Message

From: Shappley, Ned [Shappley.Ned@epa.gov]
Sent: 12/29/2020 2:57:50 PM
To: Watkins, Nealson [Watkins.Nealson@epa.gov]; Chen, Xi [Chen.Xi@epa.gov]; Dewees, Jason [Dewees.Jason@epa.gov]
Subject: RE: Sterigenics Santa Teresa facility in New Mexico

Hey folks,

I got a note from Fran that NMED did not do the sampling or analysis and that it came from a third party. I will let you know if I find out more.

Thanks,
Ned

From: Watkins, Nealson <Watkins.Nealson@epa.gov>
Sent: Tuesday, 29 December, 2020 09:45
To: Shappley, Ned <Shappley.Ned@epa.gov>; Chen, Xi <Chen.Xi@epa.gov>; Dewees, Jason <Dewees.Jason@epa.gov>
Subject: RE: Sterigenics Santa Teresa facility in New Mexico

OK. We'll keep our ears up on any potential action items.

Thanks,
Nealson Watkins
Ambient Air Monitoring Group
Air Quality Assessment Division
Office of Air Quality Planning & Standards
U.S. Environmental Protection Agency - Research Triangle Park, NC 27711 - Phone: 919-541-5522

From: Shappley, Ned <Shappley.Ned@epa.gov>
Sent: Tuesday, December 29, 2020 9:43 AM
To: Watkins, Nealson <Watkins.Nealson@epa.gov>; Chen, Xi <Chen.Xi@epa.gov>; Dewees, Jason <Dewees.Jason@epa.gov>
Subject: RE: Sterigenics Santa Teresa facility in New Mexico

Not yet, we are suppose to share the modeling files with the Region in early January so they can ground truth them as part of the Outreach strategy for the rule.

From: Watkins, Nealson <Watkins.Nealson@epa.gov>
Sent: Tuesday, 29 December, 2020 09:41
To: Chen, Xi <Chen.Xi@epa.gov>; Shappley, Ned <Shappley.Ned@epa.gov>; Dewees, Jason <Dewees.Jason@epa.gov>
Subject: RE: Sterigenics Santa Teresa facility in New Mexico

Would the data be public record? We might want to plan to work *with* R6 in getting our hands on these data, if we are wanting to see them. We can call Ruben to get started.

Thanks,
Nealson Watkins

Ambient Air Monitoring Group
Air Quality Assessment Division
Office of Air Quality Planning & Standards
U.S. Environmental Protection Agency - Research Triangle Park, NC 27711 - Phone: 919-541-5522

From: Chen, Xi <Chen.Xi@epa.gov>
Sent: Tuesday, December 29, 2020 9:36 AM
To: Shappley, Ned <Shappley.Ned@epa.gov>; Watkins, Nealson <Watkins.Nealson@epa.gov>; Dewees, Jason <Dewees.Jason@epa.gov>
Subject: RE: Sterigenics Santa Teresa facility in New Mexico

No, Ned, it was not ERG who did the analysis for them.

From: Shappley, Ned <Shappley.Ned@epa.gov>
Sent: Tuesday, December 29, 2020 9:20 AM
To: Watkins, Nealson <Watkins.Nealson@epa.gov>; Chen, Xi <Chen.Xi@epa.gov>; Dewees, Jason <Dewees.Jason@epa.gov>
Subject: RE: Sterigenics Santa Teresa facility in New Mexico

I got pinged by Chet this morning.

Doris, can we check with ERG to see if they did this analysis?

From: Watkins, Nealson <Watkins.Nealson@epa.gov>
Sent: Tuesday, 29 December, 2020 08:31
To: Shappley, Ned <Shappley.Ned@epa.gov>; Chen, Xi <Chen.Xi@epa.gov>; Dewees, Jason <Dewees.Jason@epa.gov>
Subject: RE: Sterigenics Santa Teresa facility in New Mexico

I think our managers should weigh in on us doing something. This could be an ATEST "heads-up" topic, at least, but since it came down from Mike, the DDs, Mike, and maybe Peter might already have thoughts on this. When is the next EtO stand-up meeting? I'm not in those, but maybe y'all could ask Mike about his thoughts on the situation and whether or not there is something we could or should do.

Thanks,
Nealson Watkins
Ambient Air Monitoring Group
Air Quality Assessment Division
Office of Air Quality Planning & Standards
U.S. Environmental Protection Agency - Research Triangle Park, NC 27711 - Phone: 919-541-5522

From: Shappley, Ned <Shappley.Ned@epa.gov>
Sent: Monday, December 28, 2020 4:40 PM
To: Watkins, Nealson <Watkins.Nealson@epa.gov>; Chen, Xi <Chen.Xi@epa.gov>; Dewees, Jason <Dewees.Jason@epa.gov>
Subject: RE: Sterigenics Santa Teresa facility in New Mexico

Thanks Nealson,

If we can get the actual days of sampling from NM, I have access to the modeling files for this facility. Perhaps we can send this to James to do the daily dispersions?

Did we ever find out who did this analysis?

Ned

From: Watkins, Nealson <Watkins.Nealson@epa.gov>
Sent: Wednesday, 23 December, 2020 10:26
To: Chen, Xi <Chen.Xi@epa.gov>; Shappley, Ned <Shappley.Ned@epa.gov>; Dewees, Jason <Dewees.Jason@epa.gov>
Subject: FW: Sterigenics Santa Teresa facility in New Mexico

FYI, in case y'all had not seen this.

Thanks,
Nealson Watkins
Ambient Air Monitoring Group
Air Quality Assessment Division
Office of Air Quality Planning & Standards
U.S. Environmental Protection Agency - Research Triangle Park, NC 27711 - Phone: 919-541-5522

From: Benedict, Kristen <Benedict.Kristen@epa.gov>
Sent: Wednesday, December 23, 2020 8:13 AM
To: Watkins, Nealson <Watkins.Nealson@epa.gov>
Cc: Noah, Greg <Noah.Greg@epa.gov>
Subject: FW: Sterigenics Santa Teresa facility in New Mexico

FYI

From: Koerber, Mike <Koerber.Mike@epa.gov>
Sent: Wednesday, December 23, 2020 8:09 AM
To: Wayland, Richard <Wayland.Richard@epa.gov>; Chen, Xi <Chen.Xi@epa.gov>; Benedict, Kristen <Benedict.Kristen@epa.gov>
Subject: FW: Sterigenics Santa Teresa facility in New Mexico

FYI – note that the state conducted recent monitoring for EtO (see pages 5-6 of the attachment)

From: Harlow, David <harlow.david@epa.gov>
Sent: Wednesday, December 23, 2020 7:06 AM
To: Koerber, Mike <Koerber.Mike@epa.gov>
Subject: Sterigenics Santa Teresa facility in New Mexico

Mike,

I just saw this this morning.

https://news.bloomberglaw.com/environment-and-energy/sterigenics-sued-over-ethylene-oxide-releases-in-new-mexico

What I find noteworthy is that this is not some toxic tort suit brought by a private litigant (those sorts of things are a dime a dozen) but, rather, an action brought by

the State of New Mexico itself, in state court, asserting various causes of action said to arise under state law.

There's no action item arising out of this for us, at least not right not, that I can see. Still, the complaint was apparently filed just yesterday, so we (or Region 6) may get calls from reporters, if this should pique their interest.

Heading into the new year, under new management, you all will, of course, continue to run this issue to ground from the Agency's perspective, with the commercial sterilizers NPRM, etc. But I can imagine scenarios where the Agency could down the road get roped into civil suits of this nature, particularly when brought by states. The state cites the 2014 NATA data throughout, for instance. So I wanted to bring this to your attention, in case you weren't already aware of it.

By the way, we have this particular facility's actual MIR at 70 in 1-million (300 in 1-million for allowables).

David S. Harlow
Senior Counsel
Office of Air and Radiation, USEPA
WJC-N Room 5409K
1200 Pennsylvania Avenue NW
Washington, DC 20460
202-564-1233
Harlow.David@epa.gov
5 U.S.C. § 3331

Message

From: Watkins, Nealson [Watkins.Nealson@epa.gov]
Sent: 12/23/2020 3:25:56 PM
To: Chen, Xi [Chen.Xi@epa.gov]; Shappley, Ned [Shappley.Ned@epa.gov]; Dewees, Jason [Dewees.Jason@epa.gov]
Subject: FW: Sterigenics Santa Teresa facility in New Mexico
Attachments: NM v. Sterigenics.pdf

FYI, in case y'all had not seen this.

Thanks,
Nealson Watkins
Ambient Air Monitoring Group
Air Quality Assessment Division
Office of Air Quality Planning & Standards
U.S. Environmental Protection Agency - Research Triangle Park, NC 27711 - Phone: 919-541-5522

From: Benedict, Kristen <Benedict.Kristen@epa.gov>
Sent: Wednesday, December 23, 2020 8:13 AM
To: Watkins, Nealson <Watkins.Nealson@epa.gov>
Cc: Noah, Greg <Noah.Greg@epa.gov>
Subject: FW: Sterigenics Santa Teresa facility in New Mexico

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Sent: Wednesday, December 23, 2020 8:09 AM
To: Wayland, Richard <Wayland.Richard@epa.gov>; Chen, Xi <Chen.Xi@epa.gov>; Benedict, Kristen <Benedict.Kristen@epa.gov>
Subject: FW: Sterigenics Santa Teresa facility in New Mexico

FYI – note that the state conducted recent monitoring for EtO (see pages 5-6 of the attachment)

From: Harlow, David <harlow.david@epa.gov>
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To: Koerber, Mike <Koerber.Mike@epa.gov>
Subject: Sterigenics Santa Teresa facility in New Mexico

Mike,

I just saw this this morning.

https://news.bloomberglaw.com/environment-and-energy/sterigenics-sued-over-ethylene-oxide-releases-in-new-mexico

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said to arise under state law.

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By the way, we have this particular facility's actual MIR at 70 in 1-million (300 in 1-million for allowables).

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5 U.S.C. § 3331

FILED
3rd JUDICIAL DISTRICT COURT
Dona Ana County
12/22/2020 9:47 AM
DAVID S. BORUNDA
CLERK OF THE COURT
Ashley Barreras

STATE OF NEW MEXICO
COUNTY OF DOÑA ANA
THIRD JUDICIAL DISTRICT COURT

THE STATE OF NEW MEXICO, ex rel. HECTOR BALDERAS, ATTORNEY GENERAL,	§	
Plaintiff,	§	No.: D-307-CV-2020-02629
v.	§	Beyer, Marci
STERIGENICS U.S., LLC, SOTERA HEALTH HOLDINGS, LLC, SOTERA HEALTH LLC, and SOTERA HEALTH COMPANY,	§	**VERIFIED COMPLAINT WITH JURY DEMAND AND *EX PARTE* REQUEST FOR TEMPORARY RESTRAINING ORDER AND PRELIMINARY INJUNCTION**
Defendants.	§	

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I. INTRODUCTION

1. The State of New Mexico, by its Attorney General Hector Balderas ("Plaintiff" or "New Mexico" or the "State"), brings this action against Defendants Sterigenics U.S., LLC, Sotera Health Holdings, LLC ("Sotera Holdings"), Sotera Health, LLC, and Sotera Health Company ("Sotera") (collectively, "Defendants" or "Sterigenics"), for all damages to New Mexico recoverable at law or in equity, and for declaratory and injunctive relief, to remedy Defendants' violations of law.

2. Sterigenics holds itself out as "the global leader in comprehensive sterilization solutions serving customers' industrial sterilization needs across the medical device, pharmaceutical, advanced applications, commercial, and food industries."

3. Since 1989, Defendants have owned and operated a large facility in Santa Teresa, Doña Ana County, New Mexico, at which industrial sterilization and fumigation processes have been and continue to be employed (the "Santa Teresa Plant" or the "Plant").

4. The Santa Teresa Plant is located in a business park on Airport Road in Santa Teresa, proximate to a number of residential communities and schools.

5. Doña Ana County, and Santa Teresa specifically, are minority-majority communities.

6. Since 1989, Defendants have used and continue to use substantial quantities of a highly toxic, carcinogenic air pollutant, ethylene oxide ("EtO"), in their industrial sterilization processes at the Santa Teresa Plant.

7. EtO is genotoxic (i.e., it damages DNA) and is known to cause cancer, including lymphoma, leukemia, stomach cancer, and breast cancer.

8. The National Toxicology Program, a federal program, has recognized EtO as a known human carcinogen since 2000, and as a likely human carcinogen since 1985.

9. Even at very low levels, inhalation of EtO-contaminated air significantly increases the risk of developing cancer and other adverse health effects.

10. In December 2016, the U.S. Environmental Protection Agency's ("EPA") Integrated Risk Information System ("IRIS") program released an evaluation of EtO carcinogenicity (the "2016 IRIS Evaluation"), which characterized EtO as "carcinogenic to humans" and noted that EtO is a mutagenic carcinogen that causes cancer by damaging DNA in cells, which is then duplicated when the cells divide.

11. As outlined in the 2016 IRIS Evaluation, EtO exposure increases the cancer risk because DNA damage can take place with each and every exposure that is passed on to more cells, thereby increasing the number of mutated cells.

12. Based on this concern, the 2016 IRIS Evaluation increased the EPA lifetime inhalation risk estimate by a factor of about 30.

13. In conjunction with the 2016 IRIS Evaluation, EPA has established inhalation unit risk ("IUR") estimates for exposure to EtO in ambient air in order to evaluate the potential cancer risks posed by inhalation exposure to EtO.

14. The EPA's IUR estimates for cancer mortality and incidence were based on the human data from a National Institute for Occupational Safety and Health ("NIOSH") study. This study was selected for the derivation of risk estimates because it was deemed a "high-quality" study.

15. The IUR established for EtO is .03 ug/m^3 (micrograms per cubic meter).

16. Once released into air, EtO can travel significant distances with air currents, and can remain in ambient air for over 200 days.

17. EtO emitted by Defendants from the Santa Teresa Plant has significantly deteriorated air quality in Santa Teresa and surrounding communities for decades, and has materially contributed to increased health risks suffered by residents of such communities.

18. Since 1989, Defendants have reported emitting several tons of EtO per year from the Santa Teresa Plant through controlled sources, including sterilizer vacuum pumps, acid-water scrubbers, and catalytic oxidizers.

19. However, Defendants have also caused substantial unreported, uncontrolled releases of EtO to the atmosphere from the Santa Teresa Plant as a result of their intentional or negligent subversion of environmental controls:

a. As revealed in the State's presuit investigation, due to Defendants' lax oversight in connection with sterilization operations—such as the practice of routinely leaving sterilization chamber doors ajar between sterilization cycles—EtO levels in the ambient indoor air at Defendants' Santa Teresa Plant were often elevated, as indicated by an air-quality monitoring system. To dissipate the elevated concentrations of EtO inside the Plant, Defendants caused shipping bays and large facility doors to be left open for hours, or entire days, releasing excess EtO into the atmosphere in an uncontrolled and unfiltered manner.

b. Further, during regular cleaning and maintenance operations, on an at least monthly basis, Defendants caused EtO and ethylene glycol residues built up within the sterilization chambers to be removed from sterilization equipment using a hose and

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released through an ordinary drain. This practice resulted in the uncontrolled release of EtO and ethylene glycol into the environment.

c. The Santa Teresa Plant also assisted other Sterigenics facilities in performing sterilization operations, including aeration of sterilized products. For example, Sterigenics caused shipments of sterilized devices and equipment to be delivered to the Santa Teresa Plant from the company's San Diego facility on a near-weekly basis so that such devices and equipment could be aerated for 24 hours in the Santa Teresa Plant. As these shipments had been sterilized using EtO, but not aerated, they were off-gassing EtO during the shipping, receiving, and loading phases, including at the Santa Teresa Plant, further contributing to the uncontrolled release of EtO in the State.

20. Uncontrolled emissions also escaped the Santa Teresa Plant from the sterilization back vents at the facility, which were not routed through an emission control system until as late as 2014, and through other means, which may include emissions released during mechanical failures or breakdowns impacting the Plant's emission control systems.

21. In August 2018, the EPA published results from its 2014 National Air Toxics Assessment ("NATA") study. The study compiled evidence showing that, due to Defendants' reported emissions of EtO, residents of Santa Teresa and surrounding locations are at a statistically significantly increased risk of developing cancer. The NATA study assessed the increased cancer risk due to EtO exposure in Doña Ana County based on 2014 emissions data reported by Sterigenics.

22. In 2014, Sterigenics substantially decreased its reported EtO emissions as compared to prior years; from 1989 to 2013, Defendants reported emitting thousands more pounds of EtO as compared to 2014.

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23. Accordingly, the NATA study greatly underestimates the historic impact of Defendants' EtO emissions, and the increased cancer risk in Doña Ana County.

24. The NATA data shows that, as of 2014, Doña Ana County residents in the census tract likely suffering the most exposure to EtO have a cancer risk of **214.5543 per 1 million**, which is far in excess of the national average (approximately 30 per 1 million), and that this increased risk is due to EtO exposure. For years prior to 2014, the risk is considerably higher.

25. The NATA data similarly shows that Doña Ana County residents in nearby census tracts suffer increased cancer risk due to EtO exposure.

26. Because the Santa Teresa Plant is the only significant source of EtO in the Santa Teresa region, and was the sole source of EtO taken into account with respect to the cancer risk assessment of Doña Ana County residents in the NATA study, this increased cancer risk is wholly or substantially attributable to Defendants' operations.

27. All residents of Doña Ana County (approximately 218,195 residents) are affected by Defendants' EtO emissions, according to the NATA study.

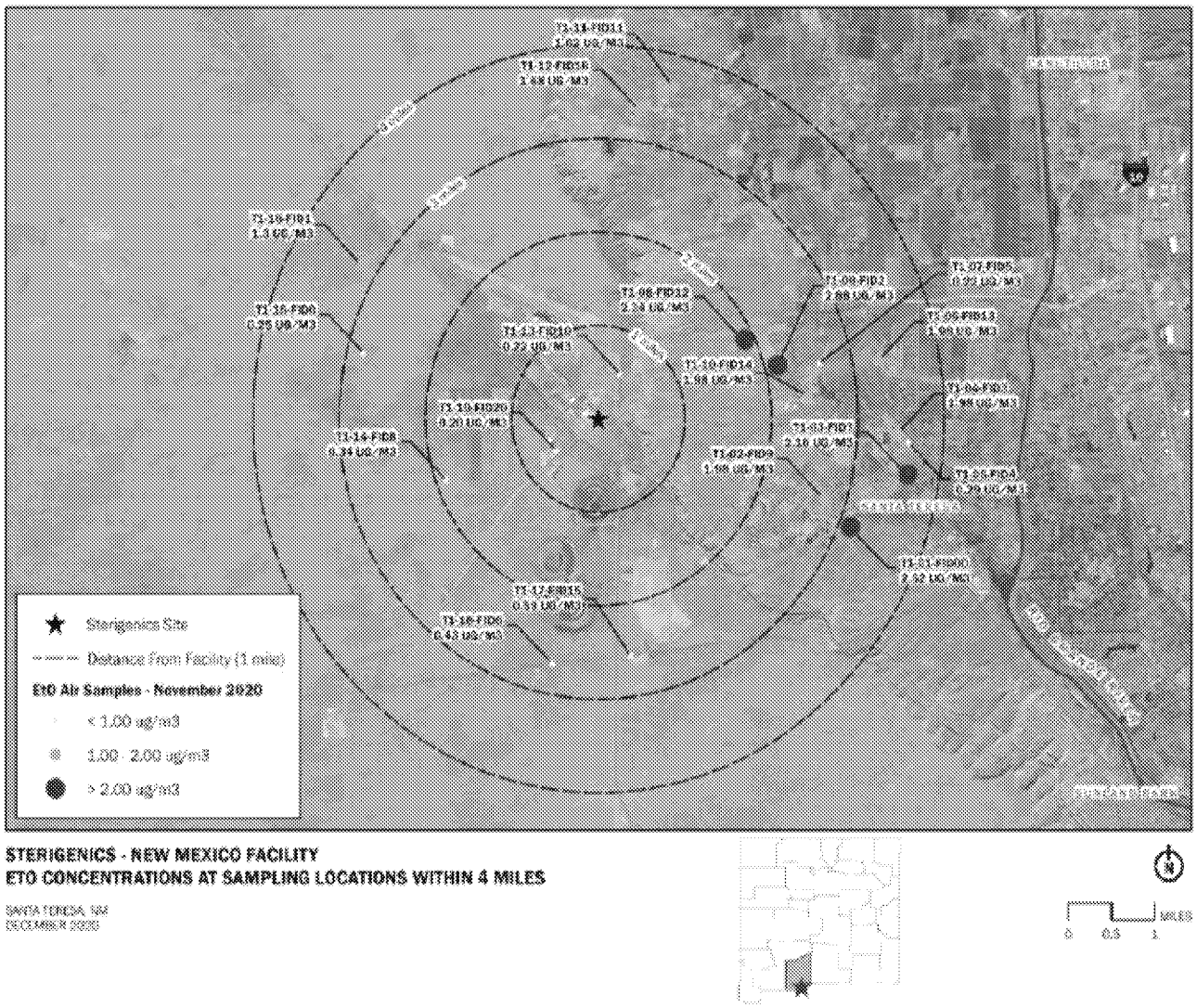
28. Defendants have reported emitting hundreds of thousands of pounds of EtO from the Santa Teresa Plant from 1989 to 2016, including at least 10,000 pounds of EtO per year from 2005 to 2013.

29. As revealed in the State's presuit investigation, however, Defendants have caused excessive uncontrolled EtO and ethylene glycol emissions into the environment in the State as a result of deficient environmental controls and intentional subversion of environmental controls.

30. Beyond the cancer risk identified by the NATA data associated with the Santa Teresa Plant, the State's presuit investigation included sampling of ambient outdoor air within a

four-mile radius of the Santa Teresa Plant for EtO. This investigation confirmed the substantial risk to New Mexico residents based on Defendants' EtO emissions.

31. Every one of the air samples collected in the presuit investigation within a four-mile radius of the Santa Teresa Plant detected ambient airborne concentrations in excess of the EPA IUR of .03 ug/m³, including one sample that was **96 times the EPA's cancer risk level** (measured at 2.88 ug/m³). A map showing the exceedances of the EPA's IUR threshold appears below:



32. In the map above, every sample indicator (yellow, orange, or red) represents an exceedance of the EPA IUR level. None of the sampling events showed EtO detections below that level.

33. Defendants' emissions of EtO from 1989 until the present have caused significant harm to New Mexico and its residents.

34. For example, Defendants' EtO emissions have severely impacted air quality in Santa Teresa and Doña Ana County. Past and future increased healthcare costs associated with Defendants' industrial activities constitute a financial loss to the State, including by increasing the cost of treating affected residents and by expenditures of State financial resources through State healthcare programs and plans.

35. Defendants' conduct has also caused property values in the affected census tracts to decline.

36. The increased risk of adverse health effects and diminution of property values in the affected communities similarly constitute injuries to New Mexico residents.

37. Through this action, the State, acting as *parens patriae* and on its own behalf, seeks all damages available under law, including compensatory and punitive damages, and all other monetary relief, declaratory relief, and injunctive relief necessary and appropriate to remedy Defendants' unlawful conduct, including a temporary restraining order and preliminary injunction requiring Defendants to cease any and all uncontrolled emissions or releases of EtO from the Santa Teresa Plant.

II. JURISDICTION AND VENUE

38. The property and conduct that are the subject of this suit all rest within the State of New Mexico. No federal subject-matter jurisdiction exists or is invoked herein.

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39. Venue is proper in Doña Ana County pursuant to NMSA 1978 Section 38-3-1 because a plaintiff resides here and the defendants are foreign corporations, and the causes of action asserted herein arose in this County.

