INDUSTRIAL CARCINOGENS

A NEED FOR ACTION
Why should you care about industrial carcinogens?

In 1775, Percivall Pott’s observation of scrotal cancer among young chimney sweeps in London marked the beginning of our understanding that industrial agents can contribute to cancer. Today, specific agents and processes in the industrial environment are some of the most well-studied and well-recognized risk factors for human cancer.

Of the 935 agents and exposure circumstances evaluated by the International Agency for Research on Cancer (IARC), over 400 are listed as carcinogenic, probably carcinogenic, or possibly carcinogenic and 40% of these are considered industrial/occupational carcinogens. According to estimates from the National Institute for Occupational Health and Safety (NIOSH), millions of U.S. workers are currently exposed to recognized carcinogens. This is cause for concern. Moreover, millions more workers may be exposed to carcinogens not yet identified because only about 2% of chemicals in U.S. commerce have been tested for carcinogenicity.

Industrial agents that increase cancer risk affect everyone, not just workers. These agents are present in our air, water, food and soil, and in products we encounter in daily life, such as:

- Pressed wood (formaldehyde)
- Paint strippers (methylene chloride)
- Cat litter (crystalline silica)

In addition to exposures through work, pollution and household products, many of us live and play near industrial facilities and hazardous waste sites. In 2006 alone, industries reporting to the Toxics Release Inventory released or disposed of 820 million pounds of known or suspected carcinogens. About 1 in 6 Americans live within 4 miles of a Superfund site.

We are exposed in many different ways to industrial agents that increase cancer risk. As such, if we want to prevent cancers associated with industrial agents, we must look at the entire lifecycles of products and materials, from manufacturing to use to disposal.

The sidebars on the following pages list the strength of the evidence linking specific cancers with exposure to industrial agents in workplaces and the general environment.

**Bladder**
- **Strong**: aromatic amines; arsenic; coal tars; metalworking fluids and mineral oils
- **Suspected**: ionizing radiation; PAHs; tetrachloroethylene

**Brain and other central nervous system**
- **Strong**: ionizing radiation
- **Suspected**: arsenic; benzene; lead; mercury; methylene chloride; non-ionizing radiation (extremely low electro-magnetic frequency, microwaves and radiowaves); N-nitroso compounds; pesticides; toluene; xylene

**Breast**
- **Strong**: Ionizing radiation
- **Suspected**: bisphenol A; dieldrin; dioxin; ethylene oxide; non-ionizing radiation; PAHs; phthalates; PCBs; DDT/DDE; hexachlorobenzene; lindane; heptachlor; triazine herbicides; organic solvents
Flawed numbers, flawed policy
Emphasizing single causes while failing to acknowledge complexity

You have probably heard statements similar to: “Public concern about environmental carcinogens is out of proportion with the true risk.” These remarks are backed-up by highly cited, yet flawed estimates of the percentage of total cancer deaths attributable to established causes of cancer.

In 1981, Sir Richard Doll and Sir Richard Peto estimated the percentage of cancer deaths that would be avoided if certain individual factors were addressed, including occupational, environmental, tobacco smoking, diet, alcohol consumption, viruses, etc. The Harvard Center for Cancer Prevention used this same method of calculating attributable fractions in 1996. Although other researchers have also published such calculations, Doll and Peto and the Harvard Center’s publications are the most widely cited sources. These publications estimated that the majority of cancers could be avoided by improvements in diet and smoking cessation while only a very small percentage of cancer deaths could be prevented by reducing exposure to cancer risks in the environment (2%) or in workplaces (4%–5%). The problem is that the approach used to reach these estimates is inherently flawed and outdated given our current understanding of how cancer develops.

