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Environmental and Occupational Causes of Cancer New Evidence, 2005–2007

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Executive Summary

What do we currently know about the occupational and environmental causes of cancer? As of 2007, the International Agency for Research on Cancer has identified 415 known or suspected carcinogens. Cancer arises through an extremely complicated web of multiple causes. We will likely never know the full range of agents or combinations of agents that cause cancer. However, we do know that preventing exposure to individual carcinogens prevents the disease. Declines in cancer rates – such as the drop in male lung cancer cases from the reduction in tobacco smoking or the drop in bladder cancer among cohorts of dye workers from the elimination of exposure to specific aromatic amines – provides evidence that preventing cancer is possible when we act on what we know. Although the overall age-adjusted cancer incidence rates in the U.S. among both men and women have declined in the last decade, rates of several types of cancers are on the rise; some of these cancers are linked to environmental and occupational exposures.

This report chronicles the most recent epidemiological evidence linking occupational and environmental exposures with cancer. Peer-reviewed scientific studies published from January 2005-June 2007 were reviewed, supplementing our state-of-the-evidence report published in September 2005. Despite weaknesses in some individual studies, we consider the evidence linking the increased risk of several types of cancer with specific exposures somewhat strengthened by recent publications, among them:

- brain cancer from exposure to non-ionizing radiation, particularly radiofrequency fields emitted by mobile telephones;
- breast cancer from exposure to the pesticide dichloro-diphenyl-trichloroethane (DDT) prior to puberty;
- leukemia from exposure to 1,3-butadiene;
- lung cancer from exposure to air pollution;
- non-Hodgkin's lymphoma (NHL) from exposure to pesticides and solvents; and
- prostate cancer from exposure to pesticides, polyaromatic hydrocarbons (PAHs), and metal working fluids or mineral oils.

In addition to NHL and prostate cancer, early findings from the Agricultural Health Study suggest that several additional cancers may be linked to a variety of pesticides.

Our report also briefly describes the toxicological evidence related to the carcinogenic effect of specific chemicals and mechanisms that are difficult to study in humans, namely exposures to bis-phenol A and epigenetic, trans-generational effects. To underscore the multi-factorial, multi-stage nature of cancer, we also present a technical description of cancer causation summarizing current knowledge in molecular biology.

We argue for a new cancer prevention paradigm, one that is based on an understanding that cancer is ultimately caused by multiple interacting factors rather than a paradigm based on dubious attributable fractions. This new cancer prevention paradigm demands that we limit exposures to avoidable environmental and occupational carcinogens in combination with additional important risk factors such as diet and lifestyle.

The research literature related to environmental and occupational causes of cancer is constantly growing and future updates will be carried out in light of new biological understanding of the mechanisms and new methods for studying exposures in human populations. However, the current state of knowledge is sufficient to compel us to act on what we know. We repeat the call of ecologist Sandra Steingraber, “From the right to know and the duty to inquire flows the obligation to act.” [1]

Introduction

The purpose of this paper is to update a report completed in 2005[2] in which we reviewed the literature regarding environmental and occupational causes of cancer. In that previous review, we noted the controversy regarding the proportion of cancer attributable to environmental exposures and the effort by British epidemiologists Doll and Peto to ascribe numerical percentage estimates to pollution and occupation. We took issue with that approach, and reviewed the evidence published in recent years that links environmental and occupational exposures to nearly thirty types of cancer. We concluded that environmental and occupational contributions to cancer in the U.S. are substantial and justify continued efforts to prevent these types of exposures.

Since our 2005 review, over one-hundred epidemiological studies have been published investigating the link between environmental and/or occupational exposures and cancer, based on our MEDLINE search. In Section I of this report, we provide a brief overview of this new literature and we describe critical evidence emerging from toxicological studies related to the carcinogenic effect of specific chemicals and mechanisms that are difficult to study in humans. We did not attempt an exhaustive summary of all the literature about risk factors for the various cancers. Readers interested in that should consult recent textbooks such as *Cancer Epidemiology and Prevention*,[3] which covers the topic in 1,392 pages, or more general review articles.

We noted in our previous review that the two main types of studies that shed light on the causes of cancer – animal studies and epidemiologic studies – each have strengths and limitations. In experimental studies on animals, the conditions of exposure and sometimes the genetic make-up of the animals are controlled by the researcher and because of these conditions, the results of animal studies may not be easily extrapolated to humans. Epidemiologic studies are sometimes referred to as animal studies where the animals are let out of their cages. This means that humans are exposed to many known and unknown factors at various stages of their relatively long life spans – they move from place to place, work at many different jobs, have different hobbies, and they also have varying genetic make-ups. Given all this, it is remarkable that epidemiologic studies provide any useful information about the causes of cancer. Yet epidemiologic knowledge is heavily relied on for policy-based decision making to protect public health.

We do not ascribe to these occupational and environmental exposures specific percentage contributions to the burden of cancer in the U.S. and we reiterate that we think this is neither possible nor advisable as a way of guiding cancer prevention policy. In the final sections of this review, we advocate moving away from a cancer prevention paradigm based on ascribing numerical percentage estimates, which typically exaggerate the importance of lifestyle factors or diet over environmental or occupational exposures, as a way of guiding policies and programs. Cancer is caused by a web of multiple factors. Diet, lifestyle, viral agents, genetics, environment and occupational exposures all can contribute to various stages in the initiation or progression of a tumor. To underscore the importance of the multi-factorial, multi-stage nature of cancer, we describe the current state of knowledge regarding the molecular biology of cancer. From this technical description it should be clear that cancer causation is extraordinarily complex. We will likely never know the full range of agents that contribute to cancer nor all the mechanisms by which each agent can exert its effect. We briefly note the political and economic barriers to changing the cancer prevention paradigm. Finally, we conclude this report by recommending, once again, that we act on what we know and prevent exposure to agents in our workplaces and environment that contribute to cancer causation.

Section I: State of the Science

Recent Cancer Trends

In January 2007, the American Cancer Society announced that for a second year in a row, cancer deaths were on the decline. The drop in cancer deaths from 556,902 in 2003 to 553,888 in 2004 represents a one-half of one percent drop, 3,014 fewer deaths. This decline in the overall cancer mortality rate translates into real lives that were extended, thanks mainly to advances in the early detection and treatment of colon and breast cancers. However, from a public health point of view, the primary goal is to prevent disease occurrence, not just to reduce death rates.

Overall U.S. age-adjusted cancer incidence rates in both men and women (all races combined) have declined over the last decade (down 0.7% in men and 0.5% in women each year from 1995-2004).[4] This decline was driven by declines in specific types of cancers such as lung cancer among men and colorectal cancer among both sexes. However, rates of the following cancers have increased: among both sexes, the last decade has seen rises in cancers of the esophagus (23.9% in men; 9.1% in women), liver (45.6% in men; 17.9% in women), pancreas (9.5% in men; 3.0% in women), kidney (19.4% in men; 24.7% in women), thyroid (52.9% in men; 64.4% in women), as well as melanoma (23.2% in men; 23.9% in women), non-Hodgkin's lymphoma (1.6% in men; 16.2% in women), and multiple myeloma (1.4% in men; 2.1% in women).[a,5] Over the same time period, testicular cancer and bladder cancer rose in men (28.3% and 3% respectively), while lung cancer (3%), brain and other central nervous system cancers (7.4%), Hodgkin's disease (20.8%) and leukemia (3.8%) rose in women.[a,5] In addition, the incidence of childhood leukemia and brain cancer has been rising steadily in the past decade.

With the exception of thyroid and kidney cancers, improved diagnostic techniques and changes in disease coding/classification do not explain the rise in rates.[6] Moreover, many of the types of cancer that have been rising in the past decade are not related to cigarette smoking but are caused by viral exposures (liver cancer), ionizing radiation (thyroid cancer), ultraviolet radiation (melanoma) or other environmental and occupational exposures (non-Hodgkin's lymphoma and leukemia).

[a]Calculated as percent change from 1995-2004 using the National Cancer Institute, Surveillance Research Program, Statistical Research Applications Branch. Surveillance Epidemiology End Results (SEER) Program. SEER*Stat Database: Delayed Adjusted Incidence, 9 Registries, 1975-2004. Accessed July 1, 2007 at http://srab.cancer.gov/delay/canques.html.

January 2005-June 2007 Literature Review

To update our 2005 review of the state of the science regarding environmental and occupational causes of cancer, we conducted a review of the peer-reviewed literature, published from January 2005-June 2007. Articles were identified through MEDLINE and focused on primary epidemiologic research studies as well as review articles when such reviews revealed new understanding regarding the state of the science. Our summary of the epidemiologic evidence regarding occupational and environmental causes of cancer over the past number of years presents the overall study findings rather than a comprehensive critique of the strength and weaknesses of each study. We do not summarize detailed results for all exposures investigated in each study, but rather focus only on the principal findings.

For several types of cancer, our 2005 review still represents the current state of the science. This is the case for cancers of the bone, cervix, thyroid as well as Hodgkin's disease, mesothelioma and soft-tissue sarcoma. Table 1 provides an overview of established and suspected risks associated with these types of cancers as presented in our 2005 paper.

For all other cancer types, new scientific updates over the last two and a half years are reviewed in detail below. Table 2 located at the end of this section provides a brief description of specific environmental and occupational risks as well as an overview of the state of the science for all cancer types, including updates described in this paper.

Bladder Cancer—The weight of the evidence regarding the risk of bladder cancer associated with ***chlorination by-products*** from water disinfection continues to grow. A bladder cancer case-control study of the effects of route of exposure to trihalomethanes (ingestion through drinking water and inhalation and dermal absorption through bathing, showering and swimming in pools) found elevated risks.[7] Specifically, the study found that individuals living in areas with residential exposure to trihalomethanes in treated water for over 30 years have a 2-fold significant increased risk of bladder cancer. Risk was also significantly elevated among those reporting longer duration showers or baths as well as among individuals who “ever” swam in swimming pools.

While ***cadmium*** is considered an established lung carcinogen, new evidence from a case-control study in Belgium suggests it is a risk for bladder cancer as well.[8] The odds of developing bladder cancer among individuals in the highest blood-cadmium exposure category were significantly elevated, a near six-fold increase in risk (OR[b]=5.7). Limited evidence regarding cadmium as a bladder carcinogen existed prior to this study, and further studies are needed to confirm these findings.

A variety of ***aromatic amines*** are considered established causes of bladder cancer. A new study suggests that when individuals are exposed to both aromatic amines and tobacco smoke (also an established cause of bladder cancer) interaction occurs (p value for interaction not statistically significant); risk substantially increases when both exposures occur, versus either exposure alone.[9] Similar interactions were also seen with exposure to smoking and polycyclic aromatic hydrocarbons (PAHs) and smoking and ***diesel exhaust***, although these findings were only suggestive and should be confirmed in additional studies. This same study also examined the interaction of these three occupational exposures when specific metabolic genes were expressed and found evidence of gene-environment interaction with glutathion S transferase (GST), N-acetyltransferase (NAT) and sulfotransferase (SULT). Although these findings illustrate the importance of studying mixtures of exposures, results are based on a very small study size and should be explored further.

[b]OR=odds ratio

New evidence regarding the risk of bladder cancer associated with ***solvents*** is primarily from a cohort study of aerospace works, which found suggestive increased risks associated with exposure to trichloroethylene (TCE) at both medium (OR=1.54) and high (OR=1.98) exposure levels, although the test for trend was not significant.[10] In this same study, risk of bladder cancer from exposure to ***mineral oils*** was also modestly elevated, but the exposure response trend was nonmonotonic (low exposure: OR=1; medium exposure: OR=1.75; high exposure: OR=1.42). These analyses did not control for tobacco smoking, an important confounding risk factor for bladder cancer.