40. This Court has subject matter jurisdiction over this case pursuant to N.M. Const. Art. VI, Sec. 13.

41. This Court has personal jurisdiction over Defendants pursuant to both NMSA 1978 Section 38-1-16(A) and New Mexico's "sufficient minimum contacts" test. *Sproul v. Rob & Charlie's, Inc.*, 2013-NMCA-072, ¶ 13, 304 P.3d 18. Defendants currently or formerly owned and/or operated at least one facility in Santa Teresa, Doña Ana County, New Mexico.

III. PARTIES

A. PLAINTIFF

42. The State of New Mexico is a body politic created by the Constitution and laws of the State; as such it is not a citizen of any state.

43. The State of New Mexico, by the Honorable Hector H. Balderas, Attorney General of the State of New Mexico, brings this suit because, in his judgment, it is in the state's interest to do so and pursuant to its inherent *parens patriae* authority to remedy an injury to its "quasi-sovereign interest" in the physical and economic health and well-being of a substantial segment of its population.

44. The Attorney General is authorized to act on behalf of the State in all actions when the interests of the State require action in his judgment, is empowered to prosecute all actions and proceedings brought by any State officer or head of a State department, board, or commission, or any employee of the State in his official capacity, and is empowered to appear before local, state,

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and federal courts to represent the State when, in his judgment, the public interest of the State requires such action. NMSA 1978 Section 8-5-2(B)-(C), (J).

45. New Mexico enjoys *parens patriae* standing in this suit because its residents have been adversely affected by the presence of EtO in the State's environment as alleged herein, including suffering property diminution, increased risks of adverse health effects, and/or suffer loss through monetary assessments or expenditures that contribute to the assessment, monitoring, and analysis of EtO and contaminants resulting from EtO emissions and to coverage for increased healthcare costs associated with EtO exposure.

46. New Mexico has spent and will continue to spend money in connection with the misconduct alleged herein, including costs associated with monitoring and assessing EtO contamination, and healthcare costs associated with New Mexico residents' exposure to Defendants' EtO emissions.

47. Further, the Attorney General has the authority to enforce the New Mexico Unfair Practices Act, NMSA 1978 §§ 57-12-1, *et seq.* ("UPA"), and the New Mexico public nuisance statute, NMSA 1978 §§ 30-8-1, *et seq.* ("Public Nuisance Statute"), to ensure the protection of New Mexico residents, natural resources, and commerce.

B. DEFENDANTS

48. Defendant Sterigenics U.S., LLC is a limited liability company organized under the laws of the State of Delaware with its principal place of business in the State of Illinois. Sterigenics U.S., LLC operates the Santa Teresa Plant.

49. Defendant Sotera Holdings is a limited liability company organized under the laws of the State of Delaware with its principal place of business in the State of Ohio. The Santa Teresa Plant is currently owned by Sotera Holdings, and has been owned by that defendant since 2018.

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50. Defendant Sotera Health, LLC is a limited liability company organized under the laws of the State of Delaware with its principal place of business in the State of Ohio. Sotera Health, LLC was formerly known as Sterigenics International.

51. Defendant Sotera Health Company is a publicly traded company organized under the laws of the State of Delaware with its principal place of business in the State of Ohio. Sotera Health Company's shares are listed on the NASDAQ exchange under ticker symbol SHC. Sotera Health Company is the parent company of each of the other Defendants.

52. The Santa Teresa Plant was originally owned by Griffith Micro Science, Inc. ("Griffith"). Griffith, along with Sterigenics International, was acquired by Ion Beam Applications S.A. ("IBA") in 1999. IBA was subsequently renamed Sterigenics International, Inc. in 2004.

IV. FACTUAL ALLEGATIONS

A. ETHYLENE OXIDE IS A DANGEROUS POLLUTANT THAT THREATENS HUMAN AND ENVIRONMENTAL HEALTH AND SAFETY

1. Physical and Chemical Properties of EtO.

53. Ethylene oxide, or EtO, is a flammable, colorless, highly penetrating gas used to sterilize or fumigate heat- and moisture-sensitive products, equipment, and devices that cannot be sterilized by steam.

54. EtO is water soluble.

55. In air or soil, EtO breaks down over time. EPA estimates that atmospheric degradation of EtO, at 25 degrees Celsius/77 degrees Fahrenheit, occurs over 69-149 days. The World Health Organization ("WHO") estimates that the "half-life of ethylene oxide in the atmosphere" is 211 days, and notes that "[n]either rain nor absorption into aqueous aerosols is capable of removing ethylene oxide from the atmosphere."

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56. At atmospheric pressure and room temperature, EtO exists as a gas due to its high vapor pressure and low boiling point.

57. Due to its high vapor pressure, EtO has a strong tendency to escape (volatilize) into air from soil or water (or other environmental media or compartment).

58. EtO is heavier and denser than air. Accordingly, the WHO reports that EtO "may travel along the ground," i.e., at a height at which emitted EtO may be inhaled, once released.

59. EtO is rapidly absorbed by the human body after inhalation or dermal exposure.

60. The half-life of EtO in the body following inhalation is 45-60 minutes. Full elimination from the body occurs within 1-7 days after exposure.

61. When EtO is present in the air continuously, EtO levels are continuously present in the bodies of those exposed.

62. Insufficient use of scrubbing technologies and other standard measures to limit or reduce emissions of potentially hazardous chemicals is responsible for most air emissions of EtO from industrial facilities, such as Defendants' Santa Teresa Plant.

63. There is no safe amount of EtO in air or other environmental media.

64. Unfiltered or uncontrolled emissions of EtO represent a significant cause for concern because much larger volumes of EtO may be released in the absence of scrubbers and other standard environmental control technologies, which serve to limit the volume of EtO released to the atmosphere.

2. Health Effects of Exposure to EtO.

65. Humans are exposed to EtO primarily by inhaling contaminated air, particularly near industrial facilities emitting EtO.

66. EtO causes a wide variety of adverse health effects in exposed persons.

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67. Studies of workers exposed to EtO as well as animal studies demonstrate that EtO exposure results in eye, skin, and mucous membrane irritation, impaired neurological functioning, increased rate of miscarriages in females and other reproductive deficiencies, low birth weight, delayed bone formation, and cancer, including an increased risk of leukemia, stomach cancer, pancreatic cancer, breast cancer, non-Hodgkin's lymphoma, Hodgkin's disease, brain tumors, lung tumors, and tumors of the tear duct.

68. Respiratory effects of EtO exposure include mucous membrane irritation, bronchitis, pulmonary edema, and emphysema.

69. Neurological effects of EtO exposure include headache, nausea, vomiting, peripheral neuropathy, impaired hand-eye coordination, memory loss, loss of balance, lethargy, numbness and weakness of the extremities, and brain lesions.

70. Fetuses in the womb are also exposed to EtO through their mothers. Animal studies of EtO exposure demonstrate that embryo and fetal toxicity, including increased incidence of resorption, reduced fetal body weight and length, and reduced skeletal ossification of the skull and sternebrae.

71. Other adverse reproductive effects of EtO exposure include decreased implantation rates, decreased testicular weights and testicular degeneration, and interference with sperm concentration, motility and drive range.

72. EtO is also genotoxic. The DNA-damaging properties of EtO have been studied for decades. It is known to be mutagenic in many organisms, from bacteriophage to mammals, and induces chromosome damage.

73. Studies of peripheral blood lymphocytes resulted in detection of chromosomal aberrations including breaks, gaps, and exchanges and supernumerary chromosomes, and other

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studies report increased incidence of SCE (sister chromatid exchange) in the peripheral lymphocytes of exposed workers and animals, which appears to be a permanent interference with the exposed organism's genetic information.

74. EtO is highly carcinogenic. The National Toxicology Program has, since 2000, recognized EtO as a known human carcinogen, and as a likely human carcinogen since 1985.

75. The WHO categorizes EtO as "carcinogenic to humans" and has acknowledged there is "strong evidence that the carcinogenicity of ethylene oxide … operates by a genotoxic mechanism."

76. According to EPA, EtO "is carcinogenic in mice and rats, inducing tumors of the lymphohematopoietic system, brain, lung, connective tissue, uterus, and mammary gland." In humans, "there is strong evidence of an increased risk of cancer of the lymphohematopoietic system and of breast cancer in females."

77. One large epidemiologic study of sterilizer workers, conducted by the NIOSH and published in 1991 in the *New England Journal of Medicine*, reported positive exposure-response trends for lymphohematopoietic cancer mortality, primarily in men and particularly for lymphoid cancer (non-Hodgkin lymphoma, myeloma, and lymphocytic leukemia) and for breast cancer mortality in women.

78. EPA characterizes EtO as "'carcinogenic to humans' by the inhalation route of exposure based on the total weight of the evidence."

79. This characterization is based on strong epidemiological evidence, extensive evidence of carcinogenicity in laboratory animals, clear evidence of genotoxicity and sufficient evidence to support a mutagenic mode of action for EtO carcinogenicity, and strong evidence that

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the key precursor events are anticipated to occur in humans and progress to tumors, including evidence of chromosome damage in humans exposed to EtO.

80. EPA classifies its confidence level in characterizing EtO as a carcinogen to humans by the inhalation route as "high."

81. EPA's conclusion that EtO is carcinogenic to humans (as distinguished from being potentially carcinogenic to humans) was announced in late 2016, as detailed further below, in connection with the 2016 IRIS Evaluation.

82. The 2016 IRIS Evaluation was an EPA program to assess the carcinogenicity of EtO. The Evaluation found that EtO is carcinogenic to humans and, in particular, that EtO is a mutagenic carcinogen that causes cancer by damaging DNA in cells, which is then duplicated when the cells divide.

83. As explained in the 2016 IRIS Evaluation, EtO exposure increases the cancer risk because DNA damage can take place with each and every exposure that is passed on to more cells, thereby increasing the number of mutated cells.

84. Based on these findings, EPA increased its inhalation risk estimate for EtO by a factor of about 30.

85. The EPA IUR (inhalation unit risk), developed in conjunction with the 2016 IRIS Evaluation, is .03 ug/m^3 (micrograms per cubic meter).

86. Exposure to EtO concentrations above the IUR threshold represents an increase in cancer risk.

B. DEFENDANTS KNEW ETO WAS A DANGEROUS POLLUTANT

87. The Santa Teresa Plant opened and began using and emitting EtO in or around 1989.

88. Over a decade earlier, in August 1977, the NIOSH issued a "Special Occupational Hazard Review with Control Recommendations for Use of Ethylene Oxide as a Sterilant in Medical Facilities."

89. The NIOSH review advised EtO users that "[r]ecent results of tests for mutagenesis have increased the concern for potential health hazards associated with exposure to EtO."

90. The review noted that "acute toxic effects of EtO in man and animals include acute respiratory and eye irritation, skin sensitization, vomiting, and diarrhea. Known chronic effects consist of respiratory irritation and secondary respiratory infection, anemia, and altered behavior."

91. Although data was limited at the time, the review further advised of the potential for carcinogenicity of EtO due to its ability to alter the structure of genetic material.

92. "[T]he alkylating and mutagenic properties of EtO are sufficient bases for concern about its potential carcinogenicity," according to NIOSH in 1977. Accordingly, NIOSH recommended that EtO be considered as "mutagenic and potentially carcinogenic to humans."

93. NIOSH recommended reducing or eliminating use of EtO for medical sterilization purposes, where alternative processes exist, to protect human health.

94. NIOSH's 1977 review identified a variety of deficiencies in sterilization facilities using EtO, including "improper or inadequate ventilation" and "poor design of the sterilization facility," among others. The review further notes that "[w]hen proper control measures are instituted, the escape of EtO into the environment will be greatly reduced."

95. NIOSH published a document entitled "Ethylene Oxide (EtO): Evidence of Carcinogenicity" in 1981, concluding that EtO should be considered a potential occupational carcinogen.

96. EtO was designated as a likely human carcinogen by the National Toxicology Program in 1985, and as a known human carcinogen by the State of California in 1987.

97. Defendants operated at least two facilities using EtO in their sterilization processes in the State of California in 1987. Accordingly, Defendants were aware that the chemical was being regulated as a carcinogen in that state before opening the Santa Teresa Plant in 1989.

98. The large, well-validated NIOSH epidemiologic study of sterilizer workers, which appeared in the *New England Journal of Medicine* and was subsequently relied upon by EPA, was published in 1991. That study examined health effects of EtO exposure in 18,254 sterilization workers in the United States, including Sterigenics workers.

99. Studies published in 2003 and 2004 by the same authors confirmed certain findings detected in the 1991 study, including that EtO exposure was associated with breast cancer in women and with hematopoietic cancer in men, with greater incidences of each positively associated with increased EtO exposure.

100. In an effort to rebut these studies and their regulatory impact, Sterigenics' Senior Vice President of Global Environmental Health & Safety, Kathleen Hoffman, issued a letter dated November 12, 2014, directed to the Science Advisory Board (SAB) of EPA.

101. In the letter, Ms. Hoffman claims that increased regulation of EtO sterilization processes would disrupt healthcare and medical device supply chains, and impose significant costs on companies in those supply chains. The letter expressly challenges the NIOSH studies referenced above because they incorporate data from workers subjected to workplace controls that have evolved over time.

102. In other words, the basis for Sterigenics' opposition to EPA's reliance on the NIOSH studies is that companies like Sterigenics have gradually reduced worker exposure to EtO,

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as required by a series of revised exposure limits issued by scientific and regulatory bodies over the past 6 decades—not that the study is inaccurate or invalid, and not that its consequences for environmental and public health regulatory purposes have been misunderstood.

103. EPA rejected Sterigenics' entreaties and cemented its reliance on the NIOSH studies in 2016, confirming that EtO is a human carcinogen by the inhalation exposure route, as described above.

104. As regulators increased their scrutiny of EtO and EtO emitters (and Sterigenics in particular) after 2016, Sterigenics continued to push back, claiming that increased regulations will result in supply chain disruptions in the healthcare and medical device industries. In light of these arguments, EPA asked the U.S. Food & Drug Administration ("FDA") to express its views on the matter.

105. In a letter dated February 5, 2020, Jeffrey Shuren, director of the FDA's Center for Devices and Radiological Health, confirmed that, in FDA's view, "EPA should establish EtO emissions limits based on the levels necessary to protect human health and the environment from EtO toxicity."

106. Dr. Shuren's letter notes that "FDA looks to EPA to set allowable limits for EtO emissions since FDA does not have the authority to do so. Contract sterilizers and medical device manufacturers must comply with the EtO standards and guidelines that EPA sets and FDA is committed to working with these entities to reduce the amount of EtO used and to explore the use of alternatives as appropriate. If a facility is unable to meet EPA emissions limits and its inability to do so could lead to product availability concerns, FDA will work with the facility and other entities in the supply chain to mitigate these concerns."

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107. Accordingly, Dr. Shuren's letter confirms that Sterigenics' supply chain disruption narrative is faulty, because FDA has committed to working with sterilizers and medical device companies to ensure emissions controls do not pose a threat to product availability.

C. DEFENDANTS' RELEASES OF ETO FROM THE SANTA TERESA PLANT SINCE 1989

108. The Santa Teresa Plant is a 105,000 square foot facility located in a business park in Santa Teresa, six miles from New Mexico's border with Mexico.

109. The Plant is located approximately 2 miles from schools, churches, and neighborhoods in Santa Teresa, home to thousands of residents, and situated among dozens of other businesses and workplaces employing over a thousand New Mexico residents.

110. From 1989 to the present, hundreds of thousands of pounds, or more, of EtO used at the Santa Teresa Plant to sterilize and/or fumigate products and devices were released into the air following the sterilization and/or fumigation process.

111. Defendants issued voluntary annual reports of EtO emissions from the Santa Teresa Plant covering the years 1994 to 2016. From 2017 onward, Defendants have declined to release such disclosures.

112. The reports that were made dramatically understate the actual EtO emissions from this facility.

113. Defendants' self-reported EtO air emissions from the Santa Teresa Plant, for the years 1994 to 2016, are as follows:

a. 1994: 250 lbs.

b. 1995: 300 lbs.

c. 1996: 640 lbs.

d. 1997: 1,100 lbs.

e. 1998: 5,970 lbs.

f. 1999: 5,318 lbs.

g. 2000: 4,675 lbs.

h. 2001: 5,044 lbs.

i. 2002: 5,026 lbs.

j. 2003: 6,752 lbs.

k. 2004: 7,123 lbs.

l. 2005: 11,756 lbs.

m. 2006: 14,759 lbs.

n. 2007: 14,022 lbs.

o. 2008: 15,439 lbs.

p. 2009: 11,485 lbs.

q. 2010: 12,421 lbs.

r. 2011: 13,068 lbs.

s. 2012: 12,362 lbs.

t. 2013: 10,082 lbs.

u. 2014: 5,761 lbs.

v. 2015: 1,003 lbs.

w. 2016: 967 lbs.

114. Notably, for the self-reported quantities set forth above, Defendants assumed very low amounts of uncontrolled or fugitive emissions of EtO (approximately 500 lbs. per year).

115. In fact, however, Defendants' routine operational and maintenance practices resulted in significant unreported, uncontrolled EtO emissions.

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116. As Defendants' own toxic release reports indicate, the Santa Teresa Plant processed and handled hundreds of thousands, and frequently over one million, pounds of EtO each year. A substantial portion of this volume was released into air through uncontrolled or fugitive releases that Defendants failed to report.

117. Indeed, prior to 2014, when Defendants rerouted nine of the sterilization back vents through the Plant oxidizer to reduce emissions from this part of the facility, all nine back vents resulted in uncontrolled emissions of EtO directly into the atmosphere.

118. According to a former Sterigenics employee, who had responsibility for loading sterilized equipment for shipping from the Santa Teresa Plant to customers, Defendants demonstrated a lack of concern for EtO emissions from the Plant in a variety of ways.

119. For example, the facility is equipped with a color-coded air quality monitoring system that indicates to employees whether the concentration of EtO in ambient air is hazardous—red, yellow, and green, indicating respectively that EtO levels are unsafe, potentially unsafe, or safe. Beginning at least as of 2008, and likely earlier, Defendants caused facility shipping bays and large doors at the Plant to be left ajar for hours, or entire days, when EtO levels were unsafe or potentially unsafe so that the gas would dissipate and escape the facility into the surrounding air, returning the monitors to "green" status.

120. Employees at the Plant were also expected to continue working even if the air quality monitoring system indicated that the levels of EtO within the facility were of concern.

121. Another former Sterigenics employee, who had responsibility for custodial services at the Plant, also indicated that as of at least 2009, and likely earlier, Defendants caused facility shipping bays and large doors to be left ajar for long periods of time when EtO levels were too high, in order to allow the pollutant to escape.

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122. That former employee further indicated that as part of his normal job duties, and beginning at least as of 2009, he had to hose down sterilization equipment on an at least monthly basis, and allow the "chamber scum" containing EtO and ethylene glycol residue to be freely washed down the drain.

123. A former Sterigenics employee also indicated that the Plant performed "favors" for other Sterigenics plants, including the San Diego facility. On an approximately weekly basis, during at least the period of 2009-2012, the San Diego facility shipped a load of sterilized equipment to the Santa Teresa Plant to aerate (and thus off-gas EtO) for a period of 24 hours.

124. As these shipments had been sterilized using EtO, but not aerated, they were off-gassing EtO during the shipping, receiving, and loading phases, including at the Santa Teresa Plant.

125. EtO emanating from the Santa Teresa Plant—whether from controlled or uncontrolled venting, stacks fitted with scrubbers and other control technologies, or uncontrolled sources such as facility doors and shipping bays, or unaerated equipment in transit—drifted from the Airport Road facility into the immediately surrounding business park and the residential communities in Santa Teresa only two miles away, and beyond.

126. As explained below, these significant emissions over a long period of time have caused a statistically significant increase in cancer risk for Santa Teresa residents.

D. DEFENDANTS' ETO RELEASES HAVE INJURED NEW MEXICO AND INCREASED THE RISK OF ADVERSE HEALTH EFFECTS IN SURROUNDING COMMUNITIES

127. In August 2018, EPA published results from its 2014 National Air Toxics Assessment study (NATA, as defined above).

128. The NATA study shows that Doña Ana County residents in the census tract likely suffering the most exposure to EtO have a cancer risk of **214.5543 per 1 million**, which is far in excess of the national average (approximately 30 per 1 million).

129. Crucially, the NATA study published in 2018 focuses on *reported EtO emissions from 2014*.

130. As alleged above, according to Defendants' self-reported emissions data, the Santa Teresa Plant released 5,761 pounds of EtO in 2014—down from over 10,000 pounds in 2013, over 12,000 pounds in 2012, and over 13,000 pounds in 2011. Further still, these reported figures do not account in any way for the uncontrolled emissions alleged above.

131. Accordingly, the 2014 data on which the cancer risk estimate is based drastically understates the actual risk in the Doña Ana County area when pre-2014 emissions levels, and unreported, uncontrolled emissions at any time, are taken into account.

132. Even setting these substantial limitations aside, the NATA study presents cause for concern.

133. The NATA study furnishes the following material facts:

a. The only point source of EtO emissions in the Santa Teresa area is the Santa Teresa Plant;

b. In 2014, the Santa Teresa Plant released at least 2.8805 tons of EtO into air (equivalent to 5,761 lbs.)—the amount reported by Defendants;

c. On a *statewide* basis, New Mexico residents have a total cancer risk (based on air emissions exposure) of 24.2145 per 1 million, which is less than the national average;

d. The 5,842 residents of census tract 35013001701, which includes Santa Teresa, have a total cancer risk (based on air emissions exposure) of 214.5543 per 1 million—*nearly ten times the statewide risk level*;

e. That census tract has a higher total cancer risk (based on air emissions exposure) than any other census tract in New Mexico;

f. Ethylene oxide emissions account for virtually all of the increased cancer risk in that census tract;

g. Residents of nearby census tracts within Doña Ana County, including 35013000600 (2,801 residents), 35013001703 (3,029 residents), 35013001705 (3,192 residents), 35013001706 (3,749 residents), 35013001707 (5,749 residents), and 35013001805 (3,958 residents), and the County-level tract (35013000000), suffer elevated total cancer risk (based on air emissions exposure), due principally to EtO emissions in the region.

134. All told, the 2014 NATA study confirms that all of the residents of Doña Ana County, New Mexico (218,195 residents as of the filing of this Complaint) suffer an increased cancer risk as a result of toxic EtO emissions from the Santa Teresa Plant—and this estimate is based on substantially reduced 2014 EtO emissions, failing to account for far higher pre-2014 emissions and for unreported, uncontrolled emissions.

135. In addition to the 2014 NATA data based on self-reported emissions from the Santa Teresa Plant, the State conducted a presuit investigation that discovered alarming levels of EtO present in the ambient outdoor air in a four-mile area surrounding the facility.

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136. This investigation included the collection and laboratory analysis of nineteen air samples. Every sample collected within the four-mile area around the Santa Teresa Plant revealed concentrations of EtO far in excess of the EPA IUR level.

137. As described above, these testing results demonstrate the presence of EtO in the Santa Teresa community's ambient air at up to **96 times the EPA's IUR cancer risk level.**

138. Defendants' conduct has injured the State and the New Mexico public in several ways.

139. First, Defendants have significantly impaired the air quality in Doña Ana County since 1989, resulting in increased public health risks.

140. Next, the Santa Teresa Plant's EtO emissions have diminished property values in the affected communities, including the census tracts identified above.

141. Further, because the Santa Teresa Plant's EtO emissions have significantly increased the cancer risk of New Mexico residents residing in census tracts near the facility, including those tracts identified above, Defendants' practices result in increased healthcare costs incurred or to be incurred by the State in connection with State-sponsored healthcare plans and programs.

142. Because Defendants' conduct has significantly increased thousands of New Mexico residents' risk of serious adverse health effects, Defendants must fund a public health monitoring program designed to detect, assess, and treat medical disorders associated with EtO exposure, under State supervision.

143. Because Defendants' conduct has created an imminent and substantial endangerment to the public, Defendants must immediately cease any and all uncontrolled emissions or releases of EtO from the Santa Teresa Plant, pending trial in this matter.

