Community risk assessment of ethylene oxide near Terumo BCT in Lakewood, Colorado

Prepared by:

Toxicology and Risk Assessment Program
Colorado Department of Public Health and Environment

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Contact:

Phone: (303) 692-2606
COLORADO
Department of Public Health & Environment
Email: cdphe_toxcall@state.co.us
www.colorado.gov/cdphe/ethylene-oxide

Summary

In response to the 2014 National Air Toxic Assessment report that used modeled data to indicate potential increased cancer risk in the area surrounding Terumo BCT, the Colorado Department of Public Health and Environment developed a plan to address concerns in the area. The department measured ethylene oxide levels in the air and then estimated associated cancer risk due to current emissions. In addition, the department evaluated actual reported cancer cases in the area to assess the potential for health effects due to past exposures. This report summarizes the results of these efforts.

Background

Terumo BCT manufactures medical devices. As part of the company's manufacturing process, Terumo BCT sterilizes medical devices at its Lakewood, Colorado facility. Like other companies that do this work, it uses ethylene oxide in the sterilization process. On August 22, 2018, the US EPA released an updated version of the National Air Toxics Assessment. Using computer modeling, that assessment showed that residents in the census tract surrounding the Terumo BCT sterilization facility in Lakewood had a higher cancer risk than residents in adjacent census tracts due to emissions of ethylene oxide from the facility. The previous NATA, indicated a much lower cancer risk. It is important to note that Terumo BCT has been operating this facility since 2001. Their emissions are well below permitted levels. The facility has not changed their process or increased emissions. The dramatic change in the potential cancer risk in the area is a result of EPA's 2016 revision of their ethylene oxide toxicity assessment which indicated an estimated 30-fold increase in cancer potency.

Although not required by existing regulation, the department asked Terumo BCT to immediately begin exploring ways to further reduce emissions from its processes. As of September 20, 2018, Terumo BCT completed the installation of new ethylene oxide controls significantly reducing their emissions.

The Terumo BCT facility is located within Jefferson County, Colorado, census tract 109.02. Using the 2010 Census and the EPA Environmental Justice Screening Tool, the total population in this area is approximately 5,358 individuals. The population of minorities in this area is 29% and the low income population is 37%. A total of 3% of the population is under age 5, and 14% is over age 64.

Environmental data

The Colorado Department of Public Health and Environment (CDPHE) performed an ambient air monitoring study for ethylene oxide in the vicinity of the Terumo BCT facility to measure the concentration in the surrounding area. All laboratory analyses were performed by Eastern Research Group (ERG) in Morrisville, NC. ERG also supplied the canisters and sampling inlets for the study. ERG is used by the U.S. Environmental Protection Agency (EPA) as a national contract laboratory for the air toxics studies and has developed methods for recent ethylene oxide sampling projects performed by EPA.

