A Literature Review and Annotated Bibliography on Bladder Cancer and Environmental and Occupational Risk Factors

Context for this Literature Review and Annotated Bibliography

The American Cancer Society estimates that in 2018, 62,380 men and 18,810 women will be diagnosed with bladder cancer in the US. Overall incidence rates of bladder cancer have declined ~6% since 1974 when the National Cancer Institute's Surveillance and Epidemiology End Results Program began national cancer surveillance. However, incidence rates are rising for some populations, particularly African American men—up 18% since 1974.

We need to do more to both cure and prevent cancer. The process by which bladder cancer develops is complex. There are multiple contributing causes, some of which can be controlled and others that cannot (e.g., genetic factors). No one factor alone is typically enough to cause the disease. This is why despite tobacco smoking being a significant risk factor for bladder cancer, not all people who smoke get the disease. As a result, there are many opportunities for prevention: take away known risk factors for the disease, and the risk of developing bladder cancer goes down.

In addition to lifestyle risk factors for bladder cancer, such as smoking tobacco, an additional pathway for bladder cancer prevention is the control of occupational and environmental risk factors that are beyond the individual's control. Yet what is the state of evidence regarding bladder cancer risk associated with the range of chemical pollutants in our environment and workplaces? This literature review and annotated bibliography identifies key authoritative reviews and studies to help answer this question and identifies key researchers who are studying the science of environmental and occupational links with bladder cancer and could help bladder cancer advocates identify opportunities for prevention.

Structure and Literature Review Method

We considered four broad categories of environmental and occupational risk factors:
- Water Pollution
- Air Pollution
- Workplace Exposures
- Consumer Products

These categories of risk factors overlap. For example, workers may be exposed to air pollutants in occupational settings including chemical fumes emitted from industrial processes or exhausts from vehicles and heavy equipment used on the job. Pollutants emitted to air eventually are deposited onto land and can ultimately contaminate drinking water sources. Nevertheless, these categories are useful for considering different prevention opportunities related to the air we breathe, the water we drink and environments where we live, work and play.

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Two tiers of publication sources were reviewed. The first tier included international and national authoritative sources: (1) the World Health Organization's International Agency for Research on Cancer's (IARC) Monographs and (2) the U.S. National Toxicology Program's (NTP) Report on Carcinogens. Both the IARC monographs and the NTP Report on Carcinogens are assessments of the state of the evidence relevant to carcinogenicity by esteemed committees of experts. The resulting classifications are based on a weight of the evidence that considers: (a) studies in human populations (b) toxicology studies and (c) mechanistic studies. NTP's classifications were included primarily for the consumer products risk factor category when IARC's reviews lacked information on specific chemicals. The second tier of publications reviewed included peer reviewed meta-analysis and systemic reviews as well as individual research studies published in the last 10 years. The research literature was queried using PubMed. Each section of the document begins with a synthesis of the literature provided. For each report/studied identified, a brief synopsis/abstract is included along with the full citation.

For each category of risk factors, a review of specific prevention-oriented strategies is provided. This review is based on technologies, policies and individual actions that have the potential to limit exposure to specific environmental and occupational chemicals associated with bladder cancer.

In addition to environmental and occupational risk factors, there are several considerations that affect risks. Genetic susceptibility is one such consideration. Literature providing examples of these important considerations are provided under Special Topics.

Water Pollution

Risk Factors

There are three waterborne exposures that affect large numbers of people and have been studied most extensively with regard to bladder cancer: inorganic arsenic, disinfection byproducts, and nitrate.

Inorganic Arsenic

IARC has determined that exposure to arsenic in drinking water is a known cause of human bladder cancer (IARC 2012). Arsenic occurs naturally in groundwater in some regions and may also result from human activities, such as use of arsenical pesticides. Studies that informed IARC's classification were primarily from epidemiological studies in parts of Southeast Asia and South America with high levels of arsenic in their drinking water (Cantor et al. 2017). In most of these studies, the levels of arsenic in the water were many times higher than those typically seen in the United States, even in areas where arsenic levels are above normal.

There remains scientific uncertainty about cancer risk associated with lower levels of exposure to arsenic in drinking water. Residential studies examining low to moderate arsenic level exposures and bladder cancer have primarily been retrospective – collecting or estimating past exposures. Because bladder cancer has such as long latency period (~40 years), it is necessary to assess historical long-term exposure patterns (Baris et al 2016). However, this is difficult because individuals change water sources throughout their lives, and/or use water sources with different arsenic concentrations throughout the day (i.e., at home, work, and school) (Cantor et al. 2017). Nevertheless, emerging evidence—including several studies conducted in New England—suggest that low-to-moderate levels of arsenic exposure may increase bladder cancer risk (Bates et al. 1995; Karagas et al. 2004; Baris et al. 2016). The largest case control study examining the association of low to moderate levels exposure to arsenic with bladder cancer risk found that risk increased with increasing water intake. This exposure was primarily among individuals that were private well users, and risk was higher among those using shallow wells. Among people using water from wells dug before 1960—when arsenical pesticides were used—those with the highest water intake levels had double the risk of bladder cancer compared to those with less intake (Baris et al. 2016). Recent ecological studies in Nova Scotia suggest increased bladder cancer risk associated with exposure to current regulatory drinking water limits for arsenic (Saint-Jacques et al. 2018).

One recent study lends mechanistic support for arsenic as a bladder carcinogen demonstrating its impact on important tumor-suppressor genes (Koutros 2018).

Disinfection Byproducts

Disinfecting water with chlorine reduces illness and death associated with waterborne microbes. However, an unintended result of the disinfection of public drinking water supplies is the formation of disinfection byproducts. When chlorine or other disinfectants react with organic matter in the water, disinfection byproducts are formed. The array of specific disinfection byproducts present in treated water depends on both treatment practices of public drinking water authorities and the characteristics of the source water. More than 700 disinfection byproducts have been identified, yet most studies

focus on bladder cancer risk associated with trihalomethanes (e.g., chloroform, dichlorobromomethane, bromoform) (Cantor et al. 2017).

IARC evaluated the carcinogenicity of specific disinfection byproducts. Chloroform (a type of trihalomethane) is considered a possible carcinogen based on sufficient evidence in experimental studies. Chloral and chloral hydrate are classified as probable human carcinogens, whereas dichloroacetic acid, trichloroacetic acid, dibromoacetic acid, bromochloroacetic acid, and MX were listed by IARC as possible human carcinogens (IARC, 2004, 2013, 2014).

Epidemiological studies have consistently observed an association between consumption of chlorinated drinking water and increased risk of bladder cancer (Cantor et al. 2017). However, the disinfection byproducts that are responsible for this risk remain unclear. As noted above, the majority of epidemiologic studies have focused on trihalomethanes. Early ecological studies finding increased risk associated with bladder cancer mortality were followed up by a series of cohort and case control studies (Cantor et al. 2017). These studies examined longer-term exposure to disinfection byproducts primarily via ingestion, which have also been subsequently evaluated in several reviews and meta-analyses. In general, risks are consistently elevated, ranging from 50% to 120%, depending on the exposure metric used (Costet et al. 2011; Villanueva et al. 2003). Multiple studies describe sex differences, documenting stronger effects among men. However, none of the individual studies had adequate power to detect associations among women (Cantor et al. 2017).

More recent studies have examined risk based on more comprehensive exposure to disinfection byproducts expanding the assessment beyond just ingestion to include dermal and inhalation exposure from showering and bathing as well as swimming pool use. One study from Spain found a 2-fold elevation in bladder cancer risk among those with the highest level of exposure to trihalomethanes considering shower duration and trihalomethane concentrations in comparison to the lowest level (Villanueva et al. 2007). Bladder cancer risk was also elevated among those who reported "ever use" of swimming pools, although risk did not increase with increasing total lifetime hours of use. In a population-based case control study in New England (Beane Freeman et al. 2017) which assessed exposure using historical information from public utilities along with residential histories, bladder cancer was elevated among people highly exposed to total trihalomethanes and brominated trihalomethanes. Risk was also elevated based on cumulative intake of chlorinated and brominated trihalomethanes beginning at age 10. There was no evidence of associations between bladder cancer risk and swimming pool use. Disinfection byproducts in swimming pools are affected by the same characteristics as drinking water. As shown above, some studies have described elevated bladder cancer risk associated with swimming pool use, but the evidence is not consistent and experts suggest this is an area requiring further study (Cantor et al. 2017).

Nitrates

Nitrate is a common drinking water contaminant arising primarily from agricultural sources, such as nitrogen fertilizers and manure and human waste. However, few studies of bladder risk associated with drinking water contaminated with nitrates have been conducted with equivocal results – several observing no association, while two studies from the Iowa Women's Health Study cohort observing elevated risk (Cantor et al. 2017). Although IARC found inadequate evidence to classify the carcinogenicity of nitrate in drinking water, it did state under conditions resulting in endogenous

nitrosation, ingesting nitrate is probably carcinogenic to humans (IARC 2010). When nitrate is ingested, N-nitroso compounds are formed as a result of metabolic transformation under certain conditions. As a consequence additional research is necessary to determine if drinking water contaminated with nitrates is a risk factor for bladder cancer.

Table 1. Water Pollutants – Evidence Summary for Bladder Cancer Risk		
Substance	**Exposure Sources**	**Strength of the Evidence**
Inorganic arsenic	Naturally occurring, contamination from the use of arsenical pesticides, other industrial contamination	Strong[1]
Disinfection byproducts	Public water supplies treated with chlorine, bromine, ozone or chloramine	Suggestive[2]
[1] Determined by the International Agency for Research on Cancer's review of the evidence [monographs included in bibliography below). Characterized in Cogliano et al. Preventable exposures associated with human cancers. J Natl Cancer Inst. 2011; 103(24):1827-39. [2]Clapp RC, Jacobs MM, Loechler EL. Environmental and occupational causes of cancer: new evidence 2005-2007. Rev Environ Health. 2008;23(1):1-37.		

Prevention Opportunities—Water Pollution

The most effective and practical way to reduce bladder cancer risks from water pollutants is to reduce exposure.

Arsenic

In the U.S., the EPA has promulgated regulatory limits for arsenic concentrations in drinking water – 10 parts per billion. EPA considers this level "acceptable," but its stated goal is for water to contain no arsenic at all. However, these regulatory limits apply only to public water sources, not household wells. Wells are usually only tested when they are newly-dug or a house is sold. However, levels of arsenic and other contaminants in groundwater can change over time.

Various methods are available to large municipal water suppliers to reduce arsenic concentrations including the development of new water sources, coagulation with iron salts and filtration as well as treatments including reverse osmosis, activated alumina, microfiltration, and ion exchange (US EPA, 2000). Counter-top filtration systems (e.g., Brita) do not filter inorganic arsenic. NSF International has certified point-of-use reverse osmosis and distillation devices for the reduction of arsenic in drinking water in residential well water. The determination of the best treatment technology should be based on testing, the consideration of other contaminants that may be present in the water, and consultation with treatment experts. Following installation of a treatment device, water quality should again be tested to verify the proper functioning of the device. After that, water should be tested at least annually to confirm treatment effectiveness. A maintenance agreement for such devices is highly recommended (Dartmouth Toxic Metals Superfund Research Program, 2018).

Biomonitoring and early bladder cancer detection have been proposed in areas where arsenic exposures remain a concern (Cantor et al. 2017). However the lack of a non-invasive bladder cancer screening option remains a significant barrier.

Disinfection byproducts

Three major classes of disinfection byproducts are regulated under the federal Clean Water Act through the Stage 1 and Stage 2 Disinfectants and Disinfection Byproducts Rule. Bladder cancer risk was among the key considerations for more stringent regulations, which went into effect in 2012. The updated rule sets maximum contaminant levels for four trihalomethanes, five haloacetic acids, chlorite and bromate (US EPA 2018). However multiple additional types of disinfection byproducts are not addressed, including halonitromethanes, iodo-acids and other halo-acids, chlorinated hydroxy furanones (e.g., MX), haloamides and haloacetonitriles, nitrosamines, and aldehydes (Richardson et al. 2007). Of concern is that many of these compounds have been shown to be mutagenic and/or genotoxic (Cantor et al. 2017). Also of concern are public water utilities using different methods of disinfection to reduce regulated disinfection byproducts (e.g., using chloramine rather than chlorine) that result in the unintended consequences producing other unregulated disinfection byproduct compounds. However, there are available methods to reduce the formation of these compounds. One approach is the removal of naturally occurring matter from the water prior to adding disinfectant chemicals (Zappa and Zavora, 2011).

Preventing exposure to disinfection byproducts requires technology interventions. It requires public utilities to routinely test for the array of both regulated and non-regulated disinfection byproducts and to adjust treatment strategies accordingly. Promoting regulation of compounds that IARC has evaluated and setting maximum contaminant levels will force utilities to reduce these contaminants and protect people who use public water supplies.

Table 2. Water Pollution Exposure Reduction Strategies (not comprehensive)	
Advocacy: *Policy and Technology Strategies*	• Advocate for EPA to set maximum contaminant levels for additional disinfection byproducts not currently covered under the Disinfectants and Disinfection Byproducts Rules. • Contact your local public water utility to request information about disinfection byproducts levels in your public drinking water. Ask whether they are utilizing best available technologies and practices to minimize the formation of disinfection byproducts. Emphasis should be placed on the use of technologies and processes that reduce or remove contaminants and precursor compounds from water rather than adding more chemicals to our drinking water.
Personal Change: *Individual-level Action Strategies*	• Disinfection byproducts, arsenic and other toxic water contaminants can be removed using residential water treatment/filtration devices. Contact a professional to determine which device is most effective. After installation, follow all maintenance and follow-up testing recommendations to ensure performance.

Air Pollution

Risk Factors

Air pollution is a complex mixture of natural and man-made substances in the air we breathe. Major sources of outdoor air pollution include industrial facilities, motor vehicles, household combustion devices such as wood fireplaces/stoves, and forest fires among others. Health studies investigating bladder cancer risk posed by air pollution have examined risk associated with regional air pollution, specific sources (such as motor vehicles or specific industrial facilities), and risk of particular substances in the air pollution mixture, such as fine particles (called $PM_{2.5}$), polyaromatic hydrocarbons and airborne metals.

Outdoor air pollution and diesel exhaust

IARC considers both outdoor air pollution and diesel exhaust as "known" human carcinogens that have a "positive association" with bladder cancer (IARC 2013, 2014). The determination related to bladder cancer was based on evidence demonstrating increased risk among workers exposed to vehicular sources of air pollution, such as truck drivers.

