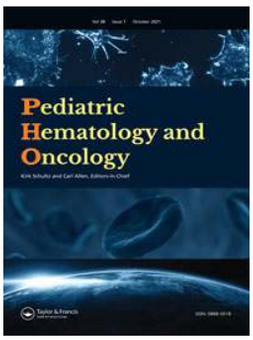

Pediatric Hematology and Oncology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ipho20

A brief review of the current knowledge on environmental toxicants and risk of pediatric cancers

Omar Shakeel, Philip J. Lupo, Simon Strong, Manish Arora & Michael E. Scheurer

To cite this article: Omar Shakeel, Philip J. Lupo, Simon Strong, Manish Arora & Michael E. Scheurer (2021): A brief review of the current knowledge on environmental toxicants and risk of pediatric cancers, Pediatric Hematology and Oncology, DOI: 10.1080/08880018.2021.1979147

To link to this article: https://doi.org/10.1080/08880018.2021.1979147

Published online: 19 Oct 2021.

PEDIATRIC HEMATOLOGY AND ONCOLOGY
https://doi.org/10.1080/08880018.2021.1979147

Taylor & Francis
Taylor & Francis Group

ARTICLE COMMENTARY

A brief review of the current knowledge on environmental toxicants and risk of pediatric cancers

Omar Shakeel[a], Philip J. Lupo[a], Simon Strong[b], Manish Arora[c] and Michael E. Scheurer[a]

[a]Department of Pediatrics, Baylor College of Medicine, Houston, Texas, USA; [b]The Oliver Foundation, Miami, Florida, USA; [c]Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, New York, USA

ABSTRACT

The incidence of pediatric cancers has steadily increased since 1975, which could suggest that other exogenous factors are accounting for an increasing proportion of cases. There has been growing concern over environmental exposures (i.e., toxicants) the on development of pediatric cancers. However, identifying environmental exposures on childhood cancer risk has been challenging because these outcomes are infrequent compared to cancer in adults, and it is difficult to estimate exposure during specific critical periods of development (e.g., pre-conception, *in utero*, early childhood) that are likely more important for childhood cancer development. Here, we summarize the International Agency for Research on Cancer (IARC) Group 1 agents (toxicants known to be carcinogenic to humans), their routes of exposure, current methods for risk mitigation, and what is known of their associations with pediatric cancer risk. Our review suggests that environmental toxicants are important and potentially modifiable risk factors that need to be more fully explored in children and adolescents.

ARTICLE HISTORY
Received 7 June 2021
Revised 24 August 2021
Accepted 7 September 2021

KEYWORDS
Pediatric cancer; environmental toxicants; pediatric oncology; epidemiology; cancer control

Each year in the United States, more than 15,000 children and adolescents are diagnosed with cancer, which is the leading cause of disease-related mortality among youth.[1] Notably, the incidence of pediatric cancers has steadily increased (approximately 0.8% per year) since 1975, resulting in a 45% increase between 1975 and 2018 (https://seer.cancer.gov/explorer/). Through large-scale sequencing efforts, we now know that approximately 10% of all cancers in children are caused by an inherited pathogenic variant.[2] Additionally, recent advances in cancer genetics have led to a better understanding and improved molecular classification of some of these cancers, which has led to improved survival in some instances. However, for most children, the underlying etiologies of their cancers remain largely unknown, suggesting that exogenous factors are accounting for an increasing proportion of cases.[1]

Specifically, there has been growing concern over environmental exposures (i.e., toxicants) on the development of pediatric cancers. The International Agency for Research on Cancer (IARC) has created monographs to help identify environmental

CONTACT Michael E. Scheurer scheurer@bcm.edu Department of Pediatrics, Baylor College of Medicine, Houston, TX 77030, USA.