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E. DEFENDANTS' PERMITS DO NOT SHIELD THEM FROM LIABILITY

144. Defendants initiated construction of the Santa Teresa Plant in 1988 without a permit in violation of law.

145. Defendants received a permit in 1989 and sought, and obtained, various modifications to the original permit over time. These permits and permit modifications contained monitoring and reporting conditions, emission and environmental control parameters, and other terms that Defendants routinely violated.

146. During the initial permit application process and subsequent modification application processes, Defendants misrepresented or omitted material information from the New Mexico Environment Department and its predecessor agency.

147. Among other misrepresentations and omissions, Defendants:

a. Failed to disclose—at any time—that they would circumvent the required environmental controls by, e.g., purposefully or negligently leaving shipping bays and other large facility doors open for hours, or longer, to dissipate elevated levels of EtO in the Plant;

b. Failed to disclose—at any time—that they would not accurately monitor and report total EtO emissions from the Plant;

c. Misrepresented or failed to disclose in the initial permit application process, in the first quarter of 1989, that significant quantities of EtO would be released from the Plant's aeration cell operations, which would not be connected to or controlled by the Plant's Deoxx scrubber;

d. Supplied incomplete and misleading air quality modeling in the first and second quarters of 1989, and modeling that included assumptions known to the company

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to be inaccurate (e.g., that emissions would occur only during the same two fixed hours in any day);

e. Made changes to the Plant's physical design after submitting permit applications in 1989, including changes to stack height;

f. Misrepresented the viability or feasibility of continuous air emission monitoring technologies in 1989 and later;

g. Underreported EtO emissions after obtaining a permit in 1989 in order to avoid implementing further environmental controls and to support the company's request to construct additional chambers.

148. Even if Defendants had lawfully obtained air quality permits, made no misrepresentations or omissions during the approval and modification processes, and complied with all permit conditions—which, as alleged above, they did not—such permits would not relieve Defendants from the obligation to otherwise comply with State law, including Defendants' common-law duties to the State, the local community in and around Santa Teresa, and the New Mexico public in general.

149. As a result of practices alleged above, Defendants have released potentially dangerous quantities of EtO through controlled and uncontrolled means into the Santa Teresa and Dona Ana County regions, have violated permit conditions requiring all EtO emissions to pass through scrubbers and other environmental control technologies, and breached other material terms on a continuous basis, including emission monitoring and reporting obligations, and otherwise violated New Mexico common and statutory law.

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F. DEFENDANTS' UNFAIR OR DECEPTIVE REPRESENTATIONS

150. Defendants' revenue streams depend on obtaining contracts from equipment manufacturers, intermediaries, and equipment users for sterilization and fumigation services.

151. To obtain such contracts, Defendants seek to assure their clients and the public that their sterilization and fumigation practices are, among other things, environmentally sound and do not subject households proximate to their facilities to unreasonable risks of harm.

152. For example, in touting the "Sustainability" of its practices, the Sterigenics website, as of 2020, claims that "[w]e focus on continuous improvements and **eliminating risk to protect people, the environment, and property**."

153. Similarly, in their "Global Corporate Sustainability and Social Responsibility Report 2017," Defendants state, *inter alia*, that "[w]e are uncompromising in our commitment to health and well-being"; "[w]e are dedicated to protecting the environment and our communities"; and "[w]e focus on continuous improvement and eliminating risk to protect people, the environment and property."

154. Defendants have long promoted the environmental safety of their EtO sterilization and fumigation practices.

155. For example, the following statement, labeled "An Unwavering Commitment to Safety and the Environment," appeared on the Sterigenics website since at least August 2014 until at least February 2018:

> While our reach is global, our commitment to customers, employees and the communities in which we operate remains local. Safety and Quality pervade our business goals, as does our commitment to environmentally responsible business practices.
>
> Sterigenics has the following Safety and Environmental policies in place:
>
> …
>
> Environmental Policy:

> Good citizenship is a key value for Sterigenics. We are dedicated to protecting the community and environment in which we work and complying with all applicable environmental regulations.
>
> Sterigenics has a complete EH&S management system for the continuous improvement and compliance with all corporate and local environmental and safety requirements. This EH&S management system also meets ISO 14001 environmental and OSHAS 18001 safety standards. Sterigenics' facilities also utilize the latest engineering solutions for safety and environmental controls. Our key environmental and safety corporate metrics show continued improvements over the past 15 years of operations.
>
> In pursuit of establishing new, environmentally responsible best practices, Sterigenics continues to focus on and improve their Sustainability Program. This program focuses resources and investments to meet the dynamic and evolving needs of our customers, while reducing our impacts on the environment. We strive to meet customers' needs and the vibrant growth of the global communities we serve.
>
> At Sterigenics, we wouldn't have it any other way.

156. These and similar representations were made for the purpose of assuring Defendants' customers and the public that Defendants' operations are adequately protective of human health and the environment.

157. Such representations were unfair and/or deceptive because Defendants knowingly failed to adequately control their EtO emissions from the Santa Teresa Plant and caused injury to New Mexico and residents situated in proximity to the Plant, resulting in, among other things, a significantly increased risk of cancer for such residents.

158. Defendants' statements were also unfair and/or deceptive because they knowingly failed to disclose Defendants' failures to adequately control their EtO emissions from the Santa Teresa Plant, and indeed their purposeful subversion of environmental controls at the Plant, and that Defendants' conduct caused injury to New Mexico and residents situated in proximity to the Plant, resulting in, among other things, a significantly increased risk of cancer for such residents.

V. CAUSES OF ACTION

FIRST CAUSE OF ACTION
PUBLIC NUISANCE

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159. New Mexico realleges and incorporates the allegations set forth in paragraphs 1 through 158 as if fully stated herein.

160. New Mexico asserts this cause of action based on its inherent *parens patriae* authority.

161. Defendants emitted, discharged, or otherwise released toxic contaminants, including EtO, from the Santa Teresa Plant from 1989 to the present, and continue to do so, in a manner that created or participated in the creation of a public nuisance that is harmful to human and environmental health and obstructs the free use of New Mexico natural resources.

162. Defendants intentionally emitted, discharged, or otherwise released unsafe amounts of toxic contaminants, including EtO, from the Santa Teresa Plant since 1989, with the knowledge that they were causing and would continue to cause environmental contamination and threaten or impair public health.

163. Defendants' conduct and the presence of EtO annoys, injures, and endangers the comfort, repose, health, and safety of others.

164. Defendants' conduct and the presence of EtO interferes with and obstructs the public's free use and comfortable enjoyment of New Mexico natural resources.

165. Defendants' conduct and the presence of EtO in New Mexico natural resources are injurious to human and environmental health.

166. An ordinary person would be reasonably annoyed or disturbed by the presence of toxic EtO that endangers human health, and degrades air quality.

167. The seriousness of the risks created by this conduct far outweighs any social utility of Defendants' conduct.

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168. The rights, interests, and inconvenience to New Mexico and the general public far outweighs the rights, interests, and inconvenience to Defendants, who profited significantly from the use of EtO for decades.

169. Defendants' conduct caused harm to the State and its citizens.

170. New Mexico has been damaged by Defendants' conduct, including Defendants' unreported, uncontrolled EtO emissions.

171. The State is incurring and will continue to incur costs and losses as a result of Defendants' conduct.

172. Defendants' conduct and the public nuisance they have created has also caused property values in the affected census tracts to decline.

173. Defendants knew their conduct in emitting, discharging, or otherwise releasing toxic EtO would cause such injuries to the State and the New Mexico public.

174. Accordingly, Defendants had a duty to cease such conduct but failed to do so.

175. Defendants also had a duty to warn about the dangers of EtO, but failed to do so.

176. As a direct and proximate result of Defendants' creation of a public nuisance, New Mexico has suffered and will suffer monetary losses, including increased past and future healthcare costs, and other damages in amounts to be proven at trial.

177. To abate the public nuisance, the State seeks an order requiring Defendants to fund a public health monitoring program designed to detect, assess, and treat medical disorders associated with EtO exposure, under State supervision.

178. Because Defendants' conduct as alleged herein was malicious, willful, reckless, and/or wanton, the State is entitled to seek, and does seek, punitive damages sufficient to punish Defendants and to deter Defendants and others from engaging in similar conduct in the future.

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SECOND CAUSE OF ACTION
VIOLATIONS OF THE NEW MEXICO PUBLIC NUISANCE STATUTE, NMSA 1978 §§ 30-8-1, *ET SEQ.*

179. New Mexico realleges and incorporates the allegations set forth in paragraphs 1 through 178 as if fully stated herein.

180. New Mexico asserts this cause of action based on its inherent *parens patriae* authority.

181. New Mexico asserts this cause of action pursuant to NMSA 1978 §§ 30-8-1, *et seq.* (the Public Nuisance Statute, as defined above).

182. The Public Nuisance Statute renders unlawful "knowingly creating, performing or maintaining anything affecting any number of citizens without lawful authority which is either (A) injurious to public health, safety, morals or welfare; or (B) interferes with the exercise and enjoyment of public rights[.]" NMSA 1978 § 30-8-1(A)-(B).

183. The Attorney General is authorized to enforce the Public Nuisance Statute in court by seeking abatement from "any person, corporation or association of persons who shall create, perform or maintain a public nuisance." NMSA 1978 § 30-8-8.

184. Defendants have knowingly created, performed, or maintained a public nuisance injurious to public health, safety, and welfare, which interferes with the New Mexico public's right to avoid dangerous, carcinogenic substances in natural resources.

185. Defendants emitted, discharged, or otherwise released toxic contaminants, including EtO, from the Santa Teresa Plant from 1989 to the present, and continue to do so, in a manner that created or participated in the creation of a public nuisance that is harmful to human and environmental health and obstructs the free use of New Mexico natural resources.

186. Defendants intentionally emitted, discharged, or otherwise released toxic contaminants, including EtO, from the Santa Teresa Plant since 1989, with the knowledge that

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they were causing and would continue to cause environmental contamination and threaten and impair public health.

187. Defendants' conduct and the presence of EtO annoys, injures, and endangers the comfort, repose, health, and safety of others.

188. Defendants' conduct and the presence of EtO interferes with and obstructs the public's free use and comfortable enjoyment of New Mexico natural resources.

189. Defendants' conduct and the presence of EtO in New Mexico natural resources are injurious to human and environmental health.

190. An ordinary person would be reasonably annoyed or disturbed by the presence of toxic EtO that endangers human health, and degrades air quality.

191. The seriousness of the risks created by this conduct far outweighs any social utility of Defendants' conduct.

192. The rights, interests, and inconvenience to New Mexico and the general public far outweighs the rights, interests, and inconvenience to Defendants, who profited significantly from the use of EtO for decades.

193. Defendants' conduct caused harm to the State and its citizens.

194. New Mexico has been damaged by Defendants' EtO emissions.

195. The State is incurring and will continue to incur costs and losses as a result of Defendants' conduct.

196. Defendants' conduct and the public nuisance they have created has also caused property values in the affected census tracts to decline.

197. Defendants knew their conduct in emitting, discharging, or otherwise releasing toxic EtO would cause such injuries to the State and the New Mexico public.

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198. Accordingly, Defendants had a duty to cease such conduct but failed to do so.

199. Defendants also had a duty to warn about the dangers of EtO, but failed to do so.

200. As a direct and proximate result of Defendants' creation of a public nuisance, New Mexico has suffered and will suffer monetary losses, including increased past and future healthcare costs, and other damages in amounts to be proven at trial.

201. To abate the public nuisance, the State seeks an order requiring Defendants to fund a public health monitoring program designed to detect, assess, and treat medical disorders associated with EtO exposure, under State supervision.

202. Because Defendants' conduct as alleged herein was malicious, willful, reckless, and/or wanton, the State is entitled to seek, and does seek, punitive damages sufficient to punish Defendants and to deter Defendants and others from engaging in similar conduct in the future.

THIRD CAUSE OF ACTION
STRICT LIABILITY

203. New Mexico realleges and incorporates the allegations set forth in paragraphs 1 through 202 as if fully stated herein.

204. New Mexico asserts this cause of action based on its inherent *parens patriae* authority.

205. Defendants' operation of the Santa Teresa Plant, including the handling, emission, discharge, and release of toxic EtO since 1989, is an ultahazardous and/or abnormally dangerous activity under New Mexico law.

206. Accordingly, Defendants are held to a heightened duty of care toward the public and those who may be injured due to Defendants' conduct, and are strictly liable for all injuries resulting from their handling, emission, discharge, or release of EtO from the Santa Teresa Plant.

207. Defendants' conduct caused harm to the State and its citizens.

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208. New Mexico suffered and continues to suffer damage from Defendants' handling, emission, discharge, and release of EtO.

209. The State is incurring and will continue to incur costs and losses as a result of Defendants' conduct.

210. Defendants' conduct and the ultrahazardous and/or abnormally dangerous activities in which they engaged have also caused property values in affected census tracts to decline.

211. As a direct and proximate result of Defendants' ultrahazardous and/or abnormally dangerous activities, New Mexico has suffered and continues to suffer monetary losses, including increased past and future healthcare costs, and other damages in amounts to be proven at trial.

212. Because Defendants' conduct as alleged herein was malicious, willful, reckless, and/or wanton, the State is entitled to seek, and does seek, punitive damages sufficient to punish Defendants and to deter Defendants and others from engaging in similar conduct in the future.

FOURTH CAUSE OF ACTION
NEGLIGENCE

213. New Mexico realleges and incorporates the allegations set forth in paragraphs 1 through 212 as if fully stated herein.

214. New Mexico asserts this cause of action based on its inherent *parens patriae* authority.

215. Defendants failed to exercise ordinary care because a reasonably careful company that knew or learned of the toxicity, carcinogenicity, harmfulness to humans, and harmfulness to the natural environment of chemicals being emitted, discharged, or otherwise released from its facility, in the manner and quantity that such emission, discharge, or release occurred at the Santa Teresa Plant, would not continue to emit, discharge, or release such chemicals in the same manner

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or quantity, would warn of the hazards introduced as a result, and at a minimum would take steps to enhance the safety of its operations as soon as possible.

216. Defendants failed to exercise ordinary care because a reasonably careful company would not continue to use EtO in mass quantities and to the extent that Defendants used and emitted, discharged, or otherwise released EtO, and would at an absolute minimum ensure that all appropriate environmental safeguards and controls were effective and in working order.

217. Defendants were grossly negligent because they failed to exercise even slight care, placing revenue and profit generation above human and environmental health and safety.

218. Defendants owed the State and its citizens a duty of care in the operation of the Santa Teresa Plant, and the use and disposal of toxic chemicals including EtO.

219. It was foreseeable to Defendants that their controlled and uncontrolled EtO emissions would end up in New Mexico's environment and result in harmful exposure of New Mexico residents in nearby workplaces and residential communities.

220. Defendants' negligent conduct and the presence of EtO in New Mexico natural resources caused injury to the physical and economic health and well-being of New Mexico citizens.

221. As a direct and proximate result of Defendants' negligent conduct, New Mexico has suffered and continues to suffer monetary losses, including increased past and future healthcare costs, and other damages in amounts to be proven at trial.

222. Because Defendants' conduct as alleged herein was malicious, willful, reckless, and/or wanton, the State is entitled to seek, and does seek, punitive damages sufficient to punish Defendants and to deter Defendants and others from engaging in similar conduct in the future.

FIFTH CAUSE OF ACTION
TEMPORARY RESTRAINING ORDER AND PRELIMINARY INJUNCTION

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223. New Mexico realleges and incorporates the allegations set forth in paragraphs 1 through 222 as if fully stated herein.

224. Absent a temporary restraining order and preliminary injunction, the State will suffer immediate and irreparable injury, loss or damage.

225. Defendants, by their actions, have caused and continue to cause an unreasonable and substantial prejudice to the public health and welfare.

226. Defendants' uncontrolled emissions of EtO, a known carcinogen, into the atmosphere near residences and places of business in Santa Teresa injure or threaten to injure the health of people living and working near the Santa Teresa Plant, have caused fear in the community due to the threat to public health, and interfere with the enjoyment and use of their homes, work places, public places, and environment.

227. As a consequence of the conduct alleged herein, Defendants have created and maintained a public nuisance and breached their duties to the State and the public.

228. Due to the urgency of the facts presented in this Complaint, and the imminent and substantial endangerment suffered by the New Mexico public as a result of Defendants' conduct, the State is without an adequate remedy at law.

229. Absent a temporary restraining order and preliminary injunction requiring Defendants to immediately cease any and all uncontrolled emissions or releases of EtO from the Santa Teresa Plant, the State will be irreparably injured, and violations of the common and statutory law as outlined herein will continue unless and until this Court grants such temporary and preliminary relief and, after trial, permanent injunctive relief.

230. The threatened injury outweighs any damage the injunction might cause Defendants.

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231. There is a substantial likelihood the State will prevail on the merits of this case.

SIXTH CAUSE OF ACTION
VIOLATIONS OF NEW MEXICO UNFAIR PRACTICES ACT, 1978 NMSA §§ 57-12-1, *ET SEQ.*

232. New Mexico realleges and incorporates the allegations set forth in paragraphs 1 through 231 as if fully stated herein.

233. This is a claim for restitution and disgorgement, injunctive relief, and civil penalties under the Unfair Practices Act. NMSA 1978 §§ 57-12-1, *et seq.*

234. Under the Unfair Practices Act, "[u]nfair or deceptive trade practices and unconscionable trade practices in the conduct of any trade or commerce are unlawful." NMSA 1978 § 57-12-3.

235. An "unfair or deceptive trade practice" is an act "specifically declared unlawful pursuant to the Unfair Practices Act, a false or misleading oral or written statement, visual description or other representation of any kind knowingly made in connection with the sale, lease, rental or loan of goods or services … by a person in the regular course of his trade or commerce, which may, tends to or does deceive or mislead any person[.]" NMSA 1978 § 57-12-2(D). Omissions of material information are actionable under the Unfair Practices Act.

236. Unfair or deceptive trade practices include, *inter alia*, representing that services have "characteristics, … uses, [or] benefits … that they do not have"; that services "are of a particular standard, quality or grade … if they are of another"; and "using exaggeration, innuendo or ambiguity as to a material fact or failing to state a material fact if doing so deceives or tends to deceive." NMSA 1978 §§ 57-12-2(D)(5), (7), (14).

237. By representing the environmental soundness of their EtO utilization and industrial sterilization and fumigation practices using EtO, Defendants made unfair and/or deceptive representations in violation of the Unfair Practices Act.

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238. Similarly, by representing the level and degree of risk to human health associated with their EtO utilization and industrial sterilization and fumigation practices using EtO, Defendants made unfair and/or deceptive representations in violation of the Unfair Practices Act.

239. As alleged above, Defendants' various environmental and human health representations—as made to the State and State employees, and as made to Defendants' customers and clients and the public—were unfair and/or deceptive because Defendants knowingly failed to adequately control their EtO emissions from the Santa Teresa Plant and caused injury to New Mexico and residents situated in proximity to the Plant, resulting in, among other things, a significantly increased risk of cancer for such residents.

240. Defendants' statements were also knowingly unfair and/or deceptive because they failed to disclose Defendants' failures to adequately control their EtO emissions from the Santa Teresa Plant and that Defendants' conduct caused injury to New Mexico and residents situated in proximity to the Plant, resulting in, among other things, a significantly increased risk of cancer for such residents.

241. Accordingly, Defendants knowingly misrepresented that their EtO sterilization and fumigation services had characteristics, uses, or benefits that they did not, in fact, possess (namely, environmental and human health protection); misrepresented that those services were of a particular standard, quality or grade (namely, protective of environmental and human health) when, in fact, they were not; and failed to state that those services would expose New Mexico communities to dangerous levels of EtO or to adverse health effects associated with EtO exposure, including cancer, in violation of the Unfair Practices Act.

242. Each unfair or deceptive trade practice alleged herein was carried out knowingly and willfully because Defendants were actually aware that their EtO sterilization and fumigation

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services posed unreasonable dangers to the environment and residents in proximity to the Santa Teresa Plant, and/or in the exercise of reasonable diligence, Defendants should have been aware that their statements were unfair and/or deceptive for those reasons.

243. Defendants' unfair or deceptive representations and omissions as alleged herein are of the type that tended to deceive and/or mislead Defendants' customers or clients, as well as New Mexico and residents of New Mexico, that Defendants' EtO sterilization and fumigation services were safe for the environment and human health.

244. The State of New Mexico seeks restitution and disgorgement under NMSA 1978 § 57-12-8(B); injunctive relief adequate to remedy Defendants' violations of the Unfair Practices Act, including an order requiring Defendants to fund a public health monitoring program designed to detect, assess, and treat medical disorders associated with EtO exposure, under NMSA 1978 § 57-12-8(B); and all recoverable penalties under NMSA 1978 § 57-12-11.

JURY DEMAND

New Mexico respectfully requests trial by jury on all claims so triable.

PRAYER FOR RELIEF

New Mexico prays for judgment against Defendants, jointly and severally, as follows:

A. Damages according to proof;

B. Declaratory relief, including an order declaring that the conduct alleged herein has violated New Mexico law;

C. Temporary and preliminary injunctive relief pending trial, including a temporary restraining order and preliminary injunction requiring Defendants to immediately cease any and all uncontrolled emissions or releases of EtO from the Santa Teresa Plant, and a permanent injunction upon conclusion of trial, including an Order prohibiting Defendants from causing,

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making, facilitating, or otherwise allowing any uncontrolled emission or release of EtO from the Santa Teresa Plant, including, but not limited to:

1. Leaving facility doors, shipping bays, or other means of egress open when not in use;
2. Leaving sterilization chamber doors, aeration room doors, and other interior doors open when not in use;
3. Allowing off-gassing associated with the storing, transporting, or handling of EtO prior to charging of sterilization chambers;
4. Allowing the off-gassing of EtO from under-controlled aeration rooms, from transfer of sterilized product from sterilizer chambers to aeration rooms, and from sterilized product removed from aeration rooms; and
5. Allowing any EtO to escape through pipes, equipment, vents, stacks, or other point sources prior to filtration or processing through fully functioning emission controls.

D. Further injunctive relief, including the award of past, present, and future costs to fully abate the public nuisance and an order requiring Defendants to fund a public health monitoring program designed to detect, assess, and treat medical disorders associated with EtO exposure;

E. An order requiring Defendants to disgorge all revenues obtained as a result of violations of the Unfair Practices Act, and to make restitution to all persons of money, property, or other things received from them in any transaction related to Defendants' violations of the Unfair Practices Act;

F. Civil penalties of $5,000 per willful violation of the Unfair Practices Act;

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G. Award of punitive damages sufficient to punish Defendants for malicious, willful, reckless, and/or wanton misconduct and to deter Defendants and others from engaging in similar misconduct in the future;

H. Litigation costs and attorneys' fees as permitted by law;

I. Pre-judgment and post-judgment interest on all monies awarded, as permitted by law;

J. Such other and further relief as the Court deems just and proper.

DATED: December 22, 2020

HECTOR H. BALDERAS,
ATTORNEY GENERAL

/s/ Jacqueline N. Ortiz
P. Cholla Khoury
Jacqueline Ortiz
Assistant Attorneys General
P.O. Drawer 1508
Santa Fe, New Mexico 87504-1508
505-717-3500 - voice
505-222-9033 - facsimile
ckhoury@nmag.gov
jortiz@nmag.gov
Attorneys for Plaintiff

ED_013218_00000022-00043

Message

From: Koerber, Mike [Koerber.Mike@epa.gov]
Sent: 7/27/2020 1:40:28 PM
To: Davis, Alison [Davis.Alison@epa.gov]
Subject: RE: Draft OIG Follow-up Response

Thank you, Alison

From: Davis, Alison <Davis.Alison@epa.gov>
Sent: Monday, July 27, 2020 9:27 AM
To: Koerber, Mike <Koerber.Mike@epa.gov>
Subject: RE: Draft OIG Follow-up Response

Please see attached

From: Koerber, Mike <Koerber.Mike@epa.gov>
Sent: Friday, July 24, 2020 9:23 AM
To: Davis, Alison <Davis.Alison@epa.gov>
Cc: Koerber, Mike <Koerber.Mike@epa.gov>
Subject: FW: Draft OIG Follow-up Response

Alison: Here's something else to talk about this morning – a draft response to the OIG on the Management Alert. I'm still waiting to hear back from Region 6 on what deadlines they are comfortable with, so the dates in red below are placeholders.

