Quarterly Surveillance Report
July 2007
Special Supplement

Cancer Cluster Investigations

Montanans are aware that cancer is becoming more common and many are concerned that environmental hazards contribute to the risk of cancer or other health problems in their communities. The Montana Department of Public Health and Human Services (DPHHS) receives inquiries and reports about potential cancer clusters every year. DPHHS has adopted a standardized protocol to ensure that each report is adequately addressed.[1] The protocol is based on a model developed by the Centers for Disease Control and Prevention.[2]

A cancer cluster is an **excess occurrence** of a single type of cancer (**case definition**) within a specified **time period** and within a defined **population at risk**, typically described by geography or some other common factor. Additional evidence for a potential cluster is cancer in a segment of the population not usually affected by that type of cancer.

The State of Montana's Cancer Cluster Investigation Protocol

Coordination: Each inquiry or report is referred to the Epidemiologist in the Cancer Control Section of DPHHS. The Epidemiologist contacts the local health jurisdiction to inform them of the report and determine who should respond.

Verification: If the DPHHS is designated to respond, the Epidemiologist creates a case definition and gathers all available information on the cases that prompted the call, including time period, location, and suspected environmental hazards, if any. The Epidemiologist verifies the reported cases in the Montana Central Tumor Registry and looks for more cases that fit the case definition. Once all cases are identified, the Epidemiologist calculates incidence rates in the community and in the state as a whole to determine whether there is an unusually high incidence in the community.

Case Definition

Cancer is a general term for cells that grow out of control, no longer perform their

[1] http://www.dphhs.mt.gov/epht/investigationprotocol.pdf
[2] http://www.cdc.gov/nceh/clusters

usual functions, and invade other tissues. Cancer as a category of disease is common: one in three residents of the US will develop cancer in his or her lifetime. Cancers are classified by site (part of the body) and histology (kind of cells affected and the way the cells behave). Specific types of cancer, as defined by site and histology, are often uncommon and many are rare. Each type of cancer has its own constellation of risk factors.

Because cancer is really many diseases, investigation of a reported cancer cluster starts with creating a case definition. For example, a general term like "leukemia" is not an appropriate case definition. There are many kinds of leukemia, each with unique age distributions and unique sets of known or suspected risk factors. The more specific the case definition, the more likely the cases are to have common risk factors. A precise case definition contributes to the possibility of discovering a risk factor because it focuses attention on a single disease process that may arise from a specific exposure.

Time Period

Cancer is complex and multifactorial (many factors interact) and develops over many years (latency period). With rare exceptions, no single event causes cancer and no single exposure or risk factor explains all cancers of a given type. Not all cases of cancer can be traced to specific exposures or risk factors. The causal process for all kinds of cancer includes multiple mutations of genetic material in a cell that result in disordered growth and function. Cells have a remarkable ability to repair mutations so multiple events over many years are usually required to cause cancer. Because of the complex causal pathways and the latency period, it is often difficult to identify events that contributed to cancer. As a preliminary step, an investigation of a potential cancer cluster might look at incidence before and after a suspected hazard was introduced into the environment.

Population at Risk

Because many potential cancer clusters are reported on the basis of suspected exposure to a local environmental hazard, the population at risk may initially be defined as people living near the hazard. However, some current residents may be newcomers and some previous residents may have left. Mobility makes it difficult to define the population at risk. The Montana Central Tumor Registry records the address at time of diagnosis for each cancer patient but that address may not reflect the true history of possible exposure. The population at risk may be refined to include only long-term residents of the area near a suspected hazard.

Excess Occurrence

Cancer occurs in all communities. The prevalence (number of cases that exist at any given time) and incidence (number of new cases diagnosed during a specified period of time) are described by either age-specific or age-adjusted rates, to take into account that cancer usually occurs in older individuals. Rates are expressed

using a common denominator, usually per 100,000 people at risk. Age-adjusted rates allow us to make accurate comparisons among communities and to judge whether there may be an unusually high incidence in a given community.

Many reported clusters are not verified so the process stops here. The most common reason a cluster is not verified is that the cases which prompted the report are diverse and do not fall into a single case definition. Another common reason a cluster is not verified is that cases have not lived in a community long enough for local conditions to have caused or contributed to their disease.

Three criteria are used to determine whether an investigation should occur:

1) three or more cases meet the case definition;
2) cases have a plausible common cause or share a common exposure; and
3) cases have lived in the area for an appropriate period of time for the common exposure to be related to their cancer.