toxicants known to increase the risk of cancers in humans.[3] These environmental toxicants include exposure to certain metals, hazardous air pollutants, radiation, food and plants, herbicides and pesticides, and occupational hazards. IARC classifies agents as carcinogenic to humans [group 1], probably carcinogenic to humans [group 2A], possibly carcinogenic to humans [group 2B], and not classifiable as to its carcinogenicity to humans [group 3].[3] The majority of these exposures have been well studied with respect to cancer risk in adults but not children. Here, we summarize the IARC Group 1 agents, their routes of exposure, current methods for risk mitigation, and what is known of their associations with pediatric cancer risk (Table 1).[3]

Metals. Exposure to cadmium, chromium, and nickel has been associated with several adult and pediatric cancers. In children, exposure to cadmium through contaminated food and water and measured in serum, urine, hair, and nails showed a significant positive association with leukemia and lymphoma.[4] Exposure to chromium measured in the ambient air was associated with increased risk of neuroblastoma and exposure estimated from parental occupations was associated with increased risk of testicular germ cell tumor.[5,6] Nickel may also be an etiological factor for childhood acute leukemia by causing oxidative DNA damage and one study showed that urinary nickel was significantly higher in patients with lymphoid and myeloid leukemia compared to controls.[7] While exposure to arsenic and beryllium have been linked to several adult cancers, studies evaluating these metals in children have either reported null results or have yet to be conducted in younger populations.

Organic Chemicals, Compounds, and Substances. Of the 20 substances linked to various adult tumors, only five have been evaluated in children and only for associations with pediatric leukemias and neuroblastoma. Hazardous air pollutants comprise most of the organic compounds and substances listed in Table 1. A recent systematic review reported that benzene exposure in children was associated with childhood leukemia and other hematological cancers.[8] Similarly, a recent meta-analysis reported that parental, *in utero*, and early-life exposure to benzene estimated from occupations, households, traffic density, and traffic-related air pollution was associated with lymphoid and myeloid leukemia.[9] A positive association was also observed between 1,3-butadiene and lymphoid leukemia in air pollutant models.[10] Exposure to polycyclic aromatic hydrocarbons (PAHs), such as benzopyrene, measured in patients exposed to vacuum dust was associated with increased risk of childhood lymphoid leukemia.[11] Additionally, a large population-based study reported an increased risk of neuroblastoma from maternal exposure to PAHs measured from community-based air pollution monitors during pregnancy.[5] Another population-based case-control study that included 35 counties in northern and central California from 2001-2006 reported that residential exposure to polychlorinated biphenyls (PCBs) measured in carpet dust was associated with a two-fold increase in risk of lymphoid leukemia.[12] A recent systematic review and meta-analysis reported that paternal daily cigarette smoking during pregnancy was related to a significantly increased risk of childhood lymphoid and myeloid leukemia.[13]

Ionizing radiation is generally classified into two categories – photons (x-radiation and gamma radiation) and particles (alpha and beta particles and neutrons) that can cause genetic damage and increase risk of cancers.[3] In children, exposure to radium

Table 1. IARC Group 1 agents exposure, risk mitigation, and cancer risk.

