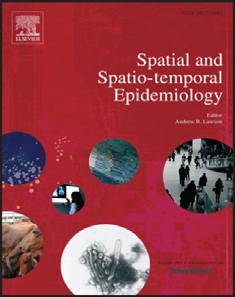
[Spatial and Spatio-temporal Epidemiology 32 (2020) 100320](https://doi.org/10.1016/j.sste.2019.100320)

Contents lists available at [ScienceDirect](http://www.ScienceDirect.com/)

Spatial and Spatio-temporal Epidemiology

journal homepage: [www.elsevier.com/locate/sste](http://www.elsevier.com/locate/sste)

High incidence of brain and other nervous system cancer identiﬁed in two mining counties, 2001–2015

Yanan Zhang, Suzanne McDermott[∗,](#_bookmark0) Bryn Davis, James Hussey

*Department of Epidemiology and Biostatistics, University of South Carolina Arnold School of Public Health, Discovery 417, 915 Greene Street, Columbia, SC 29208, United States*

a r t i c l e i n f o a b s t r a c t

*Article history:*

Received 29 July 2019

Revised 11 November 2019

Accepted 11 November 2019

Available online 21 December 2019

*Keywords:*

Brain and other nervous system cancer Incidence

Deer Lodge and Silver Bow

Two counties in Montana, Deer Lodge and Silver Bow (DL/SB), have two Superfund sites, as well as an active copper and molybdenum mine in SB. The population living in proximity to these sites are exposed to additional metals and some have been shown to be neurotoxic, especially for children; thus, this study focused on the incidence of brain and other nervous system cancers. The Montana Central Tumor Registry data was used to identify the cases in DL/SB and the remaining 54 counties of Montana (comparison group). After controlling for sex, cancer stage, and year of diagnosis, we found an incidence rate ratio for DL/SB versus comparison group of 6.28 (95% CI: 2.32–17.02) for children ages birth to 4 years, and 3.95 (95% CI: 1.66–9.38) for adults age 30–34 years. The high incidence rate of the brain cancer in the two age groups requires public health action.

© 2019 Elsevier Ltd. All rights reserved.

# Introduction

Superfund sites are the nation’s most contaminated waste sites, with about 15 million people in the U.S., including about 3.5 million children, living within one mile of a federal Superfund site ([Scorecard – The Pollution Information Site, 2011](#_bookmark38)). Metal transport can be on the order of tens of kilometers without change in environmental concentrations ([Plathe et al., 2010](#_bookmark29)), so many more people are potentially affected. One of the largest Superfund sites in the U.S. is located in and around Montana’s ﬁfth largest city, Butte, in Silver Bow county. Butte is also the home to one of the 12 largest open-pit mines in the US, and in the process of mining for the target metals, other metals are simultaneously extracted. The proximity of the Berkeley Pit, the designated Superfund site, to the active Continental Pit is shown in [Fig. 1](#_bookmark1). These sites are approximately 2 miles apart and both are located in the city limits of Butte. The distance from the center of the Berkeley Pit to the center of Butte is about 2 miles. In addition, the Anaconda Smelting site, also a Superfund designated area, is about 20 miles west of the Berkeley Pit in the neighbouring county of Deer Lodge. The distance from the Anaconda Superfund site to the center of Anaconda is about 3 miles.

Monitoring of Superfund sites is the responsibility of the Environmental Protection Agency (EPA); however, much of their

∗ Corresponding author.

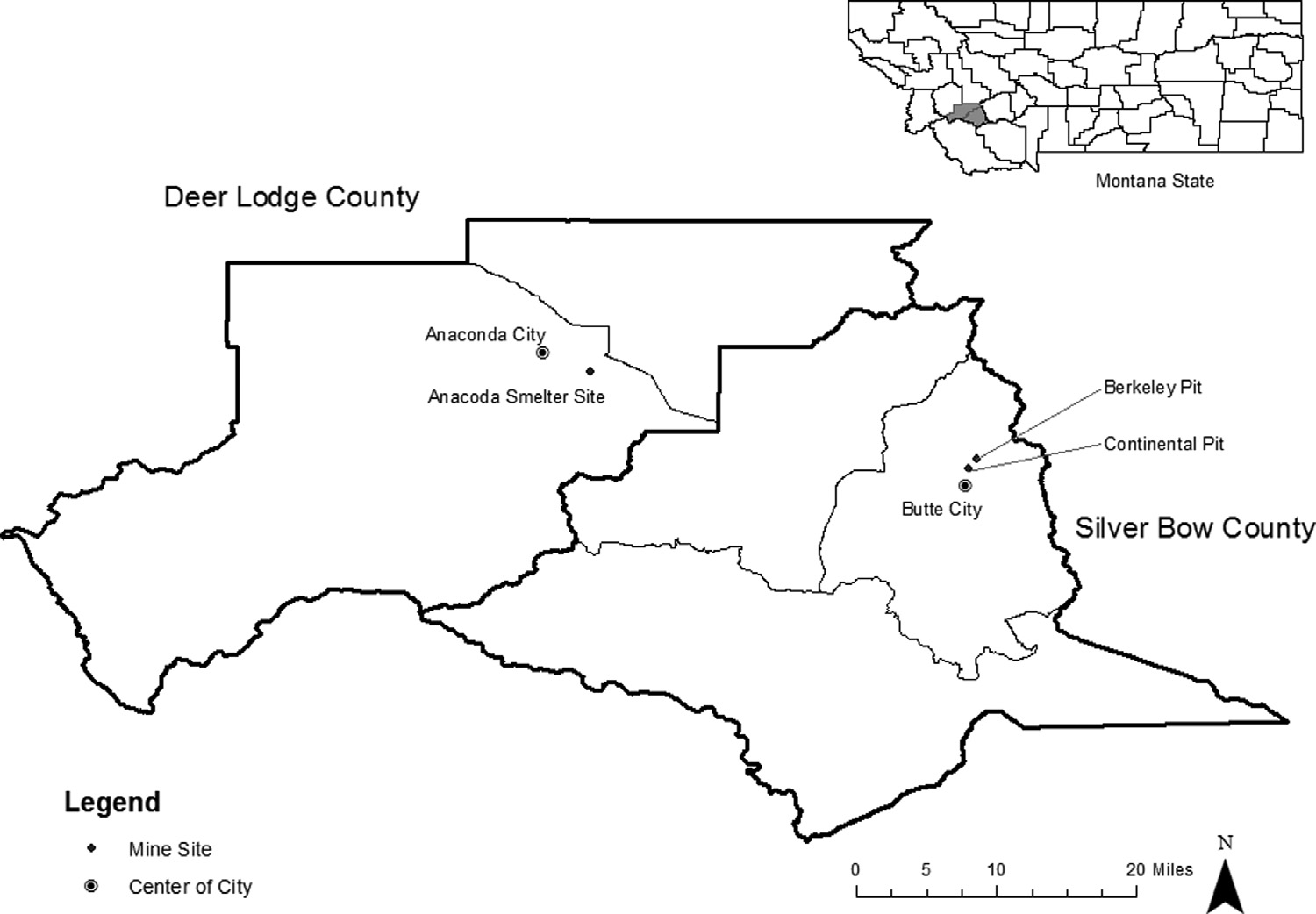
*E-mail address:* [smcdermo@mailbox.sc.edu](mailto:smcdermo@mailbox.sc.edu) (S. McDermott).