More recent research studies find conflicting evidence about the relationship between bladder cancer and diesel exhaust in part because the composition of diesel fuel is changing, as is the composition of the emissions. It may be that additional research suggests lower risk associated with newer diesel fuels (Habert and Garnier 2015). However, recent studies continue to support an increased risk of bladder cancer associated with diesel exhaust exposure including one study finding an increased risk of bladder recurrence among those that work in occupations that expose them to diesel exhaust (Wilcox et al. 2016).

To date, there have been only a few studies of bladder cancer risk and exposure to residential air pollution – i.e., exposure where people live. A pooled analysis of 15 European cohorts found no evidence of increased bladder cancer risk associated with a range of air pollution metrics (e.g., $PM_{2.5}$ absorbance/soot, traffic density at home address, etc.) (Pedersen et al. 2016). However, a number of studies have identified elevations (some not statistically significant) in bladder cancer risk associated with regional or residential air pollution (García-Pérez et al. 2013; Coli et al. 2012; Ho et al. 2010; Tsai et al. 2009; Liu et al. 2009; Latifovic et al. 2015; Castaño-Vinyals et al. 2008). These studies use primarily ecologic study designs or regional exposure metrics, which are more limited in their ability to rule out factors that impact the validity of the study (e.g., exposure misclassification). Although these studies suggest increased risk of bladder cancer associated with residential exposure to outdoor air pollution from both industrial and vehicular sources, additional research with more specific individual measures of exposure and better control of other risk factors such as tobacco smoking are needed to confirm the already-published findings regarding elevated risk observed in occupational settings.

Polycyclic Aromatic Hydrocarbons (PAHs)

Specific types of air pollutants have also been the focus research on bladder cancer risk, including polycyclic aromatic hydrocarbons (PAHs). PAHs are formed by the incomplete combustion of organic material. The major sources of air pollution – industrial facilities, residential heating sources (i.e., oil or wood heat), forest/bush fires and mobile sources – all release PAHs. Although there are dozens of individual PAHs, they are most often found as a mixture. Scientific research and environmental

regulations focus on both the mixture as well as a small minority of specific PAHs. IARC has classified several individual PAHs as known human carcinogens (IARC 2010). In specific occupational settings, IARC has found strong evidence for an increased risk of bladder among workers with high exposure to PAHs, including those exposed from coal tars and pitches as well aluminum production (IARC 2010). There is an absence of studies reporting on bladder cancer risk from residential exposure to PAHs in air pollution.

Table 3. Air Pollution – Evidence Summary for Bladder Cancer Risk		
Agents	**Exposure Sources**	**Strength of the Evidence**[1]
Air Pollution Mixture	Varied sources	Strong [characterized as "positive association" in occupational studies] by IARC
Diesel exhaust	Automobile, train, ship, construction equipment	Strong [characterized as "positive association"] in occupational studies by IARC
Polycyclic aromatic hydrocarbons (PAHs)	Products of incomplete combustion and released by industrial facilities, residential heating sources, forest/bush fires, vehicle sources	Strong for workplace settings with high exposures – coal tars/pitches and aluminum production

[1] Determined by the International Agency for Research on Cancer's review of the evidence (specific monographs included in bibliography below). Characterized in Cogliano et al. Preventable exposures associated with human cancers. J Natl Cancer Inst. 2011; 103(24):1827-39.

Prevention Opportunities

Much of the literature on strategies for intervening on air pollution is focused on reducing risk of health outcomes other than bladder cancer, in particular cardiovascular and respiratory diseases.

Policy changes and technology advances are needed to improve air quality. Individuals can also take steps to reduce their exposure to air pollution, though the effectiveness for reducing risk can be difficult for scientific studies to evaluate when health outcomes of concern are relatively infrequent. Also, personal actions to reduce exposure to air pollution are best viewed in the context of total risk; some actions to limit air pollution may actually increase related risk factors. For example, curtailing outside exercise to avoid air pollution might reduce overall exercise (Lambach et al. 2015).

Advocacy needs: Policy and Technology Strategies

Technology change and public policy are effective strategies for limiting human exposure to air pollutants, based on well-established principles of environmental protection and public health. First, sources of air pollution should be controlled at their point of origin to the greatest extent possible in order to limit emissions before they enter the ambient environment. Continued advocacy for enforcement of the Clean Air Act at the state and national levels is needed to ensure that polluting facilities are in compliance with the law and that evolving science is reflected in regulatory decisions.

Advocacy could take the form of: (a) making sure that regulatory standards ensure health protection; (b) updating and enforcing permits issued to companies to ensure the use of "best available control technologies"—including substantial and escalating fines for permit violations, and (c) advocating for continued research and adoption of alternative cleaner fuels and combustion technologies. Second, where source control measures are insufficient, strategies should focus on reducing outdoor pollutant exposure inside buildings. These include specifications in zoning and transportation policies that include provisions for residential/school/workplace setback distances from busy roads as well as the use and placement of filtered building ventilation technology, for example (Brauer et al. 2012).

Personal Change: Individual-level Action Strategies

Some evidence supports the effectiveness of individual actions to reduce exposure and health risks from air pollution. On high air pollution days, staying indoors can limit exposure, as can limiting physical exertion outdoors and near air pollution sources, including near freeways and busy roads where pollutant loads are higher (Lambach et al. 2015). Indoor air filters can reduce the infiltration of outdoor air into indoor environments (Brauer et al. 2012).

Table 4. Air Pollution Exposure Reduction Strategies (not comprehensive)	

Advocacy: *Policy and Technology Strategies*	**Federal (with state enforcement)**
	● Enforce the Clean Air Act
	   ○ Require health-protective permits for polluting industries and substantial and escalating fines for permit violations
	   ○ Ensure that emissions controls for point sources are "best available control technology"
	   ○ Pursue continual improvement in vehicle emission controls and fueling technologies
	State/Municipal
	● Enact or enforce "no-idling" policies for diesel buses, trucks, trains, boats, and heavy equipment vehicle operators
	● Convert municipal bus fleets to cleaner fuels
	● Require building set-backs in zoning/transportation policies – make sure residences, schools, hospitals, day care facilities are at least 500 ft from busy roads
	● Require building code changes to ensure that ventilation intakes are not positioned near local sources of air pollution

Personal Change: *Individual-level Action Strategies*	● Stay indoors during high pollution days ● Reduce outdoor air infiltration to indoors using filtered ventilation ● Clean indoor air with air filtration devices ● Limit physical exertion outdoors near air pollution sources and busy roads ● Use high efficiency technologies and clean fuels for heat; avoid wood burning

Workplace Exposures

Risk Factors

The association between exposure to selected chemical carcinogens, occupations or industries and bladder cancer is well established. Occupational epidemiologic investigations and authoritative agencies such as IARC have identified a number of known and suspected bladder cancer carcinogens. The literature has also identified specific occupations in which bladder cancer is elevated, yet the primary substance of concern has not been clearly established. These specific substances and occupations are reviewed below and outlined in Table 5.

Aromatic Amines

The most notable occupational bladder carcinogens are a class of chemicals called aromatic amines. These chemicals were first suspected of causing bladder cancer over 100 years ago. Exposure to aromatic amines occurs in various industrial and agricultural occupations, including use as antioxidants in the production of rubber and in cutting oils, as intermediates in azo dye manufacturing and as pesticides. The best-known associations between aromatic amines and occupational bladder cancer include jobs in the manufacturing of auramine and magenta dyes, as well as exposure to the chemicals 1- and 2-naphthylamine, benzidine, 4-aminobiphenyl, chlornaphazine (a derivative of 2-naphthylamine). IARC has classified these aromatic amines as known human carcinogens with sufficient evidence related to bladder cancer (IARC 2010b; Vineis and Pirastu 1997). Other aromatic amines for which elevated risks of bladder cancer are suspected include *ortho*-toluidine and aniline (Vineis and Pirastu 1997; Cogliano et al. 2011). Recently, two aromatic amine herbicides used for agricultural and residential weed control have been linked to increased bladder cancer risk in a large cohort of pesticide applicators (Koutros et al. 2016).

The potency of aromatic amines as bladder carcinogens is revealed in a number of studies. For example, in 1954, one study of British rubber workers exposed to 2-naphthylamine reported over a 200-fold increase in bladder cancer risk (Letašiová al. 2012; Case and Hooker 1954). In another, all 15 workers exposed to 2-naphthylamine in the distillation of the chemical in a chemical production facility developed bladder cancer (Vineis and Pirastu 1997).

Mineral Oils/Metal Working Fluids

Mineral oils are chemical mixtures prepared from crude petroleum oil. They often contain a variety of additives and become contaminated with other agents during use. Known or suspected carcinogens that may be present in mineral oils include PAHs, nitrosamines, chlorinated parparaffins, N-phenyl-2-naphthylamine, among others. IARC has classified untreated or mildly treated mineral oils as an established human carcinogen (IARC 2012). This classification was not based on evidence related to bladder cancer, but for skin cancer. However, a number of case control studies have noted an association between bladder cancer and the job of "machinist," and studies of workers using metalworking fluids and mineral oils have provided strong evidence for an association with bladder cancer. IARC's 2012 review recognized this evidence stating, "there has been sporadic and inconsistent support for an association of with bladder cancer" (IARC 2012). Subsequent to IARC's evaluation, the UK Health and Safety Executive (the primary occupational health and safety government authority in the UK) reviewed more recent evidence, including data from meta-analyses and recent research studies and

drew this conclusion: "Overall, these studies indicate clear evidence that there is an increased risk of bladder cancer arising from occupational exposure to mineral oils" (UK Health and Safety Executive 2015). Additional research studies continue to support the UK Health and Safety Executive's review, in particular for straight oils – a type of metal working fluid comprised mostly of mineral (petroleum) or vegetable oils (Friesen et al. 2009; Colt et al. 2011; Colt et al. 2014; Colin et al. 2018).

Polycyclic Aromatic Hydrocarbons (PAHs)

PAHs are formed by the incomplete combustion of carbon-containing fuels such as wood, coal and diesel, and are produced in a variety of workplaces including coal gasification, coke production, iron/steel foundries, coal-tar distillation, chimney sweeping, coal tar and pitches, use of mineral oils and metal working fluids, and creosotes among others. Most of these occupational settings and circumstances have been classified by IARC as known human carcinogens (Siemiatycki et al. 2004; Cogliano et al. 2011). Specific occupations in which PAHs have been associated with excess bladder cancer risk include painters, machinists, aluminum processing, other metal workers, textile workers, leather workers, including shoe makers, printers, hairdressers and transport workers (Siemiatycki et al. 2004).

Perchloroethylene

Perchloroethylene (also known as tetrachloroethylene or "perc") is a chlorinated solvent. Between the 1950s and 1980s, perchloroethylene was the solvent of choice in the dry cleaning industry, with lesser amounts being used for metal degreasing and in the production of chlorofluorocarbons. Today, perchloroethylene is still used extensively in dry cleaning and in other metal degreasing products, such as brake cleaners.

In 2012, IARC classified perchloroethylene as a probable carcinogen based on limited evidence of an increased bladder cancer risk in people working in the dry cleaning industry (IARC, 2014b). Since IARC's evaluation, two meta-analyses have been conducted, one of research studies of dry cleaner workers and one of studies which evaluated occupational exposure to perchloroethylene (Vlaanderen et al. 2014). There was a statistically significant 50% elevation in bladder cancer among dry cleaning workers and an 8% elevation in risk (not statistically significant) for perchloroethylene-exposed workers. The authors suggest that the absence of a significant effect for perchloroethylene-exposed workers may be due to misclassification of exposure (Vlaanderen et al. 2014).

Dioxin

Evidence has emerged that dioxin may be associated with bladder cancer. A committee of the National Academies of Science (NAS) routinely reviews evidence related to Agent Orange exposure – an herbicide used during the Vietnam War, which was contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin). Based on studies to date, in NAS recently upgraded the evidence for bladder cancer from "inadequate" to "suggestive" (NAS 2014). In their review, the NAS cites several studies, including an excess in bladder cancer mortality among workers employed in US chemical plants that manufactured Agent Orange (Steenland et al. 1999) and a recent study of Korean and Vietnam War veterans, which found a two-fold excess in bladder cancer mortality among those serving in Vietnam with the highest exposure levels to Agent Orange in comparison to those with the lowest levels of exposure (Yi et al 2014).

Industry/Occupation

As Table 5 reviews, research has found work-related bladder cancer in a long list of industries and occupations. The weight of the evidence comprises a "strong" risk in many cases; in others the evidence is at least suggestive according to IARC and other authoritative sources and seminal studies. Typically, studies in these work environments have found clear evidence of elevated risk of bladder cancer, yet the primary causal substance(s) have not been identified. Industries with a confirmed or highly probable increased risk of bladder cancer include: plastics and rubber manufacturing, aluminum production, dyestuff and chemical manufacture, pigment and paint manufacture, dry cleaning industry, cable manufacture, textile works (dyeing), leather works and shoe manufacturer and repair, the coal tar industry, and the gas industry (Cogliano et al. 2011; Siemiatycki et al. 2004; Letašiová et al. 2012; Imperial College of London and the Health and Safety Laboratory, 2007). In addition to these relatively well-established risk industries, a number of occupations have a strong or suggestive evidence supporting an increased risk of bladder cancer, including: barbers, butchers, clerks, electricians, firefighters, hairdressers, machinists, mechanics, medical occupations, metalworkers, painters, photographers, professional drivers (exposed to emissions from combustion engines,) plumbers, shoemakers and shoe repairers, tailors, and textile workers (Cogliano et al. 2011; Siemiatycki et al. 2004; Letašiová et al. 2012; Imperial College of London and the Health and Safety Laboratory, 2007).