Carcinogenic Agent	Route of Exposure	Risk Mitigation	Adult Cancer Site (Sufficient & Limited Evidence)	Pediatric Cancer Site (Limited Evidence)
Metals				
Arsenic	Consumption through food and drink and inhalation from air or cigarette smoke	Regulation by CPSC, DOT, EPA, FDA, OSHA	Lung, Kidney, Urinary Bladder, Skin, Liver, Prostate	No association
Beryllium	Inhalation from ambient air and ingestion of contaminated soil	Regulation by DOT, EPA, FDA, OSHA	Lung	No studies to date
Cadmium	Consumption through food and drink, inhalation from ambient air or cigarette smoke, and ingestion of contaminated soil	Regulation by DOT, EPA, FDA, OSHA	Lung, Kidney, Prostrate	Leukemia and Lymphoma
Chromium	Consumption through food, plants, and drink, inhalation from ambient air or cigarette smoke, and ingestion of contaminated soil	Regulation by DOT, EPA, FDA, OSHA	Lung, Nasal Cavity, and Paranasal Sinuses	Neuroblastoma, Testicular Germ Cell Tumor
Nickel	Consumption through food, drink, and consumer products and inhalation from ambient air	Regulation by DOT, EPA, FDA, OSHA	Lung, Nasal Cavity, and Paranasal Sinuses	Lymphoid and Myeloid Leukemia
Organic Chemicals, Compounds, and Substances				
4-Aminobiphenyl	Formerly used commercially as rubber antioxidant	Regulation by EPA, FDA, and OSHA	Urinary Bladder	No studies to date
Benzene	Inhalation of ambient air, present in the atmosphere from natural and industrial sources	Regulation by CPSC, DOT, EPA, FDA, OSHA	Leukemia, Multiple Myeloma, Non-Hodgkin Lymphoma	Lymphoid and Myeloid Leukemia
Benzidine	Previously used as an intermediate in production of dyeing compounds	No longer manufactured for commercial sale, production discontinued in 1976	Urinary Bladder	No studies to date
Benzopyrene	Polycyclic aromatic hydrocarbon found in ambient air from forest fires, industrial emissions, biomass fuels, motor vehicle exhaust, cooking, and tobacco smoke	Regulation by EPA, FDA	Lung	Lymphoid Leukemia, Neuroblastoma
Bisether, Chloromethyl Ether	Inhalation and dermal contact of chemical intermediates and alkylating agents in the manufacture of plastics, resins, and polymers	Regulation by EPA, Mine Safety, OSHA	Lung	No studies to date
1,3-Butadiene	Inhalation of gas used to manufacture polymers and industrial chemicals	Regulation by DOT, EPA, OSHA	Hematolymphatic Organs	Lymphoid Leukemia
Coal Emissions	Inhalation, ingestion, and dermal contact	Avoidance	Lung, Skin, Urinary Bladder	No studies to date
Dichloropropane	Inhalation and dermal contact from soil fumigant and industrial solvent	Regulation by EPA	Liver, Bile-Duct	No studies to date
Diesel/Engine Exhaust	Inhalation from combustion of fossil fuels	Regulation by EPA, Mine Safety	Lung, Urinary Bladder	No studies to date

(*Continued*)

Table 1. (*Continued*)

Carcinogenic Agent	Route of Exposure	Risk Mitigation	Adult Cancer Site (Sufficient & Limited Evidence)	Pediatric Cancer Site (Limited Evidence)
Ethylene Oxide	Inhalation and ingestion of intermediates in the production of industrial chemicals	Regulation by DOT, EPA, FDA, OSHA	Breast, Lymphoid Tumors	No studies to date
Formaldehyde	Ubiquitous in the environment and detected in air, soil, food, bottled drinking water, surface/ground water, tobacco smoke	Regulation by CPSC, USDA, HUD, DOT, EPA, FDA, OSHA	Leukemia, Nasopharynx, Paranasal Sinus	No studies to date
4,4′-Methylenebis (MOCA) (2-chloraniline)	Dermal contact of curating agent for polymers in the manufacture of rubber products	Regulation by DOT, EPA, FDA	Urinary Bladder	No studies to date
Mineral and Shale Oils	Inhalation, ingestion, and dermal contact of lubricant based oils including engine oils, transmission fluid, machine oils, processing oils	Regulation by CPSC, EPA, FDA, OSHA	Skin	No studies to date
2-Napthylamine	Inhalation of emissions from coal furnaces and cigarettes	Commercial manufacture and use banned in in the early 1970s	Urinary Bladder	No studies to date
Ortho-Toluidine	Formerly used in the manufacture of rubber chemicals, pesticide intermediates, dyes and pigments,	No longer produced in the US; however highly imported; regulation by EPA, OSHA	Urinary Bladder	No studies to date
Polychlorinated Biphenyls (PCBs)	Formerly used in the production of transformers, capacitors, paints, metal coatings	Avoidance of hazardous waste, old appliances; no longer produced in the US	Liver, Bile-Duct, Breast	Lymphoid Leukemia
Tobacco	Inhalation or absorption of cigarettes	Avoidance	Lung, Myeloid Leukemia, Colorectal, Kidney, Larynx, Liver, Nasal Cavity, Paranasal sinus, Esophagus, Oral Cavity, Ovary, Pancreas, Pharynx, Stomach, Ureter, Urinary Bladder, Breast	Lymphoid and Myeloid Leukemia
Trichloroethylene (TCE)	Formerly used for refrigerants, degreasing solvent, and surgical/inhaled anesthetic	Banned by FDA in 1977	Liver, Biliary Tract, non-Hodgkin Lymphoma, Kidney	No studies to date
Soot	Inhalation, ingestion, or dermal contact from fireplaces, furnaces, engine exhaust, particulate emissions or occupational exposures	Avoidance	Lung, Skin, Urinary Bladder	No studies to date
Vinyl Chloride	Ingestion of contaminated food and water, inhalation, dermal contact with consumer products containing , polyvinyl chloride (PVC)	Regulation by CPSC, DOT, EPA, FDA, OSHA	Liver	No studies to date