focus is on remediation, and only a subset of the population is typically monitored for toxic exposure through soil sampling and human testing. Local public health authorities with jurisdiction in the exposed areas have traditionally used aggregate data about mortality and morbidity to monitor the human health effects. This study was designed to do a more in-depth analysis of publicly available data from a statewide tumor registry to identify one potential outcome, brain and other nervous system cancers, that is associated with the speciﬁc metals identiﬁed in the Superfund cleanup and the ongoing mining in the vicinity.

This study compares the brain and other central nervous system cancer incidence experiences of two contiguous Montana coun- ties, Deer Lodge and Silver Bow (DL/SB), to all other counties in Montana. Silver Bow County is home to a large active mining site [and the Silver Bow Creek/Butte Area Superfund Site (United States Environmental Protection Agency, 2019a), and Deer Lodge County](#_bookmark26) served as home to the smelter for mining products and the Ana- [conda Smelter Superfund Site (United States Environmental Protec- tion Agency, 2018). Both sites have had ongoing remediation for](#_bookmark25) the past 36 years, following more than a century of underground [copper (Cu) mining that ended in 1982 (United States Environmen- tal Protection Agency, 2019a, 2018;](#_bookmark26) [Gammons](#_bookmark14) [et al., 2006). Shortly](#_bookmark26) after the closing of the Berkeley pit, Atlantic Richﬁeld opened a new and currently active copper and molybdenum (Mo) open pit [mining operation, the Continental pit (United States Environmen- tal Protection Agency, 2019a;](#_bookmark26) [Gammons](#_bookmark14) [et al., 2006). As a result of](#_bookmark26) exposure to historic wastes and the persistence of open pit mining

<https://doi.org/10.1016/j.sste.2019.100320>

1877-5845/© 2019 Elsevier Ltd. All rights reserved.



**Fig. 1.** Locations of Superfund sites and active mine site in Deer Lodge and Silver Bow counties, Montana.

*Note:* The locations for the center of two cities were based on population distribution.

of Cu and Mo in SB county, arsenic (As), cadmium (Cd), Cu, iron (Fe), lead (Pb), manganese (Mn), Mo, and zinc (Zn) are constantly [being released into the atmosphere (United States Environmental Protection Agency, 2019a,](#_bookmark26) [20](#_bookmark25)[18;](#_bookmark26) [Hailer](#_bookmark15) [et al., 2017).](#_bookmark26)

Metals found in these sites have neurotoxic, inﬂammatory, and carcinogenic properties ([Aschner and Costa, 2017](#_bookmark4)); however, the health effects of these exposures have not been adequately studied using epidemiologic methods. Neurotoxic impacts are known to be different when exposure occurs at different ages in humans, so the impact on children can be related to executive brain function, cognition, and behaviour ([Hsueh et al., 2017](#_bookmark16)), while in older adults the impact can be chronic conditions such as Parkinson’s or Alzheimer’s disease ([Jaishankar et al., 2014](#_bookmark17)). At all ages, there is potential to develop brain or other central nervous system cancers as a result of chronic exposure to these neurotoxic metals. An im- portant contribution to the literature focuses on the epigenetic al- [terations in brain tumors associated with heavy metals (Caffo et al., 2014). This study reported the pathway that is impacted by Cd ex-](#_bookmark5) posure, through differentiation and apoptosis and a resulting loss of expression of tumor suppressor genes and miRNA expression. In addition, data suggest that Pb, As, Cd and other metals cause oxidative stress, cell death, and neuroinﬂammation, resulting in the formation of radicals in the brain ([Mates et al., 2009](#_bookmark24)).

The epidemiologic literature about the association of metal ex- posures associated with brain and other nervous system cancer is largely limited to occupational exposures to chromium (Cr), Pb and [Cd (Schlehofer et al., 2005;](#_bookmark37) [Waisberg et al., 2003](#_bookmark34)[; Wesseling et al., 2002). Another study found elevated serum concentrations of Cd,](#_bookmark37) Fe, Mg, Mn, Pb, and Zn in patients with malignant glioma tumors compared to controls ([Arslan et al., 2011](#_bookmark6)). There are no studies that document the exposures among children with brain or other nervous system cancers. There have been a few studies on health outcomes due to metal exposures for the residents of DL/SB. The 2009 Montana cancer proﬁle reported no signiﬁcance difference in all sites cancer incidence rates for people of DL/SB (age adjusted

incidence rate (IR), cases per 100,000: SB IR = 422.6 (95% CI:

395.3–451.5); for DL IR = 411.6 (95% CI: 363.9–464.7)) when com-

pared to all Montana counties (IR = 438.0 (95% CI: 432.7–443.3))

([US National Cancer Institute, 2009](#_bookmark30)). A recently published study, authored by some members of this study, compared the cause of death in DL/SB compared to the other 54 counties of Montana dur- ing the 2000–2015 period. The selected cancers sites, reported in that study, were related to metal exposure, so the calculations re- ﬂected cancer of the stomach, liver, pancreas, bronchus and lung, skin, breast, prostate, kidney, bladder and brain. When these sites were combined, the standardized mortality rate (SMR) for cancer was 1.19, 95% CI: 1.10–1.29 ([Davis et al., 2019](#_bookmark18)).