Table 5. Occupation – Evidence Summary for Bladder Cancer Risk		
Substance	**Exposure Sources**	**Strength of the Evidence**
Aromatic amines [benzidine-based dyes, ortho-toluidine, 1, 4-nitrobiphenyl, and 2-naphthylamine, auramine, chlornaphazine]	Dye and pigment production; use in textile, paper leather, rubber, plastics, printing, paint, lacquer and dye product industries	Strong[1]
Additional aromatic amines [4-chloro-ortho-toluidine, 4,4'-methylenebis(2-chloroaniline), orthronitrotoluene MBOCA]	Dye and pigment production; pesticide production; MBOCA used to produce castable polyurethane parts	Suggestive[1,2]
Azo dyes [direct black 38, Direct blue 6]	Dye and pigment production; use in textile, paper leather, rubber, plastics, printing, paint, lacquer and dye product industries	Strong[1]
Coal tars and pitches	Production of refined chemicals and coal tar products; coke production; coal gasification; aluminum production; foundries; road paving and construction (including roofers and slaters)	Suggestive[1]
Diesel exhaust	Transportation industries including railroad, shipping and mechanic industries	Suggestive[1]
Polycyclic aromatic hydrocarbons (PAHs)/Soot	Work involving combustion of organic matter, including foundries, steel mills, fire fighting, and vehicle repair	Strong[1] for workplace settings with high exposures – coal tars/pitches and aluminum production

Circumstances	Suspected substance	Strength of the Evidence
Metal working fluids and mineral oils, untreated and mildly treated	Mineral oil production or use as a lubricant by metal workers, machinists, engineers; print industry; cosmetic; and pharmaceutical production/preparations	Strong[3]
Aluminum production	Pitch volatiles; aromatic amines	Strong[1]
Boot and shoe manufacture and repair	Leather dust; benzene and other solvents	Suggestive[2]
Coal gasification	Coal tar; coal-tar fumes; PAHs	Suggestive[2]
Dry Cleaning	Perchloroethylene	Suggestive[1]
Hair dressers/barbers	Dyes/pigments	Suggestive[1]
Firefighters	PAHs; aromatic amines; solvents	Suggestive[4]
Magenta manufacture	Magenta; ortho-toluidine; 4,4'methylene bis(2-methylaniline); ortho-nitrotoluene	Strong[1]
Painters	Pigments; solvents	Strong[2]
Printing processes	Mineral oil; dyes	Suggestive[1]
Rubber industry	Aromatic amines; solvents	Strong[1]
Textile manufacturing	Dyes/pigments	Suggestive[1]

[1] Determined by the International Agency for Research on Cancer's review of the evidence [monographs included in bibliography below) and reviewed by Cogliano VJ, Baan R, Schifano JN, et al. Preventable exposures associated with human cancers. J Jantl Cancer Inst. 2011;103(24):1827-39. [2]Characterized by Siemiatycki's review of IARC monographs. Siemiatycki J, Richardson L, Straif K, et al. Listing of occupational carcinogens. Environ Health Perspect 2004;112(15):1447-59. [3]Characterized by the UK Health and Safety Executive. [4]Characterized in Daniels et al. Mortality and cancer incidence in a pooled cohort of US firefighters from San Francisco, Chicago and Philadelphia (1950-2009). Occ Environ Med. 2014;71(6):388-397.

Prevention Opportunities

Bladder cancer can be prevented by avoiding its causes. The foundation of prevention in occupational settings is industrial hygiene techniques – see the "hierarchy of controls" (Figure 1). The hierarchy of controls shows a progression from top to bottom of the furthest upstream approach to prevention (eliminating the use of the carcinogen via process changes and/or via substitution of one chemical with a safer alternative is the most effective) to the furthest downstream and least effective approach (personal protective equipment, which can fail and may not be used as intended by the worker because it is uncomfortable, or because of other behavioral or environmental constraints). In general, prevention that depends on individual behavior changes are not the most effective strategies to control exposure to occupational carcinogens .
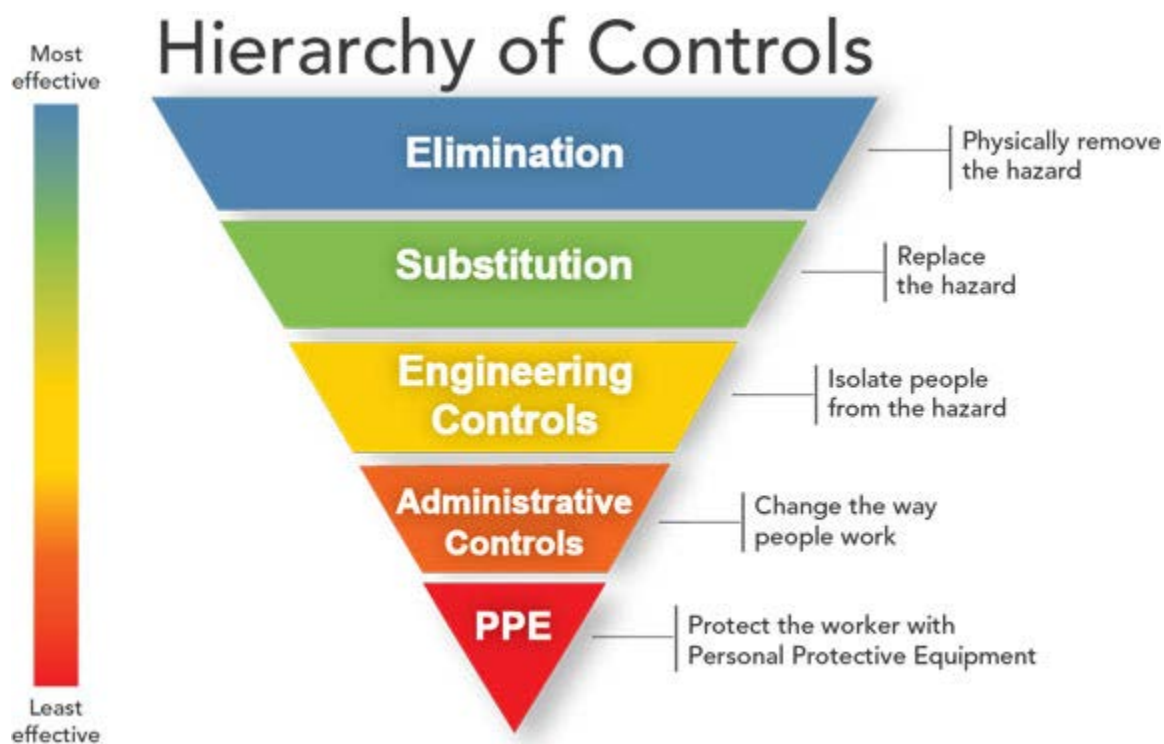
Hierarchy of Controls

Most effective

Elimination — Physically remove the hazard

Substitution — Replace the hazard

Engineering Controls — Isolate people from the hazard

Administrative Controls — Change the way people work

PPE — Protect the worker with Personal Protective Equipment

Least effective

Figure 1

An example of an upstream approach to reduce bladder cancer risk is by substituting dry cleaning with Professional Wet Cleaning. Professional Wet Cleaning does not use perchloroethylene and minimizes the use of other synthetic chemicals as it is a water-based process that cleans delicate "dry clean only" textiles (wool, silk, rayon, natural and man-made fibers) using computer-controlled washers and dryers, along with biodegradable detergents and specialized finishing equipment, to prevent fabric shrinkage and damage. In response to states and localities beginning to regulate perchloroethylene in dry cleaning, many dry cleaners have substituted other synthetic chemicals for perc. Many of these are themselves hazardous—though not as hazardous as perchloroethylene, and the marketing of them as "green" can mislead workers and customers. Policies that require or incentivize the replacement of perchloroethylene with Professional Wet Cleaning rather than substitute chemicals are advancing worker and consumer health more effectively than chemical substitution.

Occupational health and safety regulations are tools for prevention of cancer. In the US however, known carcinogens are rarely banned. OSHA typically requires employers to control workers' cancer risk via industrial hygiene techniques that fall in the middle or bottom of the hierarchy of controls (see Figure 1), such as engineering controls (i.e., ventilation), or personal protective equipment. OSHA sets its "permissible exposure limits" for workers not at 0 (i.e., no exposure is the best exposure limit for a carcinogen), but at exposure levels that pose a risk of cancer among 1 in 1,000 workers (NIOSH 2017). This may explain a decline in occupational bladder cancer risk in recent years, but not complete reductions. Moreover, OSHA has not updated regulatory standards for some known/suspected bladder carcinogens since the 1970s, including some of the aromatic amines, perchloroethylene (used in dry cleaning), and several PAHs that are involved in work settings other than coal tars/pitches, among others.

The primary prevention of occupational bladder carcinogens should logically result in lowered cancer rates. However, such reductions are not easily documented. Unfortunately, there are few follow-up studies designed to determine whether cancer rates have declined based on preventative actions taken to reduce exposure in workers (Tomatis 1997). One reason for this absence of studies is lack of resources, but others include inherent limitations of occupational and environmental health sciences, such as the multi-factorial nature of disease causation and the long latency periods for bladder cancer, which distances exposures from outcomes to an extent that all but the strongest associations may not be observed.

Table 6. Occupational Carcinogen Reduction Strategies (not comprehensive)	

Advocacy: *Policy and Technology Strategies*	**Federal**
	● Work with your unions or local occupational safety and health advocacy organizations to require OSHA to update and enforce standards under the Occupational Safety and Health Act. OSHA needs to:
	   ○ Enforce existing standards for carcinogens
	   ○ Update permissible exposure limits for carcinogens based on current science
	Corporations/Workplaces
	● Seek to identify and adopt safer substitutes for known or suspected bladder carcinogens in the workplace. Assess the hazards of the substitutes to ensure the alternative is indeed safer with regard to a range of toxicity endpoints (i.e., cancer, reproductive/developmental toxicity, endocrine disruption, neurotoxicity, dermal toxicity). Avoid regrettable substitutes.
	● Follow NIOSH's guidance regarding recommended exposure limits for carcinogens, which are set at zero.

Personal Change: *Individual-level Action Strategies*	● Know the hazard profile of the chemicals you work with ● Make sure you work in environments with adequate engineering controls (i.e., ventilating air away from you) and use personal protective equipment (i.e., gloves, suits, appropriately fitting respirators)

One recent study systematically reviewed contemporary exposure to occupational bladder carcinogens and assessed trends in incidence and mortality. The analysis found that incidence of bladder cancer from exposure to 42 out of the 61 categories of bladder carcinogens is increasing. Bladder cancer incidence rates remain highest among workers exposed to aromatic amines and PAHs (Cumberbatch et al. 2015). Some decreases were noted however, such as a decline in the incidence of bladder cancer among hairdressers, which is likely due to the restricted use of 4-aminobiphenyl in some hair dyes in 1970s (Cumberbatch et al. 2015). The researchers also found that risk of occupational bladder cancer is rising in women more than men (Cumberbatch et al. 2015). They surmised that this increase may be due to an increase in the number of women in the workforce compared to prior decades, or increased use of carcinogens in occupations with high percentages of female workers.

Chemicals in Consumer Products

This review focuses on hair dye products—the primary consumer product that has been investigated in relation to bladder cancer risk. Silverman 2017 reviews the state of the science for studies that have investigated dietary and pharmaceutical products associated with bladder cancer risk (not the focus of this literature review and annotated bibliography).

Risk Factors

Hair Dyes

Given evidence regarding bladder cancer risk associated with aromatic amines and dye chemicals, and increased risk of bladder cancer observed among hair dressers, studies have investigated risk associated with hair dye products (see Table 7). However, in its review on the topic, IARC (2010) was unable to draw a conclusion about the carcinogenicity of personal hair dye use because of conflicting evidence. New reports since the IARC evaluation continue to be inconsistent, with a positive finding for hair dye use among college educated women (but not among women without a college education) in New England (Koutros 2011), and no evidence of an association in a cohort from Shanghai (Mendelsohn 2009). The most recent meta-analysis across studies also reported no association (Turati 2014).

As discussed by Rollison et al. (2006), one possible reason for inconsistent findings and reports of no association in meta-analyses is that the individual studies are not comparable. Some studies do a better job at evaluating hair dye exposure – asking about the type (permanent, semi-permanent, etc.) and color of hair dye used, as well as about frequency and duration of use – while others ask only about 'ever vs. never' use. As noted above, the most recent meta-analysis did not find an association for use of 'any hair dye'. But interestingly, they did report a finding of elevated risk across studies that asked specifically about use of dark hair dyes (Turati 2014), which may contain higher concentrations of some specific dye chemicals than lighter colorants.

Other issues that make it difficult to draw conclusions from the current body of evidence include:
- Few studies consider risk for smokers and non-smokers separately, which could be important because cigarette smoking is another source of exposure to the bladder carcinogens that are potentially present in hair dye.
- Few studies consider the role of genetic variants. N-acetyltransferases, for example, are involved in the metabolism of aromatic amines, including 4-aminobiphenyl, a known bladder carcinogen and possible hair dye contaminant, and common genetic variants are associated with difference in acetylation capacity of these enzymes. In two US studies, a positive association between hair dye use and bladder cancer was seen among individuals classified as N-acetyltransferase-2 (NAT2) slow acetylators (Koutros 2011). Another study in Spain did not replicate this finding (IARC 2010), which could mean that the earlier findings were due to chance or could reflect differences in genotype frequencies between the populations.

Table 7. Consumer Product Chemicals – Evidence Summary for Bladder Cancer Risk		
Agents	**Consumer Product Exposure Sources**	**Summary of Evidence**
4-aminobiphenyl (4-ABP)	Possible contaminant in commonly used hair dye (Turesky et al 2003)	• 'Causes cancer of the urinary bladder' in humans, based on occupational studies. [IARC] • No non-occupational studies
ortho-**Toluidine**	Possible exposure from some hair dyes (Johansson et al 2015)	• 'Causes cancer of the urinary bladder' in humans, based on occupational studies. [IARC] • No non-occupational studies.
Disperse blue 1	Used in some hair dyes, hair mousse and toothpaste	• 'Reasonably anticipated to be a human carcinogen' based on animal studies that included benign and malignant urinary bladder tumors in male and female rats. [NTP] • No studies in humans
Benzidine	Until the 1970s, used as dye for leather products, clothes and toys, some food colors	• 'Causes cancer of the urinary bladder' in humans, based on occupational studies. [IARC] • No non-occupational studies
4,4'-Methylenebis(2-chlorobenzenamine) (MOCA)	May be present as a residual impurity in polyurethane foam and other plastic components (Rudel 2014)	• Mechanistic evidence indicates that MOCA acts like other aromatic amines that are known to cause urinary bladder cancer in humans (e.g. *ortho*-Toluidine) [IARC] • No human studies adequately evaluated cancer risk

Prevention Opportunities

Hair dyes are considered cosmetics and are regulated by the US Food and Drug Administration (FDA). Although FDA has the authority to conduct pre-market approval of "color additives" in cosmetics, additives that contain "coal tars" – common colorants in permanent and semi-permanent dye products – are exempt from these laws. According to FDA's website, FDA cannot take action against a coal-tar hair dyes, as long as the label includes a caution statement and the product comes with adequate directions for consumers to do a skin test before they dye their hair: *Caution - This product contains ingredients which may cause skin irritation on certain individuals and a preliminary test according to accompanying directions should first be made. This product must not be used for dyeing the eyelashes or eyebrows; to do so may cause blindness. (FD&C Act, 601(a))* FDA 2018).

In the 1980s, evidence demonstrating that two chemicals in coal-tar hair dye products could cause cancer in rodents resulted in FDA issuing a new regulation requiring products containing these chemicals to include a warning statement on the label: *Warning – Contains an ingredient that can penetrate your skin and has been determined to cause cancer in laboratory animals.* According to FDA's website, product manufacturers have since removed these chemicals from existing formulations FDA 2018).