Ionizing Radiation				
X and Gamma radiation	Natural, medical, atmospheric, nuclear sources	Regulation by DOE	Bone, Brain, CNS, Breast, Colon, Kidney, Leukemia, Lung, Esophagus, Skin, Stomach, Thyroid, Urinary bladder, Liver, Pancreas, Prostrate, Rectum	Lymphoid and Myeloid Leukemia, Brain, Solid Tumors
Plutonium	Radioactive metal produced in nuclear reactors	Regulation by DOT, EPA, FDA, OSHA, USNRC	Lung, Bone, Liver	No studies to date
Radon	Naturally occurring gas produced by decay of Radium, released from soil into air and groundwater	Regulation by DOT, EPA, FDA, OSHA, USNRC	Lung, Leukemia	Lymphoid Leukemia
Radium	Radioactive metal formed when uranium and thorium break down	Regulation by DOT, EPA, FDA, OSHA, USNRC	Bone, Paranasal Sinus	Lymphoid Leukemia
Strontium	Naturally occurring element found in rocks, soil, dust, coal, and oil	Regulation by DOT, EPA, FDA, OSHA, USNRC	Bone, Leukemia	Leukemia, Sarcomas
Thorium	Radioactive metallic element occurring in minerals	Regulation by DOT, EPA, FDA, OSHA, USNRC	Liver, Gall Bladder, Bile Duct, Leukemia, Pancreas, Prostate	No studies to date
Solar & UV radiation	Sun and artificial devices (sunbeds or sunlamps)	Avoidance and sunscreen	Skin, Eye	Equivocal
Food and Plants				
Aflatoxins	Consumption of contaminated foods (toxins produced by fungi that grow on grains and other agricultural crops such as corn, peanuts, tree nuts)	Avoidance; Regulation by FDA	Liver	No studies to date
Alcohol	Consumption of alcoholic beverages	Avoidance	Breast, Colorectal, Larynx, Liver, Esophagus, Oral Cavity, Pharynx, Pancreas	Leukemia, Brain, Neuroblastoma
Areca nut (Betel quid)	Chewing custom	Avoidance	Esophagus, Oral Cavity, Pharynx	No studies to date
Aristocholic Acid	Ingestion of contaminated herbal or botanical products	Avoidance; Regulation by FDA	Renal pelvis, Ureter	No studies to date
N-nitrosamines	Storage or preparation of food and tobacco products	Avoidance; Regulation by CPSC, EPA, FDA	Brain Tumors	Brain
Salted Fish	Consumption	Avoidance	Nasopharynx	No studies to date
Herbicides and Pesticides				
Tetrachlorodibenzo-p-dioxin (TCDD)	Pesticide against insects and wood-destroying fungi	Not currently produced commercially in the US	Lung, Non-Hodgkin Lymphoma, Soft Tissue Sarcoma	No studies to date
Pentachlorophenol (PCP)	Wood preservative to prevent fungal decay and insect damage in the workplace and environment	No longer produced in the US since 1980s	Non-Hodgkin Lymphoma, Nasopharyngeal, Esophageal	Leukemia, Lymphoma

(*Continued*)

Table 1. (*Continued*)