This study seeks to characterize the brain and other nervous system cancer incidence experiences of DL/SB residents, who have been historically and currently exposed to hazards from a Super- fund site and active open-pit mining. The EPA listed As and Pb the primary contaminants of concern in Butte. There are other contam- inates including Aluminum (Al), Cd, Cu, Fe, Hg, Silver (Ag) and Zn ([United States Environmental Protection Agency, 2019](#_bookmark28)b). The hy- pothesis that we tested was that the youngest age group in DL/SB had higher incidence rates for brain and other nervous system cancers compared to their age peers in the other Montana coun- ties. This hypothesis is based on the knowledge that the neurotoxic impact of the metals in the DL/SB environment can result in de- velopment of cancer when the brain is developing and maturing.

# Methods

* 1. *Data source and population studied*

The study was conducted using Montana Central Tumor Reg- istry (MCTR) data from 2001–2015. The MCTR is supported by [Centers for Disease Control and Prevention](http://dx.doi.org/10.13039/100000030) National Program for Cancer Registries and the Montana State General Fund. Information [on the MCTR can be assessed: https://dphhs.mt.gov/publichealth/ Cancer/TumorRegistry. The MCTR has a reporting requirement](https://dphhs.mt.gov/publichealth/Cancer/TumorRegistry) from hospitals, physicians, clinics, and clinical laboratories to provide personally identifying information, tumor/cancer speciﬁc data (including stage), and medical procedure information. The study received an exempt review approval, based on the de-

identiﬁcation of the case records, from the University of South Carolina Institutional Review Board in December of 2017.

The study population was restricted to white race, since the number of people from other racial groups was too low (fewer than 10 cases per age group in DL/SB) to report. All cases of brain and other nervous system cancers registered in the MCTR from 2001 to 2015 were used in the numerator. The population years at risk was calculated as the sum of estimated mid-year population from 2001 to 2015 in DL/ SB and remaining counties of Montana, [obtained from the United State Census Bureau (United States Census Bureau, 2010).](#_bookmark24) [Fi](#_bookmark1)[g. 1 indicates the location of the two](#_bookmark24) Superfund sites in Butte, Silver Bow County and in Anaconda, Deer Lodge County. The upper right corner of the map also shows the area where cases were identiﬁed compared to the remaining area of Montana where the comparison counties are located. In order to determine if the overall brain and other central nervous system cancer rate was elevated, for all ages combined, a nationally representative comparison group was deﬁned from the US Surveil- lance, Epidemiology, and End Results Program (SEER) data. The SEER 21 Incidence – Crude Rates for Additional Races, 2000–2016 database was used to calculate the standardized incidence ratio (SIR) ([National Cancer Inistitute, 2019](#_bookmark27) – Surveillance).

# Covariates

Sex was deﬁned as male or female. Age of diagnosis was grouped in ﬁve-year increments, 0–4 years, 5–9 years, …, 80–84 years, and 85 years and above. Year of diagnosis ranged from 2001 to 2015, grouped into three periods 2001–2005, 2006–2010, and 2011–2015. Four cancer stages were used: localized, regional, distant metastasis, and unknown stage. Brain and other nervous system cancer sites were deﬁned based on the SEER sites as 31,010–31,040.

* 1. *Statistical analysis*

We had information about age at diagnosis, the sex of the individual, diagnosis year, and cancer stage. We described these variables by frequency (proportion) and mean (SD) for age.

Indirect adjustment, using strata based on age group and sex, was used to obtain standardized incidence ratios (SIRs) and 95% conﬁdence intervals for DL/SB and the remaining counties sepa- rately. The number of expected cases was deﬁned by ﬁrst taking the product of SEER 21 raw incidence rate times person years of observation within a stratum, then summing this product across the strata. SIRs were then calculated by taking the ratio of the number of observed cases to the number of expected cases.

To calculate the incidence rate ratio (IRR), the incidence rate among the exposed portion of the population is divided by the in- cidence rate in the unexposed portion of the population. This IRR gives a relative measure of the effect of a given exposure and ap- proximates the rate ratio or the odds ratio if the occurrences are rare. Homogeneity of IRR across 5-year age group, sex, diagnosis year group, and cancer stage was evaluated by the Breslow–Day test, separately for each covariate. Stratiﬁed analyses were con- ducted if any inconsistency of IRR was indicated from these tests.

The crude IRR for DL/SB, compared to the remaining counties, was estimated using two-way contingency tables. An adjusted IRR was estimated by ﬁtting a generalized linear model with a log link function. In the model, the log of the probability of developing brain or nervous system cancer for person *i* was modelled as a function of the covariates, expressed as a vector, *xi* .

Thus, ln(pi) = *xiβ*. The exponential of the beta coeﬃcient that

corresponds to county of residence is the estimated adjusted IRR. These models control for age, sex, cancer stage, and year of diag-

nosis, unless stratiﬁcation by one of these variables is indicated by the Breslow–Day test.

Data management and statistical analyses were performed us- ing SAS software (version 9.4; SAS Institute Inc, Cary, NC, USA). The signiﬁcance level was set at 0.05.