Investigation: Because an investigation may require contacting patients or their families, it can be very distressing for those involved. An investigation is not undertaken unless there is persuasive evidence of a cancer cluster. If a cluster is verified, DPHHS initiates an investigation. All known risk factors are considered, including any environmental hazards that may have prompted the initial report. At this stage, DPHHS will contact health care providers of record, and possibly patients or their surviving relatives, to gather information on individual life histories, risk factors, and potential exposures to suspected hazards. If cases in the cluster cannot be explained by known risk factors, or if life histories point to a common exposure or environmental hazard, DPHHS will search for detailed information on the suspected hazard and its possible presence in the area. An epidemiologic study will be initiated if one or more of the following criteria is met:

1) an environmental hazard exists and is a biologically plausible risk for the type of cancer observed;
2) there is a high prevalence or sudden increase in cancer meeting the case definition in the area associated with the environmental hazard; or
3) there is no other explanation for the cancer cases and they share exposure to the environmental hazard.

Epidemiologic Study: If DPHHS determines that it is necessary to conduct an epidemiologic study, it will consult with specialists from appropriate agencies such as the Centers for Disease Control and Prevention, the Agency for Toxic Substances and Disease Registry, or the Environmental Protection Agency.

The Problem of Small Numbers

It is difficult to interpret incidence rates for small segments of a population such as Montana's counties. In effect, any single case of cancer might appear to be an excess. Although the occurrence of two or three cases can be very striking in a small population, it rarely indicates a cluster.

Incidence rates are computed as the number of cases divided by the number of people in the population at risk, multiplied by 100,000 to achieve a common denominator to compare rates. The table on the next page, based on data from the Montana Central Tumor Registry, shows the incidence of brain cancer in Montana and two counties, one of the larger and one of the smaller counties in the state. In 2000, five cases of brain cancer in the large county with a population of 55,716 yielded a crude (not age-adjusted) incidence rate of 9.0 per 100,000, compared the state as a whole with 73 cases and a population of more than 900,000, or a crude rate of 8.1 per 100,000. Assuming that the large county and the state have similar age distributions, it might appear that the county rate is higher than the state rate. However, if one of the five cases in the large county had been diagnosed a year earlier or later, the computed rate for 2000 would be 7.2 per 100,000, lower than the state rate. One way to deal with this variability is to use multiple year average incidence rates for comparison. The small county had only two cases of brain cancer in the five-year period, but both were diagnosed in the same year. The annual crude incidence rate was very high at 88.8 per 100,000 but the five-year average was substantially lower at 17.6 per 100,000.

It is also necessary to take into account the age structure of populations when comparing the incidence of cancer, which has a strong association with age. For example, the crude five-year average brain cancer incidence rate for Montana was 7.8 per 100,000, but when adjusted for the age distribution of the population it was 7.4 For the large county, the crude and age-adjusted rates were the same, 9.7 per 100,000. However, for the small county, the crude incidence rate was 17.6 while the age-adjusted rate was 11.2 per 100,000. The population of the small county was actually shrinking over the five-year period, and age-adjustment substantially reduced the incidence rate of cancer in this example, suggesting a reduced birth rate or out-migration of young adults and an overall aging of the county population.

Statistics based on small numbers of cases are unstable. This instability is measured by the Confidence Interval (CI) around the rate. For a 95% CI, the true cancer rate has a probability of 95% of falling within the range. For the large county, we are 95% sure that the true rate is between 5.7 and 13.7 per 100,000. The CI for the state rate, with a substantially larger population and more cases, is 6.4 to 8.4 per 100,000. Because the CI for the large county includes the state rate (5.7 to 13.7 includes 7.4), the rates are not considered statistically significantly different. Although the incidence rate for the small county appears to be substantially greater than the state rate, its CI is much larger, from 0 to 27.2, and not statistically different from the state rate.

