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Acknowledgements

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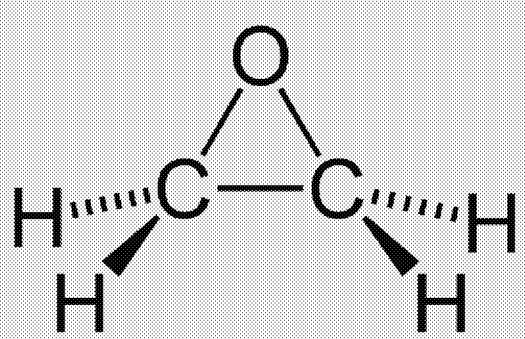

Increased Cancer Risk to Residents Near Ethylene Oxide Facilities

Susan Buchanan, MD, MPH
Director, Great Lakes Center for Children's Environmental Health
Region 5 PEHSU
University of Illinois at Chicago

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Objectives

At the end of this webinar, participants will be able to:

1) Explain why cancer risk from exposure to ethylene oxide emissions has increased

2) List alternatives to EtO for medical sterilization

3) Evaluate a patient exposed to ethylene oxide

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Outline: Ethylene Oxide (EtO)

- Background: EtO
- Alternatives to EtO for sterilization
- Summary of EtO Health Effects
- Cancer risks associated with EtO
- ATSDR Evaluation of Sterigenics Facility: Willowbrook, IL
- What can healthcare providers do?
- Action items for patients: “Aggressive self-monitoring”

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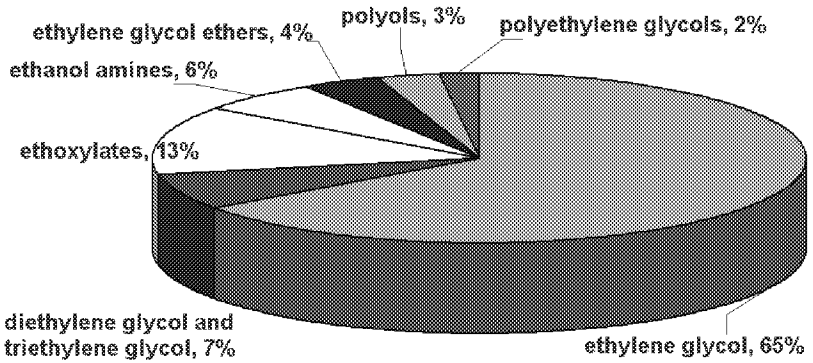
Background: Ethylene Oxide (EtO)

- Precursor for industrial chemicals (e.g. ethylene glycol), plastics, PVC pipes
- **Less than 1%** is used to sterilize medical equipment, consumer products, certain foods (e.g. spices) that can't be steam sterilized
- Used as a fumigant for some agricultural products



Source: IARC Monograph – Ethylene Oxide; https://monographs.iarc.fr/wp-content/uploads/2018/06/mono100F-28.pdf

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Background: Ethylene Oxide (EtO)

Physical properties

- High Vapor Pressure (gas at 20^0C)
- Colorless, tasteless vapor
- Odor-threshold is **500 ppm**
- Sweet, ether-like odor
- Flammable, explosive
- Reacts with water, strong acids, alkalis, and oxidizers
- Atmospheric persistence: **50-60 day half-life**; degrades to hydroxyl radicals

Source: National Library of Medicine-Toxnet. https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~7WUNLz:1
ATSDR. Medical Management Guidelines for Ethylene Oxide.
https://www.atsdr.cdc.gov/mmg/mmg.asp?id=730&tid=133

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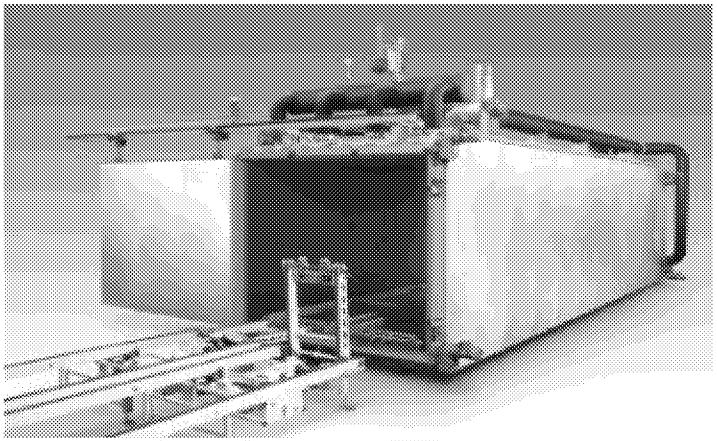
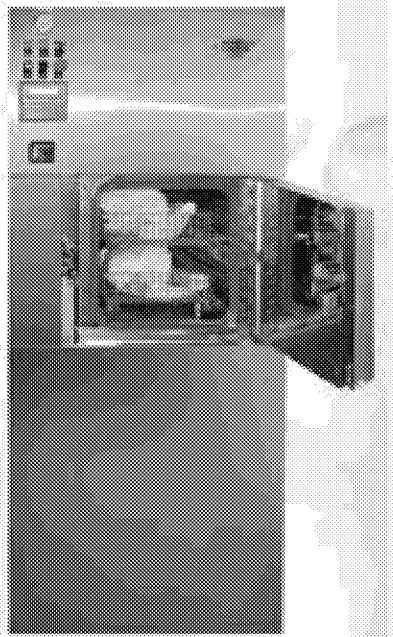
EtO Sterilization