# Results

The basic characteristics of the individuals who are registered in the Montana Central Tumor Registry during the period 2001– 2015 are shown in [Table 1](#_bookmark2). There was no signiﬁcant difference in the sex (Chi-Square = 0.0171, *p* = 0.896), age (*t* = 1.38, *p* = 0.168), or cancer stage (Fisher’s exact *p* = 0.119) between the two groups. We compared the rates of brain and other nervous system can- cers in DL/SB to both the US rates using national SEER data, and to the other counties of Montana. When we used SEER 21 as the ref- erence population, the SIRs for DL/SB and other counties were 1.09 (95% CI: 0.83–1.41) and 1.04 (0.98, 1.10), respectively. Thus, indirect standardized rates were not signiﬁcantly different when comparing

DL/SB and the remaining Montana counties to the US rates.

When comparing the incidence of brain and other nervous sys- tem cancers in DL/SB to the remaining 54 counties of Montana, the Breslow-Day test detected heterogeneity of IRR across 5-year age groups. Therefore, IRRs for DL/SB compared to the remaining coun- ties were estimated separately for each age group. The results are shown and plotted in [Fig. 2](#_bookmark3). After adjusting for sex, stage of cancer, and diagnosis year, the incidence rate ratio of brain and other ner- vous system cancers in DL/SB is 6.28 (95% CI: 2.32–17.02) for the 0–4 year age group, meaning that the risk of new cases of brain and other nervous system cancers is estimated to be more than six times as high in DL/SB compared to other Montana counites, during the study period. Similarly, the IRR in DL/SB is 3.95 (95% CI: 1.66–9.38) for the 30–34 age group. No signiﬁcant increased rates for brain and other nervous system cancers were found in any other age group included in this study.

# Discussion

We identiﬁed a signiﬁcant increased rate ratio of cancer in the brain and other nervous system for residents of DL/SB ages 0–4 years (IRR = 6.28) and ages 30–34 years (IRR = 3.95) compared to remaining counties in Montana. It is important to note that al- though the conﬁdence intervals are wide for the two age groups, the lower ends of the bounds are higher than one, giving us con- ﬁdence that an elevated risk exists. We identiﬁed this statistically signiﬁcant risk for brain and other nervous system cancer in two age groups because we explored risk in ﬁve-year age groups, since there was heterogeneity across age groups when comparing DL/SB to the remaining Montana counties. This ﬁnding is important and noteworthy since, when we did not look at age speciﬁc rates, there was no signiﬁcant difference between brain and other nervous sys- tem cancer rates compared to both the other counties of Mon- tana and the US SEER population. The age speciﬁc elevated rates of these cancers are masked by the overall brain and other nervous system cancer rates. This ﬁnding helps us understand why ongoing aggregate cancer surveillance did not identify these high rates.

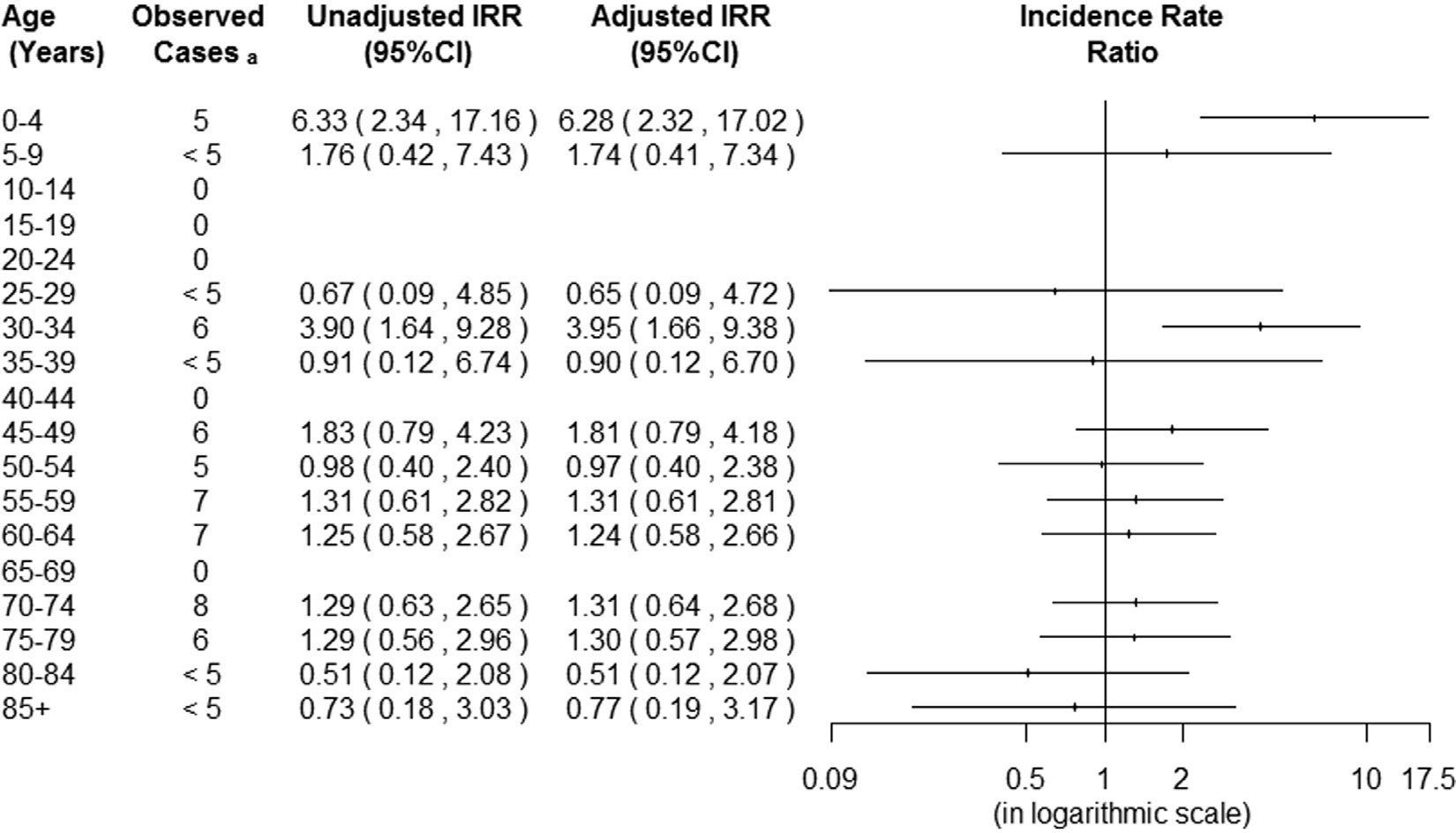
The hypothesis was supported since the IRR for children birth to age 4 years was statistically signiﬁcantly elevated. In addi- tion, the IRR for adults ages 30–34 years was also statistically signiﬁcantly elevated. These ﬁndings must be interpreted with the understanding that the number of cases for brain and other nervous system cancer in any age group is small. Brain and other nervous system cancers are the 13th most common type of cancer in Montana and they represent about 2% of all new cancer cases [in the state (Montana Department of Public Health and Human Services, 2019). Brain and other nervous system cancers incidence](#_bookmark25)