Incidence of Brain Cancer in Montana and Two Counties

	Montana				Large County				Small County			
Year	cases	population	crude rate[3]	age-adjusted rate (CI)[4]	cases	population	crude rate	age-adjusted rate (CI)	cases	population	crude rate	age-adjusted rate (CI)
1999	60	882,779	6.8	6.6	3	54,075	5.6	5.3	2	2,253	88.8	52.8
2000	73	903,157	8.1	7.8	5	55,716	9.0	9.1	0	2,158	0	0
2001	62	904,433	6.9	6.7	4	56,094	7.1	6.9	0	2,096	0	0
2002	89	909,453	9.8	9.4	10	56,554	17.8	19.3	0	2,037	0	0
2003	67	917,621	7.3	6.9	5	57,137	8.8	8.5	0	2,055	0	0
Average	70		7.8	7.4 (6.4 - 8.4)	5.4		9.7	9.7 (5.7 - 13.7)	0.5		17.6	11.2 (0 - 27.2)

We would therefore conclude that, in spite of a striking incidence of two cases in a single year in the small county, there is no excess of brain cancer there. In fact, the two cases of brain cancer were of different histologic types. One is more common in males, the other more common in females. One has bimodal age peaks (under age 10 and over age 25), the other is rare before the teens and increases linearly with age. The two types have no known risk factors in common and an initial review of cases would have placed them in different case definitions.

Cancer is becoming more common as the population ages and other causes of morbidity and mortality are brought under control. True cancer clusters are extremely rare, as are clearly identifiable environmental causes of cancer. The Montana Cancer Control Section of DPHHS uses the MCTR to monitor cancer trends in the state and to respond to public inquiries.

[3] per 100,000 total population
[4] per 100,000 population age-adjusted to the 2000 Census population; CI = 95% Confidence Interval around the point estimate

Please visit our website at www.cancer.mt.gov

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Environmental Carcinogens and Sentinel Event Monitoring

The general public and advocacy groups are very concerned about environmental pollutants causing cancer. In the United States, the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA), and internationally the International Agency for Research on Cancer (IARC), conduct research on the carcinogenic (cancer causing) potential of chemical agents.[1,2,3] The ATSDR evaluates potential human health impacts of these agents. The EPA sets permissible levels of environmental exposure and monitors compliance in the United States. The National Institute of Occupational Safety and Health (NIOSH) conducts research and makes recommendations about occupational exposures.[4] The Occupational Safety and Health Administration (OSHA) sets and enforces permissible levels of occupational exposure and specifies protective measures that must be provided for workers.[5]

In spite of extensive research, relatively few agents are classified as definite or probable human carcinogens; these are associated with 26 kinds of cancer (Table 1).[1,2,3,6] There are additional agents classified as possible or suspected human carcinogens, based on experimental studies in animals, but no evidence exists at this time to establish their carcinogenicity in humans.

The definite or probable carcinogens may increase the risk of specific kinds of cancer but, in almost all cases, the general population is exposed to much more common risk factors for those kinds of cancer. For example, 12 chemicals in Table 1 definitely increase the risk of lung cancer, and 7 probably increase the risk. However, 90% or more of all cases of lung cancer are caused by cigarette smoking. Half of the 26 cancers listed in Table 1 are caused by tobacco use (indicated by yellow in Table 1).

Two carcinogens definitely increase the risk of liver cancer and four more probably increase the risk. However, alcohol consumption and history of hepatitis B or hepatitis C infection are much more common causes of liver cancer (indicated by orange in Table 1). In addition, the most common sources of exposure to one of the carcinogens suspected to increase the risk of liver cancer (arsenic and compounds containing arsenic) are cigarette smoke and vehicle exhaust.

[1] http://www.atsdr.cdc.gov/substances/index.html
[2] EPA Integrated Risk Information System, http://cfpub.epa.gov/ncea/iris/index.cfm
[3] International Agency for Research on Cancer Monographs, http://monographs.iarc.fr/ENG/preamble/index.php
[4] http://www.cdc.gov/niosh/topics/chemical.html
[5] http://www.osha.gov/oshinfor/mission.html
[6] Report on Carcinogens, 11th Ed. US Department of Health and Human Services, Public Health Service, National Toxicology Program. 2005. http://ntp.niehs.nih.gov