Mike

Renee: My thanks to Sean, Katie, you and your team for the meeting on Monday, July 20 and our conversation on Tuesday, July 21. As follow-up, I wish to offer the following:

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Message

From: Koerber, Mike [Koerber.Mike@epa.gov]
Sent: 7/27/2020 8:46:54 PM
To: Wilson, Holly [Wilson.Holly@epa.gov]; Terry, Sara [Terry.Sara@epa.gov]; Davis, Alison [Davis.Alison@epa.gov]
CC: Lavoie, Tegan [lavoie.tegan@epa.gov]
Subject: RE: EtO Outreach Activities
Attachments: Edits to Draft response 7.27.2020 MK.docx; Response.Ethylene Oxide.5.15.2020.pdf

Ex. 5 Deliberative Process (DP)

-----Original Appointment-----
From: Koerber, Mike
Sent: Tuesday, July 21, 2020 3:44 PM
To: Koerber, Mike; Wilson, Holly; Terry, Sara; Davis, Alison
Cc: Lavoie, Tegan
Subject: EtO Outreach Activities
When: Thursday, July 23, 2020 12:00 PM-12:30 PM (UTC-05:00) Eastern Time (US & Canada).
Where: Conference Line: 919-541-4105

Message

From: Koerber, Mike [Koerber.Mike@epa.gov]
Sent: 8/23/2020 6:41:35 PM
To: Benevento, Douglas [benevento.douglas@epa.gov]; Grantham, Nancy [Grantham.Nancy@epa.gov]; Voyles, Travis [Voyles.Travis@epa.gov]; Hoverman, Taylor [hoverman.taylor@epa.gov]; Landeene, Sarah [Landeene.Sarah@epa.gov]; Idsal, Anne [idsal.anne@epa.gov]; Harlow, David [harlow.david@epa.gov]
CC: Gunasekara, Mandy [gunasekara.Mandy@epa.gov]; Davis, Alison [Davis.Alison@epa.gov]
Subject: RE: Draft Letter re: EtO
Attachments: EtO Response to congressional letters MK.docx

Here are some edits. Note, many of these additions are taken in large part from prior communications back to the OIG. The Croda text at the end of the letter is courtesy of Region 3 comms.

Mike

From: Benevento, Douglas <benevento.douglas@epa.gov>
Sent: Sunday, August 23, 2020 12:26 PM
To: Koerber, Mike <Koerber.Mike@epa.gov>; Grantham, Nancy <Grantham.Nancy@epa.gov>; Voyles, Travis <Voyles.Travis@epa.gov>; Hoverman, Taylor <hoverman.taylor@epa.gov>; Landeene, Sarah <Landeene.Sarah@epa.gov>
Cc: Gunasekara, Mandy <gunasekara.Mandy@epa.gov>
Subject: RE: Draft Letter re: EtO

Attaches is a very rough draft letter for our discussion tomorrow. What I am trying to do is:

Ex. 5 Deliberative Process (DP)

Please review the letter for accuracy and I am certain grammar will need some work. If there is anything I left out let's discuss that tomorrow.

Thanks,

Doug

From: Koerber, Mike <Koerber.Mike@epa.gov>
Sent: Saturday, August 22, 2020 4:45 PM
To: Benevento, Douglas <benevento.douglas@epa.gov>; Grantham, Nancy <Grantham.Nancy@epa.gov>; Voyles, Travis <Voyles.Travis@epa.gov>; Hoverman, Taylor <hoverman.taylor@epa.gov>; Landeene, Sarah <Landeene.Sarah@epa.gov>
Cc: Gunasekara, Mandy <gunasekara.Mandy@epa.gov>
Subject: RE: Draft Letter re: EtO

Attached please find the requested timeline. (Note, the timeline focuses on interactions in 2020, but a few key dates from 2019 are included for completeness..) Please let me know if you have any questions.

Mike

From: Benevento, Douglas <benevento.douglas@epa.gov>
Sent: Saturday, August 22, 2020 1:58 PM
To: Koerber, Mike <Koerber.Mike@epa.gov>; Grantham, Nancy <Grantham.Nancy@epa.gov>; Voyles, Travis <Voyles.Travis@epa.gov>; Hoverman, Taylor <hoverman.taylor@epa.gov>; Landeene, Sarah <Landeene.Sarah@epa.gov>
Cc: Gunasekara, Mandy <gunasekara.Mandy@epa.gov>
Subject: FW: Draft Letter re: EtO

Sarah will you set up a call with this group and anyone else that needs to be involved to discuss our response.

Ex. 5 Deliberative Process (DP)

From: Voyles, Travis <Voyles.Travis@epa.gov>
Sent: Friday, August 21, 2020 9:43 PM
To: Benevento, Douglas <benevento.douglas@epa.gov>
Cc: Hoverman, Taylor <hoverman.taylor@epa.gov>; Grantham, Nancy <Grantham.Nancy@epa.gov>
Subject: FW: Draft Letter re: EtO

Hey Doug—

Here's the current version of the letter for your review. I think the questions/headers could be removed but we left them for now so you can see. Also attaching the Sen. Coons letter, the earlier Sen. Carper/Rep. Blunt Rochester letter, and a much early Illinois Dem. Delegation + Sen. Carper letter that all discuss the OIG report.

Let us know if you have any questions.

Travis Voyles
(202) 564-6399

From: Hoverman, Taylor <hoverman.taylor@epa.gov>
Sent: Friday, August 21, 2020 7:40 PM
To: Voyles, Travis <Voyles.Travis@epa.gov>
Cc: Grantham, Nancy <Grantham.Nancy@epa.gov>
Subject: Re: Draft Letter re: EtO

That would be super helpful. Thanks, Travis!

Taylor Meredith
202-494-3662

Sent from my iPhone. Please excuse typos or brevity.

> On Aug 21, 2020, at 6:31 PM, Voyles, Travis <Voyles.Travis@epa.gov> wrote:
>
> I could quickly put in a draft letter form if that works.
>
> Travis Voyles
> (202) 564-6399
>
> ---
>
> **From:** Hoverman, Taylor <hoverman.taylor@epa.gov>
> **Sent:** Friday, August 21, 2020 6:39 PM
> **To:** Grantham, Nancy <Grantham.Nancy@epa.gov>; Voyles, Travis <Voyles.Travis@epa.gov>
> **Subject:** Fwd: Draft Letter re: EtO
>
> Ready to send to Doug?
>
> Taylor Meredith
> 202-494-3662
>
> Sent from my iPhone. Please excuse typos or brevity.
>
> Begin forwarded message:
>
> > **From:** "Koerber, Mike" <Koerber.Mike@epa.gov>
> > **Date:** August 21, 2020 at 4:54:04 PM CDT
> > **To:** "Hoverman, Taylor" <hoverman.taylor@epa.gov>
> > **Cc:** "Idsal, Anne" <idsal.anne@epa.gov>, "Moor, Karl" <Moor.Karl@epa.gov>, "Harlow,

David" <harlow.david@epa.gov>
Subject: Draft Letter re: EtO

Here is the draft letter.

Mike

From: Hoverman, Taylor <hoverman.taylor@epa.gov>
Sent: Friday, August 21, 2020 1:44 PM
To: Koerber, Mike <Koerber.Mike@epa.gov>
Cc: Idsal, Anne <idsal.anne@epa.gov>; Moor, Karl <Moor.Karl@epa.gov>; Harlow, David <harlow.david@epa.gov>
Subject: Re: David - Please review

Thanks all! Please make sure it's in a letter response format.

Taylor Meredith
202-494-3662

Sent from my iPhone. Please excuse typos or brevity.

> On Aug 21, 2020, at 10:53 AM, Koerber, Mike <Koerber.Mike@epa.gov> wrote:
>
> Yep, working on it now. Will have a draft to you this afternoon.
>
> ---
>
> **From:** Idsal, Anne <idsal.anne@epa.gov>
> **Sent:** Friday, August 21, 2020 11:53 AM
> **To:** Hoverman, Taylor <hoverman.taylor@epa.gov>; Moor, Karl <Moor.Karl@epa.gov>; Koerber, Mike <Koerber.Mike@epa.gov>
> **Cc:** Harlow, David <harlow.david@epa.gov>
> **Subject:** RE: David - Please review
>
> Good morning Taylor and Mike,
>
> Thanks for the update Taylor. Mike, would you and Alison please work on getting short and sweet responses (2-3 sentences) worked up with David and Karl's assistance?
>
> Thanks,
> Anne
>
> ---
>
> **From:** Hoverman, Taylor <hoverman.taylor@epa.gov>
> **Sent:** Friday, August 21, 2020 11:49 AM
> **To:** Moor, Karl <Moor.Karl@epa.gov>; Koerber, Mike <Koerber.Mike@epa.gov>
> **Cc:** Idsal, Anne <idsal.anne@epa.gov>
> **Subject:** RE: David - Please review

Just hopped off the phone with Doug. He would like to review a draft response on his flight back tomorrow, so can OAR please aim for a first draft by COB today? Sorry for the quick turnaround.

Taylor Meredith
Senior Advisor to the Administrator
U.S. Environmental Protection Agency
C: 202-494-3662
O: 202-566-2705

From: Hoverman, Taylor
Sent: Friday, August 21, 2020 10:25 AM
To: Moor, Karl <Moor.Karl@epa.gov>; Koerber, Mike <Koerber.Mike@epa.gov>
Cc: Idsal, Anne <idsal.anne@epa.gov>
Subject: RE: David - Please review

Team OAR –

Thank you for the quick turnaround on these. Can the team go ahead and begin drafting a letter response that would answer these questions? I think this is going to be a quick turnaround with a goal of having a response ready to send early next week.

Please call me with any questions.

Thanks again for your help with this!

Taylor Meredith
Senior Advisor to the Administrator
U.S. Environmental Protection Agency
C: 202-494-3662
O: 202-566-2705

From: Moor, Karl <Moor.Karl@epa.gov>
Sent: Friday, August 21, 2020 8:30 AM
To: Koerber, Mike <Koerber.Mike@epa.gov>
Cc: Idsal, Anne <idsal.anne@epa.gov>; Hoverman, Taylor <hoverman.taylor@epa.gov>
Subject: Fwd: David - Please review

Mike, sorry, I did not convey the timeline clearly yesterday, my fault.

Regards, Karl

Begin forwarded message:

> **From:** "Hoverman, Taylor" <hoverman.taylor@epa.gov>
> **Date:** August 20, 2020 at 17:07:26 EDT
> **To:** "Moor, Karl" <Moor.Karl@epa.gov>
> **Cc:** "Idsal, Anne" <idsal.anne@epa.gov>
> **Subject: Re: David - Please review**

Hi Karl,

Doug just called me to check in on the status of this. As I mentioned earlier, he wants to see something today. How are you guys coming along? Remember this is just a list of questions at this point, not the responses.

Give me a call with any questions.

Taylor Meredith
202-494-3662

Sent from my iPhone. Please excuse typos or brevity.

Message

From: Robinson, Jeffrey [Robinson.Jeffrey@epa.gov]
Sent: 1/10/2020 6:59:47 PM
To: Davis, Alison [Davis.Alison@epa.gov]
CC: Verhalen, Frances [verhalen.frances@epa.gov]; Casso, Ruben [Casso.Ruben@epa.gov]; Garcia, David [Garcia.David@epa.gov]
Subject: FW: EtO work status and 2020 needs - checking in.
Attachments: DRAFT R6 EtO outreach update 011020 (002).docx

Alison,

Attached is EPA Region 6's response. Thanks for reaching out to David and sorry for the delay in getting you our response.

Jeff

From: Garcia, David <Garcia.David@epa.gov>
Sent: Friday, January 10, 2020 11:24 AM
To: Robinson, Jeffrey <Robinson.Jeffrey@epa.gov>; Verhalen, Frances <verhalen.frances@epa.gov>; Casso, Ruben <Casso.Ruben@epa.gov>
Subject: Re: EtO work status and 2020 needs - checking in.

Have you all started this by any chance?

Sent from my iPhone

> On Jan 10, 2020, at 11:13 AM, Garcia, David <Garcia.David@epa.gov> wrote:
>
> I overlooked this request, pls follow up as soon as you can.
>
> Sent from my iPhone
>
> Begin forwarded message:
>
> > **From:** "Davis, Alison" <Davis.Alison@epa.gov>
> > **Date:** January 10, 2020 at 8:03:08 AM CST
> > **To:** "Garcia, David" <Garcia.David@epa.gov>
> > **Subject: EtO work status and 2020 needs - checking in.**
> >
> > Hi David,
> >
> > Checking in on where you are with the Status and Needs requires we mentioned on our last call (I sent the template out on the 23rd). If I've missed what you sent, would you resend?

Thanks.
-Alison

Message

From: Garcia, David [Garcia.David@epa.gov]
Sent: 1/31/2020 8:25:56 PM
To: Davis, Alison [Davis.Alison@epa.gov]
Subject: RE: oops - one more

Looks good

David F. Garcia, P.E.
Director
Air and Radiation Division
Ph. 214 665 7593

U.S. EPA Region 6
1201 Elm Street
Dallas, Texas

From: Davis, Alison <Davis.Alison@epa.gov>
Sent: Friday, January 31, 2020 2:07 PM
To: Garcia, David <Garcia.David@epa.gov>
Subject: oops - one more

New Mexico

Sterigenics Santa Teresa Facility (sterilizer).

- While the 2014 NATA identified the Santa Teresa Facility in New Mexico as having elevated risk. NMED and Region 6 have since confirmed that the Santa Teresa Facility installed emissions controls in 2014 that which reduced ethylene oxide (EtO) emissions to less than a risk factor of 100 in 1 million.

Message

From: Haman, Patricia [Haman.Patricia@epa.gov]
Sent: 9/17/2020 7:31:17 PM
To: Davis, Alison [Davis.Alison@epa.gov]
Subject: FW: Johnson TX CEQ letter
Attachments: 2020-08-27 EPA-Hank Johnson (EtO).pdf; JohnsonETO.pdf

This is the TX CEQ letter I was talking about and here is a copy of the EtO letter which finally went out. I spoke to John Shoaf this afternoon and he is still checking in with ORD and the OAR IO leadership whether they want to consider this responsive and close out the incoming or whether they still would like to send a unique response. According to my notes, the draft response has been with ORD for over 6 weeks – maybe 8 weeks. John is still checking.

I realized the list for the EtO TF that we have is about 6 months old so I reached out to the staffer to see if anyone else has joined. It was not on the web. I will let you know what I hear back. Pat

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

August 27, 2020

OFFICE OF CONGRESSIONAL AND
INTERGOVERNMENTAL RELATIONS

The Honorable Hank Johnson
Member of Congress
Washington, D.C. 20515

Dear Representative Johnson:

On behalf of the U.S. Environmental Protection Agency, I am writing in response to various inquiries from Members of Congress regarding ethylene oxide (EtO) emissions and EPA's response to a recent EPA Office of Inspector General (OIG) report on this matter. As EPA pursues its mission to protect public health and the environment, addressing ethylene oxide is a major priority for the Agency. While the EPA recognizes and values the important role of the OIG, in the case of this EtO report their recommendation regarding risk communication and outreach is based upon a flawed understanding of the facts, data, and the Clean Air Act. Attempts by the Agency to address OIG's concerns have been met with only a misunderstanding of the issues by OIG. At this point, the Agency cannot responsibly concur with OIG's demands.

Given the interest shown by Congress in this matter, the Agency is setting the record straight on our efforts to undertake an impactful response to EtO emissions, respond to OIG's report, and to provide meaningful and appropriate risk communication to the American people with regard to EtO. Quite simply, the OIG is recommending that the Agency provide risk communication outreach with regard to EtO emissions to certain communities where there is not the sufficient scientific data to support effective and accurate communication. Accepting the OIG recommendation would put the EPA at odds with its core mission of protecting human health and the environment and would risk undermining the Agency's current efforts to ensure meaningful and appropriate risk communication to the American people. Despite repeated conversations with the OIG, there remains a failure by the OIG to understand EPA's concerns with undertaking any such action in the arbitrary timelines and methods being recommended.

Risk communication is of critical importance to the work EPA does across our many regions, offices, and programs. This is because our mission is to protect public health and the environment, and it is impossible to effectively and efficiently pursue that mission without communicating about risk to the American people. Over the past year EPA has continued to build on our risk communication capabilities, and we will continue to support our state and local partners in their efforts to share information with the public. The Agency is committed to improving our long term ability on risk communication, but regardless of the outcome of the process with the OIG, we have plans to do direct outreach to communities in the coming months once we have better data to target appropriately.

In order to provide meaningful and appropriate risk communication, it is important to understand why the OIG recommendations are based upon a flawed understanding of the facts, data, and the Clean Air Act. The Clean Air Act directs EPA to regulate air toxics, like EtO, by setting limits on the amount that

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industrial sources can *emit* to the air, rather than by setting *ambient standards*, which are limits on the amount of a pollutant that is allowed to be present in the outdoor air. After EPA sets emission standards, the Agency is then required to review them periodically, taking into consideration advancements in pollution control technology and evaluating the level of risk that may remain following the adoption of the initial emission standards. A risk level of 1-in-10,000 is one factor EPA uses in its risk reviews of air toxics to determine whether additional controls are necessary. However, this level is *not* a regulatory number or a bright line for determining whether a given level of risk is acceptable. Other health risk measures and information are also important when making a risk determination.

EPA considered this risk information in 2018 in the most recent update to the National Air Toxics Assessment (NATA). (Note, we refer to this version of NATA as the 2014 NATA because it uses emissions data for the year 2014, the most recent available at the time.) NATA is a non-regulatory preliminary screening tool that informs our local, state, and tribal partners of air toxics levels and potential risks in their jurisdictions. NATA only tells us where to look closer—it does not provide definitive, actionable risk information. The 2014 NATA used the EPA's Integrated Risk Information System (IRIS) cancer potency value updated in 2016 to make these estimates on air toxics levels and potential risks. When the results showed that EtO was more prevalent in communities than previously realized, EPA immediately began working with state and local jurisdictions to reduce emissions from EtO facilities through the following actions:

- EPA is conducting the required residual risk and technology review for a source category containing some chemical manufacturing facilities that emit EtO. The final revised emission standards imposed on these facilities will significantly lower the amount of EtO emitted by these facilities.
- EPA is undertaking a rulemaking to revise the emission standards for the commercial sterilizer source category that were first adopted in December 1994. For the approximately 100 commercial sterilizer facilities, work is currently underway on a new technology review. Approximately one-third of these facilities are small businesses, requiring the Agency to follow additional regulatory procedures such as consultation prior to issuing a proposed rule. Additionally, as part of this rulemaking, EPA is taking the unique step of evaluating the regulation of fugitive emissions, which we believe are a significant emission source. In order to do this, the Agency needed to collect information and establish a record that would support regulation. It is our goal to have a proposed regulation for interagency review in the fall.
- EPA is working with states to learn more about emissions from specific facilities, identify opportunities for early reduction, and further support and coordination on outreach to communities. When Congress promulgated the Clean Air Act, it found that "air pollution control at its source is the primary responsibility of States and local governments." States' efforts in this regard have already led to the installation of new pollution controls that will reduce EtO emissions in Colorado, Georgia, Illinois, and Missouri. EPA has supported states in this work, and we have worked closely with both state and local governments to ensure that communities for which we have reliable risk data are informed of that risk.

With these and other steps, and in partnership with state and local governments, we have moved responsibly in using our statutory authority and other tools to address the issues surrounding EtO

emissions. It is a testament that EPA staff and our state and local partners could move so quickly to address EtO in a meaningful way.

The issues raised by the OIG in their March 31, 2020, Management Alert and subsequent report relate to whether outreach has been done in specific communities where we cannot yet reliably characterize the risk posed by EtO. By insisting that EPA must provide outreach in each of the communities based solely off of inaccurate and outdated data from a non-regulatory preliminary screening tool, the OIG has taken the position that appropriate risk communication need not include reliable data. The Agency fundamentally disagrees with that approach, and while we may agree that there is always a level of uncertainty around data, the level of uncertainty here is simply too high to allow for the responsible communication of risk. EPA cannot reliably communicate risk on the basis of raw data that may contain errors. Quality assurance of that data is imperative. The Agency's mission statement, as noted in the OIG report, states that the Agency work to ensure that "all parts of society . . . have access to ***accurate*** information sufficient to effectively participate in managing human health and environmental risks." The OIG is asking us to ignore the part of our mission statement that calls upon EPA to use reasonably accurate data in our decision making.

The Agency has explained to the OIG that using the uncertain and preliminary screening data as the basis for public outreach would be irresponsible. Not only is the data incomplete, but the OIG is recommending the Agency use it as the basis to identify the communities requiring outreach. Acting on this basis is concerning since some of the data does not include correct source information and there may not be reliable information regarding receptor sites. Instead of immediately conducting outreach, the Agency maintains it is necessary to take meaningful and appropriate actions based on the important analysis and understanding of the data. By quality checking the data, the Agency will be able to appropriately determine what is missing and fill in data gaps to better understand where outreach is necessary. For example, for many of the areas estimated to have elevated risk by the previous 2014 NATA, EPA was able to gather sufficient additional information to develop a more accurate estimate of risk and then use that information to communicate with surrounding communities. In other areas, gathering this additional information has taken longer, but the Agency has made progress and expects to be able to communicate where appropriate with surrounding communities in the months ahead.

Risk communication should reflect the most *current available* information. This is a point that EPA has continued to emphasize during our discussions with the OIG and we have noted that the previous 2014 NATA relies on emissions data that are now six years old. Emblematic of this issue is the identification by the OIG of both the Sterigenics facility in Santa Teresa, New Mexico and the Air Products Performance Manufacturing (Evonik) facility in Milton, Wisconsin as "high-priority" ethylene oxide-emitting facilities. EPA has repeatedly pointed out to the OIG that current emissions at both facilities are now about *six times lower* than in 2014, well below the 1-in-10,000 risk level. The OIG continues to insist that the Agency go to these communities with inaccurate and outdated data and use that as the basis for public outreach, which is a poor reflection either on the attention the OIG is paying to the actual facts in this matter or on their judgment.

Perhaps most importantly, the OIG has continued to ignore the role of state and local governments, many of which properly insist upon taking the lead when communicating with the public on this issue and want information to be accurate before presenting it to communities. Under the strong federal-state partnerships that have been developed through implementation of the Clean Air Act, states have primary responsibility for air pollution control with federal assistance. Most of the states with the high-risk areas identified by the 2014 NATA have expressed to EPA their desire to lead the EtO outreach efforts. As

requested, EPA is playing a necessary support role by helping with data collection and analysis, providing financial assistance, and participating in state-led public meetings.

EPA has gone to great lengths to address all issues raised by the OIG, but the OIG has instead engaged in an erratic, goal post-moving endeavor that has been unproductive, unpredictable, and frustrating. At different times during the process EPA offered solutions to resolve all outstanding issues that were seemingly accepted only to have additional, unexpected issues raised by OIG.

For example, in attempts to submit and finalize the Agency's May 15 revised corrective action plan, EPA received conflicting input and feedback from OIG staff, resulting in unnecessary delays in finalization of the corrective actions for several months. This pattern continued in subsequent discussions with the Inspector General and EPA senior officials, and in follow up issues raised by OIG staff, causing continued frustration. Significant issues were not raised during a meeting when decisionmakers on both sides were present and ready to work through the issues. Instead, one outstanding issue was raised at the meeting which EPA committed to resolve but the very next day in a phone call OIG staff raised five new issues. In good faith, the Agency provided a new revised corrective action plan to the OIG on August 7, 2020, in which we proposed to reduce the timeframe for our work by about one third, and separately provided responses to the additional issues. On August 20, 2020, the OIG informed us that all this was still not good enough.