Carcinogenic Agent	Route of Exposure	Risk Mitigation	Adult Cancer Site (Sufficient & Limited Evidence)	Pediatric Cancer Site (Limited Evidence)
Lindane	Consumption of food contaminated with pesticide residues, inhalation and dermal contact	Avoidance; Regulation by DOT, EPA, FDA, OSHA	Non-Hodgkin Lymphoma	No studies to date
Occupational Hazards				
Acid Mist	Inhalation, ingestion, or absorption through skin during manufacture of fertilizer, batteries, smelting	Regulation by OSHA	Larynx, Lung	No studies to date
Aluminum Production	Inhalation of polycyclic aromatic hydrocarbons	Regulation by OSHA	Lung, Urinary Bladder	No studies to date
Auramine Production	Inhalation or absorption through skin during manufacture of leather dyes and paints	Production discontinued in the US	Lung, Urinary Bladder	No studies to date
Asbestos	Inhalation and ingestion of silicate minerals released into the environment from industrial applications	Mining has ceased and products are being eliminated from the market; Regulation by CPSC, DOT, EPA, Mine Safety, OSHA	Larynx, Lung, Mesothelioma, Ovary, Colorectal, Pharynx, Stomach	No studies to date
Coal Production	Inhalation, ingestion, and dermal contact from large ovens used to heat coal	Regulation by DOT, EPA, FDA, OSHA	Lung, Skin, Urinary Bladder	No studies to date
Erionite	Fibrous mineral previously used for commercial purposes	No longer mined or marketed for commercial purposes	Mesothelioma	No studies to date
Hematite Mining	Inhalation from mining of iron ore	Regulation by OSHA and Mine Safety	Lung	No studies to date
Iron & Steel Founding	Inhalation of polycyclic aromatic hydrocarbons from molding, melting, and fettling	Regulation by OSHA	Lung	No studies to date
Painting	Inhalation and absorption through skin of complex chemical mixtures (organic solvents and dye products)	Avoidance	Lung, Mesothelioma, Urinary Bladder	Lymphoid Leukemia
Rubber Production	Inhalation of dust and fumes from rubber-making	Regulation by OSHA	Leukemia, Lymphoma, Lung, Stomach, Urinary Bladder, Larynx, Esophagus, Prostate	No studies to date
Silica Dust	Inhalation of silica dust from industrial and occupational settings	Regulation by OSHA and Mine Safety	Lung	No studies to date
Welding Fumes	Inhalation when metals are heated above their melting point, vaporize, then condense into fine solid particles in air		Skin	No association
Wood and Leather Dust	Inhalation from processing or manufacturing wood and leather products	Regulation by OSHA	Paranasal Sinus, Nasopharynx	Lymphoid and Myeloid Leukemia, Brain

Abbreviations: DOE: Department of Energy; CPSC: Consumer Product Safety Commission; DOT: Department of Transportation, EPA: Environmental Protection Agency, FDA: Food and Drug Administration, HUD: Department of Housing and Urban Development; OSHA: Occupational Safety and Health Administration; USNRC: United States Nuclear Regulatory Commission; USDA: United States Department of Agriculture.

and radon based on residential exposure level and time showed a linear dose-response with risk of lymphoid leukemia.[14] Strontium concentrations measured in baby teeth were significantly correlated with cancer incidence in children 0 to 4 years of age.[15] Background radiation from gamma rays estimated from geographical models may also contribute to the risk of pediatric leukemia and brain tumors.[16] Additionally, childhood survivors of the atomic bomb blasts from World War II were found to have an increased risk of leukemia and solid tumors up to 55 years after the exposure, and children exposed to radiation from the Chernobyl nuclear accident were found to have a dose-related increased risk of thyroid cancer.[17,18] Other studies, both large and small in size, have also shown an association with childhood leukemia and solid tumors and distance to nuclear power stations.[19] Even low doses of ionizing radiation from medical imaging (e.g., computed tomography scans) were associated with an increased risk of leukemia.[20] Interestingly, the association between pediatric cancer and solar and UV radiation have been largely equivocal.[21]

Food and plant-based compounds comprise another category of potentially important carcinogens to children. Maternal dietary exposure to *N*-nitroso compounds or their precursors (e.g., those found in cured meats) during pregnancy was associated with risk of childhood brain tumors.[22] Leukemia, brain tumors, and neuroblastoma have also been associated with paternal and maternal consumption of alcohol before or during pregnancy.[23] Other exposures in this category that have been associated with adult cancers have largely not been evaluated in children.