**Table 1**

Basic characteristics of individuals with cancers of the brain and other organs of the central nervous system in Montana, 2001−2015.

|  |  |  |
| --- | --- | --- |
| Characteristics  Number of cancer cases | Silver Bow and Deer Lodge  *n* = 58 | Remaining counties  *n* = 1076 |
| Sex (*n*, %) |  |  |
| Male | 35 (60.3) | 640 (59.5) |
| Female | 23 (39.7) | 436 (40.5) |
| Year (*n*, %) |  |  |
| 2001–2005 | 20 (34.5) | 343 (31.9) |
| 2006–2010 | 12 (20.7) | 346 (32.2) |
| 2011–2015 | 26 (44.8) | 387 (36.0) |
| Cancer stage (*n*, %) |  |  |
| Localized | 42 (72.4) | 872 (81.0) |
| Othera | 16 (27.6) | 204 (19.0) |
| Age (mean, SD) | 52 (24) | 56 (21) |
| Summed person-years of observation | 615,573 | 12,513,207 |

a Cases of regional, distant metastasis, and unknown stage were combined.



**Fig. 2.** Age-speciﬁc unadjusted and adjusted incidence rate ratios.

Age speciﬁc unadjusted incidence rate ratios (IRRs), adjusted IRRs and their 95% conﬁdence intervals (CIs) are shown on left. Adjusted IRRs with 95% CIs are plotted on right. a: Due to the data suppression rules, counts 1–4 are reported as *<*5 in observed cases.

for residents of DL/SB ages 0–4 years is 1.54 in 10,000 person years compared to 0.24 in 10,000 person years in the remaining counties. Similarly, incidence of brain and other nervous system cancer for residents of SB/DL aged 30–34 years is 1.84 in 10,000 person years compared to 0.47 in 10,000 person years in the remaining counties. However, the risk of brain and other nervous system cancers in very young children and adults in their prime is elevated at a level to cause concern for the residents of these two contiguous counties.

Increased risk for brain and other nervous system cancers was found in adults ages 30–34 years, who were born in the period before the Superfund sites were ﬁrst declared (1981–1985). However, without a residential history, we do not know how many of these young adults continuously lived in the DL/SB area. Further research is needed to explore associations between metal exposures and brain and other nervous system cancers, that in- cludes residential history, exposure to radiation, family history of conditions associated with brain and nervous system cancer, and other known risk factors. If address history data were available, a geospatial–temporal model could be ﬁtted to quantify the relation- ship between location of the Superfund and active mining sites

and the cases of brain cancer, while considering for correlation across spatial locations and time; and to assess the change of cancer risk and effectiveness of remediation over time. In addition, if sample sizes are suﬃcient, there is a need for analyses of inci- dence rates for subtypes of brain and nervous system cancers, and to ascertain biomarkers for metal exposures. Considering the long history of mining, continued open pit mining, and known exposure to toxic heavy metals ([Hailer et al., 2017](#_bookmark15)), cancer of the brain and nervous system should continue to be studied and monitored.

Previous studies investigating the association between heavy metal exposure and brain cancers have produced mixed re- sults ([Becker et al., 1985](#_bookmark7); [van Wijngaarden and Dosemeci 2006](#_bookmark32); [Anttila](#_bookmark31) [et al., 1996](#_bookmark8)[;](#_bookmark31) [Samkange-Zeeb et al., 2010](#_bookmark35)[; Rajaraman et al., 2006;](#_bookmark31) [Bhatti](#_bookmark9) [et al., 2009;](#_bookmark31) [Lam](#_bookmark23) [et al., 2007;](#_bookmark31) [Cocco](#_bookmark10) [et al., 1998;](#_bookmark31) [Hara et al., 2010](#_bookmark19); [Schlehofer et al., 2005](#_bookmark37); [Wesseling et al., 2002](#_bookmark37)). However, most of these studies focused on occupational exposures to metals and not chronic residential exposure to contaminated soil, water, or air. The prevailing winds in SB county are south- ward with the location of the mine north of a large residential neighbourhood ([Western Regional Climate Center, 2019](#_bookmark39)). Thus, the potential for inhalation of metals as well as skin absorption, and

hand-to-mouth transmission from both water and soil is ongoing ([Hailer et al., 2017](#_bookmark15)). Without extensive chemical analyses it is impossible to separate the exposures that are from the residue of old mining that is receiving remediation, from the exposures caused from the active mining that continues in the SB county. The MCTR does not collect information about residential history or individual exposure data, nonetheless, the risk for higher incidence of diseases associated with metal exposure to the residents of the two past and present mining counties is substantial, and the risk needs to be communicated to the population.