Table 1. Definite or Probable Human Carcinogens and Corresponding Cancers

	Lung	Oral cavity	Throat	Esophagus	Pharynx	Larynx	Nasal cavity	Naso-pharynx	Paranasal sinus	Mesothelioma	Digestive NFS †	Stomach NFS	Liver NFS	Hepato-cellular	Liver heman-giosarcoma
Cigarettes	X	X	X	X	X	X	X	X							
Second hand smoke	X						X								
Smokeless tobacco		X													
Alcohol		--		--	X	X							X		
Hepatitis													X		
Acetylaldehyde	X/cae	X/cae	X/cae	X/cae											
Acrylonitrile	X/t														
Aflatoxins														X	
4-Aminobiphenyl															
Arsenic and compounds	?/ce										?/ce		?/ce		
Asbestos	X					?				X					
Benzene															
Benzidine															
Benzo(a)pyrene	X/cse														
Beryllium and compounds	X														
1,2-Butadiene															
Butylated hydorxyanisole												?			
Cadmium and compounds	X/c														
Carbon tetrachloride													?		
Chlordane													?		
Chromium and compounds	X														
Coal tars	?										?				
Coke oven emissions	X														
1,2-Dibromo-3-chloropropane	?														
Diesel exhaust particulates	?														
Ethylene oxide												?/ce			
Formaldehyde							X/ceh	X/ceh	X/ceh						
Hexachlorobenzene								X	X						
Lead and compounds	?/c											?/ce			
2-Napththylamine															
Nickel and compounds	X						X								
PAH	?/cse														
Radium							X								
Radon	X														
Silica	X														
Soot	?/e			?/e											
Sulfuric acid mists	X					X									
Tetracholorethylene															
Tricholorethylene													?		
Uranium	X														
Vinyl chloride															X
Wood dust							X	X	X						

	Kidney	Bladder	Pancreas	Leukemia NFS	Acute myeloid leukemia	Lymophoma NFS	Non-Hodgkin lymphoma	Breast	Non-melanoma skin	Prostate	Bone NFS
Cigarettes	?	X	X		X						
Second hand smoke											
Smokeless tobacco											
Alcohol							?	X			
Hepatitis											
Acetylaldehyde											
Acrylonitrile										?/t	
Aflatoxins											
4-Aminobiphenyl		X/cs									
Arsenic and compounds	?/ce	X/ce		?/ce		?/ce			X/ce		
Asbestos											
Benzene				?/cseg	X/cseg						
Benzidine		X									
Benzo(a)pyrene									X/cse		
Beryllium and compounds				X		X					
1,2-Butadiene				X/cse		X/cse	X/cse				
Butylated hydorxyanisole											
Cadmium and compounds	?/c	?/c								?/c	
Carbon tetrachloride											
Chlordane							?				
Chromium and compounds				?							?
Coal tars	?	?		?					X		
Coke oven emissions	X	X							X		
1,2-Dibromo-3-chloropropane											
Diesel exhaust particulates											
Ethylene oxide				X/ce							
Formaldehyde											
Hexachlorobenzene											
Lead and compounds		?/c									
2-Napththylamine		X									
Nickel and compounds											
PAH									?/cse		
Radium											X
Radon											
Silica											
Soot		?/e							X/e		
Sulfuric acid mists											
Tetracholorethylene	?	?							?		
Tricholorethylene	?						?			?	
Uranium											
Vinyl chloride											
Wood dust											

Key

Primary Risk Factors for the Type of Cancer

- Tobacco
- Alcochol
- Sun
- Potential sentinel cancer

† NFS = Not Further Specified

X = documented human carcinogen

? = probable human carcinogen

Main Source of Exposure to the Chemical Agent for the Population

c = cigarette smoking

s = second-hand smoke

t = tobacco use

a = alcohol consumption

e = vehicle exhaust

h = home heating and other combustion

g = gasoline

Only cancers with Xs in the blue boxes in Table 1, without other common sources of exposure to a potential carcinogen, are believed to be *primarily* caused by exposure to that carcinogen *from an environmental exposure*: mesothelioma and asbestos; cancer of the paranasal sinus and hexachlorobenzene or wood dust; heptaocellular carcinoma and aflatoxins; and hemangiosarcoma of the liver and vinyl chloride. The associations between leukemia NFS (not further specified) and beryllium, lymphoma NFS and beryllium, and bone NFS and radium are difficult to evaluate. Leukemia, lymphoma, and bone cancer all have several subtypes, each with specific risk factors. It is likely that exposure to a carcinogen would affect only one subtype. In addition, these cancers are not rare and there are common risk factors for each of them.