Herbicides and pesticides used for food crops and in/around the home are also listed in Table 1. Pentachlorophenol (PCP) was used as an herbicide, biocide, and preservative worldwide since 1930 prior to being discontinued, and a meta-analysis suggested parental occupational exposure before pregnancy might increase the risk of leukemia and lymphoma in themselves and their children.[24] Other studies have also reported parental exposure to pesticides during pregnancy to be associated with childhood lymphoid and myeloid leukemia.[25–28] Other chemical compounds in this group, including tetrachlorodibenzo-p-dioxin (TCDD) and lindane have not been evaluated for risk of pediatric cancers.

Exposures to *occupational hazards* cause a wide range of cancers in adults.[29] Adult lung cancer from inhalation followed by skin cancer from dermal contact account for the largest proportion of cases.[30] Some occupational exposures in parents have also shown associations with pediatric cancers in their offspring. Notably painting in the home before, during, and after pregnancy was identified as a potential risk factor for childhood lymphoid leukemia.[31,32] Maternal occupational wood dust exposure from birth to diagnosis was associated with increased risk of lymphoid and myeloid leukemia, whereas paternal occupational exposure to wood dust was associated with astrocytoma in the same time period.[33] Largely, other workplace exposures have not been fully evaluated for their carcinogenic potential in children due to limited or total lack of quantitative data.[30]

In summary, environmental toxicants are important and potentially modifiable risk factors for childhood cancers. Most of these toxicants are monitored and/or regulated by federal departments, administrations, and agencies such as the Department of Energy, Consumer Product Safety Commission, Department of Transportation, Environmental Protection Agency, Food and Drug Administration, Department of

Housing and Urban Development, Occupational Safety and Health Administration, US Nuclear Regulatory Commission, and US Department of Agriculture. However, to mitigate the disease risks associated with exposure to these toxicants, parents and children should avoid exposure when possible.

Unfortunately, identifying environmental determinants for most pediatric cancers has been challenging because these outcomes are infrequent compared to cancer in adults, and it is difficult to estimate exposure during specific critical periods of development (e.g., pre-conception, *in utero*, early childhood) that are likely more important for childhood cancer development. Many of the associations reported by IARC to be carcinogenic to humans (Table 1) have yet to be fully explored in children and adolescents. Furthermore, most of these investigations have been retrospective in nature and often depend on residential information or self-reported questionnaire data to assign exposure. Notably, these exposure assessment strategies are subject to significant bias and there are currently few existing biomarkers to measure how various exposures co-occur and jointly influence pediatric cancer risk. These challenges have limited the scope of previous assessments evaluating the impact of environmental toxicants on pediatric cancer. However, given the continued increase in incidence of pediatric cancer, there is strong need to catalog the environmental risk factors more fully for cancer in children and adolescents. Additional large-scale epidemiological studies, specifically in these vulnerable populations, and the use of novel analytical tools, such as biomarkers of exposure that can pinpoint the timing of the exposure, should be utilized to further investigate these environmental exposures on pediatric cancer risk, as well as explore the dynamic of gene-environment interactions.

Funding

The author(s) reported there is no funding associated with the work featured in this article.

ORCID

Omar Shakeel http://orcid.org/0000-0002-6583-5012
Philip J. Lupo http://orcid.org/0000-0003-0978-5863
Michael E. Scheurer http://orcid.org/0000-0002-8379-6088

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;68(1):7–30. doi:10.3322/caac.21442.
2. Brodeur GM, Nichols KE, Plon SE, Schiffman JD, Malkin D. Pediatric cancer predisposition and surveillance: an overview, and a tribute to Alfred G. Knudson Jr. *Clin Cancer Res*. 2017;23(11):e1–e5. doi:10.1158/1078-0432.CCR-17-0702.
3. International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. Lyon, France; 1988.
4. Sherief LM, Abdelkhalek ER, Gharieb AF, et al. Cadmium status among pediatric cancer patients in Egypt. *Medicine (Baltimore)*. 2015;94(20):e740. doi:10.1097/MD.0000000000000740.