The Environmental Protection Agency (EPA) lists contaminants of concern in SB/DL: As, Cd, Cu, Fe, Pb, Mn, Hg, Ag, and Zn ([United States Environmental Protection Agency, 2019](#_bookmark26)a), but the only systematic testing that has been conducted in SB/DL is for As and Pb. There is no screening for Mn, Cu, and Zn, although their neurotoxic effects are documented in studies outside the US with impacts as extreme as fetal death and stillborn to intel- [lectual and developmental delay in young children (Reyes et al.,](#_bookmark33) [20](#_bookmark42)[13;](#_bookmark33) [Jomo](#_bookmark20)[va et al., 2011;](#_bookmark33) [Jomo](#_bookmark21)[va and Valko 2011; Simonsen et al.,](#_bookmark33) [2012;](#_bookmark42) [Ts](#_bookmark43)[eng 2004;](#_bookmark42) [Bhatt](#_bookmark11)[acharyya 2009;](#_bookmark42) [Shinkai](#_bookmark41) [and Kaji 2012;](#_bookmark42) [Turker et al., 2013](#_bookmark23); [Caserta et al., 2011](#_bookmark12)).

The research on the epigenetic alterations in brain tumors as- sociated with heavy metals ([Jaishankar et al., 2014](#_bookmark17)) suggests the pathway that is altered by cadmium (Cd) exposure, through differ- entiation and apoptosis, can result in loss of expression of tumor suppressor genes and miRNA expression. In addition, data suggest that Pb, As, Cd and other metals cause oxidative stress, cell death and neuroinﬂammation, resulting in the formation of radicals in the brain ([Mates et al., 2009](#_bookmark24)). The adult brain is thought to be pro- tected from toxins by the blood brain barrier and choroid plexus, nonetheless some heavy metals are able to mimic the behaviour [of essential nutrients to be transported to the brain (Bridges and Zalups, 2005). Moreover, toxic metals are capable of producing ad-](#_bookmark13) ditive, synergistic, or antagonistic interactions, generating variable biochemical changes in the brain or even reducing the essential micronutrients available ([Goyer, 1997](#_bookmark22)). Fetal exposure to metals can happen through the amniotic ﬂuid, the placenta, and the um- bilical cord; literature has demonstrated the susceptibility of pla- cental barrier to various toxic substances ([Zheng et al., 2014](#_bookmark40)). In a similar manner to the mechanism by which metals cross the blood brain barrier, they are also capable of ‘tricking’ transport proteins in the cell membranes of the placenta, allowing passage of toxic metals.

While metals induce different toxic effects at different concen- trations in the adult, they can also affect important biochemical changes during development. [Nuttall (2017)](#_bookmark28) posits two main ways that metals can affect the fetal micronutrient homeostasis. Toxic metals affect the availability of essential heavy metals through competitive chemical bonding (e.g., Pb, Cd can reduce the Zn bind- ing to proteins), and they also can cause secondary micronutrient deﬁciencies via immune response ([Lam et al., 2007](#_bookmark23)). Many metals are known to induce an acute inﬂammatory response, which in turn can affect essential micronutrient availability. Induction of an acute-phase response during pregnancy can disrupt fetal mi- cronutrient availability, due to rapid changes in protein production and micronutrient metabolism. A comprehensive review of metal mixtures and neurodevelopmental outcomes provides evidence of synergistic effects related to exposures to mixtures of As-Cd-Pb [and Mn in the presence of As, Cd, or Pb (von Stackelberg et al., 2015). Their review focused on nonspeciﬁc developmental out-](#_bookmark36) comes in children but did not report on brain and other nervous system cancer.

# Conclusion

This study uses an epidemiologic approach combined with sta- tistical methods that uncover the association of residence in DL/SB counties with extremely high risk for brain and other nervous sys- tem cancers in young children, 0–4 years, and adult ages 30–34 years. The approach used to conduct these analyses allowed for heterogeneity by age, sex, year, and stage in which the cancer was diagnosed. We found that IRRs varied by age, but not by sex, year of diagnosis (during our study period 2001–2015), or cancer stages. These ﬁndings are important since they have previously been un- derstudied and therefore not reported. The implications are sub- stantial for residents of DL/SB, and also for the millions of Amer- icans who live near a Superfund designated area or active mining sites that contain mixtures of neurotoxic metals.

# Declaration of Competing Interest

None.

# References

[Anttila,](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0001) [A., Heikkila, P., Nykyri, E., Kauppinen, T., Pukkala, E., Hernberg, S., Hem-](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0001) [minki, K., 1996. Risk of nervous system cancer among workers exposed to lead.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0001)

[J. Occup. Environ. Med. 38 (2), 131–136.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0001)

[Arslan,](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0002) [M., Demir, H., Arslan, H., Gokalp, A.S., Demir, C., 2011. Trace elements, heavy metals and other biochemical parameters in malignant glioma patients. Asian Pac. J. Cancer Prev. 12 (2), 447–451.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0002)

[Aschner, M., Costa, L.G, 2017. Environmental Factors in Neurodegenerative Diseases,](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0003)

[1. Academic Press.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0003)

[Becker, N., Claude, J., Frentzel-Beyme, R., 1985. Cancer risk of arc welders exposed to fumes containing chromium and nickel. Scand. J. Work Environ. Health 11 (2), 75–82.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0004)

[Bhattacharyya, M.H., 2009. Cadmium osteotoxicity in experimental animals: mech- anisms and relationship to human exposures. Toxicol. Appl. Pharmacol. 238 (3), 258–265.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0005)

[Bhatti,](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0006) [P., Stewart, P.A., Hutchinson, A., Rothman, N., Linet, M.S., Inskip, P.D., Ra-](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0006) [jaraman, P., 2009. Lead exposure, polymorphisms in genes related to oxidative stress, and risk of adult brain tumors. Cancer Epidemiol. Biomark. Prev. 18 (6), 1841–1848.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0006)

[Bridges, C.C., Zalups, R.K., 2005. Molecular and ionic mimicry and the transport of toxic metals. Toxicol. Appl. Pharmacol. 204 (3), 274–308.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0007)

