Cancer & Environment Network of Southwestern Pennsylvania

Year in Review:
Reflections on 2023 Peer-Reviewed Research on Cancer and Environment

A key commitment of the Cancer and Environment Network of Southwest Pennsylvania (CENSWPA) is to amplify the scientific evidence that underpins the need for preventative action on environmental causes of cancer in the region. CENSWPA is pleased to issue its 2023 "Year in Review" – reflections from the peer-reviewed research on cancer risks associated with exposure to chemical and radiological toxicants in our environment and workplaces.

CENSWPA conducts monthly searches of the scientific literature using PubMed and other web-based tools and features the full list of articles with links to the abstract on its website. An in-depth review of one of the articles is also featured in CENSWPA's Monthly Digest. CENSWPA's monthly reviews are not intended to be exhaustive, but rather an attempt to capture seminal articles to keep Network participants updated on research relevant to the Network's purpose and activities.

At the beginning of 2023, CENSWPA's Teams looked back on the annual collection of articles and identified notable highlights to include in its "Year in Review." For the 2023 list of articles, these notable topics include:

1. New insights related to childhood cancer risks associated with unconventional natural gas development and ongoing consistency in the research regarding childhood cancers linked with agricultural chemicals and air pollution.
2. The need to focus on environmental injustices related to cancer risks.
3. The significant collection of cancer risks and risk reduction opportunities represented within the built environment.
4. The importance of considering endocrine disrupting chemicals as contributors to cancer and changes in consumer product use as a prevention strategy.

Each of these topics are reviewed below. It is important to note that the majority of research studies reviewed focus on etiologic research – epidemiologic studies investigating the causal contribution of an environmental and/or occupational risk factor with cancer. Understanding this evidence is crucial, but even more crucial is acting on the knowledge to prevent future harms. Needs and opportunities for preventative action are also described in relation to this growing evidence-base.

For questions about technical terms used to describe the study results, please see CENSWPA's glossary of terms.

1. New insights related to risks associated with unconventional gas development in the region and ongoing consistency in the research regarding childhood cancers linked with air pollution and pesticides.

Children are especially vulnerable to hazardous chemicals in their environments, beginning at the fetal stage and continuing through adolescence. As explained by the U.S. Environmental Protection Agency, during these developmental periods, children's bodies are in a dynamic state of growth, with cells multiplying and organ systems developing at a rapid rate. Given the short latency period for childhood cancers to develop as compared to much longer periods for different adult cancers, children are often the sentinels of environmental harms, such as clustering events observed in Toms River Township, NJ and Woburn, MA.

Childhood cancers in the SW Pennsylvania region linked to fracking activities. CENSWPA is particularly concerned about the cancer experience in our own region. In 2023, findings from a long-awaited University of Pittsburgh School of Public Health study were released that examined the risk of childhood cancers associated with unconventional natural gas development activities (Talbot et al. 2023). This case-control study examined children born from 1990 through 2019 and subsequent cancer outcomes among those living in eight counties in Southwestern Pennsylvania with active unconventional natural gas development activities (a.k.a. fracking). Results demonstrate that children living within 1 mile of one or more fracturing wells at the time of diagnosis had a 5- to 7-fold statistically significant increased risk of developing lymphoma. A "dose-response" connection was also observed – elevated risk compared to controls was observed up to 5 miles from an active well and this risk grew stronger the closer a child's residence was to such wells. This study however did not affirm increases in childhood leukemia, which has been reported in prior studies examining risk associated with fracking activities, such as the study by Clark et al. 2022 reviewed in CENSWPA's 2022 Year in Review. In the University of Pittsburgh study, in comparison to controls, over a 7-fold increased risk of childhood leukemia was observed among those living closest to active wells (within ½ mile), but these results were not statistically significant.

Childhood Cancer and Air Pollution. There is substantial evidence linking childhood cancers, particularly leukemia, with traffic-related air pollution (see Childhood Cancer Prevention Initiative report, and CENSWPA's Year in Review from 2021 and 2022). Many of the constituents in vehicular emissions however are the same as what is seen in point source emissions. In the case-control study conducted by Malavolti et al. 2023, researchers examined childhood leukemia risk associated with living near gas stations given known risks associated with adult leukemia and exposure to benzene. Compared to children who lived greater than 1,000 meters from a gas station, children who lived less than 50 meters from a gas station experienced a 2.2-fold increase in leukemia, and nearly a 3-fold increase for those with acute lymphocytic leukemia (ALL). Risk was especially elevated, among children ages 5 and older (nearly a 5-fold increased risk among those with ALL). Zhong et al. 2023 examined exposure to PM2.5 air pollution and risk of ALL among children in California based on the use of regional air monitors. A non-statistically significant 25% elevation in risk associated with exposure to $PM_{2.5}$ was observed among non-Hispanic white children in [per 10 µg/m3 increase in $PM_{2.5}$).