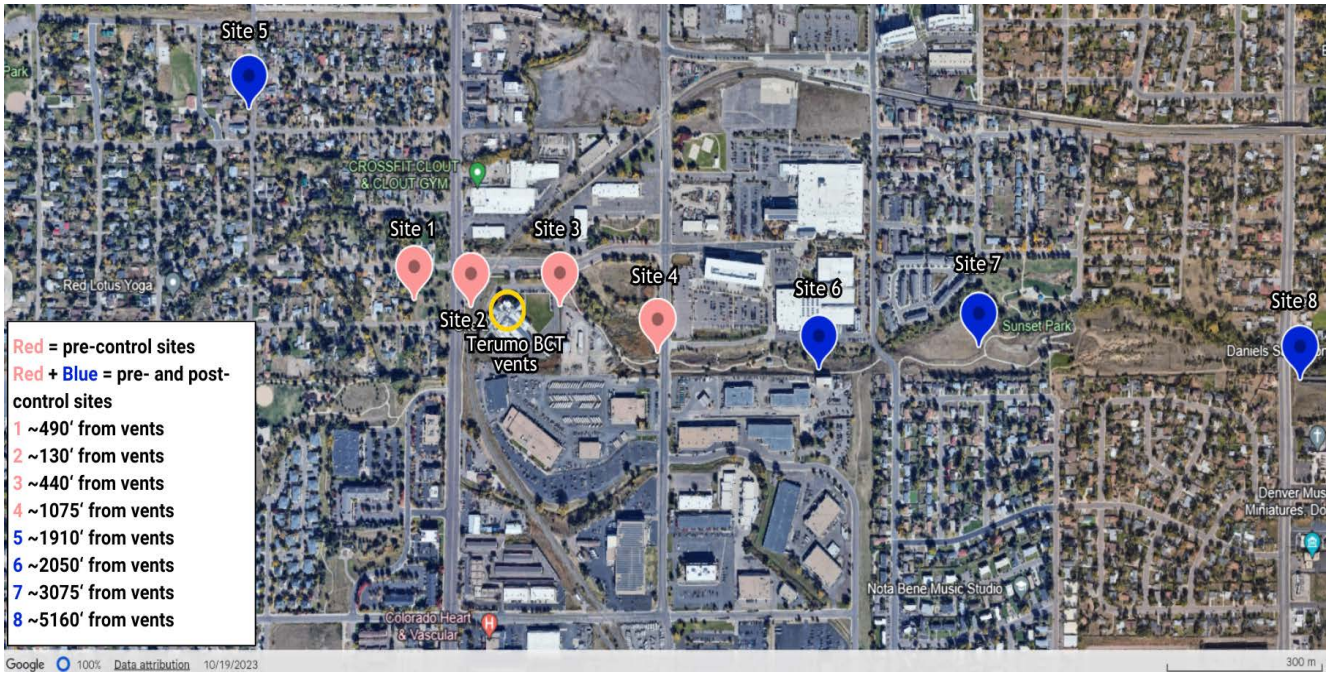

Figure 1. Map of sampling locations around Terumo BCT.

- Pre-control sampling: Sampling was performed by the Air Pollution Control Division for seven consecutive days (August 24, 2018 to August 31, 2018) at four locations west and east of the facility, ranging from 490 - 1075 feet from the vents. These locations are identified as sites 1-4 (red stars) in Figure 1.
- Post-control sampling: Additional ambient air sampling was performed for seven consecutive days after emission controls were in place (October 17, 2018 to October 24, 2018) at eight locations west and east of the facility, ranging from 1910 - 5160 feet from the vents. The locations included sites 1-4 included in the pre-control sampling, along with sites 5-8 (green stars), also shown in Figure 1. The air division used AERMOD modeling to assist with selection of these sampling sites.
- Background sampling: Sampling was conducted twice. The first background sampling event included two background samples which were taken for one 24-hour period on September 9 and 10, 2018 at the existing APCD air monitoring sites, NREL and LaCasa. The second background sampling event was conducted at those same two sites, NREL and La Casa, along with two additional background sites, Welch and Arvada. This second background event was performed for four consecutive days, from October 26, 2018 through October 30, 2018. All locations are outside of the census tracts that have elevated risks in the 2014 NATA. The locations of the background sites, along with the approximate boundary of the census tract, are shown in Figure 2.