- EtO has been used for sterilization since the 1940s
- Originally patented for preservation of spices in 1938
- Two methods of sterilization:
  - Traditional chamber (Sterigenics, hospitals, labs)
  - Gas diffusion method (hospitals, labs)
    - Plastic bag with instruments is filled with EtO gas and then placed in cabinet to diffuse





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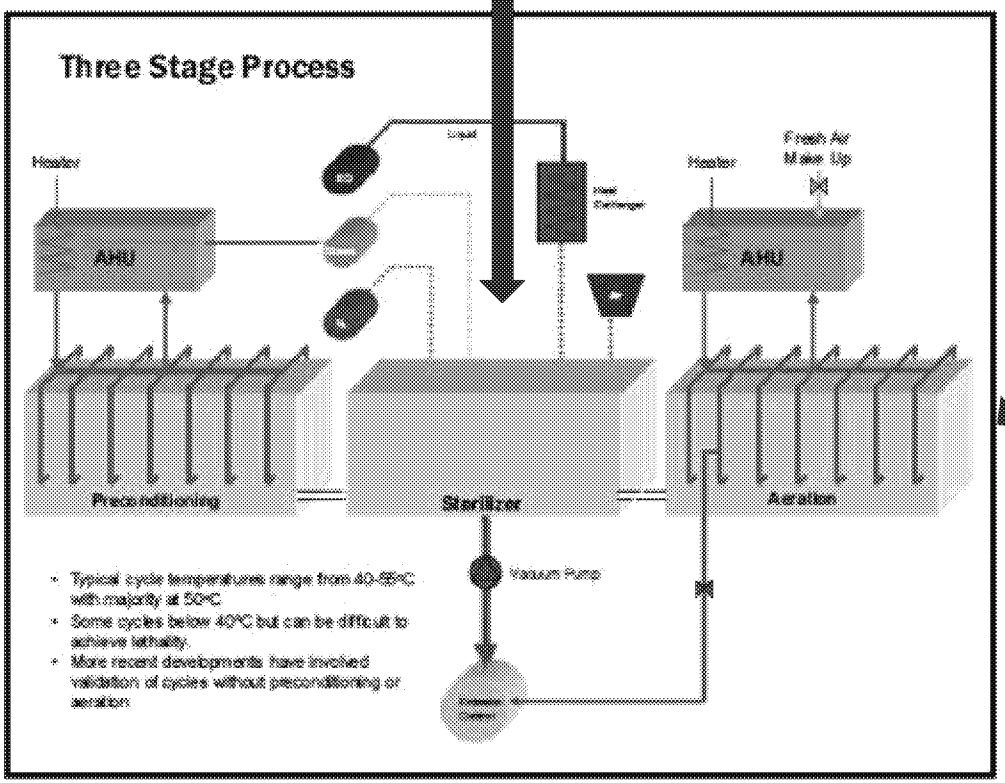
EtO Sterilization

"EO is an alkylating agent that disrupts the DNA of microorganisms, which prevents them from reproducing. The EO penetrates the breathable packaging and sterilizes all accessible surfaces."

2. Sterilization

1. Preconditioning

3. Aeration



Source: https://www.steris-ast.com/services/ethylene-oxide-sterilization/

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EtO Exposure During Sterilization

Hospital

- Changing EtO cylinders
- Tank leaks
- Part failures (valves, gaskets, etc)
- Bag transportation from sterilizer to cabinet

Industry

- Tank/gas source leaks
- Load transfers (pre and post sterilization)
- Chamber leaks
- Scrubber leak

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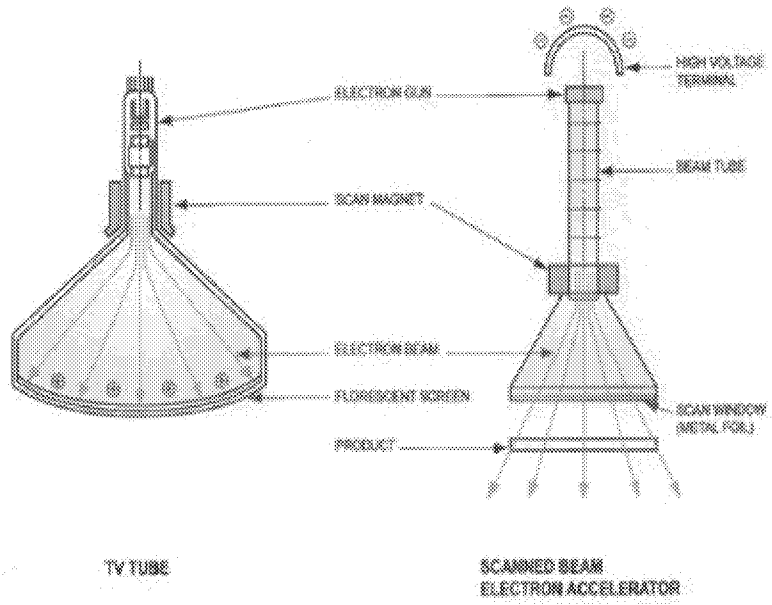
Ionizing Radiation Sterilization

- Gamma: Typically Cobalt-60
- Electron Beam: Particle Accelerator
- X-Ray: Particle Accelerator with X-ray converter

> All use ionizing radiation to damage microbial DNA



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Hydrogen Peroxide (H_2O_2)