Childhood Brain Tumors and Pesticides. Mota et al. 2023 conducted a meta-analysis of studies exploring the development of CNS tumors in children associated with exposure to pesticides. Compared to controls, they observed a 1.5-fold increase in risk for one type of CNS tumor, astrocytoma (the most frequent subtype of CNS tumors) based on exposure to all pesticide classes when exposures occurred before and during pregnancy. Both occupational exposure to pesticides as well as exposures based on residential use to pesticides were implicated. Another meta-analysis and systematic review conducted by Onyije et al.(2023) also found similar elevations in risk for brain tumors more broadly. Compared to controls, residential exposure to insecticides and herbicides during childhood were both implicated (1.5 and 2-fold increased risk, respectfully). Similar increased risks were observed for prenatal exposure to insecticides (1.5-fold increased risk). The study also reported on increased risk among children whose fathers were occupationally exposed to pesticides compared to controls, and these risks were higher among children in the U.S. compared to those in Europe, which is consistent with data from the Food and Agriculture Organization of the United Nations (FAO) demonstrating that the U.S. applies the highest level of pesticides globally. Hymel et al. (2023) examined a range of agricultural exposures and risk of childhood neuroblastoma in a systematic review and meta-analysis. Their findings from the meta-analysis reveal that children with a parent exposed to any pesticide had a 1.25-fold increased risk of being diagnosed with neuroblastoma than those not exposed to any pesticide. The meta-analysis also revealed support for a 1.5-fold increased risk associated with parental exposure to insecticides compared to those not exposed as well as a small suggestive increased risk among those living in areas near agricultural fields/crops compared to those not exposed.

Childhood Leukemia and Pesticides. Ruth et al. 2023 investigated risk of childhood leukemia (specifically acute lymphocytic leukemia (ALL) in association with parental exposure to insecticide use 1-month

before/during pregnancy. The study was strengthened by its ability to utilize controls with very clear absence of exposure to household insecticides – a problem with prior studies whereby controls still experienced some level of exposure. The study revealed excesses of ALL for 10 types of insecticidal products compared to controls. The most egregious elevated risks included an over 4-fold increased risk of ALL among mothers who used insecticide for termites compared to unexposed controls. The researchers conclude that the weight of the evidence to date, "suggest that the implementation of warning labels and public health intervention to reduce household use of [insecticides] during pregnancy is warranted." Nguyen et al. examined childhood leukemia risks associated with specific pesticides as part of a parallel investigation of risk related to electromagnetic fields as nurseries and agricultural fields are often in proximity to high tension power lines. The study is notable as it calls out specific types of pesticides, versus pesticides generically. For example, the study found increased risks (ranging from increases of ~1.3 to 1.8-fold) for childhood leukemia related to exposure to the pesticides chlorpyrifos, dimethoate, mancozeb, oxyfluorfen, oryzalin, and pendimethalin. Of particular note is "who" experienced the burden of these increased risks. The study noted that the majority of those living near these agricultural facilities were Hispanic/Latino although the study was not designed to explore racial/ethnic disparities in cancer risk. This observation points to a weakness in epidemiologic investigations in their ability to capture environmental injustices; more often than not, race is considered a confounding risk factor and thus controlled for in the analysis rather than exposing who is bearing the cancer burden.

2. The need to focus on environmental injustices related to cancer risks.

Despite the increased focus on environmental justice in the current Presidential administration and over 250 declarations naming racism as a public health crisis as passed at the state, county, and municipal level (APHA 2024), there remains a paucity in the epidemiological literature revealing the range of environmental and occupational exposure scenarios documenting disparities in cancer risk. As mentioned above, race is commonly understood as an independent risk factor for cancer. Thus, it is standard practice for studies to "control" for such risk factors that may "confound" (meaning make difficult to interpret) the association under investigation. The literature – including studies published in 2023 – clearly document *disparities in exposure* among environmental justice communities. For example, in the review of the literature conducted by Larsen et al. 2023, neighborhoods with higher proportions of low-income, non-white residents as well as same-sex couples were documented as having higher exposures to carcinogens and environments that influence cancer risk. In a similar review that focused on structural racism and lung cancer, Bonner et al. 2023, demonstrated that racial and ethnic minority groups are more likely than non-white counterparts to experience higher levels of air pollution and other known carcinogenic exposures due to segregation of neighborhoods and poor housing quality. As race was the primary focus of the review, Bonner et al. also found that racial and ethnic minority groups compared to non-white groups were more likely to have higher exposures to pesticides, silica, and asbestos. Howarth and Eiser's 2023 review documented a range of regional examples of environmental disparities in exposure, from exposure to arsenic and radioactive compounds among tribal populations who were forced to live on mining lands or downwind of nuclear facilities; to low-income, Latino farmworkers in the south exposed to a range of carcinogenic pesticides; to rural low-income often elderly white people living in areas such as SW Pennsylvania where fracking is dominant. Howarth and Eiser include cancer statistics documenting elevated cancer risks related to these experiences, such as a 10-fold prevalence of cancer among tribes living in areas contaminated by a former uranium mill.