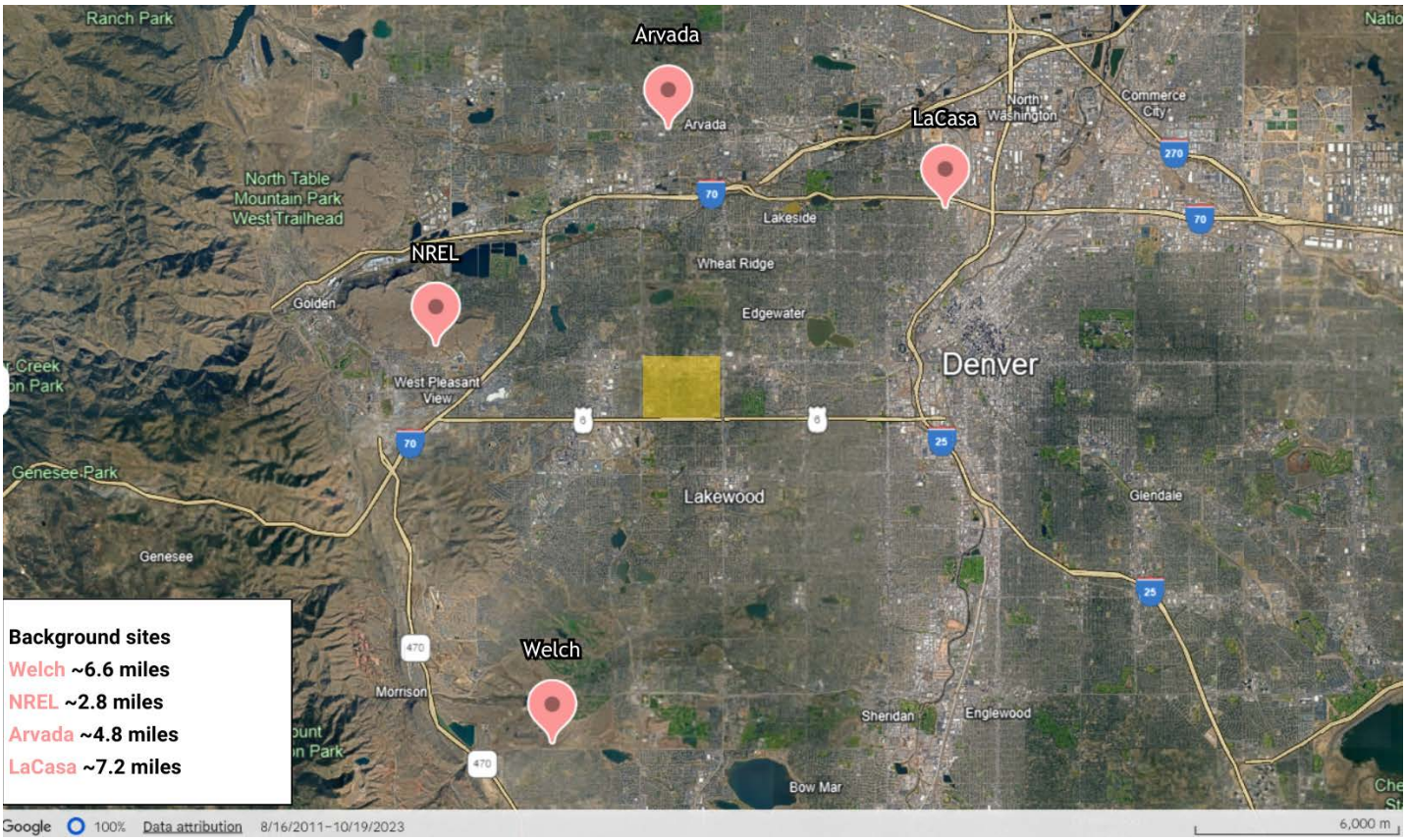

Figure 2. Map of the background sampling locations. The yellow rectangle indicates the approximate location of census tract 109.02.

Further information about the exact location of sampling sites and sampling methodology can be found in the air division's report.[1] The report also details each 24-hour sampling result. For this analysis, data were summarized by site and sampling event. For the background sites, which had an overall higher number of samples (18), a statistical method was used to handle non-detect samples in deriving the minimum and average (mean) statistics. The background data is shown in summarized in Table 1.

For all sampling locations except background sites, half of the analytical detection limit was employed when ethylene oxide was not detected for calculation of averages. Data are described using minimum, maximum, and average (mean) values in Tables 2-3.

[1] Air Pollution Control Division, 2018. Ethylene Oxide Special Air Sampling Study: Pre- and Post-Control Monitoring Report, Lakewood, CO, November 8, 2018

Table 1. Summary of background ethylene oxide concentrations.

Sampling Site	Minimum µg/m³	Mean * µg/m³	Maximum µg/m³	95% UCL µg/m³	Sample size	Detection Frequency
Background, various locations	ND (<0.082)	0.267	1.045	0.384	18	44%

NOTE: * Mean value was calculated using the Kaplan Meier non-parametric method

Ethylene oxide and its potential health implications

About ethylene oxide

Ethylene oxide is a highly reactive gas. It is used for sterilizing heat sensitive medical equipment. Ethylene oxide is also used when making antifreeze, textiles, detergents and other products, and as a fumigant for spices. If ethylene oxide is inhaled, ethylene oxide is readily absorbed into the human body and distributed throughout the body via blood circulation. Ethylene oxide leaves the body very rapidly (over 2-3 days) through urine and feces or by exhaling it.

Short-term (acute) effects associated with exposure to relatively high levels of ethylene oxide include central nervous system depression, respiratory and eye irritation, and gastro-intestinal effects. Long-term (chronic) exposure to ethylene oxide can cause respiratory and eye irritation and damage to the nervous system. There is also some evidence of effects on reproduction, including rate of miscarriages in females and decreased sperm count in males. Evidence in humans indicates that inhalation of ethylene oxide increases the risk of lymphohematopoetic cancer and, for females, breast cancer.

Non-cancer health effects

The health effects of exposure to ethylene oxide has been studied primarily in occupational settings with exposures that are much higher than would be expected in a community setting. At exposures greater than 260,000 ppb for a period of time ranging from minutes to months, workers experienced the following symptoms:

- Central nervous depression, including memory loss, dizziness, headache, lethargy, fatigue, and numbness;
- Respiratory and eye irritation, including coughing, shortness of breath, irritation of the eye, nose, and sinuses;
- Gastrointestinal effects, including vomiting and diarrhea.[2,3]

Additionally, there is limited evidence in both humans and animals that ethylene oxide exposure may result in reproductive effects.[4] In studies of occupational exposure to ethylene oxide, females showed increased rate of miscarriage, along with a higher incidence of pre- or post-term births. In laboratory animals, ethylene oxide

[2] National Research Council (US) Committee on Acute Exposure Guideline Levels. Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 9. Washington (DC): National Academies Press (US); 2010. 2, Ethylene Oxide Acute Exposure Guideline Levels. Available from: https://www.ncbi.nlm.nih.gov/books/NBK208167/

[3] Agency for Toxic Substances and Disease Registry (ATSDR). 1990. Toxicological profile for ethylene oxide. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

[4] National Research Council (US) Committee on Acute Exposure Guideline Levels. Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 9. Washington (DC): National Academies Press (US); 2010. 2, Ethylene Oxide Acute Exposure Guideline Levels. And references therein. Available from: https://www.ncbi.nlm.nih.gov/books/NBK208167/

exposure had been associated with reproductive and developmental effects, including fetus viability, size, and deformity rate, as well as rate of fetal reabsorption in females and decreased sperm count in males.