We now know that cancer is not caused from single factors, but rather from a complex, multi-factorial, multi-stage process. Cancer researchers have identified at least 6 essential alterations that unfold over time and overwhelm the natural defenses built into human cells and tissues to produce a tumor. The complex process by which cancer develops can be diagrammed as an integrated circuit, with multiple signaling pathways and feedback loops that can be altered or disrupted by many different risk factors. Professor Luc Montagnier from the Institut Pasteur said in The War on Cancer, “And what my colleagues often don’t understand is that there’s an evidence involving environmental or occupational exposures37,43
Successful cancer prevention will depend on addressing other co-occurring and interactive risk factors, including industrial exposures in our workplaces and general environment along with the broader set of social conditions that influence these exposures.

accumulation of these doses—they all add up. A little dose of radiation here, and exposure to some chemical there, a bit of something in your food, and so on... All of this adds up to create an oxidant field and it’s the totality of this field which does all the damage and may bring about a cancer." As acknowledged later by Sir Richard Doll, the calculation of attributable fractions fails to account for the fact that exposures interact with each other, that the true sum of attributable risks would have to be more than 100%, but that this is impossible to estimate as all avoidable causes are still unknown.

Science has yet to reveal the entire variety of pathways, loops and other mechanisms by which industrial agents, environmental pollutants, diet, viral exposures, genetic inheritance, lifestyle factors, reproductive factors and other cancer risks can contribute to various stages in the initiation, promotion, and progression of an individual’s cancer. Yet, we don’t need to wait for a complete understanding of the mechanisms by which cancer is caused before acting to mitigate harm.

The problem of calculating attributable fractions isn’t just a methodological issue; it’s become a programmatic and policy issue as well. Some cancer control programs have created a causal hierarchy from these calculations and therefore put more resources into addressing lifestyle and dietary risk factors while often ignoring environmental and occupational risk factors. Whereas it is true that smoking and diet are important risk factors for a number of cancers and these risks can be reduced through policy and individual behavior changes, it is also true that successful cancer prevention will depend on addressing other co-occurring and interactive risk factors, including industrial exposures in our workplaces and general environment along with the broader set of social conditions that influence these exposures.

Undoubtedly, researchers will continue to calculate uncertain and flawed estimates of how much cancer is caused by one factor or another and cancer control programs will continue to cite them.

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**Leukemia**
- **Strong:** benzene; ionizing radiation
- **Suspected:** carbon disulfide; carbon tetrachloride; butadiene; DDT; ethylene oxide; non-ionizing radiation (including electro-magnetic frequencies and radio frequencies); methyl bromide; phosphine; trichloroethylene; unspecified pesticides

**Liver and biliary**
- **Strong:** ionizing radiation; trichloroethylene; PCBs; vinyl chloride
- **Suspected:** arsenic; methylene chloride; unspecified organic solvents

**Lung cancer**
- **Strong:** air pollution (indoor and outdoor); arsenic; asbestos; beryllium; cadmium, chromium; chloromethyl ethers; coal tar and pitches; diesel exhaust; ionizing radiation (including radon); nickel; mustard gas; PAHs; silica; soot; wood dust
- **Suspected:** benzene; carbofuran; chlorpyrifos; DDT; dicamba; dieldrin; diazinon; lead; metachlor; pendimethalin

**Mesothelioma**
- **Strong:** asbestos
Although the American Cancer Society has been no exception to the use of these estimates, the organization’s 2008 Cancer Facts and Figures describes the importance of mitigating exposure to environmental and occupational risk factors,

“Although the estimated percentage of cancers related to occupational and environmental carcinogens is small compared to the cancer burden from tobacco smoking (30%) and the combination of nutrition, physical activity, and obesity (35%), the relationship between such agents and cancer is important for several reasons. First, even a small percentage of cancers can represent many deaths: 6% of cancer deaths in the United States each year corresponds to approximately 33,600 deaths. Second, the burden of exposure to occupational and environmental carcinogens is borne disproportionately by lower-income workers and communities, contributing to disparities in the cancer burden across the population. Third, although much is known about the relationship between occupational and environmental exposure and cancer, some important research questions remain. These include the role of exposures to certain classes of chemicals (such as hormonally active agents) during critical periods of human development and the potential for pollutants to interact with each other, as well as with genetic and acquired factors.”

The dose doesn’t always make the poison

Early evidence linking industrial agents to cancer among workers was revealed through studies in which exposure levels were extremely high. These occupational studies established clear linear dose-response trends—the greater the exposure, the greater the cancer risk. (Or, as the adage goes, “The dose makes the poison.”) In response to this evidence, the Occupational Health & Safety Administration (OSHA) and NIOSH created regulatory policies and programs that reduced—but did not eliminate—workers’ exposure to industrial carcinogens.