Based on the lifetime occupational histories of 1,129 cases of bladder cancer, a case-control study confirmed previously known or suggested links with bladder cancer, including exposure to paints and solvents, PAHs, diesel engine emissions, textiles, and aluminum production.[11] The study also suggests that exposure to silica and electromagnetic fields may confer an increased risk of bladder cancer, an observation found in a small number of previous studies. Although the International Agency for Research on Cancer determined in 1988 that occupation as a painter should be classified as carcinogenic (Group 1), a new study reviewing the epidemiologic evidence from 1989-2004 for bladder cancer maintains this classification, but suggests that risk was likely higher in the past decades.[12] Other studies examining specific occupations/industries and risk of bladder cancer found a modestly increased risk (with a wide confidence interval) associated with PCE exposure among dry cleaning workers in the Nordic countries and stronger evidence of increased risk among workers in the petroleum industry (OR=1.4) based on a pooled analysis of eight case-control studies.[13,14]

Brain and Other Central Nervous System Cancer—Studies are conflicting regarding the risk of brain and other central nervous system (CNS) cancers from exposure to ***non-ionizing radiation***, specifically radiofrequency fields emitted by mobile telephones. One recent case-control study reports a significant increased risk of malignant brain tumors associated with the use of analog cellular telephones (OR=2.6), digital cellular telephones (OR=1.9) and cordless telephones (OR=2.1).[15] In this study, the risk of developing a malignant brain tumor associated with using each phone device increased further when a greater than 10-year latency period was considered and similarly increased with cumulative number of hours of use. The highest risk was found for high-grade astrocytomas. When this study was pooled with an earlier case-control study, risk became much stronger, especially for the use of analog and digital cell phones.[16] In contrast, several recent studies found null results[17,18,19,20,21], including the largest study completed to date[22] and a meta-analysis of 12 studies.[23] However, several limitations in the design and conduct of these studies call into question the validity of the null findings. Critical methodological weaknesses in studies of brain cancers and mobile/cellular phones include the following: non-comparable socio-economic status among cases and controls; low and potentially unrepresentative participation rates; improper latency periods; lack of focus on the effects within the temporal lobe; and failure to distinguish tumor grades.[24,25] There are ongoing studies in the EU which may shed further light on this important issue. Although a recent study examining the effect of non-ionizing radiation from electromagnetic fields (EMF) shows no statistically significant associations between residential or occupational exposure and increased risk of brain cancer[26], there is sufficient prior knowledge to warrant continued concern regarding the risk of EMF and brain cancer.

A number of recent studies find evidence linking brain and CNS cancers with exposure to ***pesticides***. In the Agricultural Health Study, there was suggestive evidence of increased risk of brain and other CNS cancers among commercial pesticide applicators (SIR[C]=1.85), but not among private pesticide applicators.[27] In a study examining farm pesticide exposure among

[C]SIR=standardized incidence ratio

women, risk of glioma was not elevated among those who ever lived or worked on a farm, although risk was non-significantly elevated in association with multiple pesticide categories, notably carbamates (OR=3.0, including proxy respondents; OR=3.5, excluding proxy respondents).[28] In another population-based case-control study, no positive associations related to farming activities and risk of glioma were observed among women, although risk among men was significantly elevated among proxy, but not self-respondents for those who ever worked or lived on a farm as a child (OR=2.5) or an adult (OR=2.6).[29] In this study, risk among men was also significantly elevated based on exposure to specific pesticides, including bufencarb (OR=18.9), chlorpyrifos (OR=22.6), coumaphos (OR=5.9), metribuzin (3.4) and paraquat (11.1), although the increased risk estimates, in general, were based on small numbers and driven by information from proxy respondents. Given the absence of findings among self-respondents in this study, further examination of the link between gliomas and the above pesticides is needed. Although no new study examined pesticide exposure and the links with brain and CNS cancers among children, a review article did find evidence of increased risk of astrocytomas, especially when fathers or mothers were exposed prior to the child's conception.[30]

Studies regarding the risk of brain cancer associated with ***N-nitroso compounds*** from exposure to nitrate and/or nitrite find mixed results. A case-control study of childhood brain cancers found elevated risk of astrocytomas associated with in-utero exposure to nitrites via residential water source.[31] However, the study's findings are limited by the exposure assessment methodology. In another case-control study, the risk of gliomas in adults was modestly elevated, but no dose response was observed; this led the authors to conclude that the study did not support a role for drinking water and dietary sources of nitrate and nitrite in risk of adult glioma.[32]

Although studies examining the risk of brain cancer and exposure to ***hair dyes*** in occupations have yielded mixed results, a new study of women who used hair dyes revealed a 1.7 fold increased risk of gliomas.[33] This risk was stronger for women who used permanent hair dyes (OR=2.4) and for those with a more aggressive form of glioma, glioblastoma multiforme, who used dyes for a longer period of time (OR=4.9). Another study examining risk of brain tumors among children born in or after 1980 and maternal use of hair dyes (non-work related) during the five years prior to pregnancy found an 11-fold increased risk, although the findings were based on a small sample size.[34]

A number of additional studies examined specific occupations and risk of brain and central nervous system cancers. Evidence is conflicting regarding increased risk of brain and CNS cancers and employment in computer manufacturing and semiconductor fabrication.[35, 36, 37, 38] Additional evidence supports excess mortality from brain and other CNS cancers associated with PCBs based on suggestive elevations (SMR[d]=1.91) and clear dose-response relationships, although these findings are based on a small number of cases.[39] Lastly, a significant increase risk of brain cancer (OR=1.35) among fire fighters was observed in a registry-based case-control study in California.[40]

Breast Cancer—An exhaustive 2007 review of the epidemiologic literature associated with environmental pollutants and breast cancer provides a detailed assessment of the current state of knowledge.[41] Although authors of this review find vast and conflicting evidence regarding breast cancer risk associated with ***polychlorinated biphenyls*** (PCBs), their synthesis reveals an important consistency in the recent literature: women with a polymorphism in the CYP1A1 gene exhibit greater breast cancer risk when exposed to PCBs. These findings were seen more often among post-menopausal women than among pre-menopausal women.

[d]SMR=standardized mortality ratio

Additional studies support links with breast cancer and ***pesticide*** exposure. In the Agricultural Health Study, breast risk was significantly elevated among women whose husbands used specific chlorinated pesticides including dieldrin (RR[e]=2.0), chlordane (RR=1.7), aldrin (RR=1.9) and lindane (RR=1.7), but not when used by the women themselves.[42] Although authors of the 2007 review previously noted found limited support for increased breast cancer risk from organochlorine pesticide exposure, especially for DDT/DDE based on the weight of the evidence thus far, they suggest that follow-up of women now in their 50's who were exposed at an early age will yield valuable information regarding breast cancer risk associated with developmental exposure.[41] Such evidence is now emerging suggesting that the carcinogenic effect is strongest when exposure occurs before puberty or early in the woman's breast development. New evidence from a prospective study of young women in California who had their blood samples drawn in 1959-1967 found that those women under age 14 when first exposed to DDT had significant increased risk of breast cancer with increasing levels of serum *p,p'*-DDT. Women in the highest exposure category had a fivefold significant increase of risk of breast cancer.[43]

In addition to chlorinated pesticides, findings from the Agricultural Health Study also identified 2,4,5-trichlorophenoxypropionic acid (2,4,5-TP, no longer used in the U.S.) and the fungicide captan as significantly increasing the risk of breast cancer among women whose husbands used such pesticides (RR=2.0 and 2.7 respectively).[42] When this study examined breast cancer risk by menopausal status, all increased risk associated with the women's use of pesticides occurred among premenopausal women; elevated risk occurred among women using chlorpyrifos, dichlorvos, and terbufos. Although no pesticide was associated with increased breast cancer risk among postmenopausal women's use of specific pesticides, risk was elevated among postmenopausal women whose husbands used aldrin, chlordane, dieldrin, heptachlor chlorpyrifos, diazinon and malathion, 2,4,5-TP and captan. Additional evidence regarding the risk of pesticides and breast cancer emerged from the Long Island Breast Cancer Study, which found significantly increased risk of breast cancer associated with self-reported residential pesticide use, although no dose response trend was observed.[44]

Two studies were recently published adding to the mixed body of evidence regarding the risk of breast cancer associated with ***non-ionizing radiation***, principally exposure to electro-magnetic fields (EMFs). A large case-control study of occupations categorized as having high potential exposure to EMFs reported a non-significant 16% increase in breast cancer risk.[45] Risk was lower and also non-significantly elevated for occupations of lower potential exposure to EMFs. The second large case-control study, based on the Swedish population registers, found no evidence of an elevated risk of breast cancer associated with women working in occupations with high EMF exposures.[46]

Although no additional studies were identified examining the risk of breast cancer associated with dioxin, additional studies did examine risk associated with other ***combustion by-products***, specifically PAHs and environmental tobacco smoke (ETS). A new case-control study adds to the evidence linking PAH exposure with breast cancer and identified a possible link with early life exposure.[47] In this study, high PAH exposure – based on total suspended particulate (TSP) concentrations – at birth address resulted in a non-significant elevation in breast cancer risk among postmenopausal women (OR=2.42). Similar findings were observed for pre-menopausal women, although a dose response trend was observed only among post-menopausal women. Unlike pre-menopausal women, risk among postmenopausal women was also elevated across exposure levels based on TSP concentrations at menarche and at first birth address although no dose response was observed. Evidence regarding the risk of breast cancer associated with exposure to ETS is based on a review published by The California

[e]RR=relative risk

Environmental Protection Agency, which found consistent associations between breast cancer and ETS in the majority of studies examined, especially among pre-menopausal women.[48]

Although ***solvents*** have been linked to breast cancer in a number of previous occupational studies, no recent study reported strong results, including an investigation of breast cancer risk among textile workers in Shanghai.[49] Only modest elevations of breast cancer and no dose response trend associated with duration of employment were observed among a cohort of workers in an electronics factory in China with exposures to PCE and TCE.[50]

Several additional studies examining specific occupations and risk of breast cancer found a significant 41% elevation based on a meta-analysis of cancer among female flight attendants, suggesting possible links with ionizing cosmic radiation, jet fuel, EMFs from cockpit instruments, irregular work hours, and pesticides;[51] and a 14% significant increase in breast cancer risk among a historical prospective cohort of over 43,000 Norwegian nurses.[52]

Colon Cancer—Our review identified only a few studies that found increased risk of colon cancer associated with environmental and occupational exposures, namely exposures to ***pesticides***, ***dyes*** and ***hydrazine*** – a component in rocket fuel. In a nested case-control study of female textile workers in Shanghai, researchers indicated that long-term exposure (20 years or longer) to dye and dye intermediates resulted in nearly 4-fold elevation in colon cancer risk ($HR^f = 3.9$).[53] In a cohort of aerospace workers exposed to hydrazine in rocket fuels, colon cancer was elevated when exposures were lagged 20 years (RR=2.2) and risk significantly increased with increasing dose.[54] Lastly, a recent report from the Agricultural Health Study revealed a significant increase in colon cancer risk among pesticide applicators with increasing level of exposure to the herbicide dicamba. In this study, colon cancer was significantly elevated at the highest exposure-level based on both life-time exposure days (RR=3.29) and intensity-weighted lifetime exposure (RR=2.57).[55]

Esophageal Cancer—Recent studies specifically examining esophageal cancer were somewhat limited. A nested case-control study of female textile workers in Shanghai, China found significantly elevated risk of esophageal cancer associated with long-term (10 years or longer) exposure to silica dust (HR=15.8) and metals (exposure to welding dust, lead fumes and steel, HR=3.7).[56] Limited evidence from prior studies supports these associations. Although the ***solvent*** PCE is a suspected risk factor for esophageal cancer based on multiple past studies of dry cleaning and dye-house workers, a new study of dry cleaning workers in Nordic countries found no increased risk.[14] Additional studies examining specific occupations and risk of esophageal cancer found an elevated risk (OR=1.48) among California firefighters.[40]

Kidney Cancer—Additional evidence supporting the link between kidney cancer and ***solvents***, specifically TCE, was identified. In a cohort of Rocketdyne workers, a non-significant elevation of kidney cancer mortality was observed among test stand mechanics exposed to TCE (SMR=2.22).[57] In this study, mortality increased with increasing years worked as a test stand mechanic, although the statistical test for trend was not significant. In a second cohort study of Rocketdyne/ Rockwell/ Boeing workers, a significant increased risk of kidney cancer among employees exposed to high levels of TCE (RR=4.90) was observed and the test for a dose-response trend was also significant.[10]

Additional studies examining specific occupations and risk of kidney cancer found excess mortality associated with computer manufacturing among both men and women,[35] elevated