Based on the negative health effects seen in humans exposed occupationally, as well as laboratory studies of ethylene oxide inhalation in animals, the Agency for Toxic Substances and Disease Registry has developed a health-based comparison value of 90 ppb for ethylene oxide exposure over 14 weeks.[5] The levels detected in the area around Terumo BCT are all much lower than this value, and therefore, it is unlikely that non-cancer health effects would occur in workers or residents in the area.

Cancer health effects

The US EPA Integrated Risk Information System and the International Agency for Research on Cancer have characterized ethylene oxide as "carcinogenic to humans." These agencies have determined that long-term exposure to ethylene oxide may increase the risk of breast cancer and lymphohematopoietic (blood/lymph) cancers in humans. The magnitude of this increased risk depends on the magnitude of the exposure (i.e., how much is in the air) and the length of time a person is exposed.

In order to determine the risk of developing cancer from a cancer-causing substance, scientists use data from laboratory animals and humans to estimate a unit risk factor (inhalation unit risk or IUR). The unit risk factor can then be compared to an exposure concentration in order to estimate excess cancer risk from exposure to that concentration over a lifetime. In December 2016, IRIS released a revised toxicological assessment of ethylene oxide. The unit risk determined in this assessment indicated a 30-fold increase in cancer potency as compared to the previous IRIS value.

While there is scientific consensus that inhalation of ethylene oxide can cause cancer, there is not agreement on its potency. California EPA[6] has published a unit risk factor (8.8×10^{-5} $(\mu g/m^3)^{-1}$) that is approximately 100 fold lower than the IRIS value (3×10^{-3} $(\mu g/m^3)^{-1}$). Additionally, in a letter to EPA, the American Chemistry Council raised concerns with various aspects of the 2016 IRIS assessment.[7] ACC raised concerns regarding the model and statistics employed to derive the unit risk factor from scientific data, the data included (or excluded) in the model, the biological plausibility of the value, and the value of the unit risk factor compared to background or ambient levels. However, as a matter of policy, the department relies on IRIS toxicity values in making decisions about environmental risk.[8]

Cancer risk associated with measured ethylene oxide concentrations

To estimate cancer risk using the environmental data collected by the air division, we employed the IRIS unit risk factor for ethylene oxide, along with age-dependent adjustment factors. The adjustment factors are used to account for the potential for increased susceptibility to ethylene oxide exposure during early life exposures. We then calculated excess cancer risk for residential and occupational exposure scenarios depending on the likely exposure pathway at each site as shown in Table 2. The likely exposure pathways were determined by

[5] Agency for Toxic Substances and Disease Registry (ATSDR). 1990. Toxicological profile for ethylene oxide. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

[6] https://oehha.ca.gov/chemicals/ethylene-oxide

[7] www.americanchemistry.com/EO/Request-for-Correction-under-the-Information-Quality-Act-2014-NATA.pdf

[8] 2004. Colorado Department of Public Health and Environment. Policy on the use of human health toxicity values in environmental risk assessment and risk management.

examining satellite imagery of each site. Generally, within approximately 440 feet of the facility, the land-use is commercial/industrial in all directions.

Table 2. Exposure pathway used for cancer risk estimation at each sampling site.

Sampling site	Distance (direction) from Terumo BCT	Exposure pathway
5	1,910 feet (west)	Residential
1	490 feet (west)	Residential
2	130 feet (west)	Occupational
3	440 feet (east)	Occupational
4	1,075 feet (east)	Residential
6	2,050 feet (east)	Residential
7	3,075 feet (east)	Residential
8	5,160 feet (east)	Residential
Background	Various	Residential *

NOTE: * Residential pathway is more conservative, so this pathway was assumed for background.

To estimate lifetime cancer risk to residents, we used the EPA's default exposure factors[9] for residential exposure to air: exposure to the substance 24 hours per day, 350 days per year, for 26 years. Additionally, to understand potential excess cancer risk to workers in the immediate vicinity (within 440 feet), we also estimated an occupational exposure risk using EPA's default exposure factors: exposure to the substance 8 hours per day, 250 days per year for 25 years.

For both exposure scenarios (resident and worker), we calculated cancer risk based on the maximum measured concentration at each location (and background) in order to estimate the risk that would occur if exposure always occured at the reasonable maximum level. We also calculated cancer risk based on the average (mean) concentration at each location which is likely more representative of a long-term exposure. Finally, we calculated risk levels at the minimum of the measure concentration range to provide a lower estimate of exposure at each site. Also, it is important to note that we calculate an "excess cancer risk" which is defined as the additional risk due to ethylene oxide exposure above and beyond the "normal" risk of cancer from other causes. The EPA's acceptable cancer risk range is one to 100 excess cancer cases per million people.