[Caffo, M., Caruso, G., Fata, G.L., Barresi, V., Visalli, M., Venza, M., Venza, I., 2014. Heavy metals and epigenetic alterations in brain tumors. Curr. Genom. 15 (1389–2029), 457–463 Print.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0008)

[Caserta, D.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0009), [Mantovani, A.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0009), [Ciardo, F.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0009), [Fazi, A.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0009), [Baldi, M.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0009), [Sessa, M.T.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0009), [la Rocca, C.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0009), [Ronchi, A., Moscarini, M., Minoia, C., 2011. Heavy metals in human amniotic ﬂuid: a pilot study. Prenat. Diagn. 31 (8), 792–796.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0009)

[Cocco,](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0010) [P., Dosemeci, M., Heineman, E.F., 1998. Brain cancer and occupational expo- sure to lead. J. Occup. Environ. Med. 40 (11), 937–942.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0010)

Davis, B., McDermott, S., McCarter, M., Ortaglia, A., 2019. Population-based mortality data suggests remediation is modestly effect in two Montana Superfund coun- ties. Environ. Geochem. Hlth. 41 (2), 803–816. doi:[10.1007/s10653-018-0175- z](https://doi.org/10.1007/s10653-018-0175-z).

[Gammons,](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0011) [C.H., Metesh, J.J., Duaime, T.E., 2006. An overview of the mining his- tory and geology of butte, Montana. Mine Water and the Environment 25 (2), 70–75.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0011)

[Goyer, R.A., 1997. Toxic and essential metal interactions. Annu. Rev. Nutr. 17 (1), 37–50.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0012)

[Hailer, M.K., Peck, C.P., Calhoun, M.W., West, R.F., James, K.J., Siciliano, S.D., 2017. As- sessing human metal accumulations in an urban superfund site. Environ. Toxi- col. Pharmacol. 54, 112–119 1872-7077 Electronic.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0013)

[Hara, T., Hoshuyama, T., Takahashi, K., Delgermaa, V., Sorahan, T., 2010. Cancer risk among japanese chromium platers, 1976–2003. Scand. J. Work Environ. Health 36 (3), 216–221.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0014)

[Hsueh, Y.M.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0015), [Lee, C.Y.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0015), [Chien, S.N.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0015), [Chen, W.J.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0015), [Shiue, H.S.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0015), [Huang, S.R.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0015), [Lin, M.I.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0015), [Mu, S.C., Hsieh, R.L., 2017. Association of blood heavy metals with developmen- tal delays and health status in children. Sci. Rep. 7, 43608 2045-2322 Electronic.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0015)

[Jaishankar, M., Tseten, T., Anbalagan, N., Mathew, B.B., Beeregowda, K.N., 2014. Toxi- city, mechanism and health effects of some heavy metals. Interdiscip. Toxicol. 7 (2), 60–72.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0016)

[Jomova, K.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0017), [Jenisova, Z.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0017), [Feszterova, M.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0017), [Baros, S.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0017), [Liska, J.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0017), [Hudecova, D.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0017), [Rhodes, C.J.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0017), [Valko, M., 2011. Arsenic: toxicity, oxidative stress and human disease. J. Appl. Toxicol. 31 (2), 95–107.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0017)

[Jomova, K., Valko, M., 2011. Advances in metal-induced oxidative stress and human disease. ToxicologyToxicology 283 (2–3), 65–87.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0018)

[Lam, T.V., Agovino, P., Niu, X.L., Roche, L., 2007. Linkage study of cancer risk among lead-exposed workers in New Jersey. Sci. Total Environ. 372 (2–3), 455–462.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0019)

[Mates, J.M., Segura, J.A., Alonso, F.J., Marquez, J., 2009. Natural antioxidants: thera- peutic prospects for cancer and neurological diseases. Mini Rev. Med. Chem. 9 (10), 1202–1214.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0020)

Montana Department of Public Health and Human Services. Montana Central Tu- mor Registry Annual Report, Cancer in Montana 2012-2016 2019 [cited June 24, [2019. Available from https://mtcancercoalition.org/wp-content/uploads/2019/ 04/MCTR-Annual-Report\_2012-2016.pdf.](https://mtcancercoalition.org/wp-content/uploads/2019/04/MCTR-Annual-Report_2012-2016.pdf)

National Cancer Inistitute, 2019. Surveillance, epidemiology, and end results pro- gram. Cancer Query System. SEER Incidence Statistics cited May 21 Available from <https://seer.cancer.gov/canques/incidence.html>.

[Nuttall, J.R., 2017. The plausibility of maternal toxicant exposure and nutritional sta- tus as contributing factors to the risk of autism spectrum disorders. Nutr. Neu- rosci. 20 (4), 209–218.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0022)

[Plathe, K.L.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0023), [von der Kammer, F.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0023), [Hassellov, M.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0023), [Moore, J.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0023), [Murayama, M.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0023), [Hofmann, T.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0023), [Hochella, M.F., 2010. Using ﬂfff and aTEM to determine trace metal-nanoparticle associations in riverbed sediment. Environ. Chem. 7 (1), 82–93.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0023)

[Rajaraman, P., Stewart, P.A., Samet, J.M., Schwartz, B.S., Linet, M.S., Zahm, S.H., Roth-](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0024)

[man, N.,](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0024) [Yeager, M.,](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0024) [Fine, H.A.,](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0024) [Black, P.M.,](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0024) [Loeﬄer, J.,](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0024) [Shapiro, W.R.,](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0024) [Selker, R.G.,](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0024) [Inskip, P.D., 2006. Lead, genetic susceptibility, and risk of adult brain tumors. Cancer Epidemiol. Biomark. Prev. 15 (12), 2514–2520.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0024)

[Reyes, J.L., Molina-Jijon, E., Rodriguez-Munoz, R., Bautista-Garcia, P., Debray–](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0025) [Garcia, Y., Namorado Mdel, C., 2013. Tight junction proteins and oxida- tive stress in heavy metals-induced nephrotoxicity. Biomed. Res. Int., 730789 20132314-6141Electronic.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0025)