Although it is common sense to use evidence of exposure disparities, particularly those documenting increased exposure to carcinogens, as justification for the need for risk reduction interventions, efforts to pursue prevention needs are often slowed by the lack of epidemiologic evidence which is our main scientific tool to answer the question, "Are the observed exposure to toxicants in the environment associated with/a potential cause of cancer in the area of concern?" With a lack of such studies, industry, politicians and

regulators are too quick to blame other risk factors for the elevations in cancer incidence – such as lifestyle factors including obesity and smoking (Terrell and St. Julien 2022) and thus, dismissive of environmental exposure disparities. Moreover, such research gaps have direct consequences for residents as state regulators often cite a lack of evidence of adverse health outcomes when making industrial permit decisions Terrell and St. Julien 2022).

Wilkins and Schulz 2023 wrote an important commentary regarding an antiracist research and practice agenda for environmental health. The above need – making more explicit in epidemiologic studies cancer risks borne by environmental justice communities – is critical for future research to more directly tie environmental harms with health disparities. Wilkins and Shultz outline very specific recommendations for antiracist practices for engaging communities in such epidemiologic research as well as environmental health research more broadly. Such practices as written by the authors include:

1. developing mutually agreed-upon processes and principles to ensure equitable resource distribution, decision-making power, and representation;
2. supporting and amplifying new and existing leadership from within disproportionately impacted communities;
3. critically examining and addressing practices and policies that reproduce inequities both within community–academic partnerships and in environmental decision-making processes; and
4. ensuring accountability of research and funding institutions to communities who invest their time and energy to support research, by ensuring dissemination and applications of findings to support social change and environmental justice.

3. The significant collection of cancer risks and risk reduction opportunities represented within the built environment.

In 2023, the Pennsylvania Department of Health published its 10-year cancer control plan (PDOH 2023), which emphasizes the role of the built environment in shaping cancer risks and related risk reduction opportunities. Cancer risks related to the built environment are highly influenced by urban planning/land-use design decisions, which have direct impacts related to residential and industrial zoning, air quality, access to healthy foods, parks and open space. Proximity matters: studies over the last decades reveal that the closer people live to sources of known carcinogens, such as traffic-related air pollutants or emissions from industrial facilities, increased cancer risk associated with exposures are observed (see CENSWPA's Year in Review from 2021 and 2022). Other sources of concern to cancer risks in the built environment include exposure to pesticides in public parks and lands as well as the historical use of asbestos shingles on houses, which can release asbestos fibers when they deteriorate. On the flip side, proximity and access also matters to reduce cancer risks. Living close and having access to healthy food markets and sources, green space, and urban designs that influence physical activity are all important cancer prevention opportunities.

CENSWPA examined the list of research articles from 2023 with an eye towards cancer risks and risk reduction opportunities in the built environment. Much of what was found was strongly correlated to the sections featured above regarding environmental justice as well as childhood cancers. The built environment and environmental justice are significantly intertwined. As reviewed in the scoping reviews by Larsen et al. 2023, and Bonner et al. 2023, urban design decisions regarding the use of redlining – the systematic denial of services such as mortgages, insurance loans, and other financial services to residents seeking to live in specific city neighborhoods based on their race or ethnicity – has resulted in residential neighborhoods being co-located near industrial, agricultural and transportation corridors. Consequently, low-income and non-white residents in these neighborhoods routinely experience higher levels of exposure to carcinogenic air pollutants associated with emissions from vehicles, industrial activities and hazardous waste sites. Proximity was also a key driver to higher risks observed in multiple childhood cancer studies reviewed above. In the case of risk of childhood cancers associated with unconventional natural gas development activities (Talbot et al. 2023), it

was living in close proximity to active wells that was the driver for the elevated risks of childhood lymphoma. Similarly, living near gas stations (by Malavolti et al. 2023) and agricultural fields and nurseries (Nguyen et al. 2023) were associated with increased risk of childhood leukemia compared to those living further distances away.