Table 3 shows the estimated minimum, average, and maximum excess cancer cases per million people at all sampling locations before and after the installation of additional emission control at Terumo BCT, along with risk estimates for background samples. The excess cancer cases for the maximum and average exposures are also shown graphically in Figures 3 and 4, respectively.

Generally, the occupational cancer risk estimates were lower than the residential cancer risk despite measuring higher levels of ethylene oxide at the two sites that likely represented exposure to workers (sites 2 and 3). This lower risk is explained by the reduced exposure time use for the worker exposure scenario. When we compare sites 1-4 that were sampled both before and after Terumo BCT installed additional emission controls, we see that cancer risk for residents or workers fell 2-5 fold at each site. For example, at 130 feet

[9] U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Preparedness (2014). OSWER DIRECTIVE 9200.1-120, Human Health Evaluation Manual, Supplemental Guidance: Update of Standard Default Exposure Factors.

west of the facility (site 2), occupational exposure risk based on maximum exposure fell from 1,573 to 312 in a million. At 490 feet west of the facility (site 1), residential risk based on maximum exposure fell from 5,389 to 2,409 in a million.

Table 3. Summary of estimated excess cancer risk before and after installation of additional emission control at Terumo BCT. Cancer risk is given for the minimum, average, and maximum concentration for each sampling location.

		Pre-control		Post-control	
Summary statistic	**Site**	**Measured concentration µg/m³**	**Excess cancer cases per million people**	**Measured concentration µg/m³**	**Excess cancer cases per million people**
Minimum values	5			0.041 (ND)	121
	1	0.306	905	0.041 (ND)	121
	2 *	0.485	119	0.335	82
	3 *	1.739	425	0.357	87
	4	0.895	2,648	0.041 (ND)	121
	6			0.041 (ND)	121
	7			0.041 (ND)	121
	8			0.041 (ND)	121
	Background			0.041 (ND)	121
Mean values	5			0.251	743
	1	0.848	2,509	0.420	1,243
	2 *	2.996	733	0.774	189
	3 *	3.090	756	0.993	243
	4	1.289	3,814	0.507	1,500
	6			0.433	1,281
	7			0.335	991
	8			0.330	976
	Background			0.267	790
Maximum values	5			0.441	1,305
	1	1.820	5,385	0.814	2,409
	2 *	6.432	1,573	1.277	312
	3 *	4.522	1,106	2.018	494
	4	1.910	5,652	0.946	2,799
	6			0.915	2,707
	7			0.688	2,036
	8			0.858	2,539
	Background			1.045	3,092

NOTE: * Occupational (instead of residential) exposure was assessed, ND=Non-detect

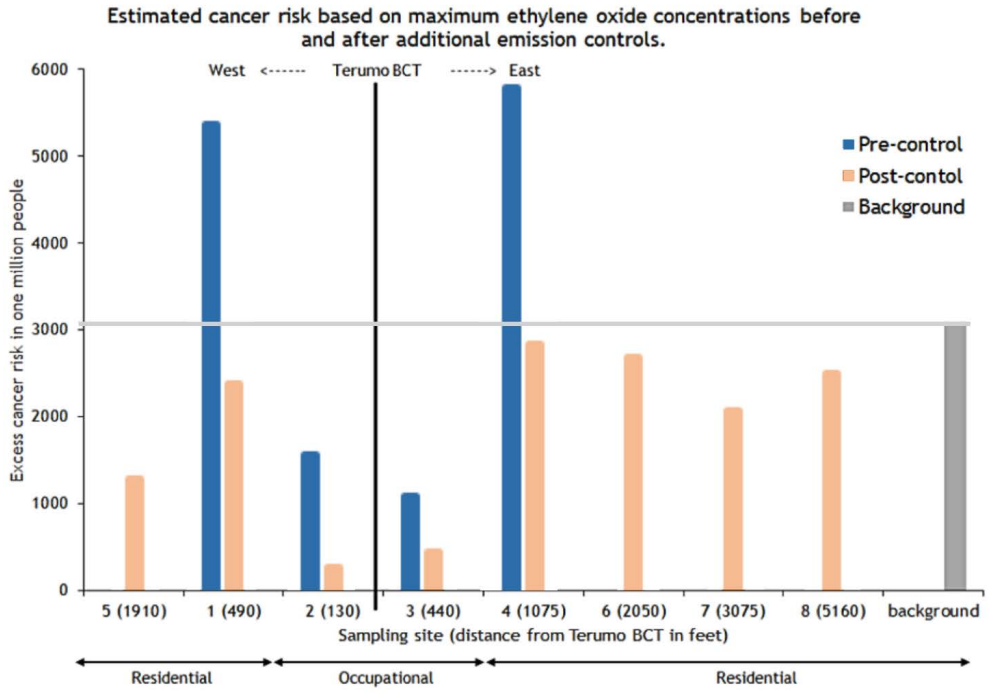

Figure 3. Estimated cancer risk based on maximum ethylene oxide concentrations before and after additional emission controls at Terumo BCT.