FDA states that it continues to monitor research on hair dye safety, but that it currently lacks reliable evidence showing a link between cancer and coal-tar hair dyes on the market today. One mechanism by which FDA could consider additional regulations for personal hair dyes is review of adverse event data (FDA 2018); the agency encourages submissions by consumers who have experienced health conditions that they believe have been caused by the use of hair dyes, see: [Adverse Event Reporting: How to Report a Cosmetic-related Problem to FDA](#).

Because of consumer concerns regarding the lack of regulatory protections to ensure the safety of cosmetics, some non-profit organizations have developed third-party evaluation and/or certification programs that screen ingredients in consumer products for the presence of chemical carcinogens and other chemical toxicants. One such program is MadeSafe, www.madesafe.org. The MADE SAFE® seal means that a product is made with safe ingredients. Some hair dye products have received a MadeSafe certification. GoodGuide®, www.goodguide.org is another resource to help identify safer hair dye products. GoodGuide rates products on a scale of 1 (bad) to 10 (good) based on the inherent hazard of chemical ingredients and full ingredient disclosure, among other factors. In addition to hair dyes, both of these resources also review a broad range of consumer products including household products, baby products, cosmetics and personal care products.

Special Topics

Gene Environment Interactions

There are several genetic polymorphisms that are associated with higher rates of bladder cancer and may confer higher risk. The presence of these polymorphisms may influence susceptibility to exposures—including smoking, workplace and environmental, leading to higher risk.

An association between the carcinogen-metabolizing enzyme, N-acetyltransferase 2 (NAT2) and bladder cancer risk has been consistently observed in epidemiologic studies and meta-analyses, especially among smokers and those exposed to several carcinogenic aromatic amines. (Silverman 2017). NAT2 is an important in the inactivation of some aromatic amines (present in both tobacco smoke and in a range of occupational settings (see above). There are two primary phenotypes for NAT2: 'fast' and 'slow' acetylators. The slow acetylator form of NAT2 may put people at increased risk of bladder cancer when they are exposed to environmental and occupational aromatic amine carcinogens because they do not metabolize the carcinogen as efficiently. Conversely studies have also demonstrated that the slow acetylator form of NAT2 may be protective in the case of some exposures, such as benzidine (Carreon et al. 2006). Genetic testing of the encoding gene *N*-acetyltransferase 2 (*NAT2*) was introduced for purposes of legal compensation or preventive activities for workers with exposure to aromatic amines, but has been criticized on ethical grounds and because of insufficient scientific evidence (Vineis and Schulte 1995).

Another study explored data on high-risk occupations associated with bladder cancer to examine specific genetic polymorphisms that interact with these exposures (Figueroa et al. 2015). Three of the 16 genetic polymorphisms examined showed additive interactive effects, including GSTM1 deletion, rs11892031 and rs798766. Among patients with occupational exposure to metal working fluids, investigators observed statistically significant additive interaction for rs798766, patients with tumors positive for FGFR3 expression.

The role of genetic variability in modulating adverse health effects of water disinfection byproducts has also been explored. Glutathione *S*-transferase (GST) theta-1 (GSTT1) may activate brominated THMs to mutagens; GST zeta-1 (GSTZ1) catalyzes the oxygenation of dichloro- and other α-haloacids, some of which are animal carcinogens, and cytochrome P450 2E1 (CYP2E1) metabolizes a wide variety of aliphatic hydrocarbons, solvents, and industrial monomers and is responsible for the primary oxidation of THMs. In a recent analysis, associations were seen between polymorphisms in these key metabolizing enzymes and s bladder cancer risk related from exposure to disinfection byproducts (Cantor et. al 2010).

Annotated Bibliography [organized by risk factor category and study type]

Water Pollution

Risk Factor Authoritative Sources

IARC (International Agency for Research on Cancer). Volume 73: Some chemicals that cause tumors of the kidney or urinary bladder in rodents and some other substances. 1999. Lyon, France. Concluded that there is sufficient evidence in animals for the carcinogenicity of chloroform and other widespread disinfection by-products (possibly carcinogenic in humans, Group 2b). Evidence from epidemiologic studies was considered inadequate despite positive associations with bladder cancer risk because of little consistency among the studies regarding measurements of chloroform specific intake.

IARC (International Agency for Research on Cancer). Volume 84: Some drinking water disinfectants and contaminants, including arsenic. 2004. Lyon, France, IARC. Arsenic classified as a known human bladder carcinogen, group 1. 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone (MX) was classified as a probable carcinogen, group 2b.

IARC (International Agency for Research on Cancer). Volume 94: Ingested nitrate and nitrate and cyanobacterial peptide toxins. 2010. Lyon France. There was inadequate evidence to determine the carcinogenicity of nitrate in drinking water. Ingestion of nitrate under conditions that result in endogenous nitrosation is probably carcinogenic to humans.

IARC (International Agency for Research on Cancer). Volume 100c: IARC monographs on the evaluation of carcinogenic risks to humans: Arsenic, metals, fibres, and dusts. 2012. Lyon, France, IARC. Classified inorganic arsenic as a group 1, known human carcinogen. The committee stated that inorganic arsenic compounds cause cancer of the urinary bladder.

IARC (International Agency for Research on Cancer). Volume 101: Some Chemicals Present in Industrial and Consumer Products, Food and Drinking-water. 2013. Lyon, France, IARC. Dibromoacetic acid, bromochloroacetic acid and dibromoacetonitrile classified as group 2B, possibly carcinogenic.

IARC (International Agency for Research on Cancer). **Volume 106: Trichloroethylene, Tetrachloroethylene, and Some Other Chlorinated Agents. 2014. Lyon, France, IARC.** Dichloroacetic acid, trichloroacetic acid were classified as group 2B, possibly carcinogenic.

Systematic Reviews/Meta-analyses/Pooled Analyses

Cantor KP, Steinmaus CM, Ward MH, et al. Water Contaminants. In M Thun, MS Linet, JR Cerhan, et al., eds. Cancer Epidemiology and Prevention. 4th ed. New York: Oxford University Press, 2017. This comprehensive review paper reviews the evidence for multiple types of water contaminants and cancer, including arsenic, disinfection byproducts, nitrates among others.

Costet N, Villanueva CM, Jaakkola JJ, et al. Water disinfection by-products and bladder cancer: is there a European specificity? A pooled and meta-analysis of European case–control studies. Occup Environ Med. 2011;68(5):379–85. For policy guidance of drinking water disinfection in Europe and because

major differences exist in water disinfection practices and DBPs occurrence between both continents, specific risk estimates for bladder cancer in relation to DBPs exposure for European populations were needed. We conducted a pooled and a two-stage random-effect meta-analyses of three European case-control studies from France, Finland, and Spain (5467 individuals: 2381 cases and 3086 controls). Individual exposure to THMs was calculated combining information on residential history, estimates of the average total THMs (TTHM) level in tap water at the successive residences and personal water consumption. A significant odds-ratio was observed for men exposed to an average residential TTHM level > 50 µg/l (OR = 1.47 (1.05; 2.05)) when compared to men exposed to levels ≤ 5 µg/l. The linear trend of the exposure-risk association was significant (p = 0.01). Risks increased significantly for exposure levels above 25 µg/l and with more than 30 years of exposure to chlorinated water, but were mainly driven by the level rather than the duration of exposure. No significant association was found among women or with cumulative exposure through ingestion. There was no evidence of a differential exposure-response relation for TTHM and bladder cancer in Europe and North America.

Richardson SD, Plewa MJ, Wagner ED, et al. 2007. Occurrence, genotoxicity, and carcinogenicity of regulated and emerging disinfection by-products in drinking water: a review and roadmap for research. Mutat Res, 636(1–3), 178–242. Here we review 30 years of research on the occurrence, genotoxicity, and carcinogenicity of 85 DBPs, 11 of which are currently regulated by the U.S., and 74 of which are considered emerging DBPs due to their moderate occurrence levels and/or toxicological properties. These 74 include halonitromethanes, iodo-acids and other unregulated halo-acids, iodo-trihalomethanes (THMs), and other unregulated halomethanes, halofuranones (MX [3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone] and brominated MX DBPs), haloamides, haloacetonitriles, tribromopyrrole, aldehydes, and N-nitrosodimethylamine (NDMA) and other nitrosamines. Alternative disinfection practices result in drinking water from which extracted organic material is less mutagenic than extracts of chlorinated water. However, the levels of many emerging DBPs are increased by alternative disinfectants (primarily ozone or chloramines) compared to chlorination, and many emerging DBPs are more genotoxic than some of the regulated DBPs.

Saint-Jacques N, Parker L, Brown P, Dummer T. Arsenic in drinking water and urinary tract cancers: a systematic review of 30 years of epidemiological evidence. Environ Health. 2014;Jun 2;13:44. This review summarizes 30 years of epidemiological studies on arsenic exposure in drinking water and the risk of bladder or kidney cancer, quantifying these risks using a meta-analytical framework. Twenty-eight studies observed an association between arsenic in drinking water and bladder cancer. Ten studies showed an association with kidney cancer, although of lower magnitude than that for bladder cancer. The meta-analyses showed the predicted risks for bladder cancer incidence were 2.7 [1.2-4.1]; 4.2 [2.1-6.3] and; 5.8 [2.9-8.7] for drinking water arsenic levels of 10, 50, and 150 µg/L, respectively. Bootstrapped randomizations confirmed this increased risk, but, lowering the effect size to 1.4 [0.35-4.0], 2.3 [0.59-6.4], and 3.1 [0.80-8.9]. The latter suggests that with exposures to 50 µg/L, there was an 83% probability for elevated incidence of bladder cancer; and a 74% probability for elevated mortality. For both bladder and kidney cancers, mortality rates at 150 ug/L were about 30% greater than those at 10 µg/L.

Villanueva CM, Cantor KP, Cordier S, et al. 2004. Disinfection byproducts and bladder cancer: a pooled analysis. Epidemiology, 15(3), 357–367. We pooled the primary data from 6 case-control studies of bladder cancer that used trihalomethanes as a marker of disinfection byproducts. The analysis included 2806 cases and 5254 controls, all of whom had measures of known exposure for at least 70% of the exposure window of 40 years before the interview. Cumulative exposure to trihalomethanes was estimated by combining individual year-by-year average trihalomethane level and daily tap water

consumption. Results included adjusted odds ratio (OR) of 1.24 in men exposed to an average of more than 1 microg/L (ppb) trihalomethanes compared with those who had lower or no exposure (95% confidence interval [CI] = 1.09-1.41). Estimated relative risks increased with increasing exposure, with an OR of 1.44 (1.20-1.73) for exposure higher than 50 microg/L (ppb). Similar results were found with other indices of trihalomethane exposure. Among women, trihalomethane exposure was not associated with bladder cancer risk (0.95; 0.76-1.20).

Villanueva CM, Fernandez F, Malats N, et al. Meta-analysis of studies on individual consumption of chlorinated drinking water and bladder cancer. J Epidemiol Community Health. 2003;57(3):166–73. Ever consumption of chlorinated drinking water was associated with an increased risk of bladder cancer in men (combined OR=1.4, 95%CI 1.1 to 1.9) and women (combined OR=1.2, 95%CI 0.7 to 1.8). The combined OR for mid-term exposure in both genders was 1.1 (95% CI 1.0 to 1.2) and for long term exposure was 1.4 (95%CI 1.2 to 1.7). The combined estimate of the slope for a linear increase in risk was 1.13 (95% CI 1.08 to 1.20) for 20 years and 1.27 (95% CI 1.15 to 1.43) for 40 years of exposure in both sexes. This meta-analysis of the best available epidemiological evidence indicates that long term consumption of chlorinated drinking water is associated with bladder cancer, particularly in men. The observed relative risk is only moderately high, but the population attributable risk could be important as the vast majority of the population of industrialised countries is potentially exposed to chlorination byproducts for long time periods.

Risk Factor Research Studies

Baris D, Waddell R, Hoover R, et al. Elevated Bladder Cancer in Northern New England: The Role of Drinking Water and Arsenic. J Natl Cancer Inst. 2016;108(9):1-9. We explored reasons for the excess of bladder cancer in New England focusing on arsenic in drinking water from private wells, which are particularly prevalent in the region. In a population-based case-control study in these three states, 1213 bladder cancer case patients and 1418 control subjects provided information on suspected risk factors. Log transformed arsenic concentrations were estimated by linear regression based on measurements in water samples from current and past homes. Bladder cancer risk increased with increasing water intake. This trend was statistically significant among participants with a history of private well use (Ptrend = .01). Among private well users, this trend was apparent if well water was derived exclusively from shallow dug wells (which are vulnerable to contamination from manmade sources, Ptrend = .002). If dug wells were used pre-1960, when arsenical pesticides were widely used in the region, heavier water consumers (>2.2 L/day) had double the risk of light users (<1.1 L/day, Ptrend = .01). Our findings support an association between low-to-moderate levels of arsenic in drinking water and bladder cancer risk in New England. In addition, historical consumption of water from private wells, particularly dug wells in an era when arsenical pesticides were widely used, was associated with increased bladder cancer risk and may have contributed to the New England excess.

Bates M, Smith A, and Cantor K. Case-control study of bladder cancer and arsenic in drinking water. Am J Epidemiol, 1995;141(6), 523–530. Mortality from several cancers, including bladder cancer, is elevated in a Taiwanese population exposed to high levels of arsenic in drinking water. Data from the Utah respondents to the National Bladder Cancer Study conducted in 1978 were used to evaluate these associations in a US population exposed to measurable, but much lower, levels of drinking water arsenic. Overall, there was no association of bladder cancer with either measure; however, among smokers, but not among nonsmokers, positive trends in risk were found for exposures estimated for decade-long time periods, especially in the 30- to 39-year period prior to diagnosis. Exposures were in

the range 0.5-160 micrograms/liter (mean, 5.0 micrograms/liter). The data raise the possibility that smoking potentiates the effect of arsenic on risk of bladder cancer. However, the risk estimates obtained are much higher than predicted on the basis of the results of the Taiwanese studies, raising concerns about bias or the role of chance.**Beane Freeman LE, Cantor KP, Barius D, et al. Bladder cancer and water disinfection by-product exposures through multiple routes: a population-based case-control study (New England, USA). Environ Health Perspect. 2017;(6)** Ingestion of disinfection byproducts has been associated with bladder cancer in multiple studies. Although associations with other routes of exposure have been suggested, epidemiologic evidence is limited. We evaluated the relationship between bladder cancer and total, chlorinated, and brominated trihalomethanes (THMs) through various exposure route using a population-based case–control study in New England (*n*=(1,213) cases; *n*=(1,418) controls). We estimated lifetime exposure to THMs from ingestion, showering/bathing, and hours of swimming pool use. Adjusted ORs for bladder cancer comparing participants with exposure above the 95th percentile with those in the lowest quartile of exposure (based on the distribution in controls) were statistically significant for average daily intake mg/d of total THMs [OR=1.53 (95% CI: 1.01, 2.32), *p*-trend=0.16] and brominated THMs [OR=1.98 (95% CI: 1.19, 3.29), p-trend=0.03]. For cumulative intake mg, the OR at the 95th percentile of total THMs was 1.45 (95% CI: 0.95, 2.2), *p*-trend=0.13; the ORs at the 95th percentile for chlorinated and brominated THMs were 1.77 (95% CI: 1.05, 2,.99), *p*-trend=0.07 and 1.78 (95% CI: 1.05, 3.00), *p*-trend=0.02, respectively. The OR in the highest category of showering/bathing for brominated THMs was 1.43 (95% CI: 0.80, 2.42), *p*-trend=0.10. We found no evidence of an association for bladder cancer and hours of swimming pool use.