Table 2 describes the primary uses for the definite or probable human carcinogens, the most common sources of exposure for the general public, and the most common occupational exposures. Some carcinogens occur naturally in the environment although exposure may be increased by human activity (e.g., aflatoxins, asbestos, beryllium, cadmium, lead, nickel, radon, silica, soot, and uranium). Others are unavoidable in everyday products. Some occupations have the potential for exposure to these agents. The EPA sets permissible levels of environmental exposure and OSHA sets permissible levels of occupational exposure. These levels are very conservative, taking into account the possibility of cumulative lifetime exposure and individual variation in sensitivity.[7]

A striking feature of Table 2 is the number of times cigarette smoking, second-hand smoke exposure, and use of other tobacco products appears in the column describing common sources of exposure for the general public.

Most people exposed to definite or probable human carcinogens are not exposed through environmental contamination or disasters. They are exposed through lifestyle choices such as tobacco and alcohol use; from common consumer products; by living in an industrialized environment where fossil fuels are used by vehicles, power plants, and heating systems; and by living in a society characterized by high consumption of manufactured goods. Apart from tobacco and alcohol, exposures to these carcinogens encountered in daily life are below levels assessed to be without risk of adverse health effects.[7] Occupational exposures may be higher but can be moderated by the appropriate use of protective equipment and observance of correct safety procedures.

There are occasional catastrophic events leading to environmental contamination at levels that increase the risk of acute toxic effects and may increase the risk of some cancers. In spite of many investigations in the United States and worldwide, there have been few documented cases of increased cancer attributable to environmental contamination. The very large nuclear reactor explosion at Chernobyl in the Ukraine in 1986 resulted in an increased incidence of thyroid cancer among individuals exposed to radioactive fallout during childhood or adolescence in regions near and downwind from the reactor site.[8]

[7] http://www.atsdr.cdc.gov/mrls/
[8] Cardis et al., 2006. *J Radiol Prot* 26:127-140.

Table 2. Human Carcinogenic Agents: Uses and Common Sources of Exposure for General Population and in Occupations

Agent	Common uses	Population exposure	Occupational exposure	Comment
Acetylaldehyde	food additive; fumigant for stored fruit crops	alcoholic beverages, tobacco smoke, auto and diesel exhaust	mechanics, gas station attendants, agricultural and food industry, spray painting	
Acrylonitrile	tobacco fumigant prior to 1978	tobacco use	tobacco workers	Use as fumigant banned in 1978
Aflatoxins	toxin produced by Aspergillus fungus on grain and other crops; mainly tropical and subtropical	contaminated food products	agricultural workers	
4-Aminobiphenyl		cigarette smoking, second hand smoke		
Arsenic and compounds	wood preservative	cigarette smoking, burning fossil fuels, contaminated water and food, smelter emissions	smelting, wood preservation, manufacture of agricultural chemicals, possibly use of agricultural chemicals	No longer produced US; pesticide use very low since 1990
Asbestos	insulation, heat and flame retardant	building materials, poorly maintained older housing, brake linings, building demolition and remodelling	construction, demolition, insulation workers, brake repair, asbestos abatement, shipyards, pipefitters, HVAC	
Benzene	solvent, gasoline additive	cigarette smoking, auto exhaust, forest fires	gas station attendants, mechanics, fire fighters	
Bezidine	dyes for leather, textiles, paper	dyed products	leather, textile, and paper workers	Banned in US 1973
Benzo[a]pyrene	see PAH			
Beryllium and compounds	electronics	cigarette smoking	mining, electronic manufacture	
1,2-Butadiene		cigarette smoke, second hand smoke auto exhaust, gasoline, burning plastics or trash	lead smelting	

Butylated hydorxyanisole	preservative in food, cosmetics, and animal feed	butter, lard, meats, cereal, baked goods, sweets, beer, vegetable oil, snack foods, flavorings, sausage, poultry, meat, chewing gum, yeast, shortening,	food producers, animal feed producers, livestock producers, fast food fry cooks	
Cadmium and compounds	batteries	cigarette smoke, contaminated food and water	smelting zinc and lead ores, welding, soldering	
Carbon tetrachloride	freon cooling systems, industrial degreaser, dry cleaning	limited	dry cleaning	banned from products for home 1985, banned as grain fumigant 1985
Chlordane	pesticide	homes treated for termites prior to 1988	agricultural pesticide application, commercial termite control	agricultural use banned 1982; all use banned in US 1988
Chromium and compounds	chrome plating, leather tanning, wood preservative, printers ink, batteries	pressure treated wood	tanning, wood treatment, printing, chrome plating	use as wood preservative phased out 1970
Coal tars, creosote	wood preservative, topical skin treatment, pesticides, roofing	over the counter skin treatments	paving, roofing, wood preserving	
Coke oven emissions	see PAH; iron making blast furnaces	residents near blast furnaces	blast furnace workers	
1,2-Dibromo-3-cholorpropane	gas additive; soil and grain fumigant; post harvest fumigant for fruits and vegetables; fruit fly insecticide; golf course treatment	persistent in air, soil, ground water, and some foods; primary exposure from contaminated ground water	none current	banned as gas additive 1977; banned as pesticide and fumigant 1984
Diesel exhaust particulates	vehicle fuel	general air pollution in areas of high diesel traffic	truck drivers, use or repair of diesel equipment; workers where diesel equipment is used	