5. Heck JE, Park AS, Qiu J, Cockburn M, Ritz B. An exploratory study of ambient air toxics exposure in pregnancy and the risk of neuroblastoma in offspring. *Environ Res*. 2013;127:1–6. doi:10.1016/j.envres.2013.09.002.
6. Togawa K, Le Cornet C, Feychting M, et al. Parental occupational exposure to heavy metals and welding fumes and risk of testicular germ cell tumors in offspring: a registry-based case-control study. *Cancer Epidemiol Biomarkers Prev*. 2016;25(10):1426–1434. doi:10.1158/1055-9965.EPI-16-0328.
7. Yang Y, Jin XM, Yan CH, Tian Y, Tang JY, Shen XM. Urinary level of nickel and acute leukaemia in Chinese children. *Toxicol Ind Health*. 2008;24(9):603–610. doi:10.1177/0748233708100091.
8. D'Andrea MA, Reddy GK. Health risks associated with benzene exposure in children: a systematic review. *Glob Pediatr Health*. 2018;5:2333794X18789275. doi:10.1177/2333794X18789275.
9. Carlos-Wallace FM, Zhang L, Smith MT, Rader G, Steinmaus C. Parental, in utero, and early-life exposure to benzene and the risk of childhood leukemia: a meta-analysis. *Am J Epidemiol*. 2016;183(1):1–14. doi:10.1093/aje/kwv120.
10. Symanski E, Tee Lewis PG, Chen T-Y, Chan W, Lai D, Ma X. Air toxics and early childhood acute lymphocytic leukemia in Texas, a population based case control study. *Environ Health*. 2016;15(1):70 doi:10.1186/s12940-016-0154-8.
11. Deziel NC, Rull RP, Colt JS, et al. Polycyclic aromatic hydrocarbons in residential dust and risk of childhood acute lymphoblastic leukemia. *Environ Res*. 2014;133:388–395. doi:10.1016/j.envres.2014.04.033.
12. Ward MH, Colt JS, Metayer C, et al. Residential exposure to polychlorinated biphenyls and organochlorine pesticides and risk of childhood leukemia. *Environ Health Perspect*. 2009;117(6):1007–1013. doi:10.1289/ehp.0900583.
13. Chunxia D, Meifang W, Jianhua Z, et al. Tobacco smoke exposure and the risk of childhood acute lymphoblastic leukemia and acute myeloid leukemia: a meta-analysis. *Medicine*. 2019;98(28):e16454. doi:10.1097/MD.0000000000016454.
14. Raaschou-Nielsen O, Andersen CE, Andersen HP, et al. Domestic radon and childhood cancer in Denmark. *Epidemiology*. 2008;19(4):536–543. doi:10.1097/EDE.0b013e318176bfcd.
15. Gould JM, Sternglass EJ, Sherman JD, Brown J, McDonnell W, Mangano JJ. Strontium-90 in deciduous teeth as a factor in early childhood cancer. *Int J Health Serv*. 2000;30(3):515–539. doi:10.2190/FTL4-HNG0-BELK-5EMH.
16. Spycher BD, Lupatsch JE, Zwahlen M, et al. Background ionizing radiation and the risk of childhood cancer: a census-based nationwide cohort study. *Environ Health Perspect*. 2015;123(6):622–628. doi:10.1289/ehp.1408548.
17. Hsu W-L, Preston DL, Soda M, et al. The incidence of leukemia, lymphoma and multiple myeloma among atomic bomb survivors: 1950-2001. *Radiat Res*. 2013;179(3):361–382. doi:10.1667/RR2892.1.
18. Cardis E, Hatch M. The Chernobyl accident-an epidemiological perspective. *Clin Oncol (R Coll Radiol))*. 2011;23(4):251–260. doi:10.1016/j.clon.2011.01.510.
19. Fairlie I. Commentary: childhood cancer near nuclear power stations. *Environ Health*. 2009;8:43 doi:10.1186/1476-069X-8-43.
20. Nikkilä A, Raitanen J, Lohi O, Auvinen A. Radiation exposure from computerized tomography and risk of childhood leukemia: Finnish register-based case-control study of childhood leukemia (FRECCLE). *Haematologica*. 2018;103(11):1873–1880. doi:10.3324/haematol.2018.187716.
21. Lombardi C, Heck JE, Cockburn M, Ritz B. Solar UV radiation and cancer in young children. *Cancer Epidemiol Biomarkers Prev*. 2013;22(6):1118–1128. doi:10.1158/1055-9965.EPI-12-1316.
22. Dietrich M, Block G, Pogoda JM, Buffler P, Hecht S, Martin SP. A review: dietary and endogenously formed N-nitroso compounds and risk of childhood brain tumors. *Cancer Causes Control*. 2005;16(6):619–635. doi:10.1007/s10552-005-0168-y.