EPA's goal has been to work with the OIG to explain the intricacies of this matter and outline why some community outreach solely based upon the 2014 NATA is inappropriate given the uncertainty of the data. We will continue to work with the OIG and continue to provide them with accurate information so they are able to understand the EPA's processes and incorporate that appropriately in their recommendations for the Agency. The Administrator has made meaningful and appropriate risk communication to the American public a top priority for the Agency, and we take that responsibility seriously. We remain concerned with the OIG's desire to present data to communities that has not been verified for accuracy and has been associated with a corrective action process seemingly designed to elide pertinent facts and to keep the matter in controversy.

EPA is continuing its regulatory work while doing everything we can to help address environmental and public health issues surrounding ethylene oxide. As demonstrated above, the actions this Administration has made and will continue to make are expected to result in meaningful reductions of air pollution in the United States, as the EPA continues its mission to protect human health and the environment. If you have further questions, you may contact me, or your staff may contact Garrett Kral in the Office of Congressional and Intergovernmental Relations at kral.garrett@epa.gov or (202) 564-9114.

Sincerely,

Joseph A. Brazauskas, Jr.
Associate Administrator

HENRY C. "HANK" JOHNSON, JR.
4TH DISTRICT, GEORGIA

COMMITTEES:

JUDICIARY

TRANSPORTATION AND INFRASTRUCTURE

Congress of the United States
House of Representatives
Washington, DC 20515–1004

SUBCOMMITTEES:

CHAIRMAN
COURTS, INTELLECTUAL PROPERTY, AND THE INTERNET

ANTITRUST, COMMERCIAL, AND ADMINISTRATIVE LAW

HIGHWAYS AND TRANSIT

AVIATION

ECONOMIC DEVELOPMENT, PUBLIC BUILDINGS, AND EMERGENCY MANAGEMENT

The Honorable Andrew Wheeler
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington DC 20460

November 15, 2019

Dear Administrator Wheeler,

We write to express our concerns regarding the recent actions by the Texas Commission on Environmental Quality (TCEQ) addressing the toxicity level of ethylene oxide (EtO). As members who represent districts that have been affected by ethylene oxide emissions, our constituents have expressed their alarm over carcinogens polluting the air. We are gravely concerned that relaxed EtO standards on state levels will threaten clean air protections nationally and further endanger the health of our constituents.

This past September, the TCEQ Toxicology, Risk Assessment, and Research Division proposed a four parts per billion health-protective concentration for ethylene oxide. We are concerned that if implemented, this change will undermine the federal standards of EtO emissions established by the Environmental Protection Agency's (EPA) Integrated Risk Information System (IRIS) Evaluation of the Inhalation Carcinogenicity of EtO.

In 2016, the EPA concluded that chronic exposure to EtO is carcinogenic to humans and can cause damage to the brain and nervous system. As the Office of Air and Radiation at the EPA works towards its imminent Advance Notice of Proposed Rulemaking (ANPRM) on the National Emission Standards for Hazardous Air Pollutants, it is vital that states do not undermine the protections established by the EPA IRIS, which has been praised by leading health and medical professionals, including the National Academy of Science.

We seek your assurance that the TCEQ toxicity assessment of ethylene oxide will not threaten the integrity of the EPA's 2016 assessment, and that you are committed to maintaining the IRIS standard, which was the product of 18 years of research and work including time for public comments.

As public servants, we have the duty to protect the interests and safety of American people, and not prioritize the bottom line of the chemical industry. We are committed to working with your agency to improve technology that can further reduce the harm of EtO emissions and foster innovation that will produce safer methods of sterilizing medical equipment.

WASHINGTON OFFICE
2240 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, DC 20515
PHONE (202) 225-1605
FAX (202) 226-0691

DECATUR OFFICE
5240 SNAPFINGER PARK DRIVE, SUITE 140
DECATUR, GA 30035
PHONE (770) 987-2291
FAX (770) 987-8721

PRINTED ON RECYCLED PAPER

Sincerely,

Rep. Henry C. "Hank" Johnson, Jr.
Member of Congress

Rep. Susan Wild
Member of Congress

Rep. Sean Casten
Member of Congress

Rep. David Scott
Member of Congress

Rep. Daniel W. Lipinski
Member of Congress

Rep. Bradley S. Schneider
Member of Congress

Rep. Bill Foster
Member of Congress

Message

From: Bremer, Kristen [Bremer.Kristen@epa.gov]
Sent: 11/10/2020 8:10:49 PM
To: Davis, Alison [Davis.Alison@epa.gov]
Subject: Risk Results Table
Attachments: Risk Results - September 2020 rev.docx

Here you go...

Kristen Bremer
Policy Analysis & Communications
U.S. EPA, Office of Air Quality Planning & Standards
Email: bremer.kristen@epa.gov
Phone: 919.541.9424
Cell: 919.321.7652

Message

From: Koerber, Mike [Koerber.Mike@epa.gov]
Sent: 12/28/2020 11:02:51 PM
To: Ross, Aftin [Aftin.Ross@fda.hhs.gov]
CC: Witt, Jon [Witt.Jon@epa.gov]; Davis, Alison [Davis.Alison@epa.gov]; Weinstock, Lewis [Weinstock.Lewis@epa.gov]; Shappley, Ned [Shappley.Ned@epa.gov]; Schwartz, Suzanne [Suzanne.Schwartz@fda.hhs.gov]
Subject: Re: Potential closure of New Mexico EtO Sterilization Facility

Aftin: Yes, we saw this suit last week. Because EPA is not party to the suit, there's not much we can say at this time. But, happy to talk anytime this week, if you want.

Mike

Sent from my iPhone

On Dec 28, 2020, at 4:09 PM, Ross, Aftin <Aftin.Ross@fda.hhs.gov> wrote:

Good afternoon everyone. I know we canceled today's bi-weekly check-in as many staff were going to be out of the office for the winter break. However, we have an urgent question for EPA that we are hoping our EPA colleagues can provide additional information on. It has come to our attention that a major EtO facility in New Mexico may close. Specifically on December 22, the New Mexico Attorney General Hector Balderas filed suit in state court against a Sterigenics facility in Santa Teresa, New Mexico. The suit seeks a temporary restraining order (TRO) and a hearing may be set for any day.

We wanted to find out if you were aware of this and any additional information you may have regarding this action (e.g. awareness of why New Mexico may be acting now and what products are sterilized there).

If it would be easier to have a quick tcon, we would be happy to schedule a time to chat tomorrow or another day this week that works for the EPA team.

Best,

Aftin

Aftin Ross, Ph.D.
Senior Project Manager
Senior Science Health Advisor
Team: All-Hazards Readiness Response and Cybersecurity (ARC)
Division: All hazards Response, Science and Strategic Partnerships (DARSS)
Office of Strategic Partnerships and Technology Innovation (OST)
Center for Devices and Radiological Health
U.S. Food and Drug Administration

WO 66, Room 5558
10903 New Hampshire Ave, Silver Spring, MD 20993
Office: 301-796-5679; Cell: 202-870-0517
aftin.ross@fda.hhs.gov
Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:
https://www.research.net/s/cdrhcustomerservice?ID=7011&S=E

<image003.png>

Message

From: Haman, Patricia [Haman.Patricia@epa.gov]
Sent: 2/4/2020 8:16:49 PM
To: Davis, Alison [Davis.Alison@epa.gov]; Cyran, Carissa [Cyran.Carissa@epa.gov]
Subject: EtO fact sheets - fyi
Attachments: OAR-8(b)EtO MON NPRM and the IRIS value 020420 peh edits.docx; OAR-8(a) EtO 020420 peh edits.docx

Here is what I submitted to my managers a short while ago and sent to my colleague to let OCSPP review as requested. I will send a full set of all of the fact sheets which go to the Administrator as soon as I have them. Just thought in case OCSPP called, you should have what they have. Pat

Patricia E. Haman
Office of Congressional Affairs
U.S. EPA
202-564-2806

Message

From: Grantham, Nancy [Grantham.Nancy@epa.gov]
Sent: 12/30/2020 4:02:36 PM
To: Gray, David [gray.david@epa.gov]; Davis, Alison [Davis.Alison@epa.gov]
Subject: RE: NM Sterigenics - Santa Teresa Facility

Thanks

From: Gray, David <gray.david@epa.gov>
Sent: Wednesday, December 30, 2020 10:45 AM
To: Davis, Alison <Davis.Alison@epa.gov>; Grantham, Nancy <Grantham.Nancy@epa.gov>
Subject: FW: NM Sterigenics - Santa Teresa Facility

FYSA

From: Garcia, David <Garcia.David@epa.gov>
Sent: Wednesday, December 30, 2020 7:46 AM
Subject: NM Sterigenics - Santa Teresa Facility

FYI, attached is information on the States (New Mexico) law suit against Sterigenics/Santa Teresa facility specific to ethylene oxide emissions. The attachment contains a fact sheet and suggested talking points in case the Region begins to get outside inquires. Please note, although this is a state only action that was filed in District Court, we are staying in communication with NMED and EPA HQ on this matter.

Jeff,
Pls refer to the attached suggested talking points.

David F. Garcia, P.E.
Director
Air and Radiation Division
Ph. 214 665 7593

U.S. EPA Region 6
1201 Elm Street
Dallas, Texas

Message

From: Koerber, Mike [Koerber.Mike@epa.gov]
Sent: 1/15/2021 2:35:28 PM
To: Harlow, David [harlow.david@epa.gov]
CC: Davis, Alison [Davis.Alison@epa.gov]
Subject: Fwd: Status Report. Sterigenics NM. DRAFT.2.docx
Attachments: Status Report. Sterigenics NM. DRAFT.2.docx

David - FYA. We made some changes to the report for New Mexico. Region 6 is reviewing internally. Hopefully, all the reports will be posted this morning.

Mike

Sent from my iPhone

Begin forwarded message:

> **From:** "Garcia, David" <Garcia.David@epa.gov>
> **Date:** January 15, 2021 at 9:24:21 AM EST
> **To:** "McAtee, Jeffrey" <McAtee.Jeffrey@epa.gov>
> **Cc:** "Ngo, Kim" <Ngo.Kim@epa.gov>, "Davis, Alison" <Davis.Alison@epa.gov>, "Robinson, Jeffrey" <Robinson.Jeffrey@epa.gov>, "Koerber, Mike" <Koerber.Mike@epa.gov>
> **Subject: FW: Status Report. Sterigenics NM. DRAFT.2.docx**
>
> Jeff,
>
> Before OAR post this on the Agency's website for EtO are you okay with this version of the report??
>
> This report addresses the Sterigenics facility located in Santa Teresa, NM and further supports our effort to address EtO emissions.
>
> David F. Garcia, P.E.
> Director
> Air and Radiation Division
> Ph. 214 665 7593
>
> U.S. EPA Region 6
> 1201 Elm Street
> Dallas, Texas
>
> ---
>
> **From:** Davis, Alison <Davis.Alison@epa.gov>
> **Sent:** Thursday, January 14, 2021 4:51 PM
> **To:** Koerber, Mike <Koerber.Mike@epa.gov>; Garcia, David <Garcia.David@epa.gov>; Verhalen, Frances <verhalen.frances@epa.gov>; Casso, Ruben <Casso.Ruben@epa.gov>
> **Subject:** Status Report. Sterigenics NM. DRAFT.2.docx
>
> All – here is a second draft, to address comments from Jeff M. and Mike. Please let me know tomorrow a.m. if you are OK with it.
> Thanks.
> -Alison

Ethylene Oxide: Technical Reviews and Outreach to Potentially Affected Communities
Status Report for Sterigenics – Santa Teresa, NM

As EPA pursues its mission to protect public health and the environment, addressing ethylene oxide (EtO) remains a major priority for the Agency. EPA's National Air Toxics Assessment (NATA), released in August 2018, identified a number of areas (census tracts) with potentially elevated risk from continuous exposure, over 70 years, to EtO in the outdoor air. NATA estimated these risks based on EtO emissions from 2014, which were the most recently available at the time.

NATA is a screening-level analysis that is intended to identify pollutants or areas for closer examination. Because of this, additional work is needed to better understand emissions in areas that NATA identified as potentially having elevated risk. EPA has been supporting its state air agency partners as they conduct that work and identify opportunities for reducing EtO emissions from individual facilities, while the Agency reviews its national regulations for industrial facilities that emit EtO. Actual risks today may be higher or lower than NATA estimated due to several factors, including updated or more refined facility emissions information, or recent facility changes such as the installation of pollution controls.

The information below describes the status of EPA's work on the Sterigenics commercial sterilization facility in Santa Teresa, New Mexico. EPA is providing this information, in part, in response to the EPA Office of Inspector General's March 31, 2020, Management Alert which called on EPA to provide information to the 25 communities that NATA identified as potentially having the highest risk from EtO emissions.

Note: For commercial sterilizers, including Sterigenics, EPA is compiling more current and complete emissions data to generate new risk estimates for ethylene oxide sterilizers across the country as part of its work to develop a proposed revision for the National Emissions Standards for Hazardous Air Pollutants for EtO sterilization facilities. EPA will share this information, which will include refined risk estimates at the census block level, with the public as part of its upcoming proposed rule.

Technical information

In its response to the OIG's report, EPA noted that it believes the OIG erroneously included the Sterigenics Santa Teresa Facility in its list of facilities for follow-up. NATA-estimated risks for the census tract near the Sterigenics facility were 200 in 1 million based on *2014* emissions data. Prior to releasing NATA, EPA learned that the facility had installed a control device that reduced ethylene oxide emissions by 83 percent between 2014 and 2016, which would be expected to reduce risk. EPA included this information on the NATA products when the assessment was released in August 2018 and documented the emissions reduction in the emissions update file, available at [HYPERLINK "https://www.epa.gov/sites/production/files/2018-08/documents/2014_nata_updates_to_emissions.pdf"]

Recent Lawsuit

The New Mexico Attorney General has filed a lawsuit against Sterigenics, alleging that the company emitted ethylene oxide "in excess of permissible limits" at the Santa Teresa facility and seeking changes to its sterilization process, along with damages and penalties. The lawsuit was filed December 22, 2020, in the Third Judicial District Court in Las Cruces, NM.

Message

From: Cyran, Carissa [Cyran.Carissa@epa.gov]
Sent: 2/19/2020 9:41:22 PM
To: Davis, Alison [Davis.Alison@epa.gov]
CC: Gantt, Brett [Gantt.Brett@epa.gov]
Subject: EtO Fact Sheets with OAR IO edits
Attachments: OAR-8(a) EtO.docx; OAR-8(b) EtO-MON-IRIS.docx; OAR-8(b) EtO-MON-IRIS (002) Clean.docx; OAR-8(a) EtO CLEAN.docx

Hi Alison,

I just wanted to flag the minor edits that OAR IO had on the EtO (a) fact sheet. Let me know if you are ok with the edits.

Thank you,

Carissa

From: Tardif, Abigale (Abbie) <Tardif.Abbie@epa.gov>
Sent: Wednesday, February 19, 2020 10:17 AM
To: Cyran, Carissa <Cyran.Carissa@epa.gov>
Subject: EtO Fact Sheets

Carissa-

Attached are the EtO fact sheets. Is there anything else we owe you?

Best,
Abbie

Abigale Tardif
Office of Air and Radiation
U.S. Environmental Protection Agency
Desk: 202-564-5643 | Cell: 202-738-7297

Message

From: Harlow, David [harlow.david@epa.gov]
Sent: 1/15/2021 2:57:20 PM
To: Koerber, Mike [Koerber.Mike@epa.gov]
CC: Davis, Alison [Davis.Alison@epa.gov]
Subject: RE: Status Report. Sterigenics NM. DRAFT.2.docx

Mike,

Thanks. I see where this revised write-up added the reference to the New Mexico court action.

David S. Harlow
Senior Counsel
Office of Air and Radiation, USEPA
WJC-N Room 5409K
1200 Pennsylvania Avenue NW
Washington, DC 20460
202-564-1233
Harlow.David@epa.gov
5 U.S.C. § 3331

From: Koerber, Mike <Koerber.Mike@epa.gov>
Sent: Friday, January 15, 2021 9:35 AM
To: Harlow, David <harlow.david@epa.gov>
Cc: Davis, Alison <Davis.Alison@epa.gov>
Subject: Fwd: Status Report. Sterigenics NM. DRAFT.2.docx

David - FYA. We made some changes to the report for New Mexico. Region 6 is reviewing internally. Hopefully, all the reports will be posted this morning.

Mike

Sent from my iPhone

Begin forwarded message:

> **From:** "Garcia, David" <Garcia.David@epa.gov>
> **Date:** January 15, 2021 at 9:24:21 AM EST
> **To:** "McAtee, Jeffrey" <McAtee.Jeffrey@epa.gov>
> **Cc:** "Ngo, Kim" <Ngo.Kim@epa.gov>, "Davis, Alison" <Davis.Alison@epa.gov>, "Robinson, Jeffrey" <Robinson.Jeffrey@epa.gov>, "Koerber, Mike" <Koerber.Mike@epa.gov>
> **Subject: FW: Status Report. Sterigenics NM. DRAFT.2.docx**
>
> Jeff,
>
> Before OAR post this on the Agency's website for EtO are you okay with this version of the report??

This report addresses the Sterigenics facility located in Santa Teresa, NM and further supports our effort to address EtO emissions.

David F. Garcia, P.E.
Director
Air and Radiation Division
Ph. 214 665 7593

U.S. EPA Region 6
1201 Elm Street
Dallas, Texas

From: Davis, Alison <Davis.Alison@epa.gov>
Sent: Thursday, January 14, 2021 4:51 PM
To: Koerber, Mike <Koerber.Mike@epa.gov>; Garcia, David <Garcia.David@epa.gov>; Verhalen, Frances <verhalen.frances@epa.gov>; Casso, Ruben <Casso.Ruben@epa.gov>
Subject: Status Report. Sterigenics NM. DRAFT.2.docx

All – here is a second draft, to address comments from Jeff M. and Mike. Please let me know tomorrow a.m. if you are OK with it.
Thanks.
-Alison

Message

From: Gantt, Brett [Gantt.Brett@epa.gov]
Sent: 2/19/2020 6:35:36 PM
To: Davis, Alison [Davis.Alison@epa.gov]; Smith, Darcie [Smith.Darcie@epa.gov]
Subject: Latest EtO pagers
Attachments: OAR-8(a) EtO Clean.docx; OAR-8(b) EtO-MON-IRIS Clean.docx

Hi Guys,
See attached.
Brett

Message

From: Bremer, Kristen [Bremer.Kristen@epa.gov]
Sent: 1/15/2021 4:50:59 PM
To: Davis, Alison [Davis.Alison@epa.gov]
Subject: RE: Thanks
Attachments: Status Report. Evonik Milton WI.pdf; Status Report. Sterigenics NM.pdf

Ex. 5 Deliberative Process (DP)

Kristen Bremer
Policy Analysis & Communications
U.S. EPA, Office of Air Quality Planning & Standards
Email: bremer.kristen@epa.gov
Phone: 919.541.9424
Cell: 919.321.7652

From: Davis, Alison <Davis.Alison@epa.gov>
Sent: Friday, January 15, 2021 11:46 AM
To: Bremer, Kristen <Bremer.Kristen@epa.gov>
Subject: Thanks

Ex. 5 Deliberative Process (DP)

Alison Davis

Senior Advisor for Public Affairs

USEPA, Office of Air Quality Planning & Standards

Research Triangle Park, NC 27711

Tel. 919-541-7587

Message

From: Tucker, Marlene [Tucker.Marlene@epa.gov]
Sent: 4/14/2021 3:35:37 PM
To: Palmer, Leif [Palmer.Leif@epa.gov]
CC: Nowell, Valerie [Nowell.Valerie@epa.gov]; Rubini, Suzanne [Rubini.Suzanne@epa.gov]; Mitchell, Ken [Mitchell.Ken@epa.gov]; Waterson, Sara [Waterson.Sara@epa.gov]; Lusky, Katy [Lusky.Kathleen@epa.gov]; Davis, Alison [Davis.Alison@epa.gov]
Subject: FW: New Mexico Sues Sterigenics Over Ethylene Oxide Emissions
Attachments: THE STATE OF NEW MEXICO ex rel HECTOR BALDERAS ATTORNEY GENERAL Plaintiff v STER.pdf

Leif,

You may recall the email below concerning the lawsuit filed by the New Mexico Attorney General against Sterigenics on 12/22/20. In light of the various lawsuits against Sterigenics involving the Cobb County Facility and the public outcry about EtO here in Georgia, it is important to pay attention to what is happening in other states that are experiencing similar issues and how state and federal courts rule in other jurisdictions. Here is a summary of the status of the lawsuit. (See the Slip opinion attached "*Memoranda Opinion and Order Remanding Case to State Court:*")

- Initially, Plaintiff (New Mexico AG) filed a lawsuit against Defendants (Sterigenics and its parent company, Sotera) in State Court alleging that that "EtO emitted by Defendants from the Santa Teresa Plant has significantly deteriorated air quality in Santa Teresa and surrounding communities for decades, and has materially contributed to increased health risks suffered by residents of such communities." Notwithstanding the fact that the Defendants had legally acquired an air quality permit, such permit would not relieve Defendants from the obligation to otherwise comply with State law, including Defendants' common-law duties to the State, the local community in and around Santa Teresa, and the New Mexico public in general (a public nuisance claim).
- Subsequently, Defendants removed the case to federal court on the basis that the action gave rise to a federal question jurisdiction. (Defendants argued that Plaintiff's "Public nuisance" claim arises under the Constitution, laws or treatise of the United States. Defendants also assert that the US District Court has supplemental subject matter jurisdiction over the remaining state law causes of action.)
- In response to the removal, Plaintiff filed a "*Motion to Remand to State Court*."
- On 04/13/2021, the US District court ruled that case should be remanded to state court. According to the court – "Under the well-pleaded complaint rule, Plaintiff, as master of its complaint, should have its lawsuit heard in state court. Put another way, Defendants have not met their burden of establishing federal question jurisdiction by a preponderance of the evidence. A remand is appropriate under these circumstances."

Regards,

Marlene Tucker

From: Tucker, Marlene
Sent: Friday, January 29, 2021 7:47 AM
To: Palmer, Leif <Palmer.Leif@epa.gov>
Cc: Rubini, Suzanne <Rubini.Suzanne@epa.gov>; Nowell, Valerie <Nowell.Valerie@epa.gov>; Mitchell, Ken <Mitchell.Ken@epa.gov>; Jenkins, Brandi <Jenkins.Brandi@epa.gov>; Marraccini, Davina <Marraccini.Davina@epa.gov>; Davis, Alison <Davis.Alison@epa.gov>; Lusky, Katy <Lusky.Kathleen@epa.gov>
Subject: New Mexico Sues Sterigenics Over Ethylene Oxide Emissions

Leif,

This story is not related to the Sterigenics facility in Cobb County, however, it may still be of interest. See summary below:

- On December 22, 2020, the New Mexico Attorney General filed a lawsuit against the medical device sterilization company Sterigenics U.S., LLC and its parent Sotera Heath Company for emitting the carcinogenic gas ethylene oxide (EtO) in excess of permissible limits. The lawsuit was filed in the state of New Mexico third Judicial district.
- The suit alleges Sterigenics' plant in Santa Teresa, New Mexico has harmed the environment and potentially threatened human health by emitting high amounts of EtO since 1989. Sterigenics' sites in Georgia and Illinois were the focus of emission concerns in 2019.
- A spokesperson for Sterigenics parent company Sotera Health called the claims baseless and said it would vigorously defend itself against the lawsuit. Law firms submitted hundreds of cases against Sterigenics last year and some observers expect the Biden administration to give momentum to the efforts.
- The New Mexico suit alleges that Sterigenics caused "substantial unreported, uncontrolled releases" of EtO oxide into the atmosphere. Specifically, the suit alleges EtO levels inside the facility were often elevated due to "lax oversight" practices such as leaving sterilization chamber doors ajar when not in use. Sterigenics allegedly lowered EtO levels inside the facility by leaving shipping bays and large doors "open for hours, or entire days."
- New Mexico is requesting a TRO - asking the court to require Sterigenics to immediately cease releasing uncontrolled EtO emissions pending trial and to fund a state-supervised public health monitoring program to detect, assess and treat medical disorders associated with EtO exposure. The lawsuit also seeks a preliminary injunction, damages and penalties.
- Writing in The National Law Review last month, lawyers from environmental specialist Beveridge & Diamond said the election of Joe Biden could increase enforcement risk for emitters of EtO. The warning is based on a belief the Biden administration could back EPA to take a harder line as part of its focus on environmental justice.