Karagas M, Tosteson T, Schned A, et al. Incidence of transitional cell carcinoma of the bladder and arsenic exposure in New Hampshire. Cancer Causes & Control. 2004;(5):465. Arsenic is a known bladder carcinogen and populations exposed to high arsenic levels in their water supply have reported elevated bladder cancer mortality and incidence rates. To examine the effects of lower levels of arsenic exposure on bladder cancer incidence, we conducted a case-control study in New Hampshire, USA where levels above 10 micro/l are commonly found in private wells. Cases of transitional cell carcinoma of the bladder cancer, newly diagnosed between July 1, 1994 and June 30, 1998 and 641 general population controls. Individual exposure to arsenic was determined in toenail clippings using instrumental neutron activation analysis. Among smokers, an elevated odds ratio (OR) for bladder cancer was observed for the uppermost category of arsenic (OR: 2.17, 95% CI: 0.92-5.11 for greater than 0.330 mcg/g compared to less than 0.06 micro/g). Among never smokers, there was no association between arsenic and bladder cancer risk. These, and other data, suggest that ingestion of low to moderate arsenic levels may affect bladder cancer incidence, and that cigarette smoking may act as a co-carcinogen.

Koutros S, Lenz O, Hewsitt SM, et al. Elevated Bladder Cancer in Northern New England: The Role of Drinking Water and Arsenic. J Natl Cancer Inst ePub March 2018. Tumor tissues from bladder cancer cases enrolled in the Maine and Vermont components of the New England bladder cancer case–control study were assembled as tissue microarrays and examined for expression of p16 and Rb. Cases (n = 424) were compared with controls (n = 1287) from all study states (ME, VT, NH), as distributions of cumulative arsenic from drinking water, as well as covariates, were similar across states. Data on cumulative arsenic from drinking water were used to evaluate the relationship between arsenic and bladder cancer risk by immunophenotype (p16-/p16+ and Rb-/Rb+) using polytomous logistic regression. Our results show that increasing arsenic intake from drinking water was associated with bladder cancer risk only when comparing patients with p16+ or Rb+ tumors with controls (representing 72.8% and 74.0% of tumors, respectively), with a strong monotonic association with increasing intake

(compared with lowest unlagged exposure, OR_{p16+} = 1.36, 95% CI = 1.47 to 1.85, P_{trend} = .004; OR_{Rb+} = 1.51, 95% CI = 1.56 to 1.94, P_{trend} = .007) (Table 1). There was no association between arsenic and p16- or Rb- bladder tumors ($P_{heterogeneity}$ by subtype = .03 for p16 and .06 for Rb). This heterogeneity was not evident across subtypes defined by stage or grade despite the relationship of these markers with stage and grade of bladder cancer.

Saint-Jacques N, Brown P, Nauta L, Boxall J, Parker L, Dummer T. Estimating the risk of bladder and kidney cancer from exposure to low-levels of arsenic in drinking water, Nova Scotia, Canada. *Environ Int*. **2018;110:95-104.** Arsenic in drinking water impacts health. Highest levels of arsenic have been historically observed in Taiwan and Bangladesh but the contaminant has been affecting the health of people globally. Strong associations have been confirmed between exposure to high-levels of arsenic in drinking water and a wide range of diseases, including cancer. However, at lower levels of exposure, especially near the current World Health Organization regulatory limit (10μg/L), this association is inconsistent as the effects are mostly extrapolated from high exposure studies. This ecological study used Bayesian inference to model the relative risk of bladder and kidney cancer at these lower concentrations-0-2μg/L; 2-5μg/L and; ≥5μg/L of arsenic-in 864 bladder and 525 kidney cancers diagnosed in the study area, Nova Scotia, Canada between 1998 and 2010. The model included proxy measures of lifestyle (e.g. smoking) and accounted for spatial dependencies. Overall, bladder cancer risk was 16% (2-5μg/L) and 18% (≥5μg/L) greater than that of the referent group (<2μg/L), with posterior probabilities of 88% and 93% for these risks being above 1. Effect sizes for kidney cancer were 5% (2-5μg/L) and 14% (≥5μg/L) above that of the referent group (<2μg/L), with probabilities of 61% and 84%. High-risk areas were common in southwestern areas, where higher arsenic-levels are associated with the local geology. The study suggests an increased bladder cancer, and potentially kidney cancer, risk from exposure to drinking water arsenic-levels within the current the World Health Organization maximum acceptable concentration.

Villanueva C, Cantor K, Kogevinas M, et al. Bladder cancer and exposure to water disinfection by-products through ingestion, bathing, showering, and swimming in pools. **Am J Epidemiol. 2007;165(2):148-156.** The authors examined whether bladder cancer risk was associated with exposure to trihalomethanes (THMs) through ingestion of water and through inhalation and dermal absorption during showering, bathing, and swimming in pools. Lifetime personal information on water consumption and water-related habits was collected for 1,219 cases and 1,271 controls in a 1998-2001 case-control study in Spain and was linked with THM levels in geographic study areas. Long-term THM exposure was associated with a twofold bladder cancer risk, with an odds ratio of 2.10 (95% confidence interval: 1.09, 4.02) for average household THM levels of >49 versus < or =8 micro g/liter. Compared with subjects not drinking chlorinated water, subjects with THM exposure of >35 micro g/day through ingestion had an odds ratio of 1.35 (95% confidence interval: 0.92, 1.99). The odds ratio for duration of shower or bath weighted by residential THM level was 1.83 (95% confidence interval: 1.17, 2.87) for the highest compared with the lowest quartile. Swimming in pools was associated with an odds ratio of 1.57 (95% confidence interval: 1.18, 2.09). Bladder cancer risk was associated with long-term exposure to THMs in chlorinated water at levels regularly occurring in industrialized countries.

Prevention Studies/Documents

EPA (US Environmental Protection Agency). Drinking Water Requirements for States and Public Water Systems: Stage 1 and Stage 2 Disinfectants and Disinfection Byproducts Rules. Accessed, April 8, 2018.

Describes the history and focus of the rule, including disinfection byproducts covered and the maximum contaminant levels for each. Links to the rule making documents and fact sheets are provided.

Moyad M. Complementary and preventive medicine. What do I tell my patients about drinking water and the risk of bladder cancer? Urol Nurs. 2003;23(5):371-377. Occupational exposure to arylamines, schistosomiasis, and especially smoking are well-known potential causes of bladder cancer. However, numerous individuals who are diagnosed with this cancer apparently have no known etiology. Increased consumption of a variety of fluids, including water, may significantly reduce the risk of bladder cancer by reducing the overall impact time of potential carcinogens on bladder tissue. However, the quality of drinking water could also have an impact on risk. Health care professionals could play a large role in preventing bladder cancer by providing patients with new data on the impact of water quantity and quality on risk.

Dartmouth Toxic Metals Superfund Research Program. Arsenic and You: Information on Arsenic in Food, Water & Other Sources. Accessed, April 8, 2018. Information on residential water filtration treatment technologies for arsenic.

Zappa L and W Zavora. Addressing disinfection by-product challenges in drinking water. WaterWorld. 2011;27(3):60. There are a number of technologies which have been evaluated and are now being employed by municipal water providers for precursor removal. Membrane filtration, activated carbon, and the enhanced coagulation process have emerged as the three most commonly applied technologies for NOM reduction. All three of these technologies have been thoroughly researched for their effectiveness relative to NOM reduction, and there are numerous technical papers which describe how these technologies can be applied to help municipalities meet their Stage 2DBPR compliance requirements.

Air Pollution

Risk Factor Authoritative Sources

IARC (International Agency for Research on Cancer). IARC Monographs on the evaluation of carcinogenic risks to humans. Volume 92. Some Non-heterocyclic Polycyclic Aromatic Hydrocarbons and Some Related Exposures. 2010. Lyon, France. The IARC working group found strong support from epidemiologic studies for an increased risk of bladder among workers with high exposure to PAHs from coal tars and pitches as well as specific industries with significant sources of PAHs, including aluminum production.

IARC (International Agency for Research on Cancer). IARC Monographs on the evaluation of carcinogenic risks to humans. Volume 109. Outdoor Air Pollution. 2013. Lyon France. The IARC working group found a "positive association" between exposure to outdoor air pollution (a complex and varying mixture of chemical pollutants) and bladder cancer. The committee's determination was primarily supported by epidemiological cohort and case-control studies of workers exposed to vehicular sources air pollution (as opposed to industrial emissions).

IARC (International Agency for Research on Cancer). IARC Monographs on the evaluation of carcinogenic risks to humans. Volume 105: Diesel and Gasoline Engine Exhaust and Some Nitroarenes. 2014. Lyon, France. The IARC working group found evidence for a "positive association" between exposure to diesel engine exhaust and bladder cancer based on a comprehensive review of existing epidemiologic studies. The most informative data on which the IARC working group based its determination included results from an analysis that pooled data from 11 European studies and found that individuals who worked in environments that exposed them to the highest category of diesel engine exhaust had a significantly increased risk of bladder cancer. The available epidemiologic data was considered too limited to assess the urinary bladder carcinogenicity of gasoline exhaust.

Systematic Reviews/Meta-analysis Sources

Habert C, Garnier R. Health effects of diesel exhaust: a state of the art. Rev Mal Respir. 2015;32(2):138-54. This review presents the state of knowledge regarding the acute and chronic toxicity of diesel engine exhaust in humans. The epidemiologic data collected during the last two decades also show limited evidence of increased risks of bladder cancer in diesel engine exhaust exposed workers. Both experimental and epidemiological studies have involved the effect of emissions from traditional diesel engine technology. Major developments in this technology have occurred recently and the toxicity of emissions from these new engines is still to be characterized. Further studies are needed to explore the link between diesel engine exhaust exposure and the risks of bladder cancer and more information is needed on the toxicity of new diesel technology emissions.

Risk Factor Research Studies

Attfield MD, Schleiff PL, Lubin JH, et al. The diesel exhaust in miners study: a cohort mortality study with emphasis on lung cancer. J Natl Cancer Inst. 2012;104(11):869-83. We undertook a cohort mortality study of 12 315 workers exposed to diesel exhaust at eight US non-metal mining facilities.

Historical measurements and surrogate exposure data, along with study industrial hygiene measurements, were used to derive retrospective quantitative estimates of respirable elemental carbon (REC) exposure for each worker. Standardized mortality ratios for lung cancer (1.26, 95% confidence interval [CI] = 1.09 to 1.44), esophageal cancer (1.83, 95% CI = 1.16 to 2.75), and pneumoconiosis (12.20, 95% CI = 6.82 to 20.12) were elevated in the complete cohort compared with state-based mortality rates, but all-cause, bladder cancer, heart disease, and chronic obstructive pulmonary disease mortality were not. The association between diesel exhaust exposure and lung cancer risk remained after inclusion of other work-related potentially confounding exposures in the models and were robust to alternative approaches to exposure derivation.

Castaño-Vinyals G, Cantor KP, Malats N, et al. Air pollution and risk of urinary bladder cancer in a case-control study in Spain. Occup Environ Med. 2008;65(1):56-60. This case-control study in Spain using 1219 incident cases and 1271 hospital controls examined the risk posed by exposure to air pollution and other potential risk factors. Emissions of polycyclic aromatic hydrocarbons and diesel from industries near the residence, as evaluated by experts, were associated with an increased risk (OR 1.29 (29% increase risk), 95% CI 0.85 to 1.98), while lower or no excess risks were observed for other pollution-related variables. These risks were higher among never smokers compared to smokers suggesting that the excess risk for all study subjects cannot be attributed to residual confounding by smoking and supports the observed associations.

Coli J, Lee BR, Thomas R. Population densities in relation to bladder cancer mortality rates in America from 1950 to 1994. Int Urol Nephrol. 2012;44(2):443-9. The study purpose is to investigate the relationship between bladder cancer mortality and population density of counties in America and to explore traffic air pollution and industrial exposures as risk factors. Bladder cancer mortality rates for white men and women from 1950 to 1994 and population densities (population per 10 square miles) of 2,248 counties were the basis of the study. A linear regression analysis was performed to evaluate the relationship between bladder cancer mortality rates and population densities after log transforming the population density data set. We found a strong association between bladder cancer mortality and population density. Correlation coefficients (R) between bladder cancer mortality rates and the population densities were R = .37, P < .001 for men and R = .28, P < .001 for women. In addition, population densities increased with increasing bladder cancer.

García-Pérez J, Fernández-Navarro P, López-Cima MF, et al. Cancer mortality in towns in the vicinity of incinerators and installations for the recovery or disposal of hazardous waste. Environ Int. 2013;51:31-44. This ecologic investigation explored excess cancer mortality due to 33 cancer types in towns situated in the vicinity of Spanish-based incinerators and installations for the recovery or disposal of hazardous waste, according to the different categories of industrial activity. Population exposure to pollution was estimated on the basis of distance from town of residence to pollution source. Risk of dying from cancer in a 5-kilometer zone around installations was assessed including characterizations of specific facilities. Special mention should be made of the results for tumors of the bladder (1.08 (8% increased risk), 1.01-1.16) in the vicinity of all such installations.

Ho CK, Peng CY, Yang CY. Traffic air pollution and risk of death from bladder cancer in Taiwan using petrol station density as a pollutant indicator. J Toxicol Environ Health A. 2010;73(1):23-32. This study investigates the relationship between air pollution and risk of death from bladder cancer using a matched case control study using deaths that occurred in Taiwan from 1997 through 2006. Individuals who resided in municipalities with high petrol station density levels were at an increased risk of death from bladder cancer compared to subjects living in municipalities with a low petrol density level;

however, the differences are not statistically significant. The findings of this study warrant further investigation of the role of vehicular air pollutant emissions in the etiology of bladder cancer development.