- Colorless, odorless liquid
- Potent oxidizing agent
  - Cell metabolism, signaling
  - Consumer applications <5%
  - Industrial applications >35%
  - Eco-friendly

$$H_2O_2(g) \rightarrow 2\ OH(g)$$

$$H_2O_2(g) + OH(g) \rightarrow H_2O(g) + HO_2(g)$$

$$HO_2(g) + OH(g) \rightarrow H_2O(g) + O_2(g)$$

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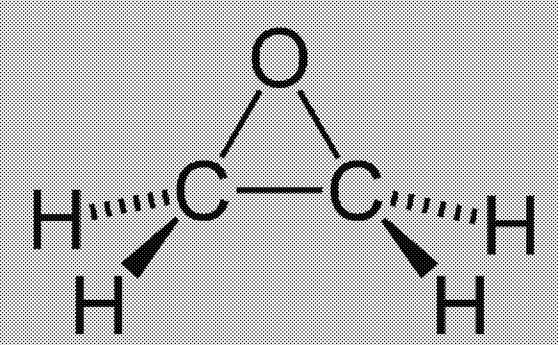

EtO and Human Health

Routes of Exposure

- Inhalation: most exposures
- Absorption via skin: rare
- Ingestion: rare
- Physiological half-life: 45-60 minutes
- Exhaled as EtO or metabolized and excreted in urine
- Completely eliminated 1-2 days after exposure has ended

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Occupational High Level EtO Exposure

Acute Respiratory Effects

- Mucous membrane irritant, bronchospasm
- Immediate local irritation of the skin, eyes, and upper respiratory tract
- Exposure to high concentrations can cause immediate or delayed pulmonary edema
- May result in sensitization response

Source: ATSDR. Medical Management Guidelines for Ethylene Oxide. https://www.atsdr.cdc.gov/mmg/mmg.asp?id=730&tid=133

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Occupational High Level EtO Exposure

Acute CNS Effects

- Central Nervous System (CNS) depressant
- Seizures, loss of consciousness, coma
- Neurological signs and symptoms may be delayed 6 hours or more after exposure
- Exposure to high concentrations can lead to respiratory paralysis and delayed peripheral nerve damage

Source: ATSDR. Medical Management Guidelines for Ethylene Oxide.
https://www.atsdr.cdc.gov/mmg/mmg.asp?id=730&tid=133

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Occupational High Level EtO Exposure

Other Acute Effects

- Nausea and vomiting
- Severe cases
  - Renal damage
  - Cyanosis
- Direct skin contact: frostbite can occur due to rapid evaporation and consequent cooling

Source: ATSDR. Medical Management Guidelines for Ethylene Oxide. https://www.atsdr.cdc.gov/mmg/mmg.asp?id=730&tid=133

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Occupational High Level EtO Exposure

Chronic effects

- Cancer
- Reproductive effects, fetal effects
- Impaired cognitive function, seizures
- Damage to liver and kidneys
- Skin allergy
- Cataracts and corneal burns
- Neuropathy in lower extremities

Source:
1- World Health Organization. Concise International Chemical Assessment Document 54; 2003. http://www.who.int/ipcs/publications/cicad/en/cicad54.pdf
2- Hazardous Substances Database; National Library of Medicine. https://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~7WUNLz:1

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Mechanism of Action in Humans/Animals

- Very potent alkylating agent
- Forms protein and DNA adducts
- Mutagenic (chromosomal aberrations)
- Carcinogenic

According to IARC:

- Limited evidence in humans for causal association with lymphatic and hematopoietic cancers.
- Limited evidence of causal association with breast cancer
- Sufficient evidence in animals of carcinogenicity
- Strong evidence that the mechanism of carcinogenicity is by a genotoxic mechanism (alkylating agent)

Source: USEPA. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide
https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/1025tr.pdf

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Carcinogenicity of EtO

- International Agency for Research on Cancer (IARC)
  - "*Carcinogenic to Humans*" (Group 1)
- National Toxicology Program (NTP) /DHHS
  - "*Known to be a Human Carcinogen*"
- Environmental Protection Agency (EPA)
  - "*Known Human Carcinogen*"

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CDC/NIOSH Occupational Studies: Ethylene Oxide

- **Cancer Mortality Study**[1]
  - Cohort of 18,235 men and women in 14 U.S. commercial sterilization facilities; initially evaluated through 1987, with follow-up 1987-1998; average EtO exposure: 4.7 ppm (1975), decreasing to <1 ppm (1986)
  - Increased mortality from **lymphoid cancers** (Non-Hodgkin lymphoma, myeloma, and lymphocytic leukemia) for men in highest cumulative exposure group; **Odds ratio = 3.76** (CI: 1.03-13.64)
  - Increased mortality from **breast cancer** in women for highest cumulative exposure group; **Odds ratio = 3.13** (CI: 1.42-6.92)

Source: [1] Steenland, K. et al., Occup. Environ. Med. 61: 2-7, 2004.

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CDC/NIOSH Occupational Studies

- **Breast Cancer Incidence[2]**
  - 7,576 women, employed in commercial sterilization facilities for average of 10.7 years
  - Average EtO exposure: 4.7 ppm (1975), decreasing to <1 ppm (1986)
  - Odds Ratio = **1.87** (CI: 1.12-3.10) for highest cumulative exposure group

