benzoic acid				
Butyraldehydes				
Carbon dioxide				
Carbon monoxide				
Cresols				
Ethyl benzene				
Formaldehyde				
Formic acid				
Hydrogen cyanide				
Nitrosamines	A (Vainio et al. 1985)			
Perylene				
Phenol				
Pyrene				
Toluene				
*Asbestos fibers	H (Selikoff, 1976)	H? (Newhouse et al. 1985)	H? (Newhouse et al. 1985) (Germani et al. 1999) (Acheson et al. 1982)	H? (Germani et al. 1999)

H = causes cancer in humans,
H? = suspected of causing cancer in humans,
A = causes cancer in animals

- Asbestos not reported in tobacco smoke
- **While few of the individual chemicals common to tobacco and fire smoke were linked to uterine cancer, there was evidence of a link between *smoking* and cervical cancer (Lovejoy, 1994; Engeland et al. 1996; Nordlund et al. 1997).

Table 7

Evidence for an Association between Substances Found in the Fire Fighting Environment and Specific Cancers

Substance	CANCER SITE					Other Sites
	Breast	Ovary	Endometrium	Uterine Cervix	Uterine Lymphoma	
Benzene	A	A				A, H
1,3–Butadiene	A	A			A, H(?)	A, H(?)
Asbestos		A(?)c H(?)				A, H
PAH(Smoke)a	A		A	H(?)		A, H(?)
Diesel Particulate						A, H(?)
Organo Chlorineb Pesticides/ (DDT)/ Estrogenic Compounds	A					A

Legend:
A=   Carcinogenic in Animals;
H   Carcinogenic in Humans;
(?)   Suggestive Evidence, Not Definite
a   Data are given for benzo (a) pyrene. Toxicity profile may very by specific substance and mode of administration
b   Data are given for DDT. Toxicity profile may vary by specific substance and mode of administration
c   Increased incidence of peritoneal tumors, including mesotheliomas.

References: National Toxicology Program (NTP); International Agency for Research on Cancer (IARC)

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