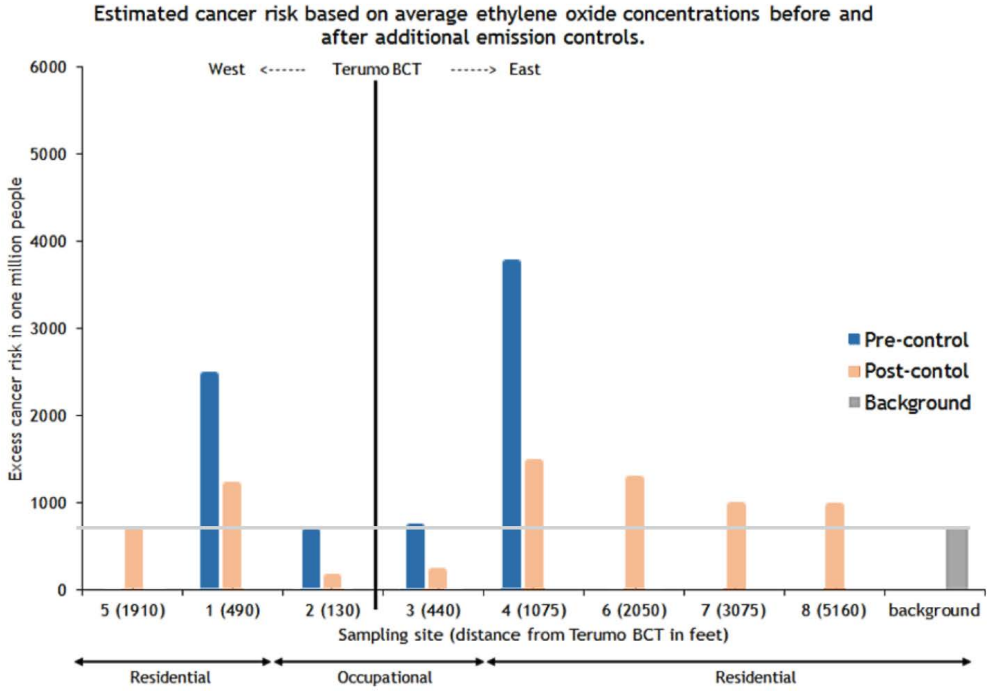

Figure 4. Estimated cancer risk based average ethylene oxide concentration before and after additional emission controls at Terumo BCT.

The excess cancer risk, based on maximum concentrations, to residents after Terumo installed additional emission controls ranged from 1,305 in a million at 1,910 feet west of the facility (site 5) to 2,799 in a million at 1,075 feet west of the facility (site 4). The estimated cancer risks from lowest to highest (based on the maximum concentration) occur at site 5, 7, 1, 8, 6, and 4. With the exception of site 8, risk levels decrease as the distance from the facility increases. For residents exposed over a lifetime to average ethylene oxide concentrations measured, the risk ranged from 743 in a million at 1,910 feet west of the facility (site 5) to 1,500 in a million at 1,075 feet east of the facility (site 4).

However, the low end of the data is confounded by a relatively high analytical detection limit. Even at ½ the detection limit, the estimated cancer risks for residential exposure are slightly higher than the acceptable range at 121 excess cancer cases per million (Table 3). That means that current standard measurement techniques are not sensitive enough to measure ethylene oxide concentrations that have associated cancer risks within the acceptable cancer risk range. In addition, the background cancer risks estimated on the sampling locations at 2.8 to 7.2 miles from the facility are 1 to 31 times higher than the acceptable cancer risk range. The source of ethylene oxide in background samples is not known, but is not thought to be associated with the Terumo facility.

With the exception of the minimum values for occupational exposure at sites 1 and 2, all other estimated risks were above the EPA acceptable cancer risk range of 1 to 100 in a million. In general, risk estimates decrease as the distance from the facility increases. Rather than compare risk estimates to the EPA acceptable cancer risk range, it is more useful to compare risk estimates around the facility to the background risk in the rest of the metro area. Considering the minimum estimates, risk estimates around the facility reach the background level within 490 feet on the west side and 1,075 on the east side. When comparing the average risk estimates, on the west side risk estimates are about 60% higher than background at 490 feet and equivalent to background by 1,910 feet from the facility. On the eastside, average risk estimates are about 2-fold higher than background at 1,075 and about 25% higher than background at 5,160 feet. Maximum risk estimates reach background levels within 490 feet on the west side and within 1,075 feet on the eastside.