Source: [2] Steenland, K. et al., Cancer Causes Control 14: 531-539, 2003

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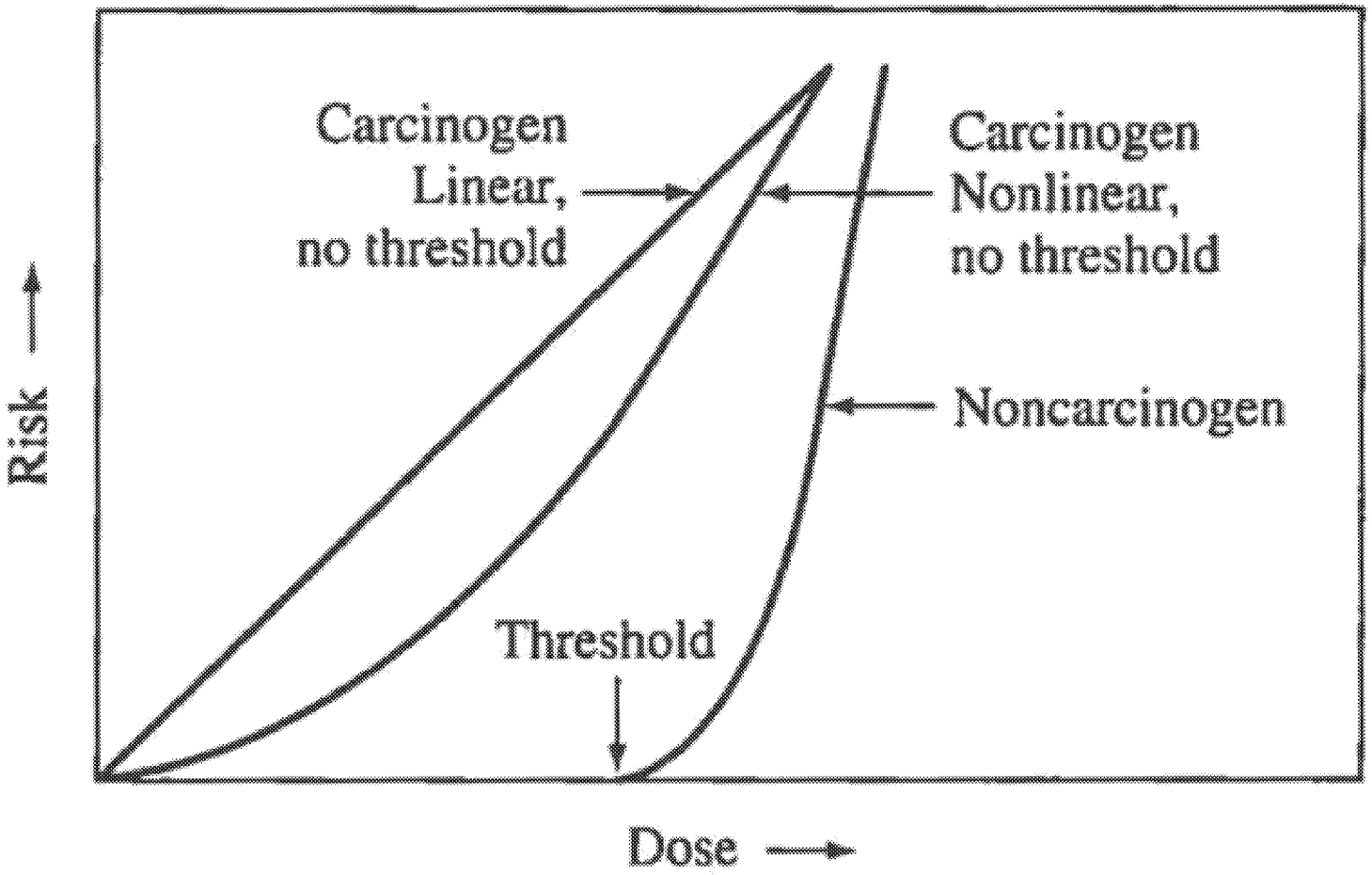
Non-Threshold Theory of Cancer Risk



Source: https://www.quora.com/What-are-the-differences-between-risk-assessment-and-environmental-impact-assessment

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EPA

EPA/635/R-16/350Fa
www.epa.gov/iris

Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide

(CASRN 75-21-8)

In Support of Summary Information on the Integrated Risk Information System (IRIS)

December 2016

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Washington, DC

Source: EPA. https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=329730

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Highlights of EtO IRIS Update 2016

- Cancer designation: from **"probably carcinogenic"** to **"carcinogenic to humans"**
- Inhalation unit risk estimate: from **1.0×10^{-4}** to **3.0×10^{-3} (per µg/m^3)** indicating a 30-50 fold greater risk
- Inhalation unit risk (IUR) is an estimate of the increased cancer risk **per unit of air concentration** from inhalation exposure to a concentration of 1 µg/m^3 for a lifetime. The IUR can be multiplied by an estimate of lifetime exposure (in µg/m^3) to estimate the lifetime cancer risk.
- The IUR (ug/m^3)$^{-1}$ is the slope of the Dose-Response curve, and correlates with the potency for a chemical to cause cancer.

Source: https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/1025tr.pdf

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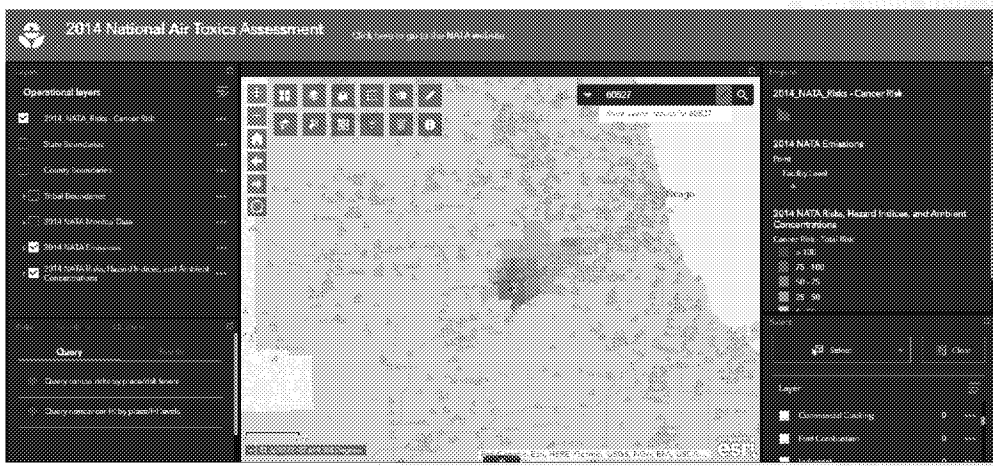
NATA: National Air Toxic Assessment that estimates cancer and noncancer risks from breathing air toxics