[f]HR=hazard ratio

risk among male food industry workers,[58] and suggestive increased risk among sawmill workers based on dermal exposure to pentachlorophenol.[59]

Leukemia—Studies continue to indicate that exposure to some ***pesticides*** increases the risk of leukemia. In the Agricultural Health Study, a suggestive elevation in risk of leukemia was observed among pesticide applicators exposed to specific organochlorine pesticides, including aldrin, chlordane, DDT, dieldrin, and toxaphene.[60] In this study a significant 2-fold increase risk of leukemia was observed among pesticide applicators exposed to heptachlor and lindane. A similar 2-fold increase in risk was observed among applicators with the highest cumulative exposure to chlordane and hepatchlor and risk rose with increasing exposure. Investigators of this study combined exposure to chlordane and heptachlor in their analysis since the chemicals are structurally similar; chlordane is metabolized into heptachlor and technical-grade products of each contain approximately 10-20% of the other compound. In this same cohort, exposure to the organophosphate fonofos resulted in 2-fold increased leukemia risk based on both life-time exposure days (RR=2.24) and intensity-weighted exposure days (RR=2.67).[61]

In a nested case-control study of members of the United Farm Workers of America, increased risk of leukemia (total leukemia) was associated with exposure to the pesticides mancozeb (OR=2.35) and toxaphene (OR=2.20) and risk was more elevated in females than in males and for granulocytic leukemia than for lymphocytic leukemia.[62] In a record linkage study in California, residence in a high pesticide-use area at the time of diagnosis was not clearly associated with acute lymphoblastic leukemia (ALL) risk, although high intensity use of the pesticides simazine and methyl bromide did result in modest increases in risk (RR=1.21 and 1.16 respectively).[63]

Evidence of exposure to ***reactive chemicals*** and subsequent leukemia risk is somewhat limited. However, a new study examining the effects of 1,3-butadiene-exposed synthetic rubber workers found increased leukemia risk associated with butadiene independent of other industrial exposures.[64] Risk remained elevated when controlling for exposure to styrene and dimethyldithiocarbamate, although exposure to dimethyldithiocarbamate also contributed independently to increases in leukemia risk. Cell type analyses revealed excesses associated with butadiene more consistently for chronic lymphocytic leukemia (CLL), although chronic myelogenous leukemia (CML) was also elevated at higher levels of exposure. A second study of this same population found evidence for a strong causal relationship between leukemia and butadiene based on high cumulative exposure and high intensity of exposure.[65] In a meta-analysis of cancer among workers in the synthetic rubber industry, investigators identified increased deaths from leukemia (meta-SMR=1.21).[66] However, workers across the 16 cohort studies examined in this meta-analysis were likely exposed to a variety of chemicals making it impossible to attribute the excess deaths specifically to butadiene exposure.

A number of studies published findings relating to geographic clustering of leukemia associated with exposure to ***metals*** and ***dioxin***. In Churchill County, Nevada tungsten and arsenic levels in urine were elevated in comparison to samples from other populations, although there were no significant differences between levels among leukemia cases and controls within Churchill County.[67] Another cluster investigation in New Zealand of a community potentially exposed to dioxin from the manufacture of the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), identified a significant elevation of CLL in two time periods.[68] However, dioxin from 2,4,5,-T production may not have been the causal agent for the increased risk of CLL during these time periods due to a lack of a sufficient latency period. Lastly, a meta-analysis examining the risk of childhood leukemia based on proximity to nuclear facilities found a 14%-21% increased risk among 0-9 year olds and a 7%-10% increased risk among 0-25 year olds, although no dose response trend was observed.[69]

New studies examining the risk of leukemia associated with ***solvents*** reported mixed evidence concerning exposure to benzene, an established cause of leukemia. A nested case-control study of the Health Watch cohort of petroleum industry workers identified a strong and significant association between leukemia and benzene exposure: each ppm-year of exposure to benzene resulted in a 10% increase in leukemia risk (based on cumulative exposure treated as a continuous variable).[70] Cell type analyses in this study revealed a seven-fold increased risk (OR=7.17) of acute nonlymphocytic leukemia (ANLL) among workers exposed for greater than 8 ppm-years and an increased risk of CLL (OR=4.52, exposure group not identified in the publication). Likewise, a historical cohort of workers in the UK exposed to benzene in 1967 or earlier found significant excesses of mortality from ANLL (SMR=183).[71] In this study, some additional cell types (acute myelogenous leukemia (AML) and CLL) and all leukemias were modestly elevated. These findings are in contrast to the cohort analysis of the Health Watch study, which revealed no increased risk of leukemia.[72] Similarly, a 56-year follow-up of workers at a Texas petroleum and chemical refinery revealed no substantial increase in leukemia mortality, although cell type analyses did suggest elevations of ALL (SMR=2.80 among men employed 10 years or longer; SMR=2.70 among men employed 20 years or longer).[73] Additional solvents reviewed included a meta-analysis of occupational exposure to TCE based on seven studies; these authors reported a small non-significant increase of leukemia (summary RR=1.11).[74]

Exposure to ***non-ionizing radiation*** continues to be associated with childhood leukemia. In a case-control study in Japan, residential power frequency magnetic fields measured in the bedrooms of children were associated with increased risk of AML and ALL combined (OR=2.6) and a significant increased risk of ALL only (OR=4.7) and the investigators note that control of confounding variables revealed no substantial difference in the results.[75]

Evidence relating to the risk of leukemia and ***hair dyes*** is somewhat strengthened by a new study which found women using black dye colors were at a 90% increased risk of developing leukemia. Sub-type analyses revealed that CLL associated with use of black hair dyes was significantly elevated (OR=3.0).[76] A lack of exposure information relating to frequency and timing of exposure limits the interpretability of these results.

Liver And Biliary Cancer—The evidence associated with ***PCBs*** as a risk factor for liver and biliary cancers was further strengthened by a long-term follow-up of a cohort of workers highly exposed to PCBs during the manufacture of electrical capacitors. This study found that mortality from liver, biliary, and gallbladder cancers were elevated (SMR=2.11), although no dose-response relationship was observed with duration of employment.[77] When this cohort was expanded to include workers with at least 90 days of potential exposure to PCBs during 1939-1977, mortality was no longer elevated among all workers combined, but remained elevated among those with higher cumulative exposure.[78] Increasing levels of exposure were significantly associated with increasing mortality when exposures were lagged by 20 years.

Laryngeal Cancer—In a multi-center case-control study, increased risk of laryngeal cancer was associated with several occupational exposures.[79] In this study, exposure to coal dust increased risk among those ever exposed. When differing durations of exposure were assessed, a clear and significant dose-response trend was observed with those in the highest exposure category experiencing significant elevations in risk. Inclusion of a 20-year lag strengthened the association based on weighted duration of exposure (based on total number of hours of exposure based on a certain job period) (OR=6.53). Other agents identified as a concern included hard alloy dusts (OR=2.23) and chlorinated solvents (OR=2.18). In another population-based case-control study, occupations with exposure to PAHs were associated with an increased risk of laryngeal cancer (OR=5.20) including a significant dose-response trend based on exposure duration.[80] Among a cohort of construction workers, exposure to asbestos

significantly increased the risk of laryngeal cancer (RR=1.9), although a dose-response trend was not observed.[81] The authors state that findings related to the link with laryngeal cancer and asbestos did not materially change after adjustment for tobacco smoke, although adjusted risk ratios are not provided. Grain millers were found to have an increased risk of laryngeal cancer in a study of Finnish food industry workers.[58]

Lung Cancer—Evidence regarding risk of lung cancer associated with ***pesticides*** continued to emerge primarily from analyses of the Agricultural Health Study. In one analysis, lung cancer risk significantly increased with increasing levels of exposure to the banned organochlorine pesticide, dieldrin, among pesticide applicators; an association was also found in an earlier analysis of this cohort study.[60] In another analysis, cancer risk associated with exposure to the carbamate pesticide carbofuran revealed a 3-fold increase in lung cancer risk (RR=3.05) among applicators in the highest exposure category when compared to those in the lowest exposure category, but not among non-exposed applicators.[82] An analysis of cancer risk associated with life-time days of exposure to metachlor at the highest level found a nonsignificant 2-fold increased risk (RR=2.37) of lung cancer.[83] Lastly, a 2-fold increased lung cancer risk was associated with the highest level of exposure to dicamba.[55]

Lung cancer has been linked with a number of ***metals***. Lung cancer mortality was modestly increased among workers at a nickel carbonyl refinery.[84] In this study, a more than 2-fold increase in lung cancer mortality was observed (SMR=231, unadjusted for potential confounding by tobacco smoking) among those employees who worked at least 5 years in the feed-handling and nickel extraction departments. This increased risk of lung cancer was confirmed in a separate analysis of the same nickel refinery cohort using combined data from two separate studies.[85] Hexavalent chromium is an established lung carcinogen, and two studies examined lung cancer mortality among chromate production workers in the U.S. and in Germany subsequent to significant process changes and enhanced industrial hygiene controls.[86,87] These studies found an absence of risk, except at high exposure levels. Sparse data precluded the control of tobacco smoke as a confounder in analyses of the U.S. cohort. An editorial critiquing these studies found evidence of increased lung cancer associated with intermediate exposures levels – below current regulatory limits – when data from both the U.S. and German cohorts were combined.[88] In response to this critique, authors of the chromate studies state that the U.S and German cohorts should not be combined due to underlying differences in the two populations.

Evidence for an increased risk of lung cancer associated with other metals was documented in a multi-center case-control study in Europe restricted to workers who had never smoked.[89] In this study, increased risk of lung cancer was observed based on exposure to non-ferrous metal dust (OR=1.73) and risk further increased among those in the highest duration and cumulative exposure categories.

The evidence regarding the risk of lung cancer related to specific and non-specific ***solvents*** continues to emerge. A follow-up study of a cohort of workers employed in shoe manufacturing found significant excess lung cancer deaths (SMR= 1.36) associated with exposure to toluene, a finding that has persisted with increasing years of follow-up of the cohort.[90] However, the investigators were not able to control for tobacco smoking. In the same multi-center case-control study in Europe noted above, occupational exposure to organic solvents generally was associated with a modest increased risk among workers who never smoked (OR=1.46) and risk did increase with increasing duration and cumulative exposure.[89]

Studies continue to identify increased risk of lung cancer associated with ***air pollution***. In a European nested case-control study of non-smokers and ex-smokers, residing near heavy traffic roads was linked to a 46% increase in lung cancer.[91] When individual pollutants were

examined, exposure to each increment of 10ppb NO_2 produced a 14% increase in lung cancer. Exposure to concentrations greater than 30ppb resulted in a 30% significant increase in lung cancer. These findings did not change after controlling for occupational factors and cotinine (a short-term marker of tobacco exposure). In another case-control study examining the risk of outdoor air pollution, women living in the group of Taiwan municipalities with the highest levels of air pollution had a 28% increased risk of lung cancer.[92] Likewise, lung cancer risk among women with prolonged residence in a highly industrialized area of northeast England (greater than 25 years) was increased by 83%.[93] Lastly, a meta-analysis of the risk of lung cancer associated with indoor air pollutants in a Chinese population found significant elevations among both sexes based on exposure to domestic coal used for heating and cooking, indoor exposure to coal dust, cooking oil vapor and ETS.[94]

We identified two additional studies examining the link between ***ionizing radiation*** and increased risk of lung cancer. In a study of U.S. radiologic technologists, limited evidence was found for an increased risk of lung cancer due to chronic low to moderate levels of exposure to ionizing radiation.[95] In this study, risk was modestly elevated among men, but not women based on a number of employment metrics adjusted for smoking. Men, but not women, who first worked as a radiologist before the age of 20 demonstrated a two-fold increase in lung cancer risk. Men and women who held patients while x-rays were taken and allowed others to take numerous (25 or more) practice x-rays on them were also at a greater risk. The second study identified was a comprehensive review of lung cancer risk associated with residential exposure to radon based on a pooled analysis of data from seven case-control studies conducted in North America.[96] The authors used sophisticated modeling and reported a significant increased risk of lung cancer with increasing residential radon concentrations. This is consistent with findings in previous studies of underground miners exposed to radon.