Limitations

In general, the uncertainties associated with any risk-based evaluation are likely to over- or underestimate environmental exposures and the associated health hazards because all aspects of the actual exposure are typically unknown. This section is not intended to be an in-depth description of all the uncertainties associated with this evaluation. Rather, the focus is to highlight the major assumptions and limitations that are specific to this evaluation and result in uncertainty.

- The estimated exposure concentrations are based on seven 24-hour samples collected over a period of one week (1 week pre-control, 1-week post-control). It is not known if these samples are representative of the concentration of ethylene oxide in air at other times of the year. This is a major uncertainty because the estimated cancer risks are based on exposures over a period of 26 years. To address this uncertainty, the maximum detected value was used to estimate cancer risks. However, a relatively large degree of uncertainty remains.
- There is the possibility of uncertainty in the pre-control air sample results due to an identified potential analytical interference by 2-butene. This interference would likely falsely increase measured concentrations leading to an overestimation of cancer risk.
- All sources of airborne ethylene oxide are unknown and background samples have an associated cancer risk that is well above the EPA acceptable cancer risk in approximately 44% of the background samples

collected. Therefore, the estimated risk in this evaluation may over- or under-represent possible contributions from the Terumo facility.

Cancer registry evaluation

In order to understand not just estimated excess cancer risk, but to also evaluate the current and historical prevalence of cancer in the community surrounding Terumo BCT, the Colorado Central Cancer Registry (CCCR) compared cancer diagnosis counts in the census tract (109.02) of the facility to expected cancer counts in the state. This analysis examined all cancers combined, and five individual types of cancer: Hodgkin's lymphoma, non-Hodgkin's lymphoma, multiple myeloma, lymphocytic leukemia, and breast cancer (females only). These cancer types were chosen due to their possible linkage to ethylene oxide exposure. All cancers among residents of this census tract diagnosed between 2000 and 2017 were included in this count as Terumo did not begin sterilizing operations at this facility until 2001. Statistical testing was not done on ratios with less than three diagnosed cases due to variability in small numbers.

Table 4. Number of cancer diagnoses in census tract 109.02 compared to expected number (statewide) for males and females from 2000 to 2017.

Population group	Cancer	Cancers diagnosed	Cancers expected	Diagnosed/ expected	95% C.I. for ratio
Males	All cancers	107	90.20	1.19	(0.97-1.43)
	Hodgkin's lymphoma	3	0.72	4.17	(0.86-12.18)
	Non-Hodgkin's lymphoma	4	3.96	1.01	(0.28-2.58)
	Multiple myeloma	1	1.13	0.79	NC
	Lymphocytic leukemia	2	1.75	1.15	NC
Females	All cancers	119	107.48	1.11	(0.92-1.33)
	Breast	36	36.94	0.98	(0.68-1.35)
	Hodgkin's lymphoma	0	0.52	0	NC
	Non-Hodgkin's lymphoma	4	3.74	1.07	(0.29-2.73)
	Multiple myeloma	1	1.08	0.93	NC
	Lymphocytic leukemia	2	1.28	1.57	NC
Females and males	All cancers	226	197.68	1.14	(1.00-1.30)
	Breast (females only)	36	36.94	0.98	(0.68-1.35)
	Hodgkin's lymphoma	3	1.04	2.87	(0.59-8.40)
	Non-Hodgkin's lymphoma	8	7.70	1.04	(0.45-2.04)
	Multiple myeloma	2	2.21	0.91	NC
	Lymphocytic leukemia	4	3.02	1.32	(0.36-3.38)

Note: Diagnosed/Expected ratios that have a 95% Confidence Interval that include the value 1.00 are not considered statistically high or low; NC = not calculated due to less than 3 diagnoses; Source: Colorado Central Cancer Registry, CDPHE, 8/17/18.

The number of cancers diagnosed among males and females individually and combined was not higher than expected at a level that is statistically significant for all cancer types in this assessment. Although the ratio in certain cases was greater than one, the confidence intervals included the number 1, indicating the ratio was within the expected statistical limits. This means we are 95% sure that the true ratio is within the confidence interval range. Table 4 displays the number of diagnosed cancers in the study area by cancer type and gender

for 2000-2017, compared to the number that would be expected based on the population of male and female Coloradoans by race/ethnicity and age. Overall, none of the five individual types of cancer were statistically different in census tract 109.02 compared to the rest of Colorado.

Conclusions

- Cancer risks based on measured air concentrations of ethylene oxide at all sampling locations (including background sample locations more than 5 miles from the facility) were elevated compared to the EPA's acceptable risk range.
- The source of ethylene oxide in background samples is not known, but is not expected to be associated with the Terumo BCT facility.
- Additional emission controls installed by Terumo BCT in September 2018 resulted in a 2- to 5-fold reduction in cancer risk in the community. However, the resulting cancer risk was still elevated compared to the EPA's acceptable risk range.
- Post-control installation, the range of cancer risk levels estimated for the area around Terumo BCT were similar to the range of background cancer risk levels from ethylene oxide measured outside of that area. Average cancer risk levels decreased to background levels within 2,000 feet west of the facility, but remained slightly elevated as far as 5,000 feet to the east of the facility.
- The incidence of all cancers combined and five individual types of cancer in the community surrounding Terumo BCT were no different than expected based on cancer rates in the remainder of Colorado for the years 2000 through 2017.