Ethylene oxide	fumigant and sterilizing agent for foods, furs, clothing, furniture, books, paper, cosmetics, railroad cars, beehives, tobacco	cigarette smoke, auto exhaust, consumer products	fumigation and sterilization workers, bee keepers	
Formaldehyde	preservative, embalming, sterilizing, insecticide, fungicide	cigarette smoking, auto exhaust, wood stoves, incinerators, kerosene heaters, outgassing from construction materials	health care workers, construction, wood products manufacture, undertakers, laboratory workers	
Hexachlorobenzene	seed fungicide for onions, sorghum, wheat, other grains	limited; contaminated fish and wildlife possible	unknown	banned as fumigant 1984; persistent and bioaccumulative
Lead and compounds	batteries, mildew prevention, matches, explosives, munitions, photocopying, photography, paint, gasoline additive	cigarette smoke, alcoholic beverages, contaminated water, old housing, persistent in environment from prior use as gasoline additive	battery production and workers, lead smelting and refining, mining, firing range, welder, demolition, photography, printing	gas additive and paint additive phased out 1970
2-Napththylamine	none current	cigarette smoke, second hand smoke	none current	Not available in US since 1967
Nickel and compounds	alloy in many metal products	food, many consumer products	mining, smelting, welding, casting, spray painting, electroplating	
PAH: Polycyclic aromatic hyrdocarbons	see coke oven emissions	cigarette smoke, second hand smoke, wood smoke, smoked BBQ or grilled foods, many food products, auto exhaust	food smokers, roofers, incinerators, food preparation	
Radium	formerly used in luminous paint	limited	limited	commercial use rare
Radon	naturally occurring in environment worldwide	outgassing from subsoil into home; deliberate exposure in alternative treatment spas	uranium and other miners	

Silica	widespread in industry	ubiquitous at low levels	mining, milling, quarrying, sand and gravel, foundries, construction, sandblasting, ceramics, electronics	
Soot	byproduct of carbon combustion	any combustion source: fireplace, furnace, auto exhaust	chimney sweeps, heating occupations, insulation, firefighter, demolition	
Sulfuric acid mists	used to produce fertilizers, batteries	burning coal	construction, battery, fertilizer, printing, paper, tannery	
Tetrachloroethylene	dry cleaning, metal cleaning, paint remover, ink, adhesive, silicone lubricant	dry cleaned clothes, laundromats	dry cleaning, metal cleaning, printing	
Tricholorethylene	industrial degreaser	common in consumer environment	metalworking	
Uranium	Nuclear power and weapons	limited	mining, processing, nuclear power plants	
Vinyl chloride	step in PVC manufacture	very low	PVC manufacturing	
Wood dust	byproduct of wood working and wood product manufacture	low	wood working, wood product manufacture	

Love Canal is the best known example of environmental contamination in the United States.[9] Love Canal was initially a mile long trench near Niagara Falls, New York that the city used as a dump from the 1920s until the 1940s. It was then leased and later purchased by a chemical company for toxic waste disposal. The company drained the canal and lined it with clay, the standard containment measure for toxic waste disposal at the time. When the city of Niagara Falls grew in the 1950s, it purchased the site back from the chemical company, built a school on the dump site, and developed a residential neighborhood along the canal, in spite of written warnings in the sales document from the chemical company describing the potential danger posed by the landfill. Eventually the Love Canal neighborhood had more than 3,000 residents and approximately 500 children attended the school built on top of the dump site. In the 1970s, residents noted odors, water quality issues, and surface contamination in the neighborhood. Residents were convinced that many health problems they perceived in their community were caused by toxins from the dump site. Environmental testing found measurable and in some cases high levels of more

[9] New York State Department of Health, 2006. Love Canal Follow-Up Health Study. http://www.health.state.NY.us/environmental/investigations/love_canal

than a dozen hazardous chemicals, including some definite or probable human carcinogens, in the ground water and storm sewers in the neighborhood. In 1978, the state of New York declared a public health emergency; this was followed by a federal declaration of emergency in the same year. Love Canal residents were relocated in 1980.