Risks of lung cancer associated with other exposures and occupations were reported. In a study of aerospace workers, both medium and high exposure to mineral oils (RR=2.00 and 1.99 respectively) were associated with increased risk of lung cancer.[10] In another cohort of aerospace workers with exposure to hydrazine in rocket fuels, lung cancer was significantly elevated when exposures were lagged 20 years (RR=2.5) and risk significantly increased with increasing dose.[54] Although investigators were not able to control for tobacco smoking in this analysis, they suggest that confounding by smoking was not appreciable based on an analysis of a subset of the cohort. Increased risk of lung cancer was associated with occupational exposure to silica in a multi-center case-control study restricted to workers who had never smoked.[89] Lung cancer was also significantly elevated among female bakers.[58]

Multiple Myeloma—Exposure to ***pesticides*** and farming as an occupation continue to be linked with multiple myeloma. In the Agricultural Health Study, a 34% increase in multiple myeloma was observed among private pesticide applicators, although no cases occurred among commercial applicators.[27] In another analysis of the Agricultural Health Study, multiple myeloma was elevated among pesticide applicators exposed to the commonly used broad-spectrum herbicide glyphosate (sold as Round-up); this association was not found in previous studies.[97] In this analysis, risk was elevated based on ever use of glyphosate (RR=2.6) and risk increased with cumulative exposure days (RR=4.4 among the highest exposure category using "never exposed" as the reference), but not with intensity of exposure.

In a population-based case-control study in Germany, multiple myeloma was strongly and significantly associated with farming with varying employment durations (OR=10.4, for employment duration of 1-10 years and OR=8.6 for employment duration of greater than 10 years) and for all durations (OR=9.2).[98] Finally, dermal exposure to the fungicide pentachlorophenol among a cohort of sawmill workers resulted in a 4-fold increased risk of

multiple myeloma based on five or more years of exposure; there was also a significant dose-response trend.[59]

Although previous studies have documented strong evidence regarding the risk of multiple myeloma associated with a variety of ***solvents***, recent studies provide mixed results. The Health Watch case-control study of petroleum workers found no evidence of an increased risk of multiple myeloma associated with exposure to benzene.[70] However, a meta-analysis of seven benzene cohort studies revealed increased risk of multiple myeloma (meta-RR=2.13).[99] Similarly, a meta-analysis of occupational exposure to TCE found no increased risk of multiple myeloma based on an examination of eight studies.[74]

A recent follow-up of employees highly exposed to PCBs from a manufacturing facility found evidence of elevated mortality from multiple myeloma (SMR=2.11).[77] When the cohort was expanded to include workers with at least 90 days of potential exposure to PCBs, the SMR was significant (SMR=1.85), but there was no evidence of a dose-response trend.[78]

There is also a suggestive link of multiple myeloma with exposure to 1, 3-butadiene among synthetic rubber workers based on modest increases in risk, although no exposure-response trend was observed.[64]

Additional occupations with increased risks of multiple myeloma based on a population-based case-control study of lymphomas in Germany included animal husbandry and agricultural workers (OR=7.2, for duration of employment greater than 10 years), maids (OR=5.9 for duration of employment greater than 10 years), building caretakers, charworkers, cleaners (OR=5.1, for duration of employment greater than 10 years), bricklayers, carpenters and other construction workers (OR=3.6 and 4.7 for 1-10 years and greater than 10 years of employment respectively), and for material handling and related equipment operators, dockers and freighthandlers (OR=3.9 and 8.1 for 1-10 years and greater than 10 years of employment respectively).[98]

Nasal/Nasopharyngeal Cancer—The recent literature related to occupational or environmental risks associated with nasal or nasopharyngeal cancers is limited to a study of textile workers and an analysis of nickel refinery workers. In a case cohort study of female textile workers in Shanghai, China, investigators identified significant elevated risk of nasopharyngeal cancer from exposure to dyes and inks as well as to acids, bases and caustics, although associations were based on a small number of cases.[100] In this study, women working with dyes for 10 years or more had a 3.6-fold increase in nasopharyngeal cancer risk although there was no evidence of a dose-response trend. Risk increased with increased duration of exposure to acids, bases and caustics (HR=2.1 for highest exposure category) and no dose response was observed related to exposure to inks. In a follow-up analysis of a cohort of nickel refinery workers using combined data from two recent studies, investigators observed significant elevations of nasal cancer mortality (SMR=870).[85] Although elevation of nasal cancer in this analysis was based on two cases, strong prior evidence identifies nickel refining as a causal risk factor of nasal cancer.[101]

Non-Hodgkin's Lymphoma—Evidence regarding the links between exposure to various ***pesticides*** and non-Hodgkin's lymphoma (NHL) continue to emerge. Substantial exposure to pesticides as a group in one population-based case-control study in Australia was associated with a 3-fold risk of NHL.[102] This same study found a greater than 3-fold non-significant increased risk of NHL associated with substantial exposure specifically to organochlorine and "other" pesticides and herbicides, and smaller elevated risk for phenoxyherbicides (OR=1.75). A cohort study of sawmill workers found evidence of increased risk of NHL, including a

significant dose-response trend based on years of dermal exposure to the fungicide, pentachlorophenol; this is likely to be contaminated with dioxin.[59]

In a study of the organochlorine insecticide, hexachlorocyclohexane (HCH) used for sheep dipping, high exposure (defined as owning one hundred or more sheep) was significantly associated with nearly a 4-fold risk of NHL (OR=3.86).[103] In this study, the HCH used was a mixture of different isomers, including around 15% of the gamma isomer, commonly known as lindane. In the Agricultural Health Study, NHL was significantly elevated among pesticide applicators with the highest level of intensity weighted lifetime days of exposure to lindane (RR=2.6) and risk rose with increasing cumulative exposure.[60]

Another analysis from the Agricultural Health Study revealed that pesticide applicators exposed to cyanazine, a triazine, had a 25% increase in NHL risk.[104] A nested case-control study of United Farm Workers of America members provided additional evidence linking exposure to 2,4-D to increased risk of NHL (OR=3.8).[62] In a case-control study of farmers in Spain, there was an 80% increase in lymphoma (including NHL, multiple myeloma and Hodgkin's disease) risk associated with exposure to non-arsenic pesticides, a broad category including multiple classes of pesticides.[105]

Studies of NHL among children exposed to pesticides remains more limited. A study of childhood cancers found no evidence of increased risk of lymphomas associated with residence in high pesticide use areas at the time of diagnosis.[63] However, the majority of studies to date that have identified elevated risks of childhood lymphomas were based primarily on parental exposure to pesticides prior to conception or during pregnancy.

While the evidence regarding the risk of NHL associated with exposure to ***dioxin*** is quite strong, a geographic cluster examination in New Zealand found limited evidence of increased cancer risk among a community potentially exposed to dioxin from the manufacture of the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T).[68] However, when a latency period is considered, the significant elevation of NHL (SIR=1.75) in the community is not clearly connected to the years of 2,4, 5-T production.

New studies further associate exposure to ***solvents*** with increased risk of NHL. A population-based case-control study in Australia reported a significant 30% increased risk of NHL with occupational exposure to non-specific solvents; the more frequent the exposure and the more years exposed, the higher the risk.[106] In another study, significant increased risk of NHL was observed in association with medium/high levels of toluene exposure (OR=1.8) and risk significantly increased with increasing duration.[107] In this same study, modestly increased risks of NHL were identified based on exposure to benzene (OR=1.6), trichloroethylene (OR=1.2), PCE (OR=1.2), styrene (OR=1.3), dichloromethane (OR=1.7), and xylene (OR=1.7), although no significant dose response trends were observed. Increased NHL risk from exposure to benzene in this study is in contrast to results from the Health Watch nested case-control study of petroleum industry workers, which found no evidence of increased risk for NHL.[70] In a large study of North American synthetic rubber workers, exposure to styrene at all levels of cumulative exposure, and adjusted for exposure to other industrial agents, was associated with increased risk although a dose-response trend was not observed.[64]

A population-based case-control study in Germany identified numerous occupations associated with significant increased risk of lymphomas, including architects, engineers and related technicians; cooks, waiters, bartenders; maids; metal processors; electrical fitters and related electrical and electronics workers; medical, dental, veterinary and related workers; sales workers; chemical processors and related workers; food and beverage processors; machinery fitters, machine assemblers, precision instrument makers; and printers.[98] Other specific

exposures associated with increased risk of NHL in other studies include PCBs[39] and personal hair dyes.[76]

Ovarian Cancer—Although our literature review revealed no additional studies investigating risk of ovarian cancer related to specific exposures, elevations were observed in various occupations. The Agricultural Health Study found increased ovarian cancer risk among women employed as private pesticide applicators (SIR=2.97).[27] This finding is notable given that previous studies have demonstrated increased risk of ovarian cancer among women exposed to triazine herbicides. Increased risk of ovarian cancer among semi-conductor/electronic storage device workers is also suggested in some, but not all studies. Specifically, in one mortality study, ovarian cancer risk was significantly elevated (RR=3.7) among women with 15 or more years since first potential exposure and five or greater years of potential exposure.[38] Lastly, a 14% elevation of ovarian cancer was observed among a cohort of Norwegian nurses.[52]

Pancreatic Cancer—We identified three studies that reported an increase in pancreatic cancer risk or mortality associated with working in specific industries. Mortality from pancreatic cancer was elevated among males working for a major computer manufacturing company.[35] Likewise excess pancreatic cancer mortality was observed among females in another semiconductor facility.[36] Lastly, a significant increase in male pancreatic cancer risk was found in a study of food industry workers.[58]

Prostate Cancer—Evidence regarding the links with ***pesticides*** and prostate cancer is becoming stronger. The majority of the new evidence is emerging from ongoing analyses of the Agricultural Health Study. In one such analysis, private pesticide applicators had elevated risk of prostate cancer (SIR=1.26) while commercial applicators had a slightly higher risk (SIR=1.37).[27] Exposure among applicators to the organophosphate pesticide phorate increased the risk of prostate cancer among those with a family history (RR=1.53), but not among those without.[108] Similarly, increased risk (RR=1.58) of prostate cancer was observed among applicators exposed to another organophosphate pesticide, fonofos, but only among those with a family history of prostate cancer.[61] Cyanazine, a triazine pesticide, was associated with a modest 23% increase in prostate cancer risk in the Agricultural Health Study.[104]

Other studies also document risk of prostate cancer associated with either pesticides or farming, although we identified two studies that found no such association.[109,110] Farming was associated with increased risk of prostate cancer among Caucasians (OR=1.8), but not among African-Americans in a population-based case-control study in South Carolina.[111] This study also found a 60% increased risk of prostate cancer among farmers who mixed or applied pesticides. A meta-analysis of prostate cancer among pesticide manufacturing workers found significantly increased risk (meta-RR= 1.28).[112] This meta-analysis found evidence of a non-significant increased risk of prostate cancer associated with several classes of pesticides, and a significantly increased risk for accidental and non-accidental exposure to phenoxy herbicides contaminated with polychlorinated dibenzodioxins and polychlorinated dibenzo-furans. Lastly, a study examining adipose tissue levels of persistent pesticides found a significant increase in prostate cancer risk based on levels of trans-chlordane (OR=3.49) and increased risk for a range of additional pesticides or their metabolites including HCB (OR=2.39), p,p' DDE (OR=2.30), and a number of chlordane metabolites.[113] When results from this study were stratified by PSA levels, risk substantially increased, especially among men with PSA levels greater than 16.5.