A fundamental built environment cancer risk reduction opportunity revealed in the 2023 research studies is zoning – the need to increase residential set-back distances from known sources of cancer harms (as well as other harms to health). Although the most protective prevention strategy is to eliminate the use or emission of known carcinogens, where we still have a dependency on their use given a lack of alternatives, then the most protective course of action is to minimize exposure. Rethinking and restructuring our zoning policies that reduce exposure to nearby residents from hazardous environmental pollutants is a crucial need to reduce cancer in the SW Pennsylvania region and beyond.

4. The importance of considering endocrine disrupting chemicals as contributors to cancer and changes in consumer product use as a risk reduction opportunity

Endocrine disrupting chemicals (EDCs) are substances that interfere with any aspect of the actions of hormones. Some EDCs can mimic hormones; others can block hormones from doing their job; while others can increase or decrease levels of hormones in our bodies by impacting how they are made, degraded or stored in our bodies. Substances considered EDCs are found in a broad range of product categories, from pesticides to children's products, cleaning solvents, flame retardants, building materials/furnishings, and food contact materials among many others. What is particularly nefarious about EDCs is that they can have effects at extremely low doses, which goes against the truism in health research, "the dose makes the poison" (i.e., the higher the dose, the worse the effect at both individual and population-levels; this is simply not true of EDCs. Extremely low doses of EDCs are enough to act like hormones in our bodies and trigger a cascade of endocrine disrupting effects, many of which have been linked to cancers.

The 2023 list of research articles developed by CENSWPA are replete with articles about cancer risks associated with exposure to ECDs. Rather than recounting findings from each of these articles, one review article is particularly useful as it outlines the state of science to date on the topic. Macedo et al. 2023 conducted a systematic review of the literature over the last 40 years. Their review focused on human studies as the majority of research on EDCs have focused mostly on cellular and animal studies.

- Breast Cancer. Macedo et al. found that the role of EDCs in breast cancer risk has been the most studied. Increased risks for breast cancer have been observed for exposure to EDCs that are heavy metals (strontium, arsenic and cadmium); exposure to per- and polyfluorinated alkyl substances (PFAS) (used in products for their oil, water, and stain resistance properties such as stain resistant carpets, waterproof textiles, etc.); and exposure to nonylphenol epoxide (used in products such as laundry and dish detergents).
- Prostate Cancer. Some pesticides are endocrine active and have been shown in studies reviewed by Macedo et al. to elevate prostate cancer risk. In addition, the review found that exposure to a range of additional EDCs increased prostate cancer risk including: phthalates (commonly used as a softening additive in plastics such as polyvinyl chloride (PVC) in products such as plastic shower curtains, toys or vinyl flooring); exposure to the heavy metal, cadmium; bisphenol-A (used in can linings and thermal receipt paper); solvents (including perchloroethylene, benzene styrene, toluene and xylene) and polychlorinated biphenols (PCBs). PCBs were banned in the 1970s, but can still be found in hazardous waste sites as well as buildings (such as schools) as they were used in caulking and electronic products.
- Ovarian Cancer. Macedo et al. found that ovarian cancer was the least studied target organ related to effects associated with exposure to EDCs. Exposure to the pesticide, cis-heptachlor epoxide; a

poly brominated flame-retardant, and dioxins were all associated with an increase in ovarian cancer risk.

- Thyroid Cancer. Macedo et al. found that studies have observed increased risks for thyroid cancer in association with exposure to PCBs, phthalates, pesticides, heavy metals (cadmium and lead), bisphenol-A and flame retardants.
- Testicular Cancer. Exposure to phthalates (specifically DEHP), PCBs and pesticides were observed in studies reviewed by Macedo et al. to increase testicular cancer risk.
- Uterine Cancer. Lastly, Exposure to PCBs, heavy metals (specifically cadmium), phthalates (specifically DEHP) and silica dust were reported in association with increased uterine cancer risk.

EDCs are in so many products as described above. Yet the study by Dairkee et al. 2023 provides support that if we stop our use of products containing EDCs, we can reduce our cancer risk. Dairkee et al. specifically looked at the issue of EDCs used in personal care products/cosmetics, which include substances such as parabens (used as preservatives) and phthalates (which can be found in hair spray, nail polish and fragrances). Researchers conducted a month-long study in which the intervention group stopped using personal care products containing ECDs while the control group kept using such products. Compared to controls, levels of these chemicals in the urine of the intervention group significantly declined and there was a complete reversal of the presence of cellular traits associated with breast cancer.

The evidence base related to risks associated with cancer and environmental exposures strengthens every year. Scientific certainty in understanding causal environmental cancer risks is seldom possible. When sufficient evidence of harm exists, society has a duty to act.

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