- 180 toxics + diesel PM
- Uses National Emissions Inventory of air toxics emissions data
- Estimates air concentrations using geographical and meteorological data modeling
- Estimates population exposures using mapping, time spent outdoors and types of activities
- Characterizes public health risk using Inhalation Unit Risk (**which had just increased for EtO)**



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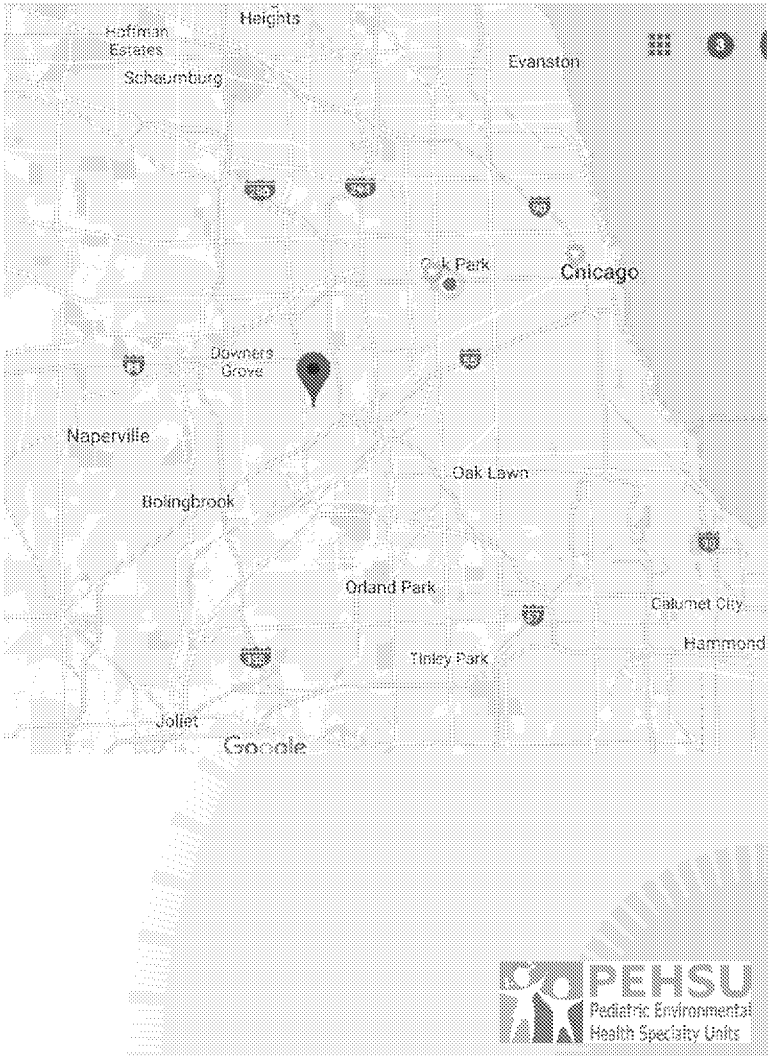
ATSDR Risk Assessment August 2018: Ethylene Oxide

Image source: Patch, Burr Ridge, August 28, 2018.
https://patch.com/illinois/burrridge/cancer-risk-tied-emissions-willowbrook-company-study

Sterigenics Facility, Willowbrook, IL

- Per day sterilizes 1,500 surgical procedure kits, 11,000 radiological syringes, and 16,000 vascular catheters
- Pollution controls include acid water scrubbers and dry bed reactors – convert EtO to ethylene glycol
- No controls on “back vents”
- Obtains permits for all its operations and **operates in full compliance with its environmental permit**



Source: Google Maps

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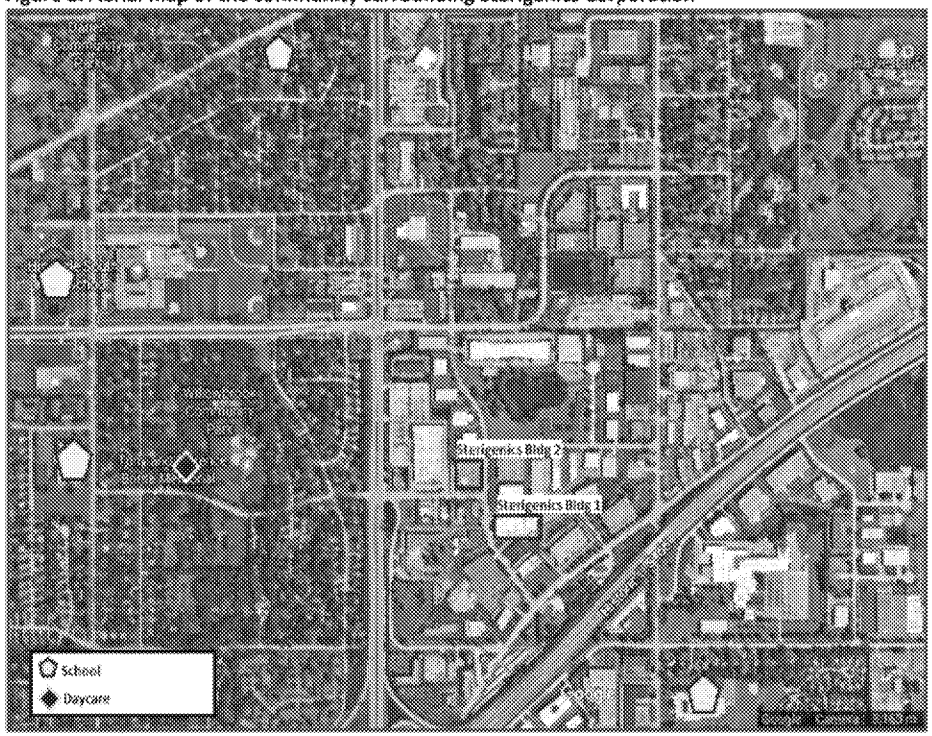
Within One Mile of Facility