Although previous studies of Vietnam veterans have found evidence of increased prostate cancer mortality, new data from the Air Force Health Study – which has followed the health status of Ranch Hand veterans who were responsible for handling and spraying Agent Orange,

an herbicide contaminated with ***dioxins*** – found no evidence of an overall increased risk of prostate cancer.[114] However, the study did find a significant increased risk of prostate cancer among those veterans with high blood dioxin levels and who served prior to 1969 (RR=2.37) – when more contaminated herbicides were used – and among veterans who served in Southeast Asia for less than 2 years (RR=2.15). Among other U.S. Air Force veterans not occupationally exposed to Agent Orange (veterans other than the Ranch Hands), there was a significant dose-response trend in prostate cancer risk associated with increasing years of service in Southeast Asia, but not with dioxin levels.[115]

A very large cohort study of workers exposed to ***PCBs*** during the manufacture of electrical capacitors revealed a positive trend for prostate cancer mortality with increasing cumulative exposure; a new finding for long-term studies of PCB-exposed workers.[78] In this study, a strong dose response was observed and the trend was significant when 10-year and 20-year exposure lags were considered. Resulting prostate cancer risks were also significant at higher exposure levels. In another study examining adipose levels of persistent organic pollutants, levels of PCB 153 (exposure defined as higher than the median PCB 153 concentration among controls) were associated with prostate cancer (OR=3.15).[113] In this same study, risk of prostate cancer associated with PCB 153 was notably high (OR=30.3) among men with PSA levels greater than 16.5.

Additional evidence supports the link between exposure to some types of ***metals*** and prostate cancer. In a case-control study, prostate cancer was associated with cadmium exposure as measured in toenails with risk especially elevated at the highest exposure level (OR= 4.7).[116] The overall dose-response trend in this study was significant. Studies are needed to validate the use of toenails as biomarkers of long-term arsenic exposure. Weak evidence supports links between prostate cancer and exposure to other non-defined metals based on two recent studies. Prostate cancer was slightly increased based on exposure to metal fumes (RR=1.11)[109] in the Netherlands Cohort Study and similarly in a case-control study in Western Australia, risk was non-significantly increased based on “non-substantial” exposure to toxic metals, but not for “substantial” exposure.[106] The association between exposure to ***metalworking fluids/mineral oils*** and increased risk of prostate cancer was further examined in a study of workers in the auto industry.[117] This study demonstrated modest elevations of prostate cancer risk with increasing cumulative exposure to soluble and straight mineral oils that occurred 5 years or more before diagnosis. The exposure-response relationship with soluble fluids was determined as non-linear with significantly increased risk occurring at the highest exposure level of 270 mg/m^3-years (RR=3.41). In contrast the exposure-response relationship between prostate cancer and straight fluids was linear resulting in a significant 12% increase in risk for every increase of 10 mg/m^3-years of cumulative exposure.

In a second study using data from this same cohort of auto-industry workers, risk of prostate cancer increased linearly with exposure to straight fluids from puberty to early adulthood (RR=2.4 per 10 mg/m^3 years of cumulative exposure).[118] The investigators also noted a strong association between exposure to straight fluids before the ages of 23 and increased risk of prostate cancer after age 50 (RR=6.46 per 4 per 10 mg/m^3 years of cumulative exposure) suggesting that early adulthood exposures are critical to prostate cancer risk later in life. These results are somewhat limited as investigators were unable to control for family history of prostate cancer.

New information about a genetic polymorphism considerably strengthens the evidence regarding the link between ***PAH*** exposure and prostate cancer. In this case-control study, no significant increased risk of prostate cancer was identified associated with lifetime cumulative PAH exposure from a variety of occupational sources, although risk was suggestively elevated based on PAH exposure via inhalation to petroleum (OR=1.12), coal (OR=1.29), “any” source

(OR=1.17), and via a cutaneous route of exposure to coal (1.48).[119] However, in this same study, a gene-environment interaction was observed associated with a polymorphism in the GSTP1 gene such that men under age 60 who carried the GSTP1 Val variant and were exposed to high levels of PAHs were at a significant increased risk of prostate cancer (OR=4.52). Evidence from other studies regarding the link between PAH exposure and prostate cancer was less compelling. Exposure to PAHs among aerospace workers resulted in a slight non-significant increased risk of prostate cancer, but only among those highly exposed[120] and results from the Netherlands Cohort study indicate no evidence of an increased risk of prostate cancer from occupational exposure to PAHs or to other combustion by-products such as diesel exhaust.[109]

Evidence regarding the risk of prostate cancer associated with ***solvents***, although limited, is emerging. A nested case-control study of occupational exposures to solvents among a cohort of workers in the aerospace industry found a significant dose-response trend of prostate cancer among workers exposed to low/moderate (OR=1.3) and high levels of TCE (2.1).[120] Increased risk of prostate cancer was associated with high levels of TCE exposure and risk increased further when exposures were lagged by 20 years. This same study found evidence of increased risk of prostate cancer associated with exposure to benzene (OR=1.5), but only based on high exposures and only when exposure was not lagged.

Additional studies examining specific occupations and/or exposures and risk of or mortality from prostate cancer found significant elevations among California firefighters (OR=1.22),[40] petroleum workers (SIR=1.18),[72] and semiconductor workers involved in facilities/laboratories (SMR=198).[38] Risk of prostate cancer was not increased based on occupational exposure to mineral oil based on results from the Netherlands Cohort Study,[109] a case-control study in Western Australia,[106] and a nested-case-control study of aerospace workers[120]; these findings are in conflict with some, but not all, previous studies. Lastly, a meta-analysis found evidence of increased risk of prostate cancer among civilian pilots, but caution should be exercised regarding these findings as the analysis did not control for confounding variables.[121]

Rectal Cancer—We identified a few studies adding to the evidence base regarding occupational and environmental risks of rectal cancer, particularly exposure to ***metals***, ***metalworking fluids***, ***PCBs*** and ***pesticides***. A study of female textile workers in Shanghai indicated that long-term exposure (20 years or longer) to metals was associated with a 2-fold elevation in rectal cancer risk.[53] In the Agricultural Health Study, exposure to chlordane and toxaphene among pesticide applicators increased the risk of rectal cancer (RR=1.7 and RR=2.0 respectively).[60] Slight elevations in rectal cancer risk were also observed among applicators exposed to aldrin, DDT, dieldrin, heptachlor and lindane. A recent follow-up of employees highly exposed to PCBs in a manufacturing facility found suggestive evidence of elevated mortality from rectal cancer (SMR=1.47).[77] When this cohort was expanded to include workers with at least 90 days of potential exposure to PCBs during 1939-1977, mortality due to rectal cancer was no longer elevated.[78] Additional evidence from a cohort mortality study of automobile manufacturing workers supports the link between metal working fluids and mineral oils and rectal cancer.[122] In this study, adjusted rectal cancer risks were elevated for all types of metal working fluids, including straight, soluble and synthetic, although the strongest and only significant increased risk was only found for straight fluids (RR=2.7) in the highest cumulative exposure category. The exposure-response relationship between rectal cancer and straight fluids was linear and lagging exposure up to 15 years further increased the risk (RR=3.2 at 40 mg/m^3-years).

Additional studies examining specific occupations and risk of rectal cancer found significant elevations among male semiconductor workers as well as in male and female combined[36] and among females working in textile maintenance operations (OR=2.3).[53]

Skin Cancer—Some evidence supports links between skin cancer and ***pesticide*** exposure, although specific pesticides have not been implicated. A study of residential pesticide exposure revealed a significant increase in melanoma among those who used indoor pesticides four or more times a year (OR=2.18) and/or those who used pesticides for ten years or more (OR=2.48); a significant dose response was observed.[123] Other studies of pesticide exposures provide mixed evidence: spouses of pesticide applicators in the Agricultural Health study had increased melanoma, while melanoma risk among applicators was not elevated.[27]

Evidence continues to link skin cancer and exposure to ***metals*** and to ***combustion by-products***. Cutaneous melanoma was also associated with copper and zinc exposure based on toenail concentrations, although caution is warranted given questions about the validity of toenails as a bio-marker of long term exposure.[124] A case-control study of chemical exposures among men identified a consistent increased risk of all skin cancer types (squamous cell carcinoma, basal cell carcinoma (both nodular and superficial multi-focal), and malignant melanoma) associated with arsenic exposure, although only malignant melanoma was significantly increased.[125] In this study, risk of malignant melanoma was also elevated for other established skin carcinogens, such as coal, PAHs, pitch and tar. Exposure to tar, pitch, soot, coal, and PAHs was associated with similarly elevated risk for squamous cell carcinoma. Risk of basal cell carcinoma was non-significantly elevated with coal exposure. A review article of oil refining workers and the risk of malignant melanoma found strong evidence of an association from multiple studies and the lack of such an association among studies funded by industry.[126]

In Air Force veterans not occupationally exposed to Agent Orange (veterans other than the Ranch Hands), there was a significant dose-response trend associated with increased melanoma risk and serum ***dioxin*** levels, although increased risk at each exposure quartile was not significantly elevated. A modest dose-response trend was also observed in relation to basal or squamous cell skin cancer and serum dioxin levels as well as increased risk of melanoma and years served in Southeast Asia.[114]

An update of a cohort mortality study of workers exposed to ***PCBs*** finds persistent evidence regarding excess mortality from melanoma (SMR= 2.43).[39] However, the strength of the evidence is somewhat limited since no exposure-response trend was observed.

Melanoma was strongly associated with exposure to ***mineral oils*** in a study of aerospace workers. Workers exposed to mineral oils at both medium (OR=2.15) and high levels (OR=3.32) were at increased risk, although risk was only significant for the high exposure category. A test for a dose-response trend was significant.[10]

Additional studies examining specific occupations and risk of melanoma found elevated risk (OR=1.50) among California firefighters;[40] high risk among Swedish women employed as educators, bank tellers, dental nurses, librarians/archivists/curators, horticultural workers and hatmakers/milliners;[127] excess risk among a cohort of petroleum workers (SIR=137);[72] excess mortality among males associated with computer manufacturing[35] and among females as well as males and females in another semiconductor facility;[36] and a 15% increase in melanoma risk among a cohort of 43,000 Norwegian nurses.[52] Lastly, a meta-analysis of cancer risk associated with employment as a female flight attendant revealed a 2-fold elevation in risk of melanoma (combined RR=2.13).[51] Studies included in this meta-analysis did not control for lifestyle factors such as time spent sun-bathing and evidence to date does not suggest a risk of

UV radiation exposure within confines of the airplane. A similar meta-analysis found evidence of increased melanoma and other skin cancer among male cabin attendants and civilian pilots.[121]

Stomach Cancer—The recent literature related to occupational and or environmental risks associated with stomach cancer is limited to studies examining workers exposed to ***PCBs*** and ***metal working fluids***. In a cohort study of workers exposed to PCBs during the manufacture of electrical capacitors, investigators found an elevation in mortality due to stomach cancer (SMR=1.53) among men.[78] In this study, a strong dose response trend was observed among all workers when considering no cumulative exposure lag and a 10-year lag (but not a 20-year lag); stomach cancer risk was higher and the dose response trend was stronger among men. Workers exposed to mineral oils within the aerospace industry had elevations of risk of stomach cancer and esophageal cancer (combined) at both medium (OR=1.73) and high (OR=1.99) exposure levels.[10]

Testicular Cancer—Recent studies of testicular cancer associated with environmental and occupational exposures were limited to studies examining specific occupations. Testicular cancer was elevated among California firefighters (OR=1.54),[40] and modestly elevated among pesticide applicators (commercial applicators, SIR=1.24 and private applicators, SIR=1.05).[27]

Section II: Understanding Critical Elements of Cancer Causation

Toxicological Evidence is Crucial for Connecting Early-life Exposures and Cancer

Over the years, more refined methods of assessing human exposure have contributed to a marked improvement in understanding not only of what agents probably cause cancer but also when people are more susceptible to carcinogenic effects. For example, one study described above in our literature review found an increased risk of female breast cancer as a result of DDT exposure prior to puberty, but not after puberty.[43] Similarly, prenatal exposure to solvents and pesticides continues to be associated with childhood leukemia and brain cancer. Previous research, especially within the field of radiation epidemiology, has repeatedly documented examples of differential cancer risk with age at exposure – such as greater risk of cancer among workers at nuclear facilities when the same dose of radiation is delivered at older ages[128, 129, 130] and increased risk of childhood leukemia from prenatal x-ray exposure, especially during the first trimester of pregnancy.[131]

However, there are limits to what we can learn from epidemiologic studies about the effects of early life exposures and the effects of low doses on cancer risk. Epidemiologic studies that examine the effects of low levels of exposure are complicated by an inability to find adequate control populations with no exposure to the agent under investigation and also by the prohibitive cost of funding prospective studies that collect exposure data decades before the onset of disease, a limitation for studies of early life exposures as well.