Now we are learning that low levels of exposure may still correspond to an increased cancer risk. Some studies of workers confirm that exposure to industrial agents increases cancer risk even when the exposure level is at or below current regulatory limits. Agents for which this is true include asbestos, benzene, and ionizing radiation. For example, research suggests that a worker exposed to benzene at an average of 1 ppm (the current OSHA regulatory level) for 40 years would nearly double his or her risk of dying from leukemia. Moreover, for some agents, the dose doesn’t always make the poison. For arsenic, multiple studies have shown that the rise in cancer risk is sharper at lower rather than higher exposure.
levels.\textsuperscript{19–21} Evidence from both mice and rat models demonstrate that animals exposed to low doses of the chemical bisphenol-A in utero develop mammary gland alterations that increase susceptibility to breast cancer later in life.\textsuperscript{22,23} A 2006 study showed that rats given one low dose in utero of bisphenol-A exhibited altered gene behavior that leads to prostate cancer in adults.\textsuperscript{24}

**Timing is critical**

The timing of exposure to industrial agents that increase cancer risk may be as important as the dose. Research has repeatedly documented examples of differential cancer risk with age at exposure:

- Studies of nuclear workers reveal that cancer risk is greater among older workers than younger workers when exposed to the same dose of radiation.\textsuperscript{25–27}
- Evidence from atomic-bomb survivors and medical irradiation studies clearly indicates an increased risk of leukemia among children exposed while in utero\textsuperscript{28–30} or post-natally.\textsuperscript{28}
- A 1999 study found that men exposed to radiation prior to impregnating their partners fathered children with an increased risk of leukemia.\textsuperscript{31}
- Evidence also indicates an increased risk of childhood leukemia from parental exposure to benzene\textsuperscript{32} and possibly to other solvents.
- A new study demonstrates that girls exposed to elevated levels of DDT before puberty—when mammary cells are more susceptible to the carcinogenic effects of hormones, chemicals and radiation—are five times more likely to develop breast cancer when they reach middle age.\textsuperscript{33}

Securing funding for large prospective studies such as the National Children’s Study will undoubtedly produce new knowledge about how the timing of exposures affects cancer risk later in life.
Failing to act on early warnings

The case of benzene

The lag between evidence of a carcinogenic effect and action taken to prevent exposure and protect workers and the public is often decades. The history of benzene and how we failed to act on early warnings of harm illustrates key reasons for delays that continue to hinder our ability to minimize exposure to industrial agents that influence or contribute to cancer.

Although reports of benzene-induced aplastic anemia were first described decades earlier, the first case report of leukemia was published in 1928. By 1939, investigators recommended substituting benzene with safer solvents based on additional case reports of benzene poisonings and associated cases of leukemia, some of which occurred at much lower exposure levels than those previously reported. In 1946, the American Conference of Governmental Industrial Hygienists (ACGIH) recommended a workplace exposure limit of 100 ppm, which was subsequently reduced to 50 ppm in 1947, 35 ppm in 1948, and 25 ppm in 1957.

Yet in spite of exposure recommendations, poisonings continued and by the mid 1970s evidence of an epidemic of leukemia associated with benzene began to emerge. In the early 1970s the first epidemiologic study documented significant excesses of mostly chronic forms of leukemia (chronic lymphocytic leukemia (CLL) and chronic myelogenous leukemia (CML)) among workers using solvents contaminated with benzene. By 1977, the results of the first cohort of workers exposed specifically to benzene (rather than solvents contaminated with benzene) were published. These workers, who were involved in manufacturing Pliofilm, a rubberized food wrap, demonstrated a 5 to 10 fold elevated risk of leukemia based on exposure to benzene considered within the recommended limits.