Appendix A - Cancer analysis methods

Cancer is a disease common within the general population, and remains at the forefront of public health concern. In Colorado, over 20,000 new cases of cancer are registered each year. On average, Coloradoans have approximately a 1 in 3 risk of developing cancer in their lifetime. Whether an individual develops a cancer during his or her lifetime depends on a variety of factors, many of which are not currently understood. This complex, multistage, process involves both external (e.g. chemical, radiation, and viruses) and internal factors (e.g., hormonal, immune conditions, and inherited mutations).

The department conducts ongoing, systematic cancer surveillance across the state to look for trends over time and to find cancer patterns in regions or groups of people. This cancer incidence surveillance is possible using data collected by the Colorado Central Cancer Registry (CCCR). All cancers diagnosed in Colorado are reported to the cancer registry, with the exception of non-melanoma skin cancers, as mandated by the Colorado law and Board of Health regulations. This invaluable data allows the CCCR to effectively answer questions about cancer incidence in communities statewide. The CCCR was used to assess the incidence of cancer in the vicinity of the Terumo BCT facility.

Data from incidence-based registries provide several benefits compared to mortality-based data. Because incidence-based registries identify each case at the time a diagnosis of cancer is reported, rather than at the time of death, a more complete count of cancers that have occurred, regardless of survival, is available. Incidence data will not be affected by differences in survival across cancer types and sites, whereas mortality data are susceptible to bias from differences in treatment and access to health care. In addition, medical records used to compile incidence-based registry statistics typically have more detailed information on cancer diagnoses (e.g., pathology reports, etc.) than is collected on death certificates, which are used to compile mortality statistics.

The epidemiological study design used in this analysis of diagnosed and expected numbers of cancer cases is descriptive and ecological. The descriptive element provides a numerical summary of disease frequency, whereas the ecological component examines entire communities or populations, rather than individuals. Ecological studies have been conducted frequently in communities adjacent to potential environmental exposures, since they are efficient and can be completed within a reasonable period of time. Ecological studies are usually viewed as exploratory and may generate hypotheses to be considered in additional studies, if appropriate.

Cancer rates from the cancer registry for men and women of comparable race/ethnic groups and ages were used to calculate the expected number of cancers for the state. A cancer rate is the number of new cancer cases diagnosed per 100,000 population per year. The population in the study area, stratified by age, gender, and race/ethnicity, was multiplied by the cancer rate for each age, gender, and race/ethnic group in the comparison population to produce the expected number of cancers. This method assures that any differences found are not due to differences in demographic composition. For example, census tracts with a higher proportion of elderly individuals would be expected to have higher cancer rates since the incidence of most cancers increases dramatically with increasing age. A diagnosed-to-expected ratio is then calculated by dividing the number of cancers diagnosed in the area by the number of expected cases. If the ratio is greater than 1, then more cancer cases than expected were reported in the area. When this occurs, the next step is to look more closely at that relationship. It is important to know if that ratio could have been higher by chance alone, so a confidence interval is calculated for the ratio. The confidence interval has a lower number (minimum value) and a higher number (maximum value). It is common to use a 95 percent confidence interval which means that we are 95 percent sure that the true ratio is within the range between the lower and higher values. If the ratio is greater than 1 but the confidence interval includes the number 1, then the ratio is within expected statistical limits. If the confidence interval does not include the number 1, then the ratio is statistically significant. A statistically significant elevated ratio means that there were more diagnosed cases than expected and that there is less than a 5 percent chance that this greater number is due to chance alone.

The following limitations of this ecological, incidence-based registry evaluation must be considered:

- This epidemiological study design used in this analysis of diagnosed and expected number of cancer cases is descriptive and ecological. Information on other potential causes of disease (such as lifestyle behaviors, occupation, genetic predisposition) is lacking.
- This study design does not allow conclusions to be made about causal associations between exposure and any single cancer or group of cancers. The study design and results only aid in determining whether the number of cancers are greater than or less than expected. This may help determine whether future studies would be useful and relevant.
- The estimates of expected cancers are a central tendency (average) of expected cases for the time period 2000-2017. Actual cancer rates for specific populations, such as in smaller cities, towns or neighborhoods, may be higher or lower than the “average expected” cancer rate.
- Statistical testing was not done on ratios with less than three diagnosed cases due to variability in small numbers.
- The geographical area of residence was used as a substitute measure of exposure. This exposure estimate may raise the likelihood of exposure misclassification, reducing the ability of the study to observe a statistically significant difference between groups.