Detailed examination of prenatal and early life exposures on later risk of cancer in humans is extremely difficult to do in practice. Investigators must try to take advantage of exposure and disease information that is not under the control of the researcher. For example, the data on DDT exposure before puberty was not originally collected with a DDT and breast cancer hypothesis in mind.[43] It was extremely fortuitous that blood samples were collected forty or fifty years ago that could be analyzed for DDT and metabolites and then linked to breast cancer cases and controls many years later. But these are exceptional circumstances in epidemiology, as opposed to toxicology or lab sciences where the researcher controls the conditions of the exposure and the animals may have a short lifespan during which the effects are seen.

Evidence is emerging from the animal toxicological literature regarding carcinogenic effects of chemicals that are difficult to study in humans. For example, there is a virtual absence of human studies examining the effects of bisphenol-A – a principal ingredient in the production of polycarbonate plastics and used in the preparation of epoxy resins. However, more than one hundred animal studies have been published, the vast majority of which have documented a range of health effects occurring at low exposure levels, including links with cancer. Studies in both mice and rat models show that animals exposed to low doses of bisphenol-A in utero develop mammary gland alterations that increase susceptibility to breast cancer later in life.[132,133] Studies in rats show similar evidence for prostate cancer, such that low dose exposure to bisphenol A in utero alters gene behavior that leads to prostate cancer later in life.[134] New lines of research in animal studies also demonstrate that these changes not only affect those exposed in utero, but animals of subsequent generations. Experiments in animals with other endocrine disrupting agents and radiation show “epigenetic trans-generational alternations,” alterations that result in tumor development and other disease states in adulthood not just in the first generation, but in all subsequent generations examined.[135] We have learned from toxicology that many agents are not mutagenic or genotoxic at low exposure levels, but can act in a myriad of other ways, such as turning on or turning off specific genes that can alter a person's susceptibility to genotoxic agents or other mechanisms involved in the progression of cancer. These studies have profound implications regarding the multi-factorial nature of cancer causation. They also point to the need to act on what we know and not wait for the “perfect” epidemiological study before considering preventive action.

The Multi-factorial Process of Cancer Causation

Due to advances in molecular biology, researchers now know that cancer develops from a complex multi-factorial web of causes. Although researchers are beginning to examine interactions among causal factors, the vast majority of epidemiological and toxicological studies continue to investigate cancer risk associated with individual factors. Although Section I provides examples of the wide variety of ways investigators examined how environmental and occupational agents can cause cancer, even these recent studies are limited by our current level of knowledge and current epidemiologic methods. There are undoubtedly other interacting factors, such as prenatal and early childhood exposures, nutrition, physical activity, genetics, and psychosocial factors such as stress, which together may ultimately be responsible for the development of cancer in ways we do not yet fully appreciate.

We provide here a brief overview of the current understanding of the steps that lead to malignant tumor formation in humans. This more technical information is presented because it illustrates that current concepts in understanding the carcinogenic process are more detailed and elaborate than they were in previous decades. We consider it important to describe some of the multiple pathways leading to human cancer in order to understand why previous reviews providing attributable fractions/percentages are too simplistic and reductionist to be useful.

The term “carcinogen” refers to any substance that can contribute to the process of tumor formation and includes mutagens (or genotoxins), co-carcinogens, and tumor promoters. The term “carcinogen” is most often associated with substances that are genotoxic (meaning: “genetic toxins”), which initiate the process of carcinogenesis by causing a mutation in DNA (i.e., as mutagens). A variety of processes occurring spontaneously inside cells can also contribute to mutagenesis and carcinogenesis, including spontaneous DNA damage as well as mistakes (errors) being made during the duplication of DNA. A “co-carcinogen” is a substance that by itself does not cause a tumor to form, but enhances the potency of a genotoxic substance. A “tumor promoter” is a substance that by itself does not cause a tumor, but enhances tumor formation when it is given (usually repeatedly) after exposure to a genotoxin.

The steps leading from carcinogen to mutation are complex, but usually follow the following sequence. (1) Most chemical carcinogens are not inherently cancer-causing without being covalently modified ("metabolized") inside cells by enzymes (notably by cytochrome P450s) into chemically reactive intermediates. This metabolism has evolved to rid the organism of toxic hydrophobic substances that accumulate in membranes and fatty tissue. Most carcinogens are hydrophobic. (2) While less toxic derivatives usually result, some metabolism leads to more toxic intermediates that react with the DNA nucleobases to form "adducts." (3) In comparison to normal nucleobases, DNA adducts are more likely to be misread during DNA synthesis, often by specialized DNA polymerases (DNAPs). For example, the carcinogen benzo[a]pyrene forms a guanine adduct, which is copied correctly by DNAP kappa (cytosine insertion) but incorrectly by DNAP eta (adenine insertion). When thymine is incorporated opposite this adenine in the next round of DNA replication, a fixed, heritable mutation results, as a G:C base pair has become a T:A base pair. Interestingly, the situation is reversed for copying UV-induced DNA damage: DNAP eta does correct insertion while DNAP kappa does incorrect insertion. (4) In most cases, though, cells avoid mutagenic DNA replication through a process called DNA repair, which removes DNA adducts and restores the sequence and integrity of DNA. DNA repair is multifaceted with many pathways, each targeted to a different kind of DNA damage.

Steps in Tumor Formation—In most cases, cells in adult humans are in a steady state, and new cells are generated (by cell division) only to replace old cells that have been lost (e.g. by injury).[136, 137, 138, 139] Cell division is tightly regulated and is overseen by the protein products of growth control genes. If these genes become mutated, a cell may lose the checks and balances necessary to insure that it divides only when it is supposed to. For example, normal cells have so-called "tumor suppressor genes," which limit cell division to those times when the cell receives a proper growth signal (e.g., to repair damaged tissue). The loss of a tumor suppressor gene by mutation may contribute to uncontrolled cell growth (cancer). A second class of genes called "proto-oncogenes" are active in the signaling pathway for cell growth; if these genes are mutated to "oncogenes", then they can potentially send their signals to grow continually rather than only when it is proper.

Evidence suggests that tumor cells are different from normal cells in at least six ways, which relate to growth control: self-sufficiency in growth signals; insensitivity to anti-growth signals; limitless replication potential; evasion of programmed cell death (apoptosis); sustained angiogenesis; and tissue invasion and metastasis.[139, 140] While a cell with a defect in any of these categories could proliferate abnormally, a cancer cell probably must have defects in all six categories.

Self-Sufficiency in Growth Signals—Normal cells divide only upon receiving a signal from a growth-triggering substance called a "mitogen." Mitogens bind to cell surface receptors and initiate a cell signaling pathway, which involves the sequential activation of a string of proteins that ultimately leads to changes in the expression of genes in the nucleus. Mutations in genes encoding proteins in many of the steps in a growth controlling signaling pathway can lead to faulty signaling, which can promote cell growth.

Mitogens are usually made in different cells than the cells that respond to the mitogen, which requires a cell surface receptor that is mitogen-specific. Some cancer cells have mutations leading them to make their own mitogens, as is the case in some cancers of the breast, prostate, colon and lung. Mitogen receptors can also be mis-regulated or increased in some stomach, brain, lung and breast tumors. Proteins downstream in a signal transduction pathway can also be affected in a way that increases cell growth.

Insensitivity to Anti-Growth Signals—Non-dividing cells are said to be in the "quiescent" or "G_0" state. Following mitogenic stimulation, a cell divides by following an orderly process called the "cell cycle", which has four stages. The dividing cell follows a complicated protocol that culminates in each daughter cell getting one copy of each chromosome. Genes encoding proteins that regulate the cell cycle are also frequently mutated in cancers. The retinoblastoma (Rb) protein is a key player in the regulation of progression through the cell cycle, and Rb is probably mutated, disrupted, or misregulated in all tumors.

Evading Programmed Cell Death (Apoptosis)—Cell division and growth is counter-balanced by cell death, which usually follows an orderly process that occurs via one of three pathways. The best studied pathway is apoptosis (pronounced: ah-pah-toe-sis) or "programmed cell death." Apoptosis can occur in normal development but cells receiving excessive DNA damage also undergo apoptosis rather than trying to survive with high levels of mutations. For example, cells in severely sunburned skin have high levels of ultraviolet light-induced DNA damage; to avoid cells with many mutations that might generate a skin cancer, these cells are killed via apoptosis. The dead cells are replaced by new cells produced in a shielded layer of cells lower in the dermis. The p53 tumor suppressor protein plays a central role in the sensing of the level of DNA damage and regulating the cellular response to this damage, including in the regulation of apoptosis. The p53 protein is mutated in ~50% of all human cancers.

Limitless Replication Potential—Human cells are able to replicate themselves a finite number of times, after which they stop dividing, leading to a state termed "senescence." Most cells that escape senescence (usually via mutations in either the Rb or p53 gene) enter a state called "crisis" and die, but a small fraction of cells circumvent crisis and become "immortal" (i.e., they multiply without limit). Though the process of immortalization is incompletely understood, one key element involves the regulation of the ends of chromosomes, which are called "telomeres." Telomeres are retained and cells become immortal when telomerase, which replicates telomeres, is overexpressed. Approximately 90% of tumors over-express telomerase, retain their telomeres, and thereby avoid senescence.

Sustained Angiogenesis—Cells in a tissue must be within ~0.2mm of a capillary blood supply in order to receive adequate oxygen and nutrients for growth. "Angiogenesis" is the term for the signaling of new blood vessel formation. Tumors remain small until they acquire the ability to trigger new capillary growth, which is termed the "angiogenesis switch". This switch may be maintained in the "on" position by various factors that are present or increased in cancer cells. Vascular endothelial growth factor (VEGF) is the best understood angiogenesis signaling factor. VEGF binds several cell surface receptors to trigger growth of new blood vessels, and is up-regulated in many tumors – a necessary (though not sufficient) step for a tumor to acquire an enhanced blood supply.

Tissue Invasion and Metastasis—Approximately 90% of all cancer deaths occur because a primary tumor acquires the capacity to release cells that then invade and grow in remote sites in the body, a process called "metastasis." Cancer cells are held together by adhesion proteins, whose expression decreases in metastatic cells. Cancer cells are held together by adhesion proteins, notably E-cadherin, whose expression decreases in metastatic cells, which are then able to leave the primary cancer site. Many other events are involved in metastasis as well.

Implications for Cancer Treatments

In recent years, knowledge of cancer genes has provided specific targets for chemotherapy with perhaps the most illustrative example being a new treatment for chronic myelogenous leukemia (CML). A high percentage of individuals with CML have a specific mutation that the drug "Gleevec" was created to selectively block. This drug effectively prevents the

progression of CML in patients with this specific type of leukemia. Other selective treatments are currently in the process of being evaluated and some researchers now hold the optimistic view that cancers will eventually become manageable chronic diseases. As two authors put it, "We envision anticancer drugs targeted to each of the hallmark capabilities of cancer; some, used in appropriate combinations and in concert with sophisticated technologies to detect and identify all stages of disease progression, will be able to prevent incipient cancers from developing, while others will cure pre-existing cancers, elusive goals at the moment."[140] Whether this vision will become reality is impossible to say with certainty. It is clearly the goal toward which most cancer research is currently directed, however.

Section III: Shifting Our Cancer Prevention Paradigm

Failing to Act on What We Know

Our review in Section I chronicles substantial evidence from the epidemiologic literature within in the last two and a half years that supports numerous links between environmental and occupational exposures and cancer risk. This literature comes after decades of solid research that has identified over 100 agents as causal or probably causal factors of cancer according to the International Agency for Research on Cancer (IARC). However, we as a society have repeatedly failed to act on this body of evidence to reduce and/or eliminate exposure to carcinogens wherever possible. Although we have made significant headway on preventing disease associated with exposure to lifestyle factors such as tobacco smoke, we have ignored the dozens of environmental and occupational agents that contribute to new cases of cancer each year.