Based on the Pliofilm study, the Occupational Health and Safety Administration (OSHA) issued an emergency temporary standard to reduce the occupational benzene exposure limit to 1 ppm over a time-weighted 8-hour average. Yet the emergency temporary standard was stayed in response to a legal challenge brought by the American Petroleum Institute, who argued that there was no increased risk of leukemia at exposures below 10 ppm. OSHA tried again, by proposing a permanent standard, and in 1978 issued a final standard that included a 1 ppm exposure limit. This final standard was also challenged by the American Petroleum Institute and in July 1980, the U.S. Supreme Court issued a decision that has continued to impede OSHA’s ability to control toxic exposures in workplaces. This court decision mandated that OSHA must first establish that “significant risk” is present and can be limited by the proposed rule before promulgating a permanent health standard. The resulting “risk assessment” process created years of additional delay and it wasn’t until 11 years after OSHA’s first attempt at issuing a 1 ppm benzene standard that the 1 ppm limit became final. Ironically, the 1 ppm limit was not based on elimination of “significant risk”, but rather economic feasibility.

One analysis estimates that continued exposure to benzene during those 11 years of regulatory delays caused nearly 300 cancer deaths. Imagine the lives saved if we heeded the 1939 recommendations to substitute benzene with a safer chemical.

Beginning in 1996, new studies were published that showed that the spectrum of lymphohematopoietic cancers are elevated among workers exposed to benzene below the 1 ppm standard. So, the debate regarding a permissible exposure level for benzene continues with mounting evidence that no safe threshold exists for this carcinogen.

Effects last generations

Studies of both animals and humans are showing that the effects of exposure to industrial agents that increase cancer risk may last for generations. One such study found that rats exposed to high levels of the fungicide vinclozolin, a known endocrine disrupting agent, while in utero developed malignant tumors at a higher frequency than non-exposed rats; the pattern held true for their offspring and their offspring’s offspring.\(^{34}\) In fact, the subsequent generations with no direct exposure to the fungicide had a higher frequency of tumor development (both malignant and nonmalignant) and a range of other diseases than those exposed while in utero. These effects seem to be transmitted across generations through epigenetic changes, such as altered methylation patterns that control whether a gene can be turned on.\(^{34}\) Human evidence reveals that women exposed to diethylstilbestrol (DES) while in utero show elevated rates of clear cell adenocarcinoma of the vagina and a range of reproductive disorders.\(^{35}\) Elevations of a number of uncommon disorders are also being observed in the granddaughters and grandsons of DES-exposed women.\(^{35}\) Rodent studies corroborate this evidence and demonstrate that the effects of maternal DES exposure are transmitted via both genetic and epigenetic mechanisms that control whether a gene can be turned on.\(^{36}\) These studies suggest that we need to seriously expand our methods to examine the range of mechanisms by which industrial agents can contribute to cancer.

The more we learn about cancer causation, the more it becomes evident that cancer prevention programs need to include not only a focus on fewer and lower exposures, but also safer exposures. We can make exposures to industrial agents less hazardous by promoting green chemistry, alternatives assessment and phase-out or “sunsetting” of agents that contribute to cancer.

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**Prostate**  
- **Suspected:** aromatic amines; arsenic; cadmium; dioxin; bisphenol A; metal working fluids; PAHs; chlorinated, organophosphorous and unspecified pesticides

**Rectal**  
- **Strong:** Metal working fluids and mineral oils  
- **Suspected:** chlorination by-products; toluene; xylene

**Soft tissue sarcoma**  
- **Strong:** dioxin; ionizing radiation; vinyl chloride

**Skin**  
- **Strong:** arsenic; coal tars; creosotes; ionizing radiation; metalworking fluids and mineral oils; PAHs

**Stomach**  
- **Strong:** asbestos; metal working fluids and mineral oils  
- **Suspected:** coal dust; ionizing radiation; lead; nickel; unspecified solvents; unspecified pesticides

**Testicular**  
- **Suspected:** chlorinated insecticides

**Thyroid**  
- **Strong:** ionizing radiation

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Exposures in the real world

Mixtures, not single agents

When an industrial agent is tested for toxicity, it is usually studied by itself; it is not tested for how it interacts with other agents. But most of us are exposed to multiple industrial agents at low concentrations in the food we eat, the air we breathe and the materials we encounter. Although more studies are beginning to examine how chemicals and genes interact, practical limits in epidemiology often mean that researchers can examine the interaction of only two or three agents at a time. Yet the biological effects of exposure to 20 different industrial agents are probably very different from the effects of two or three.