Latifovic L, Villeneuve PJ, Parent ME, et al. <u>Bladder cancer and occupational exposure to diesel and gasoline engine emissions among Canadian men</u>**. Cancer Med. 2015; 4(12):1948-62**. The purpose of this study was to investigate the association between occupational exposure to diesel and gasoline emissions and bladder cancer in men using data from the Canadian National Enhanced Cancer Surveillance System; a population-based case-control study. This analysis included 658 bladder cancer cases and 1360 controls with information on lifetime occupational histories and a large number of possible cancer risk factors. A job-exposure matrix for engine emissions was supplemented by expert review to assign values for each job across three dimensions of exposure: concentration, frequency, and reliability. Relative to unexposed, men ever exposed to high concentrations of diesel emissions were at an increased risk of bladder cancer (OR = 1.64, 0.87-3.08), and those with >10 years of exposure to diesel emissions at high concentrations had a greater than twofold increase in risk (OR = 2.45, 1.04-5.74). Increased risk of bladder cancer was also observed with >30% of work time exposed to gasoline engine emissions (OR = 1.59, 1.04-2.43) relative to the unexposed, but only among men that had never been exposed to diesel emissions.

Liu CC, Tsai SS, Chiu HF, et al. <u>Ambient exposure to criteria air pollutants and risk of death from bladder cancer in Taiwan</u>**. Inhal Toxicol. 2009;21(1):48-54.** To investigate the relationship between air pollution and risk of death from bladder cancer, the authors conducted a matched case-control study using deaths that occurred in Taiwan from 1995 through 2005. Data on all eligible bladder cancer deaths were obtained from the Bureau of Vital Statistics of the Taiwan Provincial Department of Health. Classification of exposure to municipality air pollution was based on the measured levels of nitrogen dioxide and sulfur dioxide. The results of the present study show that there is a significant positive association between the levels of air pollution and bladder cancer mortality. The adjusted odds ratios (95% confidence interval) were 1.37 (1.03-1.82) for the group with medium air pollution level and 1.98 (1.36-2.88) for the group with high air pollution level when compared to the group with the low air pollution level. Trend analyses showed statistically significant trend in risk of death from bladder cancer with increasing air pollution level.

Pedersen M, Stafoggia M, Weinmayr G, et al. <u>Is There an Association Between Ambient Air Pollution and Bladder Cancer Incidence? Analysis of 15 European Cohorts</u>**.** E**ur Urol Focus. 2016; S2405-4569(16)30166-3.** Data from 15 population-based cohorts enrolled between 1985 and 2005 in eight European countries (N=303,431; mean follow-up 14.1 yr) was examined. There was no evidence of an association between exposure to outdoor air pollution levels (exposure to nitrogen oxides (NO_2 and NO_x), particulate matter (PM) with diameter <10µm (PM_{10}), <2.5µm ($PM_{2.5}$), between 2.5 and 10µm ($PM_{2.5-10}$), $PM_{2.5absorbance}$ (soot), elemental constituents of PM, organic carbon, and traffic density at baseline home addresses) at place of residence and risk of bladder cancer.

Tsai SS, Tiao MM, Kuo HW, et al. <u>Association of bladder cancer with residential exposure to petrochemical air pollutant emissions in Taiwan</u>**. J Toxicol Environ Health A. 2009;72(2):53-9.** This study investigates the relationship between petrochemical air pollution and risk of death due to bladder cancer based on a matched cancer case-control Taiwan from 1995 through 2005. Data on all eligible bladder cancer deaths were obtained from the Bureau of Vital Statistics of the Taiwan Provincial Department of Health. The proportion of a municipality's total population employed in the petrochemical industry in a municipality was used as an indicator of a resident's exposure to air

emissions from the petrochemical industry. Subjects who lived in the group of municipalities characterized by the high levels of petrochemical air pollution had a significantly higher risk of death attributed to bladder cancer than subjects in the group that lived in municipalities with the lowest petrochemical air pollution levels, after controlling for possible confounders. The findings of this study warrant further investigation of the role of petrochemical air pollution in the etiology of bladder cancer.

Wilcox AN, Silverman DT, Friesen MC, et al. Smoking status, usual adult occupation, and risk of recurrent urothelial bladder carcinoma: data from The Cancer Genome Atlas (TCGA) Project. Cancer Causes Control. 2016;27(12):1429-1435. We evaluated whether smoking status and usual adult occupation are associated with time to urothelial bladder carcinoma (UBC) recurrence for 406 patients with muscle-invasive bladder cancer submitted to The Cancer Genome Atlas (TCGA) project. Data on time to recurrence were available for 358 patients over a median follow-up time of 15 months. Of these, 133 (37.2%) experienced a recurrence. Current smokers who smoked for more than 40 pack-years had an increased risk of recurrence compared to never smokers (HR 2.1 (110% increased risk), 95% CI 1.1, 4.1). Additionally, employment in a high-risk occupation was associated with a shorter time to recurrence (log-rank p = 0.005). We found an increased risk of recurrence for those employed in occupations with probable diesel exhaust exposure (HR 1.8 (80% increased risk), 95% CI 1.1, 3.0) and for those employed in production occupations (HR 2.0, (100% increased risk) 95% CI 1.1, 3.6).

Prevention Studies/Documents

Brauer M, et al. Develop with Care - 2012 Environmental Guidelines for Urban and Rural Land Development in British Columbia. Supporting Information -- Air Quality. University of British Columbia, School of Population and Public Health. 2012. This document has been prepared for use by local governments, the development community, landowners and environmental organizations as a comprehensive guide to maintaining environmental values during the development of urban and rural lands. This appendix outlines specific policy provisions relevant to public health protections associated with air pollution exposures.

Laumbach R, Meng Q, Kipen H. What can individuals do to reduce personal health risks from air pollution? J Thoracic Dis. 2015;7(1):96-107. This article reviews the evidence for individual risk reduction strategies associated with air pollution. Personal exposure to ambient air pollution can be reduced on high air pollution days by staying indoors, reducing outdoor air infiltration to indoors, cleaning indoor air with air filters, and limiting physical exertion, especially outdoors and near air pollution sources. Careful consideration is especially warranted when interventions may have unintended negative consequences.

Workplace Exposures

Risk Factor Authoritative Sources

IARC (International Research on Cancer). IARC Monograph Evaluation Carcinogenic Risk to Humans. Volume 99: Some Aromatic Amines, Organic Dyes and Related Exposures. 2010b. Lyons, France, IARC.

IARC (International Research on Cancer). IARC Monographs on the evaluation of carcinogenic risks to humans. Volume 92: Some Non-heterocyclic Polycyclic Aromatic Hydrocarbons and Some Related Exposures. 2010c. Lyon, France. The IARC working group found strong support from epidemiologic studies for an increased risk of bladder among workers with high exposure to PAHs from coal tars and pitches as well as specific industries with significant sources of PAHs, including aluminum production.

IARC (International Research on Cancer). IARC Monograph Evaluation Carcinogenic Risk to Humans. Volume 100F: Chemical Agents and Related Occupations. 2012. Lyon, France, IARC. This monograph updates a number of previously published volumes relevant to occupational risk factors and bladder cancer, including the broad range of aromatic amines, mineral oils, as well as work in specific industries and occupation including iron and steel foundry, rubber manufacturing and painting.

IARC (International Research on Cancer). IARC Monographs on the evaluation of carcinogenic risks to humans. Volume 105: Diesel and Gasoline Engine Exhaust and Some Nitroarenes. 2014. Lyon, France. The IARC working group found evidence for a "positive association" between exposure to diesel engine exhaust and bladder cancer based on a comprehensive review of existing epidemiologic studies. The most informative data on which the IARC working group based its determination included results from an analysis that pooled data from 11 European studies and found that individuals who worked in environments that exposed them to the highest category of diesel engine exhaust had a significantly increased risk of bladder cancer. The available epidemiologic data was considered too limited to assess the urinary bladder carcinogenicity of gasoline exhaust.

IARC (International Agency for Research on Cancer). IARC Monographs on the evaluation of carcinogenic risks to humans. Volume 106: Trichloroethylene, Tetrachloroethylene, and Some Other Chlorinated Agents. 2014b. Lyon, France, IARC. The IARC working group classified tetrachloroethylene (perchloroethylene as a probable human carcinogen (group 2A) and noted positive associations related to cancer of the bladder.

NAS (National Academies of Science). Veterans and Agent Orange: Update 2014. 514-29. Bladder cancer was moved from "inadequate or insufficient" evidence of association up to "limited or suggestive" evidence of association.

UK Health and Safety Executive. Industrial Injuries Advisory Council Information note: Bladder cancer and mineral oils. May 2015. The Council reviewed the state of the evidence regarding bladder cancer and mineral oil/metalworking fluid exposures. The review focused on research published since IARC's review in 2012. The council found, "indicate clear evidence that there is an increased risk of bladder cancer arising from occupational exposure to mineral oils."

Systematic Reviews/Meta-analysis Sources

Calvert GM, Ward E, Schnorr TM, Fine LJ. <u>Cancer risks among workers exposed to metalworking fluids: A systematic review.</u> A J Ind Med. 1998;33(3):282-292. This review of the literature on cancer risks in workers exposed to metal-working fluids concluded that there is substantial evidence for an increased risk of bladder cancer. With increased duration of exposure the relative risk (RR) for bladder cancer was 2.9 for drill press operatives, 2.3 for turners and 3.1 for machine tool operators

Cogliano VJ, Baan R, Schifano JN, et al. <u>Preventable exposures associated with human cancers.</u> J Natl Cancer Inst. 2011;103(24):1827-39. The International Agency for Research on Cancer (IARC) Monograph series, which has classified human carcinogens for more than 40 years, recently completed a review to provide up-to-date information on the cancer sites associated with more than 100 carcinogenic agents. Based on IARC's review, we listed the cancer sites associated with each agent and then rearranged this information to list the known and suspected causes of cancer at each site. We also summarized the rationale for classifications that were based on mechanistic data. This information, based on the forthcoming IARC Monographs Volume 100, offers insights into the current state-of-the-science of carcinogen identification.

Cumberbatch MG, Cox A, Teare D., et al. <u>Contemporary Occupational Carcinogen Exposure and Bladder Cancer: A Systematic Review and Meta-analysis.</u> JAMA Oncol. 2015;1(9):1282-90. The goal of this systematic review and meta-analysis is to identify contemporary risks associated with bladder cancer. Despite manufacturing and legislative changes to workplace hygiene, many BCs still arise through occupational carcinogen exposure. Meta-analysis revealed increased BC incidence in 42 of 61 occupational classes and increased BC-specific mortality in 16 of 40 occupational classes. Reduced incidence and mortality were seen in 6 of 61 and 2 of 40 classes, respectively. Risk varied with sex and was greatest in men (standardized incidence ratio, 1.03 [95% CI, 1.02-1.03]; P < .001]). From the 1960s to the 1980s, there was a steady decline in standardized incidence ratio (SIR) for both sexes. This trend reversed from the 1980s, as in the decade 2000 to 2010 the SIR increased to 1.13 (95% CI, 1.07-1.19) for men and 1.27 (95% CI, 1.12-1.43) for women. In contrast, mortality risk declined for both sexes from the 1960s to the 1990s. The overall risk of BC mortality was also greater for men (standardized mortality ratio [SMR], 1.32 [95% CI, 1.18-1.48]) than for women (SMR, 1.14 [95% CI, 0.80-1.63]). Limitations include possible publication bias, that reports stratify workers mostly by job title not task, that not all studies adjusted for smoking, and that the population was mostly derived from Western nations. The profile of contemporary occupations with increased BC risk is broad and differs for incidence and mortality. Currently the incidence seems to be increasing, and this increase is occurring faster in women than men. Improved detection mechanisms and screening are possible reasons for this. Workers with aromatic amine exposure have the highest incidence, while those exposed to polycyclic aromatic hydrocarbons and heavy metals have the greatest mortality.

Harling M, Schablon A, Schedlbauer G, et al. <u>Bladder cancer among hairdressers: a meta-analysis.</u> Occup Environ Med. 2010;(5):351-8. We conducted a meta-analysis to determine summary risk ratios (SRRs) for the risk of bladder cancer among hairdressers. Studies were identified by a MEDLINE, EMBASE, CENTRAL search and by the reference lists of articles/relevant reviews. Statistical tests for publication bias and for heterogeneity as well as sensitivity analysis were applied. In addition, the study quality and the risk of bias were assessed using six criteria. 42 studies were included and statistically significantly increased risks around 1.3–1.7 were found for all but one analysis. The SRR increased with duration of employment from 1.30 (95% CI 1.15 to 1.48) for 'ever registered as hairdresser' to 1.70 (95%

CI 1.01 to 2.88) for 'job held ≥10 years'. No difference was found between the risk for smoking-adjusted data (SRR 1.35, 95% CI 1.13 to 1.61) and no adjustment (SRR 1.33, 95% CI 1.18 to 1.50). Studies assessed as being of high quality (n=11) and of moderate quality (n=31) showed similar SRRs. There was no evidence of publication bias or heterogeneity in all analyses. In summary, our results showed an increased and statistically significant risk for bladder cancer among hairdressers, in particular for hairdressers in jobs held ≥10 years. Residual confounding by smoking cannot be totally ruled out. Because of the long latency times of bladder cancer it remains an open question whether hairdressers working prior to 1980 and after 1980, when some aromatic amines were banned as hair dye ingredients, have the same risk for bladder cancer.

Guha N, Steenland NK, Merletti F, et al. Bladder cancer risk in painters: a meta-analysis. Occup Environ Med. 2010;(8):568-73. The International Agency for Research on Cancer has classified occupational exposure as a painter as 'carcinogenic to humans', largely based on increased risks of bladder and lung cancer. A meta-analysis, including more than 2900 incident cases or deaths from bladder cancer among painters reported in 41 cohort (n=2), record linkage (n=9) and case-control (n=30) studies, was conducted to quantitatively compare the results of the different study designs and the potential confounding effect of smoking as well as other occupational exposures. The summary relative risk (meta-RR, random effects) for bladder cancer in painters was 1.25 (95% CI 1.16 to 1.34; 41 studies) overall and 1.28 (95% CI 1.15 to 1.43; 27 studies) when including only smoking adjusted risk estimates. The elevated risk persisted when restricted to studies that adjusted for other occupational exposures (meta-RR 1.27; 95% CI 0.99 to 1.63; 4 studies). The results remained robust when stratified by study design, gender and study location. Furthermore, exposure-response analyses suggested that the risk increased with duration of employment. There was no evidence of publication bias. Taken together, these results support the conclusion that occupational exposures in painters are causally associated with the risk of bladder cancer.