An unfortunate case in point is the story of Swann Park in Baltimore, Maryland. As early as 1973, the International Agency for Research on Cancer evaluated evidence implicating arsenic as a causal factor of several types of cancer, including lung and skin cancers; evidence that was revisited in 1987 resulting in the classification of arsenic as a group 1 agent, "carcinogenic to humans." In 1981, a Johns Hopkins University researcher identified extremely high levels of arsenic in a South Baltimore park and evidence that this contamination from a nearby pesticide manufacturing plant was likely related to the high lung cancer death rate among men in the surrounding neighborhood.[141] The study reported results of soil testing by an EPA-certified laboratory that uncovered high levels of arsenic throughout the area, the highest of which were found near the northern edges of Swann Park, an area where the factory loaded train cars with arsenic-based pesticides, and along a half-mile stretch of rail line that ran adjacent to a residential community. High levels of arsenic corresponded with areas of high lung cancer mortality. Results from this study were widely disseminated through an academic journal, professional conferences, an original report, and presentations to EPA, as well as through stories in the local newspaper, but no one acted on the information. Cancer incidence and mortality were not subsequently monitored nor were additional soil samples taken; that is, until April 2007 when soil sampling revealed arsenic levels remain at more than 100 times that which is considered safe.[142] The city finally closed Swann Park and is now working with the state's Department of the Environment to remediate the environmental contamination that has plagued this community for decades.

The failure to translate knowledge of a carcinogenic effect into preventive measures is an issue that continues to affect millions of workers. A well-known example is the case of benzene. As early as the 1920s, scientists knew benzene caused cancer. However, it was not until some twenty years later that officials instituted 100ppm as the "permissible" exposure level, which was lowered to 10ppm in 1978, and 1 ppm 1990. As a renowned benzene researcher noted, the evolution of what was considered a permissible level of benzene was not driven by dramatic improvements in scientific knowledge regarding the mechanisms by which benzene caused cancer, but rather was the result of a continued struggle for health by unions, workers,

physicians, and scientists against powerful economic interests.[143, 144] The debate regarding a permissible exposure level for benzene exposure continues with mounting evidence that there is no safe threshold for this carcinogen.

Attributable Fractions: Hindering Comprehensive Cancer Prevention

Rather than emphasizing action on what we know and minimizing exposures to carcinogens wherever possible, some well-meaning scientists have attempted to devise better methods of attributing the percentage of cancer cases caused by single exposures and produced results that paradoxically can be used to justify inaction. The British Health and Safety Executive (HSE) released a draft workshop report on "The Burden of Occupational Cancer in Great Britain" in June, 2005. They recognized that the long-cited estimate of the occupational proportion of cancer deaths by Doll and Peto (4%, with a range from 2-8%) was 25 years out of date.[145] Researchers contracted by the HSE are reviewing the occupational cancer literature, estimating the fraction of each type of cancer attributable to occupational exposures, and then summarizing the percentages of each that were due to these exposures in Britain. The six cancers in this draft report included lung cancer, bladder cancer, non-melanoma skin cancer, sinonasal cancer, leukemia and mesothelioma. Estimates of the portion attributable to occupational exposures for these and several other cancers are expected to be released in the coming year.

Some limitations of the HSE approach to estimating the occupational cancer burden are similar to those of the Doll and Peto approach. For example, the HSE calculations are based largely on studies of workers who are known to have high exposures to known or likely human carcinogens. This does not take into account widespread low exposures to known human carcinogens, exposures to suspected carcinogens without good human studies to date, or other aspects of work such as lack of exercise and general air pollution. Furthermore, the HSE draft does not consider unknown carcinogens or effects of mixed exposures about which information is still emerging. Nor does the analysis take into account that most cancers arise from a complicated collection of multiple exposures, not exposure to single agents. As a result, the HSE draft estimates are very likely underestimates of the true occupational cancer burden in Great Britain.

Based on present knowledge it is quite unlikely that the HSE or any other group of scientists could come up with a "true" estimate of cancer cases caused by occupational exposures. The best that can be done is to calculate some lower bound estimates that might help inform policy decisions. For example, the HSE currently estimates up to 6,000 annual cancer deaths may be due to occupational exposures. This may change somewhat when new estimates are released in the coming year. Even this low estimate represents an enormous amount of potentially preventable tragedy each year.

The danger in producing calculations such as this is that they become "reified" as if they are true then get played off against cigarette smoke, unhealthy diet and other "lifestyle" cancer risk factors. We have seen this happen in the U.S. over the past twenty-five years and it would be regrettable if there were another round of this in Great Britain as a result of the HSE draft.

The Politics and Economics of Cancer Prevention

The Baltimore example and the documentation of the ongoing and avoidable cancer toll from occupational exposures to agents such as benzene or asbestos illustrate another problem with cancer prevention: there are large political and economic stakes involved. Public agencies frequently fail to do their jobs because their leaders recognize the political minefields they may tread, and they may fear personal or organizational retaliation if they take strong stands. As most people involved with primary prevention in public health know all too well, prevention is often under-resourced in public agency budgets and virtually non-existent in the private for-

profit sector. There are non-governmental organizations that have filled the void with respect to primary prevention of some diseases, including some cancers, but the overall picture is skewed toward screening, treatment, and support for survivors. Given the enormous human and economic costs involved with cancer – direct and indirect costs were estimated at $172 billion in the U.S. in 2002 – and rising incidence, this lack of emphasis on primary prevention demands an explanation.

The President of the Institute of Medicine, Dr. Harvey Fineberg, addressed this in a 2006 lecture at the UCLA School of Public Health entitled "Why Prevention is a Hard Sell."[146] He listed some of the reasons as follows: "There is no drama in prevention; non-events are not counted; statistical lives don't have immediacy; prevention is not profitable; prevention often runs against commercial interests; it may conflict with personal preferences or religious beliefs; and there is declining trust in leaders and institutions, challenging people's willingness to follow guidelines." While all of these reasons have some salience in understanding cancer prevention, the economic reasons loom largest.

There are extraordinary profits in the pharmaceutical industry in general, and chemotherapeutic drugs currently in use or on the horizon are some of the most profitable. A Forbes magazine story in 2004 quoted a clinician at a cancer treatment center in New York as saying that ten years earlier, he could extend the life of one of his patients by 11.5 months on average with a drug that cost $500; in 2004, he could extend the life of a patient with the same diagnosis 22.5 months, at a cost of $250,000. The goal of many current cancer treatment protocols is to repeat this experience with more and more types of cancer. Targeted chemotherapy, as described by Hanahan and Weinberg, is the Holy Grail of pharmaceutical companies, and the number of people living with cancer in the U.S. is expected to double in the next two decades. These trends are likely to greatly increase profits in this industry. Those who seek to prevent or reduce the magnitude of these profits risk being swept aside by industry representatives and their political and scientific spokespeople.

Conclusion

We consider the scientific literature linking environmental and occupational exposures to cancer to be substantial and getting stronger as time goes on. One of us (R.C.) has been reviewing this literature for over thirty years. In the 1970s there were approximately a dozen substances or exposures that were considered "established" human carcinogens by international agencies. That number now approaches 100, with many more considered "likely" to cause cancer in humans. As we noted in our previous review, incidence rates for many types of cancer in the U.S. continue to rise, although we welcome the apparent decline in lung cancer in males and soon in females. The cancer burden, defined as the number of people living with cancer, with the attendant economic and human costs, will inevitably continue to grow. This justifies urgent action to limit exposures to avoidable environmental and occupational carcinogens and to find safer alternatives to present chemical and physical risks. To repeat the call of ecologist Sandra Steingraber, "From the right to know and the duty to inquire flows the obligation to act."[1]

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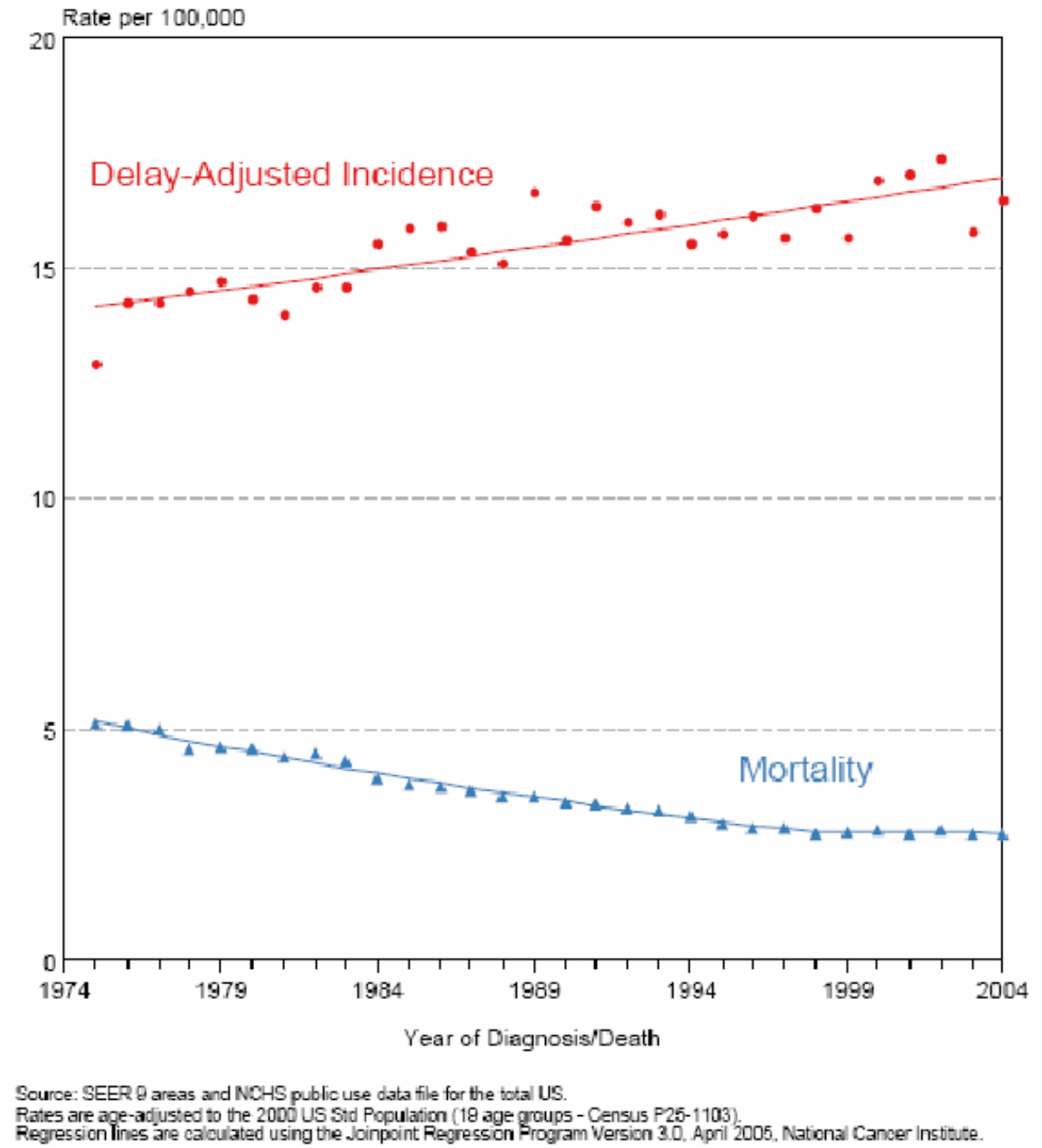

1. . SEER Delay-Adjusted Incidence and US Mortality All Childhood Cancers, Under 20 Years of Age Both Sexes, All Races, 1975-2004

Table 1
Evidence Unchanged Since 2005 Review

Cancer Type	Causal Evidence Regarding Involuntary Environmental or Occupational Exposures	
	Strong*	Suspected**
Bone	Ionizing radiation	
Cervical	Endocrine Disruptors (DES)	Non-specified solvents; Tetrachloroethylene; Trichloroethylene
Hodgkin's disease		Chlorophenols; Phenoxy acid herbicides; Other pesticides; Trichloroethylene
Mesothelioma	Asbestos	
Soft tissue sarcoma	Dioxin; Ionizing radiation; Vinyl chloride	Arsenic; Chlorophenols; DDT; Phenoxy acid herbicides; Unspecified pesticides
Thyroid	Ionizing radiation	

* Strong causal evidence of a causal link is based primarily on a Group 1 designation by the International Agency for Research on Cancer

** Suspected evidence of a causal link is based on our assessment that results of epidemiologic studies is mixed, yet positive findings from well-designed and conducted studies warrant precautionary action and additional scientific investigation.