See link to the story below:

https://www.medtechdive.com/news/new-mexico-sues-sterigenics-over-ethylene-oxide-emissions/592953/

See story below with complaint attached:
https://www.nmag.gov/uploads/PressRelease/48737699ae174b30ac51a7eb286e661f/AG_Balderas_Files_Lawsuit_Against_Chemical_Company_for_Historical_Pollution.pdf

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2021 WL 1391298
Only the Westlaw citation is currently available.
United States District Court, D. New Mexico.

THE STATE OF NEW MEXICO, ex rel. HECTOR BALDERAS, ATTORNEY GENERAL, Plaintiff,

v.

STERIGENICS U.S., LLC, SOTERA HEALTH HOLDINGS, LLC, SOTERA HEALTH LLC, and SOTERA HEALTH COMPANY, Defendants.

Civ. No. 20-1355 KG/KRS
|
Filed 04/13/2021

MEMORANDUM OPINION AND ORDER REMANDING CASE TO STATE COURT

Since 1989, Defendants have used ethylene oxide (EtO), a toxic gas, at their Santa Teresa Plant to sterilize and fumigate, *inter alia,* medical devices. At the end of December 2020, Plaintiff filed a lawsuit in the Third Judicial District Court, Dona Ana County, State of New Mexico, alleging state law claims against Defendants for harmful EtO emissions. Defendants subsequently removed the case to federal court on the basis that the action gives rise to federal question jurisdiction. In response to the removal, Plaintiff filed the instant "The State of New Mexico's Motion to Remand" (Motion to Remand). (Doc. 4). The Motion to Remand is now fully and timely briefed. *See* (Docs. 14-17). Having considered the briefing, the Complaint (1-2), the controlling law, and for the following reasons, the Court grants the Motion to Remand.

I. The Complaint (Doc. 1-2)

A. Summary of Factual Allegations

Plaintiff alleges that "[s]ince 1989, Defendants have used and continue to use substantial quantities" of EtO "in their industrial sterilization processes at the Santa Teresa Plant." (Doc. 1-2) at ¶ 6. Plaintiff maintains that EtO is "a highly toxic, carcinogenic air pollutant...." *Id.* In fact, according to Plaintiff, "[t]he National Toxicology Program, a federal program, has recognized EtO as a known human carcinogen since 2000, and as a likely human carcinogen since 1985." *Id.* at ¶ 8. Also, in 2016, the United States Environmental Protection Agency's (EPA) Integrated Risk Information System "program released an evaluation of EtO carcinogenicity, noting "that EtO is a mutagenic carcinogen that causes cancer by damaging DNA in cells, which is then duplicated when the cells divide." *Id.* at ¶ 10.

Plaintiff alleges that "EtO emitted by Defendants from the Santa Teresa Plant has significantly deteriorated air quality in Santa Teresa and surrounding communities for decades, and has materially contributed to increased health risks suffered by residents of such communities." *Id.* at ¶ 17. According to Plaintiff, in 2018, "the EPA published results from its 2014 National Air Toxics Assessment" study which found that "residents of Santa Teresa and surrounding locations are at a statistically significantly increased risk of developing cancer" due to EtO exposure. *Id.* at ¶ 21.

Plaintiff contends that Defendants know that EtO is a dangerous air pollutant. *See id.* at ¶¶ 87-107. Even so, Plaintiff asserts that "Defendants have long promoted the environmental safety of their EtO sterilization and fumigation practices." *Id.* at ¶ 154. Plaintiff alleges that "[d]uring the initial permit application process and subsequent modification application processes, Defendants misrepresented or omitted material information from the New Mexico Environment Department and its predecessor agency." *Id.* at ¶ 146. Plaintiff maintains that

> [e]ven if Defendants had lawfully obtained air quality permits, made no misrepresentations or omissions during the approval and modification processes, and complied with all permit conditions ... such permits would not relieve Defendants from the obligation to otherwise comply with State law, including Defendants' common-law duties to the State, the local community in and around Santa Teresa, and the New Mexico public in general.

Id. at ¶ 148.

B. Causes of Action

Plaintiff filed suit in state court bringing several state law causes of action. Relevant to this Motion to Remand, Plaintiff brings a common law public nuisance cause of action and a cause of action under the New Mexico public nuisance statute, NMSA 1978, § 30-8-1 (2004 Repl. Pamp.).

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New Mexico courts recognize that "common law public nuisance is similar to the New Mexico public nuisance statute, Section 30-8-1." *State ex rel. Vill. of Los Ranchos de Albuquerque v. City of Albuquerque* (*City of Albuquerque II*), 1994-NMSC-126, ¶ 52, 119 N.M. 150; *see also City of Albuquerque v. State ex rel. Vill. of Los Ranchos de Albuquerque (City of Albuquerque I)*, 1991-NMCA-015, ¶ 15, 111 N.M. 608 (deeming "it unnecessary to distinguish between" statutory public nuisances and common law public nuisances). Section 30-8-1 provides that "[a] public nuisance consists of knowingly creating, performing or maintaining anything affecting any number of citizens without lawful authority which is ... injurious to public health...."

II. The Notice of Removal (Doc. 1)

Defendants contend that this Court has federal question jurisdiction because Plaintiff's public nuisance claims "arise[ ] under the Constitution, laws, or treatises of the United States." 28 U.S.C. § 1331. Specifically, Defendants assert that Plaintiff's allegation that the Santa Teresa Plant's harmful levels of EtO emissions "constitute a public nuisance raise a substantial federal question...." (Doc. 1) at ¶ 27. Defendants also assert that the Court has supplemental subject matter jurisdiction over the remaining state law causes of action. *See* 28 U.S.C. § 1367(a).

III. Discussion

A defendant can remove a state case to federal district court if the federal district court would have original jurisdiction over the matter. 28 U.S.C. § 1441(a). However, "[s]ince federal courts are courts of limited jurisdiction, [courts] presume no jurisdiction exists absent an adequate showing by the party invoking federal jurisdiction." *Dutcher v. Matheson*, 733 F.3d 980, 985 (10th Cir. 2013) (citation omitted). "As the parties removing this case to federal court, [Defendants] bear the burden of establishing jurisdiction by a preponderance of the evidence." *Id.*

"Congress has authorized the federal district courts to exercise original jurisdiction in 'all civil actions arising under the Constitution, laws, or treaties of the United States,' 28 U.S.C. § 1331...." *Gunn v. Minton*, 568 U.S. 251, 257 (2013). "To determine whether [a] claim arises under federal law, [courts] examine the 'well[-]pleaded' allegations of the complaint and ignore potential defenses...." *Devon Energy Prod. Co., L.P. v. Mosaic Potash Carlsbad, Inc.*, 693 F.3d 1195, 1202 (10th Cir. 2012) (quoting *Beneficial Nat'l Bank v. Anderson,* 539 U.S. 1, 6 (2003)). "Under the 'well-pleaded complaint' rule, 'a suit arises under federal law only when the plaintiff's statement of his own cause of action shows that it is based on federal law.' " *Id.* (citation and internal quotation marks omitted). "This rule 'makes the plaintiff the master of the claim.' " *Id.* (quoting *Caterpillar Inc. v. Williams,* 482 U.S. 386, 392 (1987)). In other words, "[b]y omitting federal claims from a complaint, a plaintiff can [generally] guarantee an action will be heard in state court." *Id.* (quoting *Qwest Corp. v. City of Santa Fe,* 380 F.3d 1258, 1264 n. 1 (10th Cir. 2004)).

"Under the 'artful pleading' doctrine, however, a plaintiff may not defeat removal by failing to plead federal questions that are essential elements of the plaintiff's claim." *Turgeau v. Admin. Rev. Bd.*, 446 F.3d 1052, 1060 (10th Cir. 2006) (citation omitted). Similarly, a recognized exception to the well-pleaded complaint rule occurs when "there is a substantial, disputed federal-law issue necessarily embedded in [the plaintiff's] state-law claims." *Devon Energy Prod. Co., L.P.*, 693 F.3d at 1203-04. As the United States Supreme Court in *Gunn* recognized, only a "slim" category of cases with their origins in state law can arise under federal law. *Gunn*, 568 U.S. at 258. In those cases, "federal jurisdiction over a state law claim will lie if a federal issue is: (1) necessarily raised, (2) actually disputed, (3) substantial, and (4) capable of resolution in federal court without disrupting the federal-state balance approved by Congress." *Id.*

"[A] few important principles" mark "[t]he narrow boundaries of the substantial question category" of federal question jurisdiction. *Becker v. Ute Indian Tribe of the Uintah & Ouray Rsrv., 110* F.3d 944, 947 (10th Cir. 2014). First, "the mere presence of a federal issue in a state cause of action does not automatically confer federal-question jurisdiction." *Id.* (quoting *Merrell Dow Pharm. Inc. v. Thompson,* 478 U.S. 804, 813 (1986)). Second, federal question jurisdiction cannot "depend solely on 'a federal defense, ... even if the defense is anticipated in the plaintiff's complaint, and even if both parties concede that the federal defense is the only question truly at issue.' " *Id.* (quoting *Caterpillar Inc.,* 482 U.S. at 393). "Finally, if a claim does not present 'a nearly pure issue of law, one that could be settled once and for all and thereafter would govern numerous ... cases,' but rather is 'fact-bound and situation-specific,' then federal question jurisdiction will generally be inappropriate." *Id.* at 947-48 (quoting *Empire Healthchoice Assurance, Inc. v. McVeigh,* 547 U.S. 677, 700-01 (2006)).

Defendants argue first that the public nuisance claims necessarily raise a federal issue. Defendants contend that an

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essential element of the statutory public nuisance claim is that the public nuisance occurred "without lawful authority." *See* NMSA 1978, § 30-8-1. In this case, Defendants assert that to determine whether the use and emission of EtO at the Santa Teresa Plant was "without lawful authority" one must apply and interpret federal EPA regulations promulgated under the Clean Air Act that control the industrial use of EtO, including Defendants' permit to operate the Santa Teresa Plant. Defendants conclude that this need to apply and interpret federal regulations necessarily raises a federal question.

Although the "without lawful authority" language appears to be an element of a statutory public nuisance claim, New Mexico courts have found that language provides a defense. *See State ex rel. Smith v. Riley*, 1997-NMCA-063, ¶¶ 8-9, 12, 123 N.M. 453 (concluding, in alternative, that "Petitioners have not stated a claim under Section 30-8-1 because they have not alleged that Respondents did not have lawful authority"). In the context of public works projects that may constitute a public nuisance, the New Mexico Court of Appeals promulgated the following rules:

> If the public works project is in existence and poses a present nuisance, due authorization is a qualified defense; courts may or may not decide that despite the defense the project is still a nuisance. However, if the project has yet to be constructed and is challenged as an anticipatory nuisance in fact, due authorization—as we have defined it in this opinion—is an absolute defense; courts will summarily conclude that there is no basis for a finding of nuisance.

City of Albuquerque II, 1994-NMSC-126 at ¶ 63 (emphasis added). In promulgating those rules, the New Mexico Court of Appeals referred to Section 30-8-1's "without lawful authority" language to formulate the issue in that case: "In a complicated project like the building of a bridge, does the fact that it complies with lawful authority preclude any claim of public nuisance?" *Id.* at ¶ 62. The New Mexico Court of Appeals then observed that "[a]s this [public nuisance] statute relates to public works projects, 'lawful authority' is synonymous with 'due authorization' as we have defined it above: conformance with all the federal, state, and local laws, rules, and regulations pertinent to that particular project." *Id.* In a related case, the New Mexico Court of Appeals determined that "the City's constitutional and statutory authority to construct public highways and bridges constitutes a valid defense to a claim of nuisance per se under either" statutory or common law public nuisance law. *City of Albuquerque I*, 1991-NMCA-015 at ¶ 15 (emphasis added).

From those New Mexico cases, one could reasonably conclude that the "without lawful authority" language in the public nuisance statute can provide the basis for a defense and is not an element of a public nuisance claim. Such a defense does not "necessarily" raise a federal issue. *See Schumacher v. Sterigenics U.S., LLC*, 394 F. Supp. 3d 837, 844 (N.D. Ill. 2019) (noting that "[a]lthough Defendants may ultimately choose to defend against Plaintiffs' claims by introducing evidence that they complied with federal law, it is well settled that this would not be a basis for the exercise of federal jurisdiction").

Assuming for the sake of argument that Plaintiff has "necessarily" raised a federal issue in its public nuisance claims, the next issue in determining if a substantial federal question exists is whether the parties actually dispute the federal issue. Here, Plaintiff does not assert in their public nuisance causes of action that Defendants violated any federal regulations or federal statute. Instead, Plaintiff simply alleges that Defendants knowingly created and maintained a public nuisance by injuring the health of the public through its emission of toxic levels of EtO. Plaintiff's public nuisance "claims can succeed without reference to any federal statute" or regulation. *Id.* at 845. In other words, even if a jury found that Defendants "complied with federal standards, the jury could nevertheless determine that state [public nuisance] common law [and the state statutory public nuisance law] impose[ ] a standard of care higher than that expressly required by federal law." *Id.* For these reasons, the federal issue, whether Defendants had lawful authority for their EtO emissions under EPA regulations and the Clean Air Act, is not actually disputed in this case.

Even so, Defendants argue that the public nuisance claims raise substantial issues of federal law related to the application and interpretation of EPA regulations. Defendants maintain that the outcome of the public nuisance claims will impact "the entire medical products sterilization industry that is essential to the supply of medical products [in] the United States." (Doc. 14) at 17. Moreover, Defendants maintain that "the determination will impact the regulatory framework that Congress and the EPA established to govern air emissions generally and, specifically, the use and emission of E[t]O by medical sterilization facilities in the United States." *Id.*

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The public nuisance claims, however, do "not present 'a nearly pure issue of law, one that could be settled once and for all and thereafter would govern numerous ... cases,'...." *Becker*, 770 F.3d at 947-48 (citation omitted). Rather, the public nuisance claims raise a factual question specific to the Santa Teresa Plant: whether Defendants knowingly created, performed, or maintained a situation at the Santa Teresa Plant that produced harmful EtO emissions resulting in injury to the health of the public in the Santa Teresa area. *See* NMSA 1978, § 30-8-1. This "fact-bound and situation-specific" question does not constitute a "substantial" federal question. *Becker*, 770 F.3d at 948 (citation omitted) (stating that under those circumstances "federal question jurisdiction will generally be inappropriate").

Finally, Defendants argue that the Court's exercise of subject matter jurisdiction will not upset any congressionally approved balance of federal and state judicial responsibilities. This last requirement for substantial federal question jurisdiction "focuses principally on the nature of the claim, the traditional forum for such a claim, and the volume of cases that would be affected." *New York ex rel. Jacobson v. Wells Fargo Nat'l Bank, N.A.*, 824 F.3d 308, 316 (2d Cir. 2016). In addition, "[a]bsent a special state interest in a category of litigation, or an express congressional preference to avoid federal adjudication, federal questions that implicate substantial federal interests will often be appropriately resolved in federal rather than state court." *Id.*

In particular, Defendants note that the Clean Air Act provides a private right of action for any "person," including States, for violations of emission standards or limitations, and permits. 42 U.S.C. §§ 7604(a)(1) and (3), and 7602(e). The Clean Air Act also gives federal district courts original jurisdiction over those actions. *Id.* at § 7604(a). Yet, the Clean Air Act also provides that nothing "shall preclude or deny the right of any State ... to adopt or enforce (1) any standard or limitation respecting emissions of air pollutants or (2) any requirement respecting control or abatement of air pollution; except that" the State "may not adopt or enforce any emission standard or limitation which is less stringent than the standard or limitation under such plan or section." *Id.* at § 7416. Furthermore, nothing in the citizen suit provision "or in any other law of the United States shall be construed to prohibit, exclude, or restrict any State ... from—(1) bringing any enforcement action or obtaining any judicial remedy or sanction in any State or local court...." *Id.* at § 7604(e).

To summarize, while the Court has subject matter jurisdiction over any lawsuit brought by a State alleging violations of EPA regulations and the Clean Air Act, States also have the right to require even more stringent air pollution requirements than the Clean Air Act and to bring suit in state court to enforce those requirements. Hence, Congress expressly contemplated state lawsuits, like this one, which allege public nuisance claims based on the emission of air pollutants that exceed EPA and Clean Air Act requirements. *See Bell v. Cheswick Generating Station*, 734 F.3d 188, 198 (3d Cir. 2013) (acknowledging that circuit courts "have affirmed decisions granting plaintiffs relief against sources of air pollution under state law nuisance theory;" *Her Majesty The Queen In Right of the Province of Ontario v. City of Detroit*, 874 F.2d 332, 342–43 (6th Cir. 1989) (holding that "plain language of the [Clean Air Act's] savings clause ... clearly indicates that Congress did not wish to abolish state control"); *Mayor & City Council of Baltimore v. BP P.L.C.*, 388 F. Supp. 3d 538, 563 (D. Md. 2019), *as amended* (June 20, 2019), *aff'd,* 952 F.3d 452 (4th Cir. 2020), *cert. granted,* 141 S. Ct. 222 (2020) (noting that "language of these provisions unequivocally demonstrates that 'Congress did not intend the federal causes of action under [the Clean Air Act] to be exclusive' ") (citation and internal quotation marks omitted).

The Court further recognizes that public nuisance claims are typically of a state nature and traditionally tried in state court. *See McDougall v. CRC Indus., Inc.*, 2021 WL 810635, at *9 (D. Minn.) (noting that "[p]ublic nuisance claims have traditionally been the purview of the state"); *City of Philadelphia v. Beretta U.S.A., Corp.*, 126 F. Supp. 2d 882, 893 (E.D. Pa. 2000), *aff'd,* 277 F.3d 415 (3d Cir. 2002) (observing that "public nuisance claim ... seeks to exert traditional state power"). Given that the Clean Air Act allows for more stringent state limitations on emissions and state lawsuits to enforce those limitations, forcing Plaintiff to litigate, in federal court, its more exacting state public nuisance claims, claims traditionally brought by States in state court, would upset the congressionally approved balance of federal and state judicial responsibilities set forth in the Clean Air Act.

For all of the above reasons, Plaintiff's public nuisance claims do not "necessarily depend[ ] on resolution of a substantial question of federal law" and, thus, do not fall within the "slim" category of state law cases arising under federal law. *Gunn*, 568 U.S. at 258; *Empire Healthchoice Assurance, Inc.*, 547 U.S. at 690. As such, the Court cannot conclude that Plaintiff artfully drafted the Complaint to avoid federal

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jurisdiction. Under the well-pleaded complaint rule, Plaintiff, as master of its complaint, should have its lawsuit heard in state court. Put another way, Defendants have not met their burden of establishing federal question jurisdiction by a preponderance of the evidence. A remand is appropriate under these circumstances.

IT IS ORDERED that

1. The State of New Mexico's Motion to Remand (Doc. 4) is granted; and

2. this lawsuit is remanded to the Third Judicial District Court, Dona Ana County, State of New Mexico.

All Citations

Slip Copy, 2021 WL 1391298

End of Document

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Message

From: Robinson, Jeffrey [Robinson.Jeffrey@epa.gov]
Sent: 2/24/2021 9:09:04 PM
To: Rimer, Kelly [Rimer.Kelly@epa.gov]; Morris, Mark [Morris.Mark@epa.gov]
CC: Verhalen, Frances [verhalen.frances@epa.gov]; Davis, Alison [Davis.Alison@epa.gov]
Subject: DRAFT OIG-listed EtO facility profiles 1-12-21 fv (002).pptx
Attachments: DRAFT OIG-listed EtO facility profiles 1-12-21 fv (002).pptx

Message

From: Casso, Ruben [Casso.Ruben@epa.gov]
Sent: 5/11/2021 8:06:36 PM
To: Davis, Alison [Davis.Alison@epa.gov]
Subject: RE: Sterigenics - NM

Thanks.

From: Davis, Alison <Davis.Alison@epa.gov>
Sent: Tuesday, May 11, 2021 3:06 PM
To: Casso, Ruben <Casso.Ruben@epa.gov>
Cc: Branning, Amy <Branning.Amy@epa.gov>
Subject: RE: Sterigenics - NM

I don't think OGC is assigned to a particular facility. But Amy Branning is the attorney working on the sterilizers rule. Copying her here

---

From: Casso, Ruben <Casso.Ruben@epa.gov>
Sent: Tuesday, May 11, 2021 3:44 PM
To: Davis, Alison <Davis.Alison@epa.gov>
Subject: Sterigenics - NM

Alison – Do you know who is the OGC staff attorney assigned to Sterigenics in Santa Teresa, NM? -Ruben

Message

From: Koerber, Mike [Koerber.Mike@epa.gov]
Sent: 5/18/2020 2:26:56 PM
To: Garcia, David [Garcia.David@epa.gov]
CC: Davis, Alison [Davis.Alison@epa.gov]
Subject: RE: EtO Mtg with Doug
Attachments: Response.Ethylene Oxide.5.15.2020.pdf

David: After some back-and-forth, the attached response was sent to the OIG on Friday afternoon. Alison and I are planning to discuss this on the Thursday afternoon call.

Mike

From: Garcia, David <Garcia.David@epa.gov>
Sent: Monday, May 18, 2020 8:02 AM
To: Koerber, Mike <Koerber.Mike@epa.gov>
Subject: EtO Mtg with Doug

Good Morning Mike,

Any update with your last mtg with Doug B regarding IG report?

David F. Garcia, P.E.
Director
Air and Radiation Division
Ph. 214 665 7593

U.S. EPA Region 6
1201 Elm Street
Dallas, Texas

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

May 15, 2020

OFFICE OF
THE ADMINISTRATOR

MEMORANDUM

SUBJECT: Response to Office of Inspector General Management Alert "Prompt Action Needed to Inform Residents Living Near Ethylene Oxide-Emitting Facilities About Health Concerns and Actions to Address Those Concerns," Report No. 20-N-0128 (March 31, 2020)

FROM: Douglas Benevento, Associate Deputy Administrator

TO: Katie Butler, Acting Assistant Inspector General for Audit and Evaluation
Office of Audit and Evaluation
Office of Inspector General

Thank you for the opportunity to respond further to the recommendation identified in the subject Management Alert report from EPA's Office of Inspector General (OIG). Specifically, the OIG recommended that EPA:

> *Improve and continue to implement ongoing risk communication efforts by promptly providing residents in all communities near the 25 ethylene oxide-emitting facilities identified as high-priority by the EPA with a forum for an interactive exchange of information with the EPA or the states regarding health concerns related to exposure to ethylene oxide.*

Although we were surprised by, and disagree with, both the tone and substance of the report, we offer a proposed corrective action plan with milestones in the interest of resolving this matter.

This proposed plan was developed based on two guiding principles:

First, risk communication must rely on accurate information. Indeed, the agency's mission statement, as you noted in the report, states that the Agency work to ensure that "all parts of society ... have access to accurate information sufficient to effectively participate in managing human health and environmental risks." The report misses the part of the mission statement that includes providing access to *accurate* information.

As we noted in prior correspondence, because the National Air Toxics Assessment (or NATA) provides *screening level* results which have inherent uncertainties, additional work is necessary to more fully understand the risks that NATA identified as being potentially elevated in certain areas.