- 19,271 residents
- Hinsdale South High School
- Gower West Elementary
- Day care center

Figure 2. Aerial map of the community surrounding Sterigenics Corporation



Source: Google Earth

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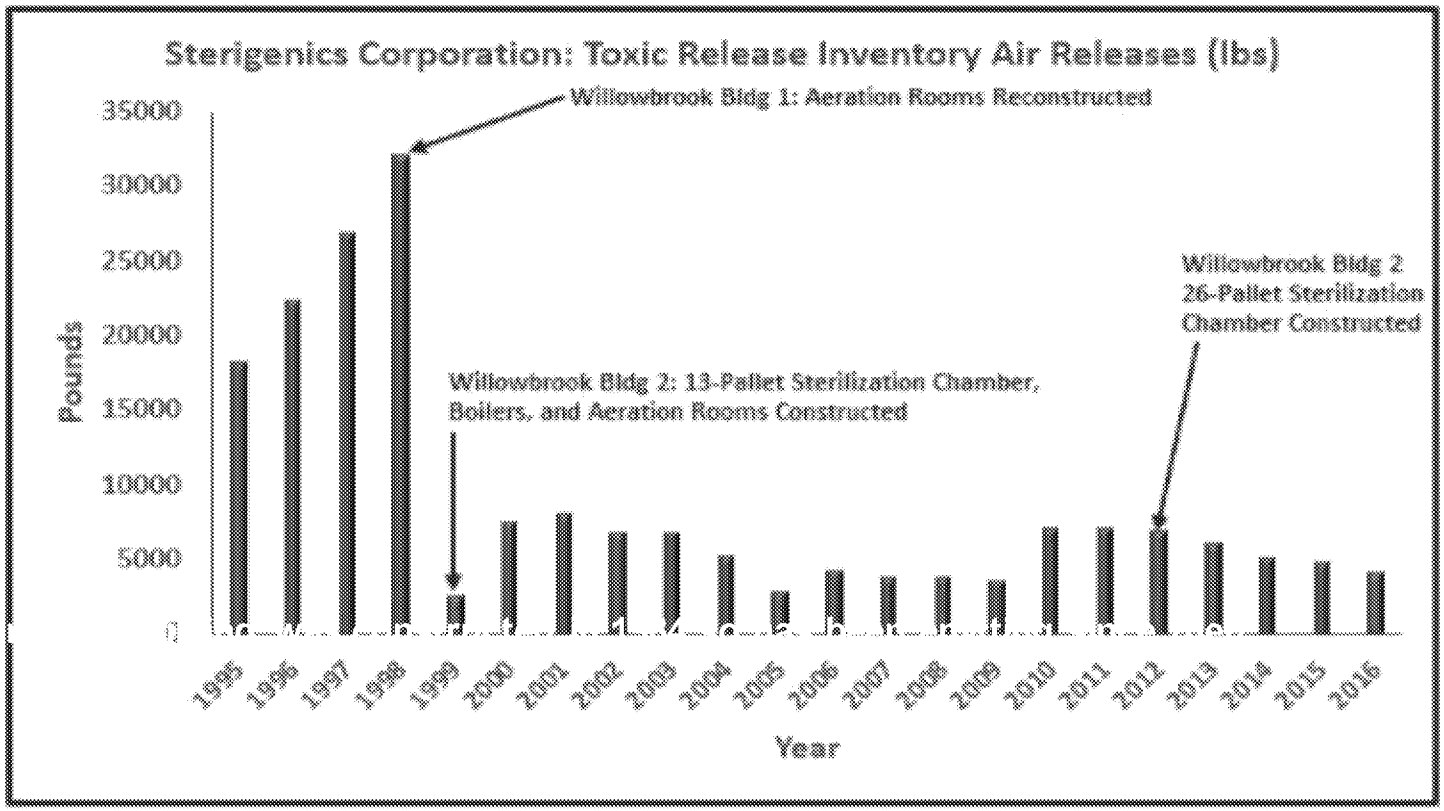
Emissions from Sterigenics Facility

Figure 1. TRI Total Air Emissions Reported (in pounds), by Sterigenics Corporation for Ethylene Oxide, 1995-2016



[a]*Source: Toxic Release Inventory (TRI): https://www.epa.gov/enviro/tri-overview*

[b]*Dates for facility constructed and upgrades were identified according to Illinois EPA (2017) DRAFT/PROPOSED Clean Air*