In spite of nearly 30 years of intensive study, there is no evidence of increased cancer incidence among former Love Canal residents, compared to residents of Niagara County as a whole or to residents of the state of New York. There is no evidence of greater cancer mortality or total mortality among former Love Canal residents. Some adverse health effects were noted in the Love Canal studies, primarily increases in low birth weight, preterm birth, and the incidence of birth defects.

If exposures as large as those that occurred at Love Canal did not result in measurable increases in cancer incidence or mortality, it is unlikely that exposures on a smaller scale would cause an increase in cancer incidence or mortality elsewhere. Nevertheless, public health officials remain vigilant about the possibility of both catastrophic events and low-level but cumulative exposures that could increase cancer incidence. There are two strategies to accomplish this: maintaining routine surveillance of cancer incidence and watching for sentinel events.

Sentinel Events

Sentinel events are "occurrences of unexpected disease or disorders that are *known to result from specific, recognized causes* of likely relevance to the situation or setting," provided they occur *in the absence of established risk factors*.[10,11] For example, lung cancer would not be attributed to a chemical exposure in a patient with a history of heavy smoking. In contrast, hemangiosarcoma of the liver, an extremely rare kind of cancer, has no confirmed risk factors except occupational exposure to vinyl chloride.[12] This was discovered when four employees of a single plastics manufacturing plant were diagnosed with hemagniosarcoma of the liver within a period of six years.[13] The cases were reported by the plant physician and the company medical director.[12] The incidence in the general population was approximately 25 cases per year in the United States, or about one case in 10 million people. In a factory that had been open only since 1938 and averaged fewer than 250 employees, four cases in six years was an extremely high incidence of such a rare cancer. A number of epidemiologic studies were conducted over the next decade. The cause was traced to exposure to vinyl chloride, a gas produced during the manufacture of PVC plastics.

[10] http://www.atsdr.cdc.gov/csem/cluster/definition.html
[11] CDC Environmental Public Health Indicators Project, http://www.cdc.gov/nceh/indicators/pdfs/ephi.pdf
[12] http://www.inchem.org/documents/iarc/suppl7/vinylchloride.html
[13] Creech and Johnson. 1974. *J Occup Med* 16:150-151

Sentinel events may alert public health officials to "a preventable disease, disability or untimely death whose occurrence serves as a warning signal...an indication that an environmentally induced health effect may have occurred and implies that some action should be considered."[14] The clearest examples of sentinel events are communicable and infectious diseases or other acute events such as poisoning.[15]

In acute situations, specific causal events can usually be identified. Examples include increased incidence of whooping cough due to a breakdown of vaccination coverage;[16] increased incidence of severe gastrointestinal disease traced to ground beef contaminated with E. coli;[17] or increased incidence of methemoglobinemia in infants caused by nitrate contamination of drinking water.[18]

The common factors in these examples are

- The increased incidence of disease over background incidence can be detected quickly,
- The latency period (time between exposure and development of disease) is short,

  and

- The cause is well-defined.

Sentinel cancer events are much more difficult to define and monitor. Like other diseases, all cancers occur at background incidence rates, although some kinds of cancer may be very rare. A measurable increase over the background incidence rate may be cause for concern. This increase is usually defined as a statistically significant excess in time and space. However, in relatively small populations, such as Montana or individual counties within the state, modest fluctuations in incidence rates are rarely statistically significant. Therefore the Montana Department of Public Health and Human Services uses additional criteria to evaluate changes in cancer incidence (see next section).

Defining the time parameter is difficult for cancer because the latency period -- from exposure to a potential carcinogen to the development of cancer -- is usually many years or even decades. A truly causative exposure may have occurred so long ago that the patient no longer recalls it, or perhaps was not even aware of it at the time. A more common situation is that a patient may attribute his or her cancer to a recent exposure that occurred after the cancer process was already well underway but not yet diagnosed.