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We believe this follow-up work must be conducted prior to significant public outreach. It is critically important that we provide residents information that is as detailed and up to date as possible when communicating risk. Public engagement based on dated, preliminary, uncertain information is irresponsible and undermines the Agency's credibility.

Second, state leadership is essential to deal effectively with local air toxics issues, like ethylene oxide. The approach for action and public engagement in each area must be tailored to, and focused on, the specific community and the specific facility. States, who have primary responsibility for air pollution prevention and air pollution control under the Clean Air Act, are best positioned to lead this work. Under the second prong of the Agency's two-pronged approach for addressing emissions of ethylene oxide in response to the most recent NATA, we are continuing to support state-led efforts to not only conduct additional, more refined investigations, but also carry out appropriate outreach with affected communities. And, as we noted in prior correspondence, these efforts have already led to significant emission reductions and public health benefits in several areas.

In keeping with these guiding principles, we offer the following two-part corrective action plan with milestones: (1) conduct additional, more refined investigation of risk and (2) conduct outreach to affected communities.

Part 1. Conduct additional, more refined investigation of risk

a. Regions 2, 3, 4, 5, 7 and 8 (15 facilities/areas)
   Milestone: Technical work has already been completed or is well underway for these facilities/areas. EPA will post quarterly status reports on these additional, more refined investigations to the Agency's/Regions' Ethylene Oxide website beginning September 30, 2020.

b. Region 6 (9 facilities/areas)[1]
   Milestone: EPA Region 6 will work with the states of Texas and Louisiana on facility/area-specific technical assessments. Information on the assessments will be posted to the Agency's/Regions' Ethylene Oxide website beginning with the Agency's December 31, 2020 quarterly progress report.

   Longer Term Milestone: EPA will complete additional, more refined investigations of risk for all high-risk areas identified by the most recent NATA (i.e., the 24 facilities/areas) by June 30, 2021.

[1] EPA believes the OIG erroneously included one facility -- the Sterigenics Santa Teresa Facility in New Mexico -- in its report. EPA clearly noted in its NATA documentation that this facility installed a control device and had reduced ethylene oxide emissions by 83% between 2014 and 2016 – prior to the NATA release. No further technical assessment or public outreach is believed necessary at this time. See https://www.epa.gov/sites/production/files/2018-08/documents/2014_nata_updates_to_emissions.pdf

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Part 2. Conduct outreach to affected communities[2]

a. Regions 2, 3, 4, 5, 7 and 8 (15 facilities/areas)
   Milestone: Public outreach has already occurred or is planned for these facilities/areas. Any additional outreach for these facilities/areas should proceed as planned and as appropriate – in accordance with local directives related to COVID-19. EPA will post quarterly status reports of outreach activities to the Agency's/Regions' Ethylene Oxide website beginning September 30, 2020.

b. Region 6 (9 facilities/areas)
   Milestone: EPA Region 6 will work with the states of Texas and Louisiana to explore appropriate communication tools and assist the states in developing facility/area-specific outreach information. Descriptions of the tools, information, and outreach activities will be posted to the Agency's/Regions' Ethylene Oxide website beginning with the Agency's December 31, 2020 quarterly progress report.

   Milestone: Most of the facilities of interest in Region 6 are chemical plants. By May 29, 2020, EPA must issue a final review of the National Emissions Standards for Hazardous Air Pollutants for Miscellaneous Organic Chemical Manufacturing (known as "the MON), which addresses ethylene oxide emissions at some chemical plants. EPA will reach out to Texas and Louisiana to offer them an opportunity to participate in a public webinar in June 2020 (after the MON is issued). EPA would cover the requirements of the rule; the states would be given an opportunity to discuss MON-affected chemical plants in their jurisdictions.

   Longer Term Milestone: EPA will complete initial outreach for all high-risk areas identified by the most recent NATA (i.e., the 24 facilities/areas) by June 30, 2021. Please note this initial outreach would lead to an open and appropriate ongoing communication with surrounding communities.

If you have any questions concerning our proposed corrective action with milestones, please contact Michael Koerber, Deputy Director, Office of Air Quality Planning & Standards, (919) 541-5557.

[2] In light of the COVID-19 crisis, EPA is not able to convene or support in-person public meetings for the foreseeable future. As we noted in prior correspondence, effective public outreach can occur in many forms. At any time, public meetings ("forums for an interactive exchange of information with the EPA") may not be the best approach for initial public outreach in all areas. Holding such in-person meetings now could put the public at increased risk of contracting the virus that causes COVID-19. EPA will continue to explore a wide variety of appropriate communication tools, including targeted webinars, website postings, virtual open houses, local distribution of printed materials, and partnering with existing outreach efforts by state or local governments.

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Message

From: Smith, Darcie [Smith.Darcie@epa.gov]
Sent: 6/2/2020 8:34:45 PM
To: Davis, Alison [Davis.Alison@epa.gov]
Subject: FW: Revised EtO Plan
Attachments: EtO Technical Assessment Options DRAFT 6-2-20.docx

Don't know if you were planning on commenting, but you weren't on Fran's email, so here you go.

Darcie Smith
U.S. EPA, OAQPS, ATAG
919.541.2076
smith.darcie@epa.gov
please consider the environment before printing this email

From: Verhalen, Frances <verhalen.frances@epa.gov>
Sent: Tuesday, June 02, 2020 4:30 PM
To: Garcia, David <Garcia.David@epa.gov>; Robinson, Jeffrey <Robinson.Jeffrey@epa.gov>; Casso, Ruben <Casso.Ruben@epa.gov>; Koerber, Mike <Koerber.Mike@epa.gov>; Bordelon, David <David.Bordelon@WestonSolutions.com>; Weinstock, Lewis <Weinstock.Lewis@epa.gov>; Smith, Darcie <Smith.Darcie@epa.gov>
Subject: Revised EtO Plan

Depending on the decision by the IG, here is the draft R6 plan for EtO activities that I revised based on the discussion earlier today. Please let me know if there are other changes.

Fran

Frances Verhalen, P.E., Chief
Air Monitoring & Grants Section
US Environmental Protection Agency
1200 Elm Street, Suite 500 (MC 6ARPM)
Dallas, TX 75270
214-665-2172
verhalen.frances@epa.gov

Message

From: Verhalen, Frances [verhalen.frances@epa.gov]
Sent: 6/3/2020 10:59:01 AM
To: Davis, Alison [Davis.Alison@epa.gov]
Subject: FW: Revised EtO Plan
Attachments: EtO Technical Assessment Options DRAFT 6-2-20.docx

Incorrect addressee

Frances Verhalen, P.E., Chief
Air Monitoring & Grants Section
US Environmental Protection Agency
1200 Elm Street, Suite 500 (MC 6ARPM)
Dallas, TX 75270
214-665-2172
verhalen.frances@epa.gov

From: Verhalen, Frances
Sent: Tuesday, June 02, 2020 3:30 PM
To: Garcia, David <Garcia.David@epa.gov>; Robinson, Jeffrey <Robinson.Jeffrey@epa.gov>; Casso, Ruben <Casso.Ruben@epa.gov>; Koerber, Mike <Koerber.Mike@epa.gov>; Bordelon, David <David.Bordelon@WestonSolutions.com>; Weinstock, Lewis <Weinstock.Lewis@epa.gov>; Smith, Darcie <Smith.Darcie@epa.gov>
Subject: Revised EtO Plan

Depending on the decision by the IG, here is the draft R6 plan for EtO activities that I revised based on the discussion earlier today. Please let me know if there are other changes.

Fran

Frances Verhalen, P.E., Chief
Air Monitoring & Grants Section
US Environmental Protection Agency
1200 Elm Street, Suite 500 (MC 6ARPM)
Dallas, TX 75270
214-665-2172
verhalen.frances@epa.gov

Message

From: Davis, Alison [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=1C309F42D5D44D18A52B027BD0112778-ADAVIS06]
Sent: 1/14/2021 6:23:09 PM
To: Verhalen, Frances [verhalen.frances@epa.gov]; Casso, Ruben [Casso.Ruben@epa.gov]
Subject: Please review ASAP
Attachments: Status Report. Sterigenics NM. DRAFT.docx

Importance: High

Fran,
As I mentioned, we are finally posting the OIG status reports tomorrow – but there is no report for NM. Given the recent interest in that facility, it seems like we should do something. Please have a look at the attached and let me know if it would work for the NM facility. I tweaked the common intro language a tiny bit to avoid implying we were doing outreach. But I do think including the note that more risk info is coming would be helpful.

Please let me know your edits.
Thanks.
-Alison

Alison Davis
Senior Advisor for Public Affairs
US EPA, Office of Air Quality Planning & Standards
Research Triangle Park, NC 27711
Desk: 919-541-7587
Mobile: 919-624-0872

Message

From: Davis, Alison [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=1C309F42D5D44D18A52B027BD0112778-ADAVIS06]
Sent: 1/14/2021 6:43:46 PM
To: Koerber, Mike [Koerber.Mike@epa.gov]
Subject: Status report for New Mexico facility - please read
Attachments: Status Report. Sterigenics NM. DRAFT.docx

Importance: High

Hey Mike,
As I was prepping the OIG status reports for posting, I remembered that R6 did not submit one for the Sterigenics New Mexico facility. Given the recent news on that facility, it seems like we need one. I threw something together based on the language that's posted on the NATA Map. Fran and Ruben have OKd it – they're checking with David Garcia. Would you have a look and let me know what you think? We could skip it and just respond to questions -but at least this way, we are signaling that new risk info will be coming for that facility.

Thanks.
Alison

Message

From: Davis, Alison [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=1C309F42D5D44D18A52B027BD0112778-ADAVIS06]
Sent: 1/15/2021 5:04:26 PM
To: Payne, Melissa [Payne.Melissa@epa.gov]
Subject: Four more
Attachments: Status Report Sterigenics Willowbrook IL.pdf; Status Report. Sterigenics NM.pdf; Status Report. Evonik Milton WI (1).pdf

Davis, Alison has shared a OneDrive for Business file with you. To view it, click the link below.

Status Report.Edwards Lifesciences.AnascoPR.pdf

Kristen is checking the last W Va one. Will send in a minute. We are clear to post when you are ready

Alison Davis
Senior Advisor for Public Affairs
USEPA, Office of Air Quality Planning & Standards
Research Triangle Park, NC 27711
Tel. 919-541-7587

Ethylene oxide: Technical Reviews and Outreach to Potentially Affected Communities

Status Report -- Sterigenics US LLC, Willowbrook, Ill.

As EPA pursues its mission to protect public health and the environment, addressing ethylene oxide (EtO) remains a major priority for the Agency. EPA's National Air Toxics Assessment (NATA), released in August 2018, identified a number of areas (census tracts) with potentially elevated risk from continuous exposure, over 70 years, to EtO in the outdoor air. NATA estimated these risks based on EtO emissions from 2014, which were the most recently available at the time.

NATA is a screening-level analysis that is intended to identify pollutants or areas for closer examination. Because of this, additional work is needed to better understand emissions in areas that NATA identified as potentially having elevated risk. EPA has been supporting its state air agency partners as they conduct that work and identify opportunities for reducing EtO emissions from individual facilities, while the Agency reviews its national regulations for industrial facilities that emit EtO. Actual risks today may be higher or lower than NATA estimated due to several factors, including updated or more refined facility emissions information, or recent facility changes such as the installation of pollution controls.

The information below describes the technical analyses conducted for Sterigenics Willowbrook, as part of the follow-up work conducted since NATA was issued in August 2018. It also summarizes outreach to nearby communities about the NATA results. EPA is providing this information, in part, in response to the EPA Office of Inspector General's March 31, 2020, Management Alert which called on EPA to provide information to the 25 communities that NATA identified as potentially having the highest risk from EtO emissions.

Note: For commercial sterilizers, EPA is compiling more current and complete emissions data to generate new risk estimates for ethylene oxide sterilizers across the country as part of its work to develop a proposed revision for the National Emissions Standards for Hazardous Air Pollutants for EtO sterilization facilities. EPA will share this information, which will include refined risk estimates at the census block level, with the public as part of its upcoming proposed rule.

Technical reviews conducted:

Sterigenics operated a commercial sterilizer that used EtO to sterilize medical equipment and other products in Willowbrook, Ill. from 1984 to 2019.

- **Closure**: Sterigenics announced it was permanently closing its Willowbrook location in September 2019, resulting in EtO emission reductions of more than 4,600 pounds per year. The facility had been subject to a State of Illinois seal order, issued in February 2019, which prohibited EtO use. Before the closure, Sterigenics received a construction permit from Illinois EPA to install new technology that would have achieved 99.9% control.

ED_013218_00000536-00001

- **Air Monitoring**: EPA conducted initial short-term air sampling over three days in May 2018. EPA conducted additional monitoring at eight sites from November 2018 to March 2019. The highest average EtO concentrations were observed at the two sites closest to Sterigenics (100 meters).
- **Risk Assessment**: EPA conducted a risk assessment, presented the results at the public meeting in Burr Ridge, Ill. on May 29, 2019 and posted a summary of the results to the Web. EPA posted the full risk assessment report to the Web on August 16, 2019.

Outreach conducted:

- **Websites**: EPA developed a Willowbrook-specific website in August 2018. Illinois EPA also has a website to keep stakeholders informed.
- **Public Meetings**: EPA attended a public meeting convened by Willowbrook Mayor Frank Trilla on August 28, 2018. EPA led public meetings on November 28, 2018 and May 28, 2019 to update the community. These meetings were organized with community and local officials' participation. Illinois EPA held a public meeting on August 1, 2019 to answer questions about Sterigenics' draft construction permit.
- **Meetings with Local Officials**: On September 28, 2018, November 29, 2018, and May 28, 2019, EPA held in-person meetings with elected officials and/or staff from the State of Illinois, the Village of Willowbrook and/or DuPage County. Representatives from Senator Durbin, Senator Duckworth and Congressman Lipinski's offices also attended the meetings. EPA held numerous meetings with village and state officials, along with congressional staff, about data from air monitoring near the Willowbrook facility. The agency also participated in numerous calls from individual officials at their request.
- **Meetings with Community Groups**: EPA held a series of webinars to present monitoring results and educate the local community about topics such as air toxics, risk assessment and EPA's rulemaking process. In addition, the agency held a meeting with community group leaders on May 28, 2019, to discuss risk assessment results so the groups could prepare to ask questions at the May 29, 2019 public meeting.

Message

From: Davis, Alison [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=1C309F42D5D44D18A52B027BD0112778-ADAVIS06]
Sent: 4/29/2020 1:08:07 AM
To: Koerber, Mike [Koerber.Mike@epa.gov]
Subject: RE: Region 6 info
Attachments: DELIBERATIVE.OIG Response Draft2.ad comments.docx

Some preliminary thoughts. We definitely should discuss. Thanks for the opportunity to review.

From: Koerber, Mike <Koerber.Mike@epa.gov>
Sent: Tuesday, April 28, 2020 5:22 PM
To: Davis, Alison <Davis.Alison@epa.gov>
Subject: RE: Region 6 info

Here's the latest draft. Comments welcome. Let's talk on Wednesday morning.

Mike

From: Davis, Alison <Davis.Alison@epa.gov>
Sent: Tuesday, April 28, 2020 11:53 AM
To: Koerber, Mike <Koerber.Mike@epa.gov>
Subject: Region 6 info

Here is the info from David Garcia – they just followed up on the CAG information, which is pasted below this note.

A couple of things jump out here: LDEQ reached out to permittees – see letter, attachment1; and LEAN posted detailed information on their website five days after NATA was issued (see attachment 1). You may recall that, at David Gray's request, Kelly and Darcie spent some time walking Wilma Subra and Mary Lee Orr through the NATA results re. EtO – shortly before NATA went out, as I recall. Kelly will know that for certain.

Pinging Katie on Wisconsin info now.

I'm available to chat before 1, between 230 and 3, and after 4.
Thanks .
Alison

CAG info:
Community Activist Groups:
Sasol LC – Has Community Advisory Panel http://www.sasolnorthamerica.com/louisiana
Union Carbide Taft –Has Community Advisory Panel https://corporate.dow.com/en-us/locations/louisiana
Eastman (formerly Taminco_ - None identified. They do have a CAP for the Longview Texas facility
Evonik (formerly Air Products – Has Community Advisory Panel
BCP St. Gabriel – None identified

From: Garcia, David <Garcia.David@epa.gov>
Sent: Tuesday, April 28, 2020 11:43 AM
To: Davis, Alison <Davis.Alison@epa.gov>
Subject: FW: EtO Information for David

Alison,

Per your request, attached is response to your additional questions regarding EtO state outreach/material. Please note, we are reaching out to LDEQ, to see if we can get more insight as to whether the companies have a CAG. Upon receipt I will forward additional information.

David F. Garcia, P.E.
Director
Air and Radiation Division
Ph. 214 665 7593

U.S. EPA Region 6
1201 Elm Street
Dallas, Texas

From: Verhalen, Frances <verhalen.frances@epa.gov>
Sent: Monday, April 27, 2020 4:38 PM
To: Robinson, Jeffrey <Robinson.Jeffrey@epa.gov>
Subject: EtO Information for David

Jeff, here is summary of EtO information for David.

Fran

Frances Verhalen, P.E., Chief
Air Monitoring & Grants Section
US Environmental Protection Agency
1200 Elm Street, Suite 500 (MC 6ARPM)
Dallas, TX 75270
214-665-2172
verhalen.frances@epa.gov

Appointment

From: Tsirigotis, Peter [Tsirigotis.Peter@epa.gov]
Sent: 6/9/2021 6:01:43 PM
To: Tsirigotis, Peter [Tsirigotis.Peter@epa.gov]; Koerber, Mike [Koerber.Mike@epa.gov]; Culligan, Kevin [Culligan.Kevin@epa.gov]; Lassiter, Penny [Lassiter.Penny@epa.gov]; Cozzie, David [Cozzie.David@epa.gov]; South, Peter [South.Peter@epa.gov]; Fruh, Steve [Fruh.Steve@epa.gov]; McLamb, Marguerite [McLamb.Marguerite@epa.gov]; Witt, Jon [Witt.Jon@epa.gov]; Witosky, Matthew [Witosky.Matthew@epa.gov]; Spells, Charlene [Spells.Charlene@epa.gov]; Ferguson, Gregory [ferguson.gregory@epa.gov]; Mills, Kathy [Mills.Kathy@epa.gov]; Parker, Barrett [Parker.Barrett@epa.gov]; Lessard, Patrick [Lessard.Patrick@epa.gov]; Sasser, Erika [Sasser.Erika@epa.gov]; Rimer, Kelly [Rimer.Kelly@epa.gov]; Morris, Mark [Morris.Mark@epa.gov]; Saili, Katerine [saili.katerine@epa.gov]; Vasu, Amy [Vasu.Amy@epa.gov]; Petesch, Theresa (Tess) [petesch.theresa@epa.gov]; Dowd, Gregory [Dowd.Gregory@epa.gov]; Wayland, Richard [Wayland.Richard@epa.gov]; Johnson, Steffan [johnson.steffan@epa.gov]; Shappley, Ned [Shappley.Ned@epa.gov]; Noonan, Jenny [Noonan.Jenny@epa.gov]; Davis, Alison [Davis.Alison@epa.gov]; Bremer, Kristen [Bremer.Kristen@epa.gov]; Jones, Rhea [Jones.Rhea@epa.gov]; Wilson, Holly [Wilson.Holly@epa.gov]; Ndoh, Tina [Ndoh.Tina@epa.gov]; Wood, Anna [Wood.Anna@epa.gov]; Anderson, Lea [anderson.lea@epa.gov]; Marks, Matthew [Marks.Matthew@epa.gov]; Weatherhead, Darryl [Weatherhead.Darryl@epa.gov]; Langdon, Robin [Langdon.Robin@epa.gov]; Branning, Amy [Branning.Amy@epa.gov]; Srinivasan, Gautam [Srinivasan.Gautam@epa.gov]
CC: Senter, Stephen [Senter.Stephen@epa.gov]; Brown, Annette [Brown.Annette@epa.gov]; Joseph, Wanda [joseph.wanda@epa.gov]; Hunt, Virginia [Hunt.Virginia@epa.gov]; Blatcher, Tonya [Blatcher.Tonya@epa.gov]; Mozingo, Kristal [Mozingo.Kristal@epa.gov]; Michelsen-Correa, Stephani [michelsen-correa.stephani@epa.gov]; Feinberg, Stephen [Feinberg.Stephen@epa.gov]

Subject: EtO and Commercial Sterilizers Meeting
Attachments: OAQPS-EtO Sterilizers Meeting Request.docx; EtOSterilizersBriefing.OAQPS.06.15.21.docx
Location: Microsoft Teams Meeting

Start: 6/15/2021 5:00:00 PM
End: 6/15/2021 5:45:00 PM
Show Time As: Tentative

Required Attendees: Koerber, Mike; Culligan, Kevin; Lassiter, Penny; Cozzie, David; South, Peter; Fruh, Steve; McLamb, Marguerite; Witt, Jon; Witosky, Matthew; Spells, Charlene; Ferguson, Gregory; Mills, Kathy; Parker, Barrett; Lessard, Patrick; Sasser, Erika; Rimer, Kelly; Morris, Mark; Saili, Katerine; Vasu, Amy; Petesch, Theresa (Tess); Dowd, Gregory; Wayland, Richard; Johnson, Steffan; Shappley, Ned; Noonan, Jenny; Davis, Alison; Bremer, Kristen; Jones, Rhea; Wilson, Holly; Ndoh, Tina; Wood, Anna; Anderson, Lea; Marks, Matthew; Weatherhead, Darryl; Langdon, Robin; Branning, Amy; Srinivasan, Gautam
Optional Attendees: Senter, Stephen; Brown, Annette; Joseph, Wanda; Hunt, Virginia; Blatcher, Tonya; Mozingo, Kristal; Michelsen-Correa, Stephani; Feinberg, Stephen

6/15: Meeting materials attached
6/9: Scheduled for 6/15 at 1:45 PM

Microsoft Teams meeting

Join on your computer or mobile app
Click here to join the meeting

Or call in (audio only)
Ex. 6 Personal Privacy (PP) United States, Washington DC

Phone Conference ID: Ex. 6 Personal Privacy (PP)
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By participating in EPA hosted virtual meetings and events, you are consenting to abide by the agency's terms of use. In addition, you acknowledge that content you post may be collected and used in support of FOIA and eDiscovery activities.

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OAR Meeting Request Form
For Peter Tsirigotis

Date of this Request: June 8, 2021

Scheduling Point of Contact: Annette Brown 919-541-0532
Technical Point of Contact: Penny Lassiter, SPPD Director

Subject: EtO and Commercial Sterilizers Meeting

Purpose: To present the new risk modeling results and to discuss the schedule for the rulemaking and other related items.