23. Infante-Rivard C, El-Zein M. Parental alcohol consumption and childhood cancers: a review. *J Toxicol Environ Health B Crit Rev*. 2007;10(1–2):101–129. doi:10.1080/10937400601034597.
24. Zheng R, Zhang Q, Zhang Q, Yang L, Zhang Z, Huang F. Occupational exposure to pentachlorophenol causing lymphoma and hematopoietic malignancy for two generations. *Toxicol Ind Health*. 2015;31(4):328–342. Published online January 11doi:10.1177/0748233712472520.
25. Patel DM, Jones RR, Booth BJ, et al. Parental occupational exposure to pesticides, animals and organic dust and risk of childhood leukemia and central nervous system tumors: findings from the International Childhood Cancer Cohort Consortium (I4C). *Int J Cancer*. 2020;146(4):943–952. doi:10.1002/ijc.32388.
26. Bailey HD, Fritschi L, Infante -Rivard C, et al. Parental occupational pesticide exposure and the risk of childhood leukemia in the offspring: findings from the childhood leukemia international consortium. *Int J Cancer*. 2014;135(9):2157–2172. doi:10.1002/ijc.28854.
27. Wigle DT, Turner MC, Krewski D. A systematic review and meta-analysis of childhood leukemia and parental occupational pesticide exposure. *Environ Health Perspect*. 2009;117(10):1505–1513. doi:10.1289/ehp.0900582.
28. Chen M, Chang C-H, Tao L, Lu C. Residential exposure to pesticide during childhood and childhood cancers: a meta-analysis. *Pediatrics*. 2015;136(4):719–729. doi:10.1542/peds.2015-0006.
29. Cogliano VJ, Baan R, Straif K, et al. Preventable exposures associated with human cancers. *J Natl Cancer Inst*. 2011;103(24):1827–1839. doi:10.1093/jnci/djr483.
30. Loomis D, Guha N, Hall AL, Straif K. Identifying occupational carcinogens: an update from the IARC Monographs. *Occup Environ Med*. 2018;75(8):593–603. doi:10.1136/oemed-2017-104944.
31. Bailey HD, Milne E, Klerk ND, et al. Exposure to house painting and the use of floor treatments and the risk of childhood acute lymphoblastic leukemia. *Int J Cancer*. 2011;128(10):2405–2414. doi:10.1002/ijc.25572.
32. Bailey HD, Metayer C, Milne E, et al. Home paint exposures and risk of childhood acute lymphoblastic leukemia: findings from the Childhood Leukemia International Consortium. *Cancer Causes Control*. 2015;26(9):1257–1270. doi:10.1007/s10552-015-0618-0.
33. Volk J, Heck JE, Schmiegelow K, Hansen J. Parental occupational organic dust exposure and selected childhood cancers in Denmark 1968–2016. *Cancer Epidemiol*. 2020;65:101667. doi:10.1016/j.canep.2020.101667.