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Dozens of occupations (e.g. fire-fighters, painters, rubber manufacturing, hair-dressers, barbers, construction workers) are surrogates for the study of chemical mixtures and evidence from multiple studies of these occupations show increased cancer risk. Similarly, air pollutants and water pollutants contain a mixture of known carcinogens and show evidence of increased cancer risk. Even cigarette smoke is a mixture of several carcinogens and other toxic materials.

New methods are needed to understand the cancer risks associated with exposure to chemical mixtures. Although studies are beginning to reveal the interaction of chemical mixtures on a molecular level and new statistical methods are under development, it will take many years before experimental science fully reveals the effect of mixtures. Fortunately, we can still take action to reduce the cancer risk that mixtures may pose.

Acting on what we know

A crucial strategy in the prevention of cancer is to stop putting industrial agents that increase cancer risk in our workplaces and environments in the first place. Yet of the tens of thousands of industrial chemicals in use in the United States today, the National Toxicology Program has published long-term carcinogenicity studies of only 556 chemicals.
We need to act through policy and market-based approaches to identify safer technologies and chemical alternatives to industrial agents that increase cancer risk. We also need to adopt stronger regulations to protect workers and communities from these agents and to enhance our state and federal agencies’ enforcement capacity.

Although the Toxic Substances Control Act (TSCA) was established to regulate toxic chemicals before and after they enter commerce, evidence to date suggests we have too often failed to uncover information and then use what we’ve learned to protect public and worker health. In order to prevent future cases of cancer, there needs to be greater emphasis on the pre-market testing of new chemicals and post-market testing of those chemicals in use.

A second priority strategy for preventing cancer is to eliminate or drastically reduce exposure to known and suspected carcinogenic agents. Dr. Harold Freeman, Director of the NCI Center to Reduce Cancer Health Disparities said, “To win the war against cancer, we must apply what we know at any given time to all people.” But recent studies have shown that people of color, recent immigrants and the poor are far more likely to work with industrial agents that increase cancer risk, have less access to institutions that protect them, and suffer disproportionately from exposure to environmental contaminants linked with cancer where they live. If we want to reduce the overall cancer burden, it is essential that these disparities be eliminated.

Cancer prevention programs too often focus on what individuals can do for themselves—exercise, eat healthy foods, and stop smoking. But individual actions are not enough to keep industrial agents that increase cancer risk out of the air and water or lower the legal exposure limits for industrial agents. We need to act through policy and market-based approaches to identify safer technologies and chemical alternatives to industrial agents that increase cancer risk. We also need to adopt stronger regulations to protect workers and communities from these agents and to enhance our state and federal agencies’ enforcement capacity.

We also need to act on early warnings. Based on IARC’s evaluations, you might believe that certain cancers, such as breast cancer, prostate cancer, brain cancer and cancers of the digestive system, are unrelated to exposures to industrial agents. Yet research has produced abundant evidence that these cancers are associated with exposure to a range of industrial agents. Some of this evidence comes from animal studies.
A short prescription for cancer prevention

**INDUSTRIAL CARCINOGENS**

We need a comprehensive U.S. cancer prevention agenda that promotes health, prevents cancer and protects the most vulnerable members of society. To implement such an agenda, we must:

- **Avoid** using attributable fractions as the basis of determining priorities for cancer prevention programs and policies.

- **Eliminate** exposure disparities related to race, income and immigration status.

- **Support** cancer research that captures the complex web of cancer causation including multiple exposures, low dose effects, and how early life exposures and other critical windows of vulnerability can increase cancer risk.

- **Acknowledge** that scientific certainty is seldom possible and that from our duty to inquire flows an obligation to take preventative action when evidence of harm is sufficient.

- **Create** a new system to manage chemicals that avoids introducing industrial agents that increase cancer risk into our workplaces and environment, expands toxicity testing of new and existing industrial agents, and acts on early warnings of harm.

- **Act** through policy and market-based effort that identify safer alternatives to industrial agents that increase cancer risk and other exposure mitigation techniques.
REFERENCES