Imperial College of London and the Health and Safety Laboratory. 2007. The burden of occupational cancer in Great Britain. Technical Annex 5: Bladder cancer. Prepared for the UK Health and Safety Executive. This reports trends in incidence and mortality for bladder cancer as well as a review of occupational risk factors. The main objective of the report is to update attributable fractions for occupational bladder cancer.

Letašiová S, Medveďová AŠovčíková A, et al. Bladder cancer, a review of the environmental risk factors. Environ Health. 2012, 11(Suppl):S:11. The aim of this review is to investigate the links between various environmental risk factors and cancer of the bladder.A systematic literature search was performed using PubMed, Science Direct, Scopus, Scholar Google and Russian Google databases to identify reviews and epidemiological studies on bladder cancer risk factors associated with the environment published between 1998 and 2010. Only literature discussing human studies was considered. Results: Smoking, mainly cigarette smoking, is a well known risk factor for various diseases, including bladder cancer. Another factor strongly associated with bladder cancer is exposure to arsenic in drinking water at concentrations higher than 300 μg/l. The most notable risk factor for development of bladder cancer is occupational exposure to aromatic amines (2-naphthylamine, 4-aminobiphenyl and benzidine) and 4,4'- methylenebis(2-chloroaniline), which can be found in the products of the chemical, dye and rubber industries as well as in hair dyes, paints, fungicides, cigarette smoke, plastics, metals and motor vehicle exhaust. Other studies show that hairdressers and barbers with occupational exposure to hair dyes experience enhanced risk of bladder cancer. Although the number of chemicals related to

occupational exposure is still growing, it is worth noting that it may take several years or decades between exposure and the subsequent cancer.

Rota M, Bosetti C, Boccia S. et al. Occupational exposures to polycyclic aromatic hydrocarbons and respiratory and urinary tract cancers: an updated systematic review and a meta-analysis to 2014. Arch Toxicol. 2014; 88:1479. We updated a previous systematic review by reviewing in details cohort studies on workers employed in selected industries with potential PAH exposure published between 2006 and 2014, and we summarized through a meta-analytic approach the main results of all available cohort studies published between 1958 and 2014 investigating cancers of the respiratory and urinary tracts. In the meta-analysis, a borderline increase risk was also observed for cancer of the bladder in the aluminum production (pooled RR 1.28, 95 % CI 0.98–1.68 from 10 studies) and in iron and steel foundries (pooled RR 1.38, 95 % CI 1.00–1.91 from 9 studies). This updated review and meta-analysis confirm the increased risk from respiratory tract and bladder cancers in selected PAH-related occupations.

Siemiatycki J, Richardson L, Straif K, et al. Listing of occupational carcinogens. Environ Health Perspect 2004;112(15):1447-59. Based largely on the evaluations published by the International Agency for Research on Cancer, and augmented with additional information, the present article represents an attempt to summarize, in tabular form, current knowledge on occupational carcinogens, the occupations and industries in which they are found, and their target organs. We have considered 28 agents as definite occupational carcinogens, 27 agents as probable occupational carcinogens, and 113 agents as possible occupational carcinogens. These tables should be useful for regulatory or preventive purposes and for scientific purposes in research priority setting and in understanding carcinogenesis.

Takkaouche B, Regueira-Mendez C, Montes-Martinez A. Risk of cancer among hairdressers and related workers: a meta-analysis. Int J Epidemiol. 2009;38(6):1512-31. We retrieved studies by systematically searching Medline and other computerized databases, and by manually examining the references of the original articles and monographs retrieved. We also contacted international researchers working on this or similar topics to complete our search. We included 247 studies reporting relative risk (RR) estimates of hairdresser occupation and cancer of different sites. Study-specific RRs were weighted by the inverse of their variance to obtain fixed and random effects pooled estimates. The pooled RR of occupational exposure as a hairdresser was 1.30 (95% CI 1.20-1.42) for bladder cancer. The results restricted to those studies carried out before the ban of two major carcinogens from hair dyes in the mid-1970s were similar to the general results. Hairdressers have a higher risk of cancer than the general population. Improvement of the ventilation system in the hairdresser salons and implementation of hygiene measures aimed at mitigating exposure to potential carcinogens at work may reduce the risk.

Tomatis L, Huff J, Hertz-Picciotto I, et al. Avoided and avoidable risks of cancer. Carcinogenesis. 1997;1:98-105. There is disagreement, however, regarding the proportion of cancer risks attributable to specific etiological factors, including diet, occupation and pollution. Estimates of attributable risks are largely based today on unverified assumptions and the calculation of attributable risks involves taking very unequal evidence of various types of factors and treating them equally. Effective primary prevention resulting in a reduction of cancer risk can be obtained by: (i) a reduction in the number of carcinogens to which humans are exposed; or (ii) a reduction of the exposure levels to carcinogens. Exposure levels that could be seen as sufficiently low when based on single agents, may actually not be safe in the context of the many other concomitant carcinogenic and mutagenic exposures.

Vineis P and Pirastu R. Aromatic amines and cancer. Cancer Causes Control. 1997; 8:346-355.
Epidemiological evidence on the relation between aromatic amines and cancer risk is reviewed. Seven arylamines have been classified by the International Agency for Research on Cancer: benzidine-based dyes and MOCA (4,4'-methylene bis 2-choloroaniline) were considered 'probably' carcinogenic, Group 2A, because of a high level of evidence in experimental animals; two occupational chemicals (2-naphthylamine and benzidine), one drug (Chlornaphazine), and two manufacturing processes (manufacture of auramine and magenta) were included in Group 1 on the basis of 'sufficient' evidence of carcinogenicity in humans. Occupational exposures to aromatic amines explain up to 25 percent of bladder cancers in some areas of Western countries; these estimates might be higher in limited areas of developing countries. Aromatic amines contaminate the ambient air as a component of environmental tobacco smoke. There is increasing evidence that the excess of bladder cancer in smokers is attributable to aromatic amines rather than to other contaminants of tobacco smoke such as polycyclic aromatic hydrocarbons (PAH). A modulating role in the risk of bladder cancer associated with exposure to aromatic amines is played by metabolic polymorphisms, such as the N-acetyltransferase genotype, raising important social and ethical issues.

Vlaanderen J, Straif K, Guha N, et al. Tetrachloroethylene Exposure and Bladder Cancer Risk: A Meta-Analysis of Dry-Cleaning-Worker Studies. Environ Health Perspect. 2014;122(7):661-666. We assessed the epidemiological evidence for the association between tetrachloroethylene exposure and bladder cancer from published studies estimating occupational exposure to tetrachloroethylene or in workers in the dry-cleaning industry. Random-effects meta-analyses were carried out separately for occupational exposure to tetrachloroethylene and employment as a dry cleaner. We qualitatively summarized exposure–response data because of the limited number of studies available. The meta-relative risk (mRR) among tetrachloroethylene-exposed workers was 1.08 (95% CI: 0.82, 1.42; three studies; 463 exposed cases). For employment as a dry cleaner, the overall mRR was 1.47 (95% CI: 1.16, 1.85; seven studies; 139 exposed cases), and for smoking-adjusted studies, the mRR was 1.50 (95% CI: 0.80, 2.84; 4 case–control studies). Our meta-analysis demonstrates an increased risk of bladder cancer in dry cleaners, reported in both cohort and case–control studies, and some evidence for an exposure–response relationship. Although dry cleaners incur mixed exposures, tetrachloroethylene could be responsible for the excess risk of bladder cancer because it is the primary solvent used and it is the only chemical commonly used by dry cleaners that is currently identified as a potential bladder carcinogen. Relatively crude approaches in exposure assessment in the studies of "tetrachloroethylene-exposed workers" may have attenuated the relative risks.

Risk Factor Research Studies

Case RAM and ME Hooker. Tumour of the urinary bladder as an occupational disease in the rubber industry in England and Wales. Br J Prev Soc Med. 1954;8(2):39-50. Study investigates (1) whether there is an increased risk of tumour of the bladder in workmen engaged in rubber occupations compared with the total male population of England and Wales; (2) whether this risk persists in areas where the particular antioxidant under consideration is known to have been used; and (30 whether risk demonstrates a temporal change with 1935-36 as a pivotal point. The study demonstrated reasonably good statistical evidence that in the period between 1936-1951, there is an occupational risk of dying of bladder tumour among males employed in the rubber occupation.

Colt JS, Friesen MC, Stewart PA, et al. A Case-Control Study of Occupational Exposure to Metalworking Fluids and Bladder Cancer Risk Among Men. Occup Environ Med. 2014; 71(10):667-74.
Metalworking has been associated with an excess risk of bladder cancer in over 20 studies.

Metalworking fluids (MWFs) are suspected as the responsible exposure, but epidemiological data are limited. We investigated this association among men in the New England Bladder Cancer Study using state-of-the-art, quantitative exposure assessment methods. Cases (n=895) and population controls (n=1031) provided occupational histories during personal interviews. We computed ORs and 95% CIs relating bladder cancer risk to a variety of exposure metrics, adjusting for smoking and other factors. Non-metalworkers who had held jobs with possible exposure to mineral oil were analysed separately. Bladder cancer risk was elevated among men who reported using straight MWFs (OR=1.7, 95% CI 1.1 to 2.8); risk increased monotonically with increasing cumulative exposure (p=0.041). Use of soluble MWFs was associated with a 50% increased risk (95% CI 0.96 to 2.5). ORs were non-significantly elevated for synthetic/semisynthetic MWFs based on a small number of exposed men. Non-metalworkers holding jobs with possible exposure to mineral oil had a 40% increased risk (95% CI 1.1 to 1.8). Exposure to straight MWFs was associated with a significantly increased bladder cancer risk, as was employment in non-metalworking jobs with possible exposure to mineral oil. These findings strengthen prior evidence for mineral oil as a bladder carcinogen.

Colt JS, Karagas MR, Schwenn M, et al. Occupation and bladder cancer in a population-based case-control study in Northern New England. Occ Environ Med. 2011;68(4):239-249. We used data from a large, population-based case-control study in Maine, New Hampshire, and Vermont to examine relationships between occupation, industry and bladder cancer risk. Male precision metalworkers and metalworking/plasticworking machine operators had significantly elevated risks and significant trends in risk with duration of employment (precision metalworkers: OR 2.2, 95% CI 1.4 to 3.4, p(trend) = 0.0065; metalworking/plasticworking machine operators: OR 1.6, 95% CI 1.01 to 2.6, p(trend) = 0.047). Other occupations/industries for which risk increased significantly with duration of employment included: for men, textile machine operators, mechanics/repairers, automobile mechanics, plumbers, computer systems analysts, information clerks, and landscape industry workers; for women, service occupations, health services, cleaning and building services, management-related occupations, electronic components manufacturing and transportation equipment manufacturing. Men reporting use of metalworking fluids (MWF) had a significantly elevated bladder cancer risk (OR 1.7, 95% CI 1.1 to 2.5).

Colin R, Grzyebyk M, Wild P, et al. Bladder cancer and occupational exposure to metalworking fluid mist: a counter-matched case-control study in French steel-producing factories. Occup Environ Med 2018 Jan 26 [Epub ahead of print]. A nested case-control study on bladder cancer was set up in a cohort of workers from six French steel-producing factories. Three controls were randomly selected for each incident bladder cancer case and matched on age at diagnosis and counter-matched on a surrogate measure of exposure to MWFs derived from a job-exposure matrix. Cases (n=84) and controls (n=251) were face-to-face interviewed. In the 25 years before diagnosis, ORs increased significantly with duration of exposure to straight MWFs (OR=1.13 (1.02-1.25)) and increased with frequency-weighted duration of exposure to straight MWFs (OR=1.44 (0.97-2.14)). These results remained valid after adjusting for duration of smoking, average number of cigarettes smoked per day, time since smoking cessation and exposure to polycyclic aromatic hydrocarbons (PAHs). ORs also increased with soluble MWFs but not significantly.

Friesen MC, Costello S, Eisen EA. Quantitative Exposure to Metalworking Fluids and Bladder Cancer Incidence in a Cohort of Autoworkers. A J Epidemiol; 2009;169(12):1471-1478. The authors report results from the first cohort study to examine bladder cancer incidence in relation to quantitative exposures to metalworking fluids (MWFs), based on 21,999 male Michigan automotive workers, followed from 1985 through 2004. Cox regression was used to estimate hazard ratios based on categorical exposure variables for straight, soluble, and synthetic MWFs, as well as duration of exposure

to ethanolamines and nitrosamines. Increased bladder cancer risk was associated with straight MWFs but not with any other exposure. The hazard ratio increased with cumulative exposure to a maximum of 2-fold observed at 75 mg/m(3)-year straight MWF exposure (lagged 20 years).

Koutros S, Silverman DT, Alavanja MC, et al. 2016. Occupational exposure to pesticides and bladder cancer risk. Int J Epidemiol, 45(3),792–805. We observed associations with bladder cancer risk for two imidazolinone herbicides, imazethapyr and imazaquin, which are aromatic amines. Ever use of imazaquin (RR = 1.54, 95% CI: 1.05, 2.26) was associated with increased risk whereas the excess risk among users of imazethapyr was evident among never smokers (RR in highest quartile vs non-exposed = 3.03, 95% CI: 1.46, 6.29, P-interaction = 0.005). We also observed increased risks overall and among never smokers for use of several chlorinated pesticides including chlorophenoxy herbicides and organochlorine insecticides.veral associations between specific pesticides and bladder cancer risk were observed, many of which were stronger among never smokers, suggesting that possible risk factors for bladder cancer may be more readily detectable in those unexposed to potent risk factors like tobacco smoke.

Steenland K, Piacitelli L, Deddens J, et al. Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibezo-p-dioxin. J Natl Cancer Inst. 1999;5(91):779-786. In 1997, the International Agency for Research on Cancer classified 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) as a group 1 human carcinogen, based largely on four highly exposed industrial cohorts that showed an excess of all cancers combined. In this study, we extended the follow-up period for the largest of these cohorts by 6 years and developed a job-exposure matrix. Bladder cancer was also statistically significantly elevated considering those workers restricted to TCDD exposure for more than 1 year and analyzed for the period of 20 years or more of potential latency, the SMR for all cancers was 1.29 (95% CI 1.10–1.51).

Yi SW, Ryu SW Ohrr H, et al. Orange exposure and risk of death in Korean Vietnam veterans: Korean Veterans Health Study. Int J Epidemiol. 2014;43:1825-1834. Agent Orange (AO) was a mixture of phenoxy herbicides, containing several dioxin impurities including 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Various military herbicides, including AO, were sprayed by the US military and allied forces for military purposes during the Vietnam War. This study was performed to identify the associations between the AO exposure and mortality in Korean Vietnam veterans. The mortality from all causes of death was elevated with AO exposure. The deaths due to all sites of cancers combined and some specific cancers, including cancers of the stomach, small intestine, liver, larynx, lung, bladder and thyroid gland, as well as chronic myeloid leukaemia, were positively associated with AO exposure.