Table 2
Summary of Environmental and Occupational Links with Cancer

Category	Carcinogenic Agent	Source/Uses	Strong*	Suspected**
Aromatic Amines	Benzidine, 2-naphylamine, 4,4′-methylenebis 2-choloraniline (MOCA), chlornaphazine heterocyclic aromatic amines	Used as antioxidants in the production of rubber and cutting oils, as intermediates in azo dye manufacturing, and as pesticides. Common contaminant in chemical and mechanic industries and aluminum transformation and an air contaminant from tobacco smoking. Used widely in the textile industry and as hair dyes.	Bladder (Benzidine, 2-naphylamine, 4,4′-methylenebis 2-choloraniline (MOCA), chlornaphazine)	Prostate (heterocyclic aromatic amines)
Chlorination Byproducts	Trihalomethanes	Trihalomethanes include chloroform, bromodichloromethane, chlorodibromomethane, and bromoform. Result from the interaction of chlorine with organic chemicals. Several halogenated compounds may form from these reactions although trihalomethanes are the most common. Brominated by-products are also formed from the reaction of chlorinated by-products with low levels of bromide in drinking water.		Bladder; Rectal
Environmental Tobacco Smoke	Contains more than 50 known carcinogens	Environmental tobacco smoke (ETS), also known as passive smoke, is a combination of smoke emitted from the burning end of a cigarette, cigar, or pipe, and smoke exhaled by the smoker	Lung; Breast	
Metals	Arsenic	Is produced commercially as a by-product of nonferrous metal production, primarily from copper production, comprising greater than 10% of dust content in some smelter operations. Inorganic arsenic is primarily used to preserve wood, but is also used as a pesticide mainly on cotton plants.	Bladder; Lung; Skin; Soft tissue sarcoma (angiosarcoma of the liver)	Brain/CNS; Kidney; Liver & Biliary; Prostate; Soft tissue sarcoma
	Beryllium	Used in the nuclear, aircraft and medical devices industry. Used also as an alloy or in specialty ceramics for electrical and electronic applications. Found as a contaminant in the combustion of coal and fuel oil.	Lung	

Category	Carcinogenic Agent	Source/Uses	Strong*	Suspected**
	Cadmium	Occurs naturally in ores together with zinc, lead and copper. Used as stabilizers in PVC products, color pigment, several alloys and now most commonly in re-chargeable nickel-cadmium batteries. Also present as a pollutant in phosphate fertilizers.	Lung	Pancreatic; Kidney; Prostate
	Chromium	Chromium is used in steel and other alloy production. Chromium III and Chromium VI are used in chrome plating, the manufacture of dyes and pigments, leather tanning and wood preserving.	Lung; Nasal and Nasopharynx	
	Lead	Used primarily in the production of batteries, ammunition, metal products such as solder and pipers and devices to shield X-rays. Lead is also found in gasoline, paints, ceramic products, caulking, and pipe solder, but has been reduced dramatically in the US.		Brain/CNS; Lead; Kidney; Stomach
	Mercury	Used to produce chlorine gas and caustic soda, and is also used in thermometers, dental fillings, and batteries. Mercury salts are sometimes used in skin lightening creams and as antiseptic creams and ointments. Elemental mercury is transformed to methylmercury by microorganisms in water and soil.		Brain/CNS
	Nickel	Used primarily as an alloy in stainless steel. Also used in nickel plating and battery production.	Lung; Nasal and Nasopharynx	Laryngeal; Pancreatic; Stomach
Metalworking Fluids &/or Mineral Oils	Straight oils, soluble oils, synthetic and semi-synthetic fluids	Used in a variety of industries including metal machining, print press operating and cotton and jute spinning.	Bladder; Laryngeal; Lung Nasal and Nasopharynx (mineral oils); Rectal; Skin; Stomach;	Esophageal; Pancreatic; Prostate
Natural Fibers/Dust	Asbestos	An inorganic naturally occurring fibrous silicate particle used primarily in acoustical and thermal insulation. Asbestos fibers can be divided into two groups: chrysotile (most widely used) and amphibole which include amosite, crocidolite, anthophyllite, actinolite and tremolite fibers.	Laryngeal; Lung; Mesothelioma;	

Category	Carcinogenic Agent	Source/Uses	Strong*	Suspected**
	Silica	An inorganic particle used in foundries, brick-making and sandblasting.	Lung	
	Talc containing asbestiform fibers	A mineral used in the manufacture of pottery, paper, paint and cosmetics	Lung	
	Wood dust	Used primarily in carpentry, joinery and in furniture and cabinetry making	Lung; Nasal and Nasopharynx	Laryngeal
Pesticides	Herbicides, Fungicides & Insecticides [For specific pesticides, see Section 1 of this paper and Clapp et al 2005 (Reference #1 in citation list]	Used for preventing, destroying, repelling or mitigating any pest or in use as a plant regulator, defoliant or desiccant. The majority of pesticides as registered with the U.S. EPA are used in agricultural applications, although residential application is also an important source.		Brain/CNS; Breast; Colon; Hogkin's; Leukemia; Lung; Multiple Myeloma; NHL; Ovarian; Pancreatic; Kidney; Soft tissue sarcoma; Stomach; Testicular
Petrochemicals and Combustion By-Products	Petroleum products, motor vehicle exhaust (including diesel), polycyclic aromatic hydrocarbons (PAHs), soot, and dioxins	Petrochemicals are derived from natural gas or petroleum and used to produce a variety of other chemicals and materials including pesticides, plastics, medicines and dyes. Substances can be produced as the building blocks for other products, but mainly result from the incomplete combustion of burning coal, oil, gas (diesel exhaust), household waste, tobacco and other organic substances. Dioxins are a class of chemical that are the by-products of combustion processes containing chlorine and carbon-based chemicals such as polyvinyl chloride (PVC) plastics. Dioxins are also created during the chlorine-bleaching processes for whitening paper and wood pulp.	Lung (PAHs, air pollution including diesel exhaust, soot, dioxin); NHL (dioxin); Soft tissue sarcoma (dioxin); Skin (PAHs)	Bladder (PAHs); Breast (dioxin); Esophageal (soot); laryngeal (PAHs); Multiple Myeloma (dioxin); Prostate (dioxin & PAHs)
Radiation	Ionizing radiation	Any one of several types of particles and rays given off by radioactive material, high-voltage equipment, nuclear reactions and stars. Alpha and beta particles, X-rays and gamma rays are radiation particles of concern to human health.	Bone; Brain & Central Nervous System; Breast; Leukemia; Liver & Biliary; Lung; Multiple Myeloma; Soft tissue sarcoma; Skin; Thyroid	Bladder; Colon; Nasal & nasopharynx; Ovarian; Stomach
	Non-ionizing	Comprised of microwaves and electro-magnetic frequencies including radio waves and extremely low-frequency electromagnetic fields.		Brain; Breast; Leukemia

Category	Carcinogenic Agent	Source/Uses	Strong*	Suspected**
	Ultraviolet radiation	Ultraviolet radiation is part of the solar radiation emitted by the sun.	Skin	
Reactive Chemicals	Butadiene	Used in the production of polymers for the manufacture of styrene-butadiene rubber for tires, nitrile rubber for hoses, gaskets, adhesives and footwear; acrylonitrile-butadiene-styrene polymers for parts, pipes, and various appliances; and styrene-butadiene latexes for paints and carpet backing.		Leukemia
	Ethylene oxide	Used as a sterilant, disinfectant and pesticide. It is also used as a raw ingredient in making resins, films and antifreeze.	Leukemia	Breast
	Formaldehyde	Used primarily in the production of urea, phenol or melamine resins for molded products such as appliances, electric controls, and telephones; in particle-board, plywood and in surface coatings.		Nasal and Nasopharynx
	Mustard Gas	Produced and used primarily in World War I as a chemical warfare agent.	Lung	Laryngeal
	Vinyl Chloride	Vinyl chloride is used in polyvinyl resins for the production of plastic pipes, floor coverings, and in electrical and transportation applications.	Liver & Biliary; Soft tissue sarcoma (angiosarcoma of the liver)	
	Sulfuric Acid	Used widely in industry for the production of isopropanol, ethanol; treatment of metals; and the manufacture of soaps, detergents and batteries.	Laryngeal	Lung
Solvents	Benzene	Used as an intermediate in the production of plastics, resins and some synthetic and nylon fibers. Also used to make some types of rubbers, lubricants, dyes, detergents, drugs and pesticides. Is also found in crude oil, gasoline and cigarette smoke.	Leukemia; NHL	Brain/CNS; Lung; Nasal & nasopharynx; Multiple Myeloma
	Carbon Tetrachloride	Used primarily in various industrial applications. Before being banned, was also used in the production of refrigeration fluid and propellants for aerosol cans, as a pesticide, as a		Leukemia

Category	Carcinogenic Agent	Source/Uses	Strong*	Suspected**
		cleaning fluid and degreasing agent, in fire extinguishers, and in spot removers.		
	Methylene Chloride	Used primarily as a solvent in industrial applications and as a paint strippers. It may also be found in some aerosol and pesticide products and in the production of photographic film.		Brain/CNS; Liver & Biliary
	Styrene	Used in the production of rubber, plastic, insulation, fiberglass, pipes, automobile parts, food containers and carpet backing.		NHL
	Toluene	Used in the production of paints, paint thinners, fingernail polish, lacquers, adhesives and rubber. Also used in some printing and leather tanning processes.		Brain/CNS; Lung; Rectal
	Trichloroethylene (TCE)	Used mainly for degreasing metal parts. Previous used as a dry cleaning agent. TCE may be found in printing inks, varnishes, adhesives, paints and lacquers. Important contaminant in the general environment as a result of emissions & leakage from industrial settings.	Liver & Biliary; Kidney	Cervical; Hodgkin's; Leukemia; NHL; Kidney
	Tetrachloroethylene (PCE)	Used to degrease metal parts and as a solvent in a variety of industrial applications. Since 1930s used by an increasingly large percentage of U.S. dry-cleaning operations.		Bladder; Cervical; Esophageal; NHL; Kidney
	Xylene(s)	Used as a cleaning agent, a thinner for paint and in paint and varnishes. Used in printing rubber and leather industries and found in small amounts in gasoline and airplane fuel.		Brain/CNS; Rectal
Other	Creosotes	Includes coal tar and coal tar pitch formed by high-temperature treatment of wood, coal or from the resin of the creosote bush. Wood creosote was historically used as a disinfectant, laxative and cough treatment. Coal tar products are used in medicine, animal and bird repellents and pesticides. Coal tar creosote is widely used as a wood preservative. Coal tar, coal tar pitch and coal tar	Bladder (coal tars); Lung; Skin	

Category	Carcinogenic Agent	Source/Uses	Strong*	Suspected**
		pitch volatiles are used in roofing, road paving, aluminum smelting and coking.		
	Endocrine Disruptors	A number of chemicals capable of mimicking the body's natural hormones. See: http://www.ourstolenfuture.org/Basics/chemlist.htm	Breast (DES); Cervical (DES)	Breast; Prostate; Testicular
	Hair dyes	Coloring products used on hair. Hair dyes usually fall into 1 of four categories: temporary, semi-permanent, demi and permanent. Chemical agents used in dyes are specific to the color and the degree of permanency.		Bladder; Brain/CNS; Leukemia; Multiple Myeloma; NHL
	Nitrosamines & N-nitroso compounds	A class of chemicals that forms as a result when amines and nitrosating agents chemically react. Are found in the rubber, metal and agricultural industries, and in cosmetics and foods such as fried bacon and cured meats.		Brain/CNS
	Polychlorinated Biphenyls (PCBs)	Used as coolants and lubricants in transformers, capacitors and other electrical equipment. PCBs were banned in the US in 1977.	Liver & Biliary	Breast; NHL

* Strong causal evidence of a causal link is based primarily on a Group 1 designation by the International Agency for Research on Cancer.

** Suspected evidence of a causal link is based on our assessment that results of epidemiologic studies is mixed, yet positive findings from well-designed and conducted studies warrant precautionary action and additional scientific investigation.