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EPA Samples May 2018

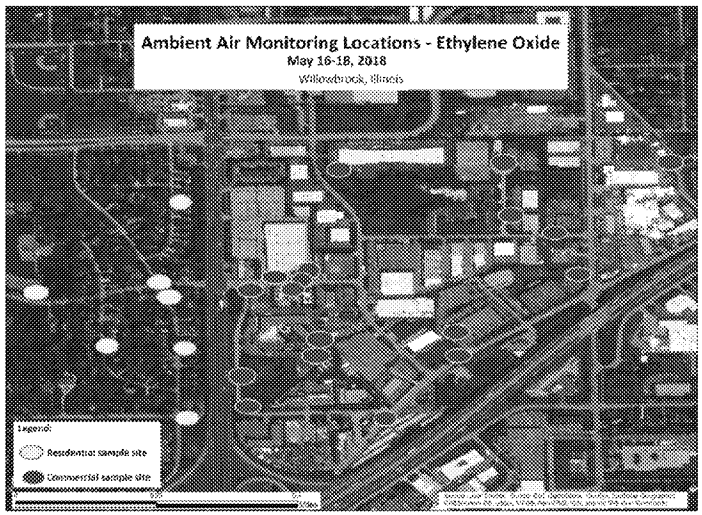
- 26 locations
- 12 hour samples, grab samples

Table 2. Statistical distribution of residential and commercial EtO air sampling*

Statistics	Grab samples (µg/m³)	12-hour samples (µg/m³)
Min	0.16	0.34
25th Percentile	0.24	0.69
50th Percentile	0.45	1.56
75th Percentile	1.34	4.39
90th Percentile	2.28	8.26
95th Percentile	4.27	8.44
99th Percentile	4.33	8.96
Max	4.34	9.09
Mean	1.07	3.02
Geo Mean	0.62	1.74

**N=21 grab samples, 18 12-hour samples*

Figure 4. Ambient air samples near the Sterigenics facility, Willowbrook, IL



Source: U.S. EPA, Region 5

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Letter Health Consultation

"Evaluation of Potential Health Impacts from Ethylene Oxide Emissions"

STERIGENICS INTERNATIONAL, INC.

WILLOWBROOK, ILLINOIS

AUGUST 21, 2018

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Agency for Toxic Substances and Disease Registry
Division of Community Health Investigations
Atlanta, Georgia 30333

https://www.atsdr.cdc.gov/HAC/pha/sterigenic/Sterigenics_International_Inc-508.pdf

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Cancer Risk

- ATSDR CREG (Cancer Risk Evaluation Guide): estimate of concentration of a carcinogen at which there is an elevated risk for one additional case of CA per one million people exposed over a lifetime = 0.00021 µg/m^3 or

0.02 µg/m^3 (for cancer risk of 1 in 10,000 from EtO)

Table 3. Range of measured and modeled EtO concentrations: U.S. EPA Cancer Risk Estimates

Statistics	Modeled 5-year (µg/m^3)	Modeled cancer risk range	12-hour samples (µg/m^3)	Measured cancer risk range*
Minimum	0.03	1.3E-04	0.16	7.9E-04
Maximum	13.32	6.7E-02	4.34	4.5E-02
Mean	0.32	1.6E-03	1.04	1.4E-02
Geometric Mean	0.18	9.1E-04	0.61	7.7E-03

**Cancer risk was calculated to estimate what long term exposures to the 12-hour concentration could look like if sustained long term and does not represent actual exposures.*

- ATSDR used RME (reasonable maximal exposure) for residential exposure for 33 years over 78 year lifetime to calculate cancer risk: **6.4 x10^{-3} or 6.4 cancers per 1,000 residents**.

- For workers in nearby commercial facilities: **2.1 x 10^{-3}**

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ATSDR Health Consultation

- *"If these measured and estimated concentrations represent chronic exposures in the surrounding community (with higher exposures likely for workers of the facility),* ***EtO emissions from the Sterigenics Corporation poses a public health hazard****."*

Clean Air Act permit:

- Issued by Illinois EPA 2015
- Per Sterigenics representative: "Sterigenics recently completed a voluntary upgrade at the Willowbrook facility in July 2018 that reduces the current ethylene oxide emissions by over 90 percent."