[Samkange-Zeeb, F., Schuz, J., Schlehofer, B., Berg-Beckhoff, G., Blettner, M., 2010. Comparison of studies on mobile phone use and risk of tumors. J. Clin. Oncol. 28 (7), e123.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0026)

[Schlehofer, B., Hettinger, I., Ryan, P., Blettner, M., Preston-Martin, S., Little, J., Ar- slan, A.,](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0027) [Ahlbom, A.,](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0027) [Giles, G.G.,](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0027) [Howe, G.R.,](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0027) [Menegoz, F.,](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0027) [Rodvall, Y.,](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0027) [Choi, W.N.,](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0027) [Wahrendorf, J., 2005. Occupational risk factors for low grade and high grade glioma: results from an international case control study of adult brain tumours. Int. J. Cancer 113 (1), 116–125.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0027)

Scorecard - The Pollution Information Site, 2011. Pollution Locator. GoodGuide cited May 21, 2019. Available from <http://scorecard.goodguide.com/env-releases/land/>.

[Shinkai, Y., Kaji, T., 2012. Cellular defense mechanisms against lead toxicity in the vascular system. Biol. Pharm. Bull. 35 (11), 1885–1891.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0029)

[Simonsen, L.O., Harbak, H., Bennekou, P., 2012. Cobalt metabolism and toxicology – a brief update. Sci. Total Environ. 432, 210–215 1879-1026Electronic.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0030)

[Tseng, C.H., 2004. The potential biological mechanisms of arsenic-induced diabetes mellitus. Toxicol. Appl. Pharmacol. 197 (2), 67–83.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0031)

[Turker, G., Ozsoy, G., Ozdemir, S., Barutcu, B., Gokalp, A.S., 2013. Effect of heavy metals in the meconium on preterm mortality: preliminary study. Pediatr. Int. 55 (1), 30–34.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0032)

United States Census Bureau. Population and Housing Unit Estimates 2010 [[cited May 21, 2019. Available from https://www.census.gov/content/census/en/ programs-surveys/popest/data/data-sets.2010.html/.](https://www.census.gov/content/census/en/programs-surveys/popest/data/data-sets.2010.html/)

United States Environmental Protection Agency. Anaconda Co. Smelter Anaconda, [MT 2018 [cited May 21, 2019. Available from https://cumulis.epa.gov/supercpad/ cursites/csitinfo.cfm?id=0800403.](https://cumulis.epa.gov/supercpad/cursites/csitinfo.cfm?id=0800403)

United States Environmental Protection Agency, 2019a. Silver Bow Creek/Butte Area Butte. Cleanup activities a, MT cited May 21, 2019. Available from [https://cumulis.epa.gov/supercpad/SiteProﬁles/index.cfm?fuseaction=second.](https://cumulis.epa.gov/supercpad/SiteProfiles/index.cfm?fuseaction=second.Cleanup&id=0800416&bkground)

[Cleanup&id=0800416#bkground.](https://cumulis.epa.gov/supercpad/SiteProfiles/index.cfm?fuseaction=second.Cleanup&id=0800416&bkground)

United States Environmental Protection Agency, 2019b. Superfund site: Sil- ver bow creek/ Butte Area Butte. MT b cited May 21, 2019. Avail- [able from https://cumulis.epa.gov/supercpad/SiteProﬁles/index.cfm?fuseaction= second.Healthenv&id=0800416#Contam.](https://cumulis.epa.gov/supercpad/SiteProfiles/index.cfm?fuseaction=second.Healthenv&id=0800416&Contam)

US National Cancer Institute. State cancer proﬁles: incidence rate report for Montana by county 2009 [cited June 24, 2019. Available from [https://statecancerproﬁles.cancer.gov/incidencerates/index.php?stateFIPS= 30&cancer=001&race=00&sex=0&age=001&type=incd&sortVariableName= rate&sortOrder=default#results.](https://statecancerprofiles.cancer.gov/incidencerates/index.php?stateFIPS=30&cancer=001&race=00&sex=0&age=001&type=incd&sortVariableName=rate&sortOrder=default&results)

[van](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0035) [Wijngaarden, E., Dosemeci, M., 2006. Brain cancer mortality and potential oc- cupational exposure to lead: ﬁndings from the national longitudinal mortality study, 1979–1989. Int. J. Cancer 119 (5), 1136–1144.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0035)

[von](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0036) [Stackelberg, K., Guzy, E., Chu, T., Henn, B.C., 2015. Exposure to mixtures of met- als and neurodevelopmental outcomes: a multidisciplinary review using an ad- verse outcome pathway framework. Risk Anal. 35 (6), 971–1016.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0036)

[Waisberg, M., Joseph, P., Hale, B., Beyersmann, D., 2003. Molecular and cellular mechanisms of cadmium carcinogenesis. Toxicology 192 (2–3), 95–117.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0037)

[Wesseling, C., Pukkala, E., Neuvonen, K., Kauppinen, T., Boffetta, P., Partanen, T., 2002. Cancer of the brain and nervous system and occupational exposures in ﬁnnish women. J. Occup. Environ. Med. 44 (7), 663–668.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0038)

Western Regional Climate Center. Prevailing Wind Direction [cited May 21, 2019. [Available from https://wrcc.dri.edu/Climate/comp\_table\_show.php?stype=wind\_ dir\_avg.](https://wrcc.dri.edu/Climate/comp_table_show.php?stype=wind_dir_avg)

[Zheng,](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0039) [G., Zhong, H., Guo, Z., Wu, Z., Zhang, H., Wang, C., Zhou, Y., Zuo, Z., 2014. Levels of heavy metals and trace elements in umbilical cord blood and the risk of adverse pregnancy outcomes: a population-based study. Biol. Trace Elem. Res. 160 (3), 437–444.](http://refhub.elsevier.com/S1877-5845(19)30130-3/sbref0039)