Prevention Studies/Documents

NIOSH (National Institute for Occupational Safety and Health). Current Intelligence Bulletin 68: Occupational Carcinogen Policy. July 2017. Outlines NIOSH's occupational carcinogen policy, including a brief description of prior policies that connects to OSHA's policies for setting standards for carcinogens.

NIOSH (National Institute for Occupational Safety and Health). Hierarchy of Controls. Accessed, April 8, 2018. Description of the Hierarchy of industrial hygiene controls as shown in Figure 1.

Consumer Products

Risk Factor Authoritative Sources

IARC (International Agency for Research on Cancer). IARC Monographs on the evaluation of carcinogenic risks to humans. Volume 73: Nitrilotriacetic acid and its salts. 1999. Lyon, France. The working group concluded that nitrilotriacetic acid and its salt are possibly carcinogenic to humans based on animal studies (including benign and malignant bladder tumors in male and female rats). There were no studies of nitrilotriacetic acid in humans.

IARC (International Agency for Research on Cancer). 2010. IARC Monographs on the evaluation of carcinogenic risks to humans. Volume 92: Some Non-heterocyclic Polycyclic Aromatic Hydrocarbons and Some Related Exposures. 2010. Lyon, France. The working group concluded that creosotes are probably carcinogenic to humans based on animal studies and on limited evidence from human studies of occupations with creosote exposure. One Swedish study reported increased bladder cancer with work in occupations with creosote exposure.

IARC (International Agency for Research on Cancer). IARC Monographs on the evaluation of carcinogenic risks to humans. Volume 99: Occupational Exposures of hairdressers and barbers and personal use of hair colourants. 2010. Lyon France. The working group concluded that the evidence for personal hair dye use as a cause of bladder cancer in humans was inadequate – that is, too conflicting. Occupational exposure as a hairdresser or barber was considered probably carcinogenic, on the other hand, based on evidence of increased bladder cancer risk among male hairdressers.

IARC (International Agency for Research on Cancer). IARC Monographs on the evaluation of carcinogenic risks to humans. Volume 100F: Chemical Agents Related to Occupation. 2012. Lyon France. The working group concluded: (a) 4-aminobiphenyl 'causes cancer of the urinary bladder', based primarily on studies of male workers in 4-aminobiphenyl production and in the rubber industry; (b) *ortho*-Toluidine 'causes cancer of the urinary bladder', with the most informative study based on workers producing chemicals for use in the rubber industry; (c) benzidine 'causes cancer of the urinary bladder', based primarily on studies of workers in benzidine production and in the dye industry. One of these studies reported a reduction in bladder cancer incidence at a benzidine manufacturing plant after measures to reduce exposure were implemented. (d) 4,4'Methylenebis(2-chlorobenzenamine) is carcinogenic to humans based on animal studies (including bladder tumors in female dogs) and on evidence that this chemical acts similarly to other aromatic amines such as *ortho*-Toluidine that are known human bladder carcinogens.

NTP (National Toxicology Program) Report on Carcinogens, 14th Edition. 2016. Research Triangle Park, NC: United States https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html
- **2,2-bis(bromomethyl)-1,3-propanediol (BBMP):** Reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from animal studies (including urinary bladder tumors with oral exposure in male rats). No studies in humans.
- **Disperse blue 1**: Reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from animal studies, including benign and malignant urinary bladder tumors in male and female rats with dietary administration. Used in hair-color formulations, as a fabric dye, for coloring plastics, and in some personal care products including hair mousse and toothpaste. No studies in humans.

Systematic Reviews/Meta-analyses

Turati, F., Pelucchi, C., Galeone, C., Decarli, A., & La Vecchia, C. Personal hair dye use and bladder cancer: a meta-analysis. Ann Epidemiol. 2014;24(2):151-159. This most recent meta-analysis of personal hair dye use and bladder cancer included 14 case-control and two cohort studies published between 1968 and 2012. Studies were primarily of North American populations, though there were a few from Asia and Europe and one from Hawaii. The authors report no evidence of an association between personal hair dye use and bladder cancer across the studies, but it is not clear that the meta-analysis approach is appropriate. The authors don't provide any assessment of quality of the individual studies, and they included a study which evaluated bladder cancer mortality. For a disease with a high survival rate, mortality may not be comparable to incidence. Importantly, despite the increase in the number of studies, these authors did not or were not able to consider potentially more susceptible sub-groups, including smokers and those with the NAT2 slow acetylation phenotype.

Kelsh MA, Alexander DD, Kalmes RM, Buffler PA. Personal use of hair dyes and risk of bladder cancer: a meta-analysis of epidemiologic data. Cancer Causes Control. 2008;19(6):549-558. A meta-analysis of 11 case-control and one cohort study found no association for ever use of personal hair dye and bladder cancer, and little evidence for use of permanent hair dye or for duration or frequency of use. The authors note the need for more studies that examine smokers and non-smokers separately and that consider possibly more susceptible sub-groups (e.g. NAT2 slow acetylators).

Rollison, D.E., Helzlsouer, K. J., Pinney, S.M. Personal hair dye use and cancer: a systematic literature review and evaluation of exposure assessment in studies published since 1992. J Toxicol Environ Health B Crit Rev. 2006; 9(5):413-439. A critical review of two case-control and one cohort study published since IARC's 1993 review showed that the evidence for personal hair dye use and bladder cancer remained inconsistent. The authors carefully considered variation in the quality of exposure assessment across studies and noted that at least one study that did a good job assessing exposure found that longer duration of permanent hair dye use was associated with increased bladder cancer risk and that use, duration and frequency of permanent hair dye were associated with higher risk among NAT2 slow acetylators (but not rapid acetylators). However, no association was seen for duration of permanent hair dye use and bladder cancer in another study with similarly strong exposure assessment.

Risk Factor Research Studies

Johannson GM, Jönsson BA, Axmon A, et al. Exposure of hairdressers to ortho- and meta-toluidine in hair dyes. Occup Environ Med. 2015; 72(1):77-63. Carcinogenic aromatic amines derived from hair dyes have recently received new attention. One of these is ortho (o)-toluidine, which is classified as carcinogenic to humans. We measured eight potentially carcinogenic aromatic amines in the blood of 295 hairdressers, 32 users of hair dyes and 60 controls. The study was restricted to female non-smokers. For hairdressers, o- and m-toluidine concentrations increased significantly with the weekly number of hair waving (p=0.020) and permanent hair dyeing treatments (p=0.026), respectively. o-Toluidine and m-Toluidine concentrations also tended (p=0.076 and 0.080, respectively) to increase with the frequency of light-colour permanent hair dye treatments. Hairdressers who use light-colour permanent hair dyes, other permanent hair dyes and hair waving treatments seem to be exposed to o- and m-toluidine as indicated by associations with the number of treatments performed. Analyses of hair waving and hair dye products should be performed to identify the possible sources of exposure to o- and m-toluidine.

Koutros S, Silverman DT, Baris D, et al. Hair dye use and risk of bladder cancer in the New England bladder cancer study. Int J Cancer. 2011;129(12):2894-904. This large study included 1193 bladder cancer cases identified from cancer registries and hospital pathology departments of Maine, Vermont, and New Hampshire and 1418 age, sex and state-matched controls randomly selected from DMV and CMS records. For the study population as a whole, there was no evidence of increased bladder cancer risk with hair dye use. When the authors looked separately at women with and without a college degree, however, they observed elevated bladder cancer risk with permanent hair dye use, but only among the college educated women. There was also a suggestion of higher risk among college-educated women with the NAT2 slow acetylation phenotype who exclusively used permanent dye. Since there is not a clear hypothesis for why the association between hair dye use and bladder cancer would differ with level of education, these results should be treated with caution.

Mendelsohn JB, Li QZ, Ji BT, et al. Personal use of hair dye and cancer risk in a prospective cohort of Chinese women. Cancer Sci. 2009;100(6):1088-91. This analysis considered 73,366 in the Shanghai Women's Health Study. Women in study were free of cancer when they enrolled and answered questions about hair dye use. After following these women for an average of 7 years, the study did not find a significant association with bladder cancer. However, the exposure assessment did not capture type (e.g. permanent, semi-permanent) or color of dyes used, and the authors chose to classify women who had not used hair dye within the past three years as "never users," which could potentially mask an association with bladder cancer due to earlier exposures. Further, the authors were not able to consider potentially more susceptible sub-groups identified in earlier studies, including smokers and those with the NAT2 slow acetylation phenotype.

Shakhssalim, N., Hosseini, S. Y., Basiri, A., et al. Prominent bladder cancer risk factors in Iran. *Asian Pac J Cancer Prev. 2010;11*(3):601-606. The study included 692 bladder cancer cases from five provinces in Iran, identified from the Iranian cancer registry, and 692 neighborhood controls matched on age and gender. The authors reported a positive association between hair dye use (at least once a year) and bladder cancer, but there are several concerns about the study design and data analysis that limit meaningful interpretation of this study. For example, 40% of cases but only 20% of controls had hair dye use questions answered by a proxy (close relative). The analysis controlled for smoking, but ex-smokers were grouped together with current smokers and the analysis did not appear to control for the matching variables (age and gender) which would introduce bias into the results.

Tao, L., Day, B. W., Hu, B., et al. Elevated 4-aminobiphenyl and 2,6-dimethylaniline hemoglobin adducts and increased risk of bladder cancer among lifelong nonsmokers--The Shanghai Bladder Cancer Study. Cancer Epidemiol Biomarkers Prev. 2013; 22(5): 937-945. The study included 494 bladder cancer cases from the Shanghai Cancer registry diagnosed between 1995 and 1998 and 499 age- and sex-matched controls randomly selected from a registry of Shanghai residents. The authors found that among individuals who had not smoked regularly for at least the past two years, having high levels vs no or low levels of 4-ABP hemoglobin adducts in blood was associated with 2x higher odds of bladder cancer. Because the finding was among non-smokers, it may reflect an association with other potential sources of 4-ABP exposure, such as hair dye contaminated with 4-ABP. However, the study population was 80% male and hair dye use and other potential 4-ABP sources were not actually assessed.

Prevention Studies/Documents

[FDA] US Food and Drug Administration. Hair Dyes. Accessed July 30, 2018 at: https://www.fda.gov/Cosmetics/ProductsIngredients/Products/ucm143066.htm

Gene Environment Interactions

Carreon T, Ruder AM, Schulte PA, et al. NAT2 slow acetylation and bladder cancer in workers exposed to benzidine. **Int J Cancer. 2006;118:161–8.** This study expands a previous study of NAT2 polymorphisms and bladder cancer in male subjects occupationally exposed only to benzidine. A protective association was observed for the slow NAT2 genotype (bladder cancer OR = 0.3; 95% CI = 0.1 = 1.0) after adjustment for cumulative benzidine exposure and lifetime smoking. Individuals carrying NAT1wt/*10 and NAT1*10/*10 showed higher relative risks of bladder cancer (OR = 2.8, 95% CI = 0.8-10.1 and OR = 2.2, 95% CI = 0.6-8.3, respectively). No association was found between GSTM1 null and bladder cancer. A meta-analysis risk estimate of case-control studies of NAT2 acetylation and bladder cancer in Asian populations without occupational arylamine exposures showed an increased risk for slow acetylators. The lower limit of the confidence interval (OR = 1.4; 95% CI = 1.0-2.0) approximated the upper confidence interval for the estimate obtained in our analysis. These results support the earlier finding of a protective association between slow acetylation and bladder cancer in benzidine-exposed workers, in contrast to its established link as a risk factor for bladder cancer in people exposed to 2-naphthylamine and 4-aminobiphenyl. Study findings suggest the existence of key differences in the metabolism of mono- and diarylamines.

Cantor KP, Villanueva CM, Silverman DT, et al. Polymorphisms in *GSTT1, GSTZ1,* and *CYP2E1, Disinfection By-products, and Risk of Bladder Cancer in Spain*. **Environ Health Perspect. 2010;118(11):1545-1550.** In this study we investigated the combined influence of DBP exposure and polymorphisms in glutathione S-transferase (GSTT1, GSTZ1) and cytochrome P450 (CYP2E1) genes in the metabolic pathways of selected by-products on bladder cancer in a hospital-based case-control study in Spain. THM exposure was positively associated with bladder cancer: adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were 1.2 (0.8-1.8), 1.8 (1.1-2.9), and 1.8 (0.9-3.5) for THM quartiles 2, 3, and 4, respectively, relative to quartile 1. Associations between THMs and bladder cancer were stronger among subjects who were GSTT1 +/+ or +/- versus GSTT1 null (P(interaction) = 0.021), GSTZ1 rs1046428 CT/TT versus CC (P(interaction) = 0.018), or CYP2E1 rs2031920 CC versus CT/TT (P(interaction) = 0.035). Among the 195 cases and 192 controls with high-risk forms of GSTT1 and GSTZ1, the ORs for quartiles 2, 3, and 4 of THMs were 1.5 (0.7-3.5), 3.4 (1.4-8.2), and 5.9 (1.8-19.0), respectively.

Silverman D, Koutros S, Figueroa JD, et al. Bladder cancer. In M Thun, MS Linet, JR Cerhan, et al., eds. Cancer Epidemiology and Prevention. 4th ed. **New York: Oxford University Press, 2017.** This comprehensive review appraises the state of the evidence for the broad range of risk factors that have been investigated in their relationship with bladder cancer.

Vineis P and Schulte PA. Scientific and ethical aspects of genetic screening of workers for cancer risk: the case of the N-acetyltransferase phenotype. **J Clin Epidemiol. 1995;48:189–97.** This paper addresses scientific and ethical issues involved in the use of genetic screening techniques which intend to identify individuals that have more than average susceptibility to develop cancer from workplace chemical exposures. The case in point is the genetic polymorphism for N-acetyltransferase activity and the risk of bladder cancer in workers exposed to carcinogenic arylamines. The acetyltransferase polymorphism is related to the metabolic activation and deactivation of carcinogenic arylamines. Any genetic screening test for cancer susceptibility must be based upon sound science. For example, it must be demonstrated that a specific metabolic phenotype is a risk factor for cancer and, further, that the available tests accurately classify the subjects as to the phenotype. If there is a poor correspondence between phenotype and genotype, or a large intra-individual variability in phenotype, misclassification may

result. Also, bias, arising as a consequence of enzyme induction by specific substrates, must be ruled out. Genetic screening of workers for susceptibility to cancer seems to us an ethically unacceptable and premature, application of the science.