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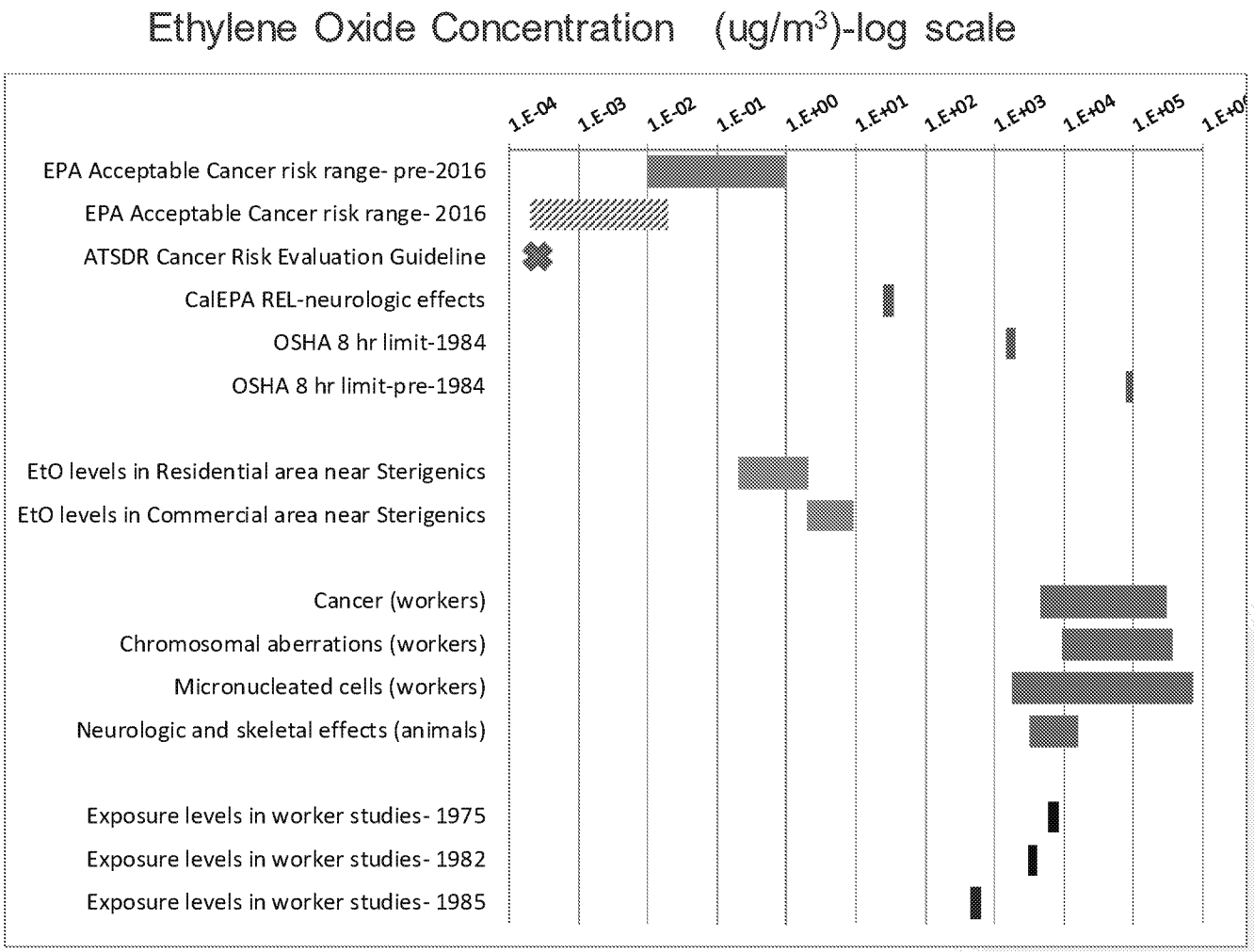
Comparison of Exposure and Effects Levels



EtO levels near Sterigenics are above cancer evaluation criteria, but below health effect levels from workers and animal studies

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CDC/ATSDR Conclusions

- Based on available environmental data, there is *an increased risk for specific cancers based on long-term exposure (>30 years)* for residents and off-site workers in the Willlowbrook community surrounding the Sterigenics facility.

- Exposure to recently measured EtO concentrations are not expected to cause other health problems, such as neurologic and respiratory.

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Under scrutiny for use of harmful chemical, Sterigenics to test emissions control upgrades

People protested Aug. 31 at Sterigenics in Willowbrook asking officials to stop its operations and leave the area. (Kimberly Fornek/Pioneer Press)

Source: Chicago Tribune, September 5, 2018.
https://www.chicagotribune.com/suburbs/burr-ridge/news/ct-dhd-sterigenics-d86-tl-0913-story.html

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Cancer Risk Tied To Emissions From Willowbrook Company: Study

Source: Patch, Burr Ridge, August 28, 2018.
https://patch.com/illinois/burrridge/cancer-risk-tied-emissions-willowbrook-company-study

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Clinical Evaluation of EtO Exposure

What Can Healthcare Providers Do?

Diagnostic Considerations

- No established guidance for medical surveillance with routine history, physical, or diagnostic testing
  - Specific tests for the presence of EtO in blood or urine are not generally useful
- Consider routine lab tests (e.g. CBC, CMP) to detect blood cell abnormalities
- Continue routine preventive screenings, including screening for breast cancer per established guidelines

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Action Items for Patients

Aggressive Self-Monitoring

- Contact your physician for health-related concerns
- Diagnostic testing will be done on a case-by-case basis
- American Cancer Society has basic information about cancer, including cancer screening and preventive actions: https://www.cancer.org/healthy.html
- CDC resources to basic cancer education information: https://www.cdc.gov/cancer
- Continue regular cancer screening: https://www.cdc.gov/cancer/breast/pdf/BreastCancerScreeningGuidelines.pdf

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Additional Resources

- **USEPA: Sterigenics Willowbrook Facility**
  https://www.epa.gov/il/sterigenics-willowbrook-facility
- **Illinois EPA: Sterigenics**
  https://www2.illinois.gov/epa/topics/community-relations/sites/sterigenics/Pages/default.aspx
- **DuPage County: Sterigenics Information**
  https://www.dupageco.org/EDP/Waste_Recycling_and_Energy/58548/
- **Village of Willowbrook, Sterigenics Issues**
  http://www.willowbrookil.org/index.aspx?NID=302

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Questions?

Thank you!

References

1) ATSDR. Toxicological profile for ethylene oxide. December 1990. U.S. Public Health Service. https://www.atsdr.cdc.gov/toxprofiles/tp137.pdf

2) ATSDR. Medical Management Guidelines for Ethylene Oxide. https://www.atsdr.cdc.gov/mmg/mmg.asp?id=730&tid=133

3) IARC. Monographs on the Evaluation of Carcinogenic Risks to Humans- Ethylene Oxide. Volume 100F. International Agency for Research on Cancer; World Health Organization; Lyon France. 2012. https://monographs.iarc.fr/wp-content/uploads/2018/06/mono100F-28.pdf

4) NIOSH. NIOSH Pocket Guide to Chemical Hazards & Other Databases. Department of Health & Human Services, Centers for Disease Prevention & Control. National Institute for Occupational Safety & Health. DHHS (NIOSH) Publication No. 2005-151 (2005)

5) USEPA. Integrated Risk Information System (IRIS)- Ethylene oxide https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=329730

6) USEPA. Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/1025tr.pdf

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