[14] Rothwell et al. 1991. *Environ Health Perspec* 94:261-263.
[15] http://www.cdc.gov/ncphi/disss/nndss/nndsshis.htm; http://www2a.cdc.gov/NIOSH-Chartbook/ch2/ch2-9.asp
[16] http://www.epi.hss.state.ak.us/bulletins/docs/b1990_24.htm
[17] http://www.dhs.ca.gov/ps/dcdc/cm/950519cm.htm
[18] http://www.atsdr.cdc.gov/HAC/PHA/laborat/lab_p2.html

Defining the space parameter is relatively simple: being close to a source of exposure. However, applying the space parameter in cancer studies can be difficult because people may move between the time they are exposed to a potential carcinogen and the time they are diagnosed. People who are exposed to a potential local risk factor and then move away may not identified in a retrospective study. People who have recently moved to the area where they are diagnosed often incorrectly attribute their cancer to local conditions.

The ADSTR Consensus Statement on Sentinel Cancers provides the following definition and examples of sentinel cancers:

"Statistically significant excess in time-space patterns of the incidence of the following conditions identified via general surveillance:

- -- bladder cancer in
  - -- lifetime non-smokers with no occupational chemical exposures
  - -- young children
  - -- human and co-resident pet diagnosed concurrently
  - -- genetically unrelated co-resident humans diagnosed concurrently
- -- three or more cases in a time-space cluster of primary liver cancer in adult lifetime non-drinkers with no history of hepatitis and no occupational chemical exposures."[19]

Bladder and liver cancers are especially sensitive to environmental carcinogens because these organs process many chemicals the body is exposed to. They are not perfect sentinel cancers, however, because many common exposures such as smoking, second-hand smoke, alcohol, hepatitis, and vehicle exhaust also increase the risk of these cancers. Each of these common risk factors must be ruled out before a case of bladder or liver cancer can be considered a potential sentinel event. The respiratory system is potentially exposed to many airborne carcinogens, but the vast majority of respiratory cancers are caused by smoking and many of the remainder are caused by exposure to second-hand smoke or radon. It is extremely difficult to sort out which respiratory cancers might have been caused by other carcinogens. Many such exposures occur in an occupational setting. Before respiratory cancers can be attributed to exposure to occupational or other environmental carcinogens, the much more common risk factors of smoking, second-hand smoke, and radon must be ruled out.

Cancer Surveillance and Cancer Cluster Investigation

Montana DPHHS uses the Montana Central Tumor Registry (MCTR) to monitor the background incidence rates of cancers and to watch for increases over background incidence rates. The MCTR has excellent data on the incidence rates of cancers in Montana and can track time trends and regional variation. The MCTR receives reports of

[19] Shy et al. 1994. *Environ Health Perspec* 102:316-317

all cases of cancer diagnosed or treated in Montana and of cases of cancer in Montana residents diagnosed or treated in most other states.

The Montana DPHHS has a formal system to respond to reports of perceived excesses in cancer incidence rates that may be suspected to be caused by environmental exposures.[20] Inquiries about perceived excesses come to the DPHHS through several channels. Some inquiries are directed to the MCTR staff. Other inquiries are relayed from the Public Information Office, the Governor's Consumer Hotline, or the offices of other public officials.

In response to any inquiry, the MCTR staff assesses cancer incidence rates in the area of concern compared to the state as a whole. Most inquiries are resolved by providing comparisons of county and state incidence rates, documenting no local excess in cancer incidence. If the inquiry requires additional consideration, the Cancer Cluster Investigation Team is convened to examine the evidence that prompted the inquiry, the comparative incidence rates prepared by the MCTR staff, and other facts about the situation. The Team uses the Cancer Cluster Investigation Protocol to determine if further investigation is needed. Three conditions must be met for the team to proceed with an investigation:

- There must be three or more cases of a specific kind of cancer meeting a stringent case definition (two cases for extremely rare types of cancer), occurring within a defined geographic region and defined time period, provided the patients have lived in the area for an appropriate period of time;
- The cases cannot be explained by the existence of documented risk factors;
- There must be a plausible exposure common to all the cases.

In the past several years, an average of one inquiry per month has been received through all channels. The Cancer Cluster Investigation Team has been convened an average of twice a year. No excess cancer incidence was found in response to any inquiry. The data and underlying science did not support the need to proceed with an investigation in response to any inquiry.

Please visit our website at www.cancer.mt.gov

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[20] http://www.dphhs.mt.gov/PHSD/cancer-control/documents/CancerClusterinvestigationprotocol506.pdf