- Next ADP Milestone:
- If applicable, due date to: OP __/__/__ (_ days review); OMB: __/__/__ (days review);
- Legal deadline: (specify court-ordered, settle agreement, court promise, etc.) due date _ _/__/___;
- Other firm deadline:

First possible date for meeting: June 15, 2021
Last possible date for meeting: June 17, 2021
Duration: 1 hour

Requested Audio / Video (*Mark with "X" appropriate communication line*)

_X_ **Video Location(s):**
List video locations needed (e.g., RTP, DC, Regions)– HQ will set up a bridge if needed
____ **HQ Conference Line:**
If requested, HQ staff will provide in meeting invite

Invitees (please list by Office and in Outlook format, e.g. *Last, First*):

Office/Org	Name (*Last, First*)
OAQPS:	Tsirigotis, Peter; Koerber, Mike; Culligan, Kevin; Lassiter, Penny; Cozzie, David; South, Peter; Fruh, Steve; McLamb, Marguerite; Witt, Jon; Witosky, Matthew; Spells, Charlene; Ferguson, Gregory; Mills, Kathy; Parker, Barrett; Lessard, Patrick; Sasser, Erika; Rimer, Kelly; Morris, Mark; Saili, Katherine; Vasu, Amy; Weatherhead, Darryl, Langdon, Robin; Petesch, Theresa (Tess); Dowd, Gregory; Wayland, Richard; Johnson, Steffan; Shappley, Ned; Noonan, Jenny; Davis, Alison; Bremer, Kristen; Jones, Rhea; Wilson, Holly; Ndoh, Tina; Wood, Anna
OGC:	Anderson, Lea; Branning, Amy, Srinivasan, Gautam; Marks, Matthew
Schedulers to Cc:	Senter, Stephen; Brown, Annette; Joseph, Wanda; Hunt, Virginia;

HQ Meeting Briefing Materials: Must provide to OAQPS IO by 5:00pm, 2 days before meeting

Appointment

From: Tsirigotis, Peter [Tsirigotis.Peter@epa.gov]
Sent: 3/1/2022 4:27:24 PM
To: Tsirigotis, Peter [Tsirigotis.Peter@epa.gov]; Koerber, Mike [Koerber.Mike@epa.gov]; Sasser, Erika [Sasser.Erika@epa.gov]; Lassiter, Penny [Lassiter.Penny@epa.gov]; Rimer, Kelly [Rimer.Kelly@epa.gov]; Michelsen-Correa, Stephani [michelsen-correa.stephani@epa.gov]; Vasu, Amy [Vasu.Amy@epa.gov]; Woody, Matt [Woody.Matt@epa.gov]; Witt, Jon [Witt.Jon@epa.gov]; Fruh, Steve [Fruh.Steve@epa.gov]; Moeller, Njeri [Moeller.Njeri@epa.gov]
CC: Jones, Rhea [Jones.Rhea@epa.gov]; Ward, Hillary [Ward.Hillary@epa.gov]; Cozzie, David [Cozzie.David@epa.gov]; Palmer, Angela.D [Palmer.Angela.D@epa.gov]; Mozingo, Kristal [Mozingo.Kristal@epa.gov]; Bass, Katherine [Bass.Katherine@epa.gov]; Joseph, Wanda [joseph.wanda@epa.gov]

Subject: EtO Commercial Sterilizer Revised Risk Results
Attachments: OAQPS Meeting Request_Tsirigotis_EtO Sterilizer Risk Results_Feb 28 2022_revised dates.docx; EtO_2022_Risk_Results_Briefing_for PT 3 3 2022_DRAFT_DELIBERATIVE_DO_NOT_DISTRIBUTE.pptx
Location: Microsoft Teams Meeting

Start: 3/3/2022 7:30:00 PM
End: 3/3/2022 8:00:00 PM
Show Time As: Tentative

Required Attendees: Koerber, Mike; Sasser, Erika; Lassiter, Penny; Rimer, Kelly; Michelsen-Correa, Stephani; Vasu, Amy; Woody, Matt; Witt, Jon; Fruh, Steve; Moeller, Njeri
Optional Attendees: Jones, Rhea; Ward, Hillary; Cozzie, David; Palmer, Angela.D; Mozingo, Kristal; Bass, Katherine; Joseph, Wanda

3/3 – Briefing materials attached

Microsoft Teams meeting

Join on your computer or mobile app
Click here to join the meeting

Join with a video conferencing device
sip:teams@video.epa.gov
Video Conference ID: Ex. 6 Personal Privacy (PP)
Alternate VTC instructions

Or call in (audio only)
Ex. 6 Personal Privacy (PP) United States, Washington DC
Phone Conference ID: Ex. 6 Personal Privacy (PP)
Find a local number | Reset PIN

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Learn More | Meeting options

[SEQ CHAPTER \h \r 1]OAQPS Meeting Request Form
For Peter Tsirigotis

Date of this Request: 2/28/22

Scheduling Point of Contact: Katherine Bass, 919-541-0518
OAQPS Point of Contact: Erika Sasser, 919-541-3889
Lead Technical Point of Contact: Amy Vasu 919-541-0107

Subject: EtO Commercial Sterilizer Revised Risk Results

Purpose: Share revised EtO commercial sterilizer risk results that are based on recent ICR responses.

- Next ADP Milestone: (specify early guidance, options selection, etc.); meeting scheduled on: __/__/__;
- If applicable, due date to: OP __/__/__ (_ days review); OMB: __/__/__ (days review);
- Legal deadline: Settlement agreement due date is __/__/__.
- Other firm deadline: Need to brief Joe Goffman by 3/10/22, prior to briefing Regional Offices the week of 3/13/2022, consistent with pre-proposal outreach schedule.

First possible date for meeting: 3/2/2022
Last possible date for meeting: 3/4/2022
Duration: 30 minutes

Requested Audio / Video (*Mark with "X" if requested*)
___X__ **Video Location(s):** Teams call
List video locations needed (e.g., Microsoft Office Teams, RTP, DC, Regions)– HQ will set up a bridge if needed
____ **HQ Conference Line:**
If requested, HQ staff will provide in meeting invite

Invitees (please list by Office and in Outlook format, e.g. *Last, First*):

Office/Org	Name (*Last, First*)
OAQPS:	Tsirigotis, Peter; Koerber, Mike; Sasser, Erika; Lassiter, Penny; Rimer, Kelly; Michelsen-Correa; Vasu, Amy; Woody, Matt; Witt, Jonathan; Fruh, Steve; Moeller, Njeri
Cc:	Jones, Rhea; Ward, Hillary; Cozzie, David
Schedulers to Cc:	Palmer, Angela; Mozingo Kristal; Bass, Katherine; Joseph,Wanda;

Meeting Briefing Materials: Must provide to OAQPS IO by 4:00pm, 1 day before meeting.

Revised 7/2021

Message

From: Koerber, Mike [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=9C513901D4FD49F9AB101A6F7A7A863E-KOERBER, MIKE]
Sent: 12/29/2020 1:57:09 PM
To: Ross, Aftin [Aftin.Ross@fda.hhs.gov]
CC: Schwartz, Suzanne [Suzanne.Schwartz@fda.hhs.gov]
Subject: RE: Response Requested by 11am EST: EPA Availability to Discuss Potential closure of New Mexico EtO Sterilization Facility

Aftin: Any of those times are okay. Also, our EPA regional office talked with the state of New Mexico yesterday. So, I'll be able to share what they learned.

Mike

From: Ross, Aftin <Aftin.Ross@fda.hhs.gov>
Sent: Monday, December 28, 2020 7:11 PM
To: Koerber, Mike <Koerber.Mike@epa.gov>
Cc: Witt, Jon <Witt.Jon@epa.gov>; Davis, Alison <Davis.Alison@epa.gov>; Shappley, Ned <Shappley.Ned@epa.gov>; Schwartz, Suzanne <Suzanne.Schwartz@fda.hhs.gov>
Subject: Re: Response Requested by 11am EST: EPA Availability to Discuss Potential closure of New Mexico EtO Sterilization Facility

Thank you.

Best,

Aftin

Get Outlook for iOS

From: Koerber, Mike <Koerber.Mike@epa.gov>
Sent: Monday, December 28, 2020 6:55:29 PM
To: Ross, Aftin <Aftin.Ross@fda.hhs.gov>
Cc: Witt, Jon <Witt.Jon@epa.gov>; Davis, Alison <Davis.Alison@epa.gov>; Shappley, Ned <Shappley.Ned@epa.gov>; Schwartz, Suzanne <Suzanne.Schwartz@fda.hhs.gov>
Subject: Re: Response Requested by 11am EST: EPA Availability to Discuss Potential closure of New Mexico EtO Sterilization Facility

Thanks, Aftin. I'll get back to you by 9:00 am tomorrow.

Mike

Sent from my iPhone

> On Dec 28, 2020, at 6:34 PM, Ross, Aftin <Aftin.Ross@fda.hhs.gov> wrote:
>
> Good evening. Would EPA have availability to meet at any of the following times tomorrow afternoon for 15-30 mins:
> 1pm EST

130pm EST
2pm EST

If you could let us know your availability by 11am EST tomorrow we would appreciate it. Should you not have availability at the proposed time, please propose an alternate meeting time.

Best,

Aftin
Get Outlook for iOS

From: Ross, Aftin <Aftin.Ross@fda.hhs.gov>
Sent: Monday, December 28, 2020 6:14:11 PM
To: Koerber, Mike <Koerber.Mike@epa.gov>
Cc: Witt, Jon <Witt.Jon@epa.gov>; Davis, Alison <Davis.Alison@epa.gov>; Weinstock, Lewis <Weinstock.Lewis@epa.gov>; Shappley, Ned <Shappley.Ned@epa.gov>; Schwartz, Suzanne <Suzanne.Schwartz@fda.hhs.gov>
Subject: Re: Potential closure of New Mexico EtO Sterilization Facility

Thanks Mike. We would like to chat and I will offer some meeting times for tomorrow afternoon a little later this evening.

Best,

Aftin

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From: Koerber, Mike <Koerber.Mike@epa.gov>
Sent: Monday, December 28, 2020 6:02:51 PM
To: Ross, Aftin <Aftin.Ross@fda.hhs.gov>
Cc: Witt, Jon <Witt.Jon@epa.gov>; Davis, Alison <Davis.Alison@epa.gov>; Weinstock, Lewis <Weinstock.Lewis@epa.gov>; Shappley, Ned <Shappley.Ned@epa.gov>; Schwartz, Suzanne <Suzanne.Schwartz@fda.hhs.gov>
Subject: Re: Potential closure of New Mexico EtO Sterilization Facility

Aftin: Yes, we saw this suit last week. Because EPA is not party to the suit, there's not much we can say at this time. But, happy to talk anytime this week, if you want.

Mike

Sent from my iPhone

> On Dec 28, 2020, at 4:09 PM, Ross, Aftin <Aftin.Ross@fda.hhs.gov> wrote:
>
> Good afternoon everyone. I know we canceled today's bi-weekly check-in as many staff were going to be out of the office for the winter break. However, we have an urgent question for EPA that we are hoping our EPA colleagues can provide additional information on. It has come to our attention that a major EtO facility in New Mexico may close. Specifically on December 22, the New Mexico Attorney General Hector Balderas filed suit in state court against a Sterigenics facility in Santa Teresa, New

Mexico. The suit seeks a temporary restraining order (TRO) and a hearing may be set for any day.

We wanted to find out if you were aware of this and any additional information you may have regarding this action (e.g. awareness of why New Mexico may be acting now and what products are sterilized there).

If it would be easier to have a quick tcon, we would be happy to schedule a time to chat tomorrow or another day this week that works for the EPA team.

Best,

Aftin

Aftin Ross, Ph.D.
Senior Project Manager
Senior Science Health Advisor
Team: All-Hazards Readiness Response and Cybersecurity (ARC)
Division: All hazards Response, Science and Strategic Partnerships (DARSS)
Office of Strategic Partnerships and Technology Innovation (OST)
Center for Devices and Radiological Health
U.S. Food and Drug Administration

WO 66, Room 5558
10903 New Hampshire Ave, Silver Spring, MD 20993
Office: 301-796-5679; Cell: 202-870-0517
aftin.ross@fda.hhs.gov

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https://www.research.net/s/cdrhcustomerservice?ID=7011&S=E

<image003.png>

Message

From: Koerber, Mike [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=9C513901D4FD49F9AB101A6F7A7A863E-KOERBER, MIKE]
Sent: 5/24/2021 4:49:50 PM
To: Carbonell, Tomas [Carbonell.Tomas@epa.gov]
Subject: New Mexico EtO Court Case
Attachments: draft sterigenics briefing material.docx

Hi, Tomas. My apologies for not raising this during today's OAQPS Weekly. (You mentioned that you were talking with OGC later today about SJV and thought I should get this on your radar in case it comes up.)

In a nutshell, the New Mexico State District Court has requested EPA to submit an amicus brief by June 6 in a case the NM Attorney General brought against Sterigenics in December 2020 concerning ethylene oxide emissions and their impact on surrounding communities. The key issue the court has raised is primary jurisdiction. As discussed in the attached paper Ex. 5 AC/DP

Ex. 5 AC/DP

Mike

From: Srinivasan, Gautam <Srinivasan.Gautam@epa.gov>
Sent: Thursday, May 20, 2021 1:03 PM
To: Koerber, Mike <Koerber.Mike@epa.gov>
Subject: paper for Joe 1-1

Hi Mike- Per our chat earlier this week, attached is a paper about the state court case re a Sterigenics facility in New Mexico. This is the paper we intend to use with Melissa, so it is more than the blurb you requested. But this will give you a full sense of the context and issues. Hopefully the paper is self-explanatory, but let me know if you have any questions.

Jonathan Witt and Kelly Rimer have been very helpful on the technical side, so special thanks to them.

PS- The paper is final despite being titled draft.
++++++++++++++++++++++++++++
(202) 564-5647 (o)
(202) 695-6287 (c)

Message

From: Koerber, Mike [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=9C513901D4FD49F9AB101A6F7A7A863E-KOERBER, MIKE]
Sent: 6/22/2021 9:18:04 PM
To: Mike Koerber (Koerber.Mike@epa.gov) [Koerber.Mike@epa.gov]; mikekoerber1@gmail.com
Subject: FW: For review and input: Recommendation for 2017 Sterilizer EtO data for national risk estimates
Attachments: Recommendation for 2017 Sterilizers data in national risk work.docx

---

From: Ward, Hillary <Ward.Hillary@epa.gov>
Sent: Tuesday, June 22, 2021 5:02 PM
To: Koerber, Mike <Koerber.Mike@epa.gov>
Cc: Vasu, Amy <Vasu.Amy@epa.gov>
Subject: For review and input: Recommendation for 2017 Sterilizer EtO data for national risk estimates

Hi Mike,

I'm following up on an outstanding item from the ATDAT. I previously mentioned that Marc's group developed options for handling 2017 EtO data. The approach they've outlined relies on publicly available info. AQAD prepared the attached pager for your review and input. Primary contact is Marc Houyoux. Chet is on leave , but aware of the pager.

Copying Amy as EtO coordinator.

Hillary Ward
USEPA, Office of Air Quality Planning and Standards
919.541.3154

Message

From: Koerber, Mike [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=9C513901D4FD49F9AB101A6F7A7A863E-KOERBER, MIKE]
Sent: 5/2/2022 10:33:42 PM
To: Vasu, Amy [Vasu.Amy@epa.gov]
Subject: Re: Does this work? -- with Sterigenics, Santa Teresa, NM
Attachments: image001.png; EtO Sterilizer National Webinar for SLTs Part 1_May 2 2022_revised 2.pptx

Okay. Thank, Amy.

Sent from my iPhone

On May 2, 2022, at 6:17 PM, Vasu, Amy <Vasu.Amy@epa.gov> wrote:

I revised the footnote to add the link to the OIG management alert update (shown in attached slide deck and below). The revised footnote for slide 12 would be:

** This facility no longer has elevated risk; however, in the 2018 NATA, it was identified has having elevated risk. As part of the Office of the Inspector General (OIG) management alert, EPA has committed to outreach to the community near this facility. Additional information is available at: https://www.epa.gov/hazardous-air-pollutants-ethylene-oxide/inspector-general-follow-ethylene-oxide-0

From: Vasu, Amy
Sent: Monday, May 2, 2022 6:00 PM
To: Koerber, Mike <Koerber.Mike@epa.gov>
Cc: Noonan, Jenny <Noonan.Jenny@epa.gov>; Bremer, Kristen <Bremer.Kristen@epa.gov>; Rimer, Kelly <Rimer.Kelly@epa.gov>
Subject: Does this work? -- with Sterigenics, Santa Teresa, NM

Hi Mike,

I've added Sterigenics, Santa Teresa, NM to the table (revised slide 12 shown below), with the following footnote:

> **This facility no longer has elevated risk; however, in the 2018 NATA, it was identified has having elevated risk. As part of the Office of the Inspector General (OIG) management alert, EPA has committed to outreach to the community near this facility.

Would you like any changes to this?

Thank you,

Amy

Message

From: Koerber, Mike [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=9C513901D4FD49F9AB101A6F7A7A863E-KOERBER, MIKE]
Sent: 8/1/2022 10:01:04 PM
To: Anderson, Lea [anderson.lea@epa.gov]
CC: Rimer, Kelly [Rimer.Kelly@epa.gov]; Branning, Amy [Branning.Amy@epa.gov]; Vasu, Amy [Vasu.Amy@epa.gov]
Subject: Re: Followup from our call and next steps

Thanks Lea!

Sent from my iPhone

On Aug 1, 2022, at 5:37 PM, Anderson, Lea <anderson.lea@epa.gov> wrote:

The statements below are consistent with our long-standing views on the 100-in-a-million risk threshold and factually accurate. Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Lea Anderson (she/her/hers)
(202) 564-5571

From: Koerber, Mike <Koerber.Mike@epa.gov>
Sent: Monday, August 1, 2022 4:40 PM
To: Anderson, Lea <anderson.lea@epa.gov>; Rimer, Kelly <Rimer.Kelly@epa.gov>; Branning, Amy <Branning.Amy@epa.gov>; Vasu, Amy <Vasu.Amy@epa.gov>
Subject: RE: Followup from our call and next steps

Thanks, Lea, for responding. Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Mike

Mike Koerber
o. 919-541-5557
c. 919-450-6478
he/him/his

From: Anderson, Lea <anderson.lea@epa.gov>
Sent: Monday, August 1, 2022 11:01 AM
To: Rimer, Kelly <Rimer.Kelly@epa.gov>; Koerber, Mike <Koerber.Mike@epa.gov>; Branning, Amy <Branning.Amy@epa.gov>; Vasu, Amy <Vasu.Amy@epa.gov>
Subject: RE: Followup from our call and next steps

Ex. 5 AC/DP

Ex. 5 AC/DP

Lea Anderson (she/her/hers)
(202) 564-5571

From: Rimer, Kelly <Rimer.Kelly@epa.gov>
Sent: Saturday, July 30, 2022 3:23 PM
To: Koerber, Mike <Koerber.Mike@epa.gov>; Rimer, Kelly <Rimer.Kelly@epa.gov>; Branning, Amy <Branning.Amy@epa.gov>; Anderson, Lea <anderson.lea@epa.gov>; Vasu, Amy <Vasu.Amy@epa.gov>
Subject: RE: Followup from our call and next steps

This works for me.

Thanks,
Kelly

From: Koerber, Mike <Koerber.Mike@epa.gov>
Sent: Saturday, July 30, 2022 12:04 PM
To: Rimer, Kelly <Rimer.Kelly@epa.gov>; Branning, Amy <Branning.Amy@epa.gov>; Anderson, Lea <anderson.lea@epa.gov>; Vasu, Amy <Vasu.Amy@epa.gov>
Subject: FW: Followup from our call and next steps

I'd appreciate your review of the response below to a comment from the CEO of BD – see July 29 email at the bottom of this string from Tom Polen to Joe Goffman. Thank you!

COMMENT: There is one additional item that I wanted to raise that we didn't touch on yesterday but is a topic which I have increasingly heard discussed. This is the perceived impact of how a risk screening tool threshold which has not been set as a standard or regulation is being used by state and federal regulators (and right or wrong industry perception that this is a result of the plaintiffs bar) in the absence of having gone through the formal rulemaking process. I am sure this has been thoroughly considered - Is there a position or communication that has been put out on this topic that can be referenced?

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Mike Koerber
o. 919-541-5557
c. 919-450-6478
he/him/his

From: Goffman, Joseph <Goffman.Joseph@epa.gov>
Sent: Friday, July 29, 2022 4:44 PM
To: Koerber, Mike <Koerber.Mike@epa.gov>
Cc: Carbonell, Tomas <Carbonell.Tomas@epa.gov>
Subject: FW: Followup from our call and next steps

Hi, Mike. Would you mind connecting with these gentlemen or having the right person on our team do so to serve as a point of contact and to address the issue in the second bullet? Ex. 5 Deliberative Process (DP)
Ex. 5 Deliberative Process (DP)

Thanks.

Joseph Goffman
Principal Deputy Assistant Administrator
Office of Air and Radiation
U.S. Environmental Protection Agency

From: Goffman, Joseph
Sent: Friday, July 29, 2022 4:40 PM
To: Tom Polen <tom_polen@bd.com>; Rakosnik, Delaney <rakosnik.delaney@epa.gov>
Cc: Todd Spangler <Todd_Spangler@bd.com>
Subject: RE: Followup from our call and next steps

Hi, Tom. Nice to meet you, Todd. I will have the appropriate colleagues here connect on both items below. Thanks for getting in touch with me.

Best,

Joe

Joseph Goffman
Principal Deputy Assistant Administrator
Office of Air and Radiation
U.S. Environmental Protection Agency

From: Tom Polen <tom_polen@bd.com>
Sent: Friday, July 29, 2022 4:03 PM
To: Goffman, Joseph <Goffman.Joseph@epa.gov>; Rakosnik, Delaney <rakosnik.delaney@epa.gov>
Cc: Todd Spangler <Todd_Spangler@bd.com>
Subject: Followup from our call and next steps

Joe, It was good to meet you yesterday, I very much appreciate the open and transparent discussion and the opportunity to work together. As a follow-up:

- We appreciate the opportunity to coordinate communications and work together so that negative impacts to patients care and medical device supply are prevented (that we remain very concerned about and see as an extremely high risk given much todays environment of lower than usual inventories in the supply chain, labor constraints and limited sterilization capacity). Todd Spangler (VP, Government Affairs) will take the lead from BD and is copied. Thank you in advance for connecting him with the right people at EPA.

- There is one additional item that I wanted to raise that we didn't touch on yesterday but is a topic which I have increasingly heard discussed. This is the perceived impact of how a risk screening tool threshold which has not been set as a standard or regulation is being used by state and federal regulators (and right or wrong industry perception that this is a result of the plaintiffs bar) in the absence of having gone through the formal rulemaking process. I am sure this has been thoroughly considered - Is there a position or communication that has been put out on this topic that can be referenced?

Tom

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****
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****
Corporate Headquarters Mailing Address: BD (Becton, Dickinson and Company) 1 Becton Drive Franklin Lakes, NJ 07417 U.S.A.

Message

From: Vasu, Amy [Vasu.Amy@epa.gov]
Sent: 9/27/2021 10:02:20 PM
To: Koerber, Mike [Koerber.Mike@epa.gov]
Subject: R6 file with dates for emission data -- RE: R6 and EtO data/community outreach timing -- FW: Following up regarding R6 commercial sterilizer emissions data -
Attachments: Region_6_EtO_EmissionsFile_09212021.xlsx

Mike,

Attached is the emission modeling file we sent to R6. Dates for facility emissions data, by emission point, are shown in columns R & S (highlighted in yellow). Dates range from 2020-2021 for some emission point/facility data to as old as a mix of data, for example, for Isomedix, Tarrant, TX, where fugitive emissions data range from 2009 for some processes to 2020-2021 for other processes. I do not have expertise with regard to the processes and emissions data beyond what I read from the file. Charlene would be able to provide a more refined explanation.

Thank you,

Amy

From: Koerber, Mike <Koerber.Mike@epa.gov>
Sent: Monday, September 27, 2021 5:31 PM
To: Vasu, Amy <Vasu.Amy@epa.gov>
Subject: RE: R6 and EtO data/community outreach timing -- FW: Following up regarding R6 commercial sterilizer emissions data -

Thanks, Amy. Yes, I saw the message from David Garcia. I'm not sure what he is referring to. I may call him to learn more.

Mike

From: Vasu, Amy <Vasu.Amy@epa.gov>
Sent: Monday, September 27, 2021 5:19 PM
To: Koerber, Mike <Koerber.Mike@epa.gov>
Subject: R6 and EtO data/community outreach timing -- FW: Following up regarding R6 commercial sterilizer emissions data -

Mike,

Ex. 5 Deliberative Process (DP)

Thank you,

Amy

From: Vasu, Amy
Sent: Monday, September 27, 2021 5:15 PM
To: Beal, Madeline <Beal.Madeline@epa.gov>
Subject: Following up regarding R6 commercial sterilizer emissions data -

Hi Madeline,

The data are the most current data we have for each facility, some from 2020-2021, some of different years for the same facility (e.g., 2019-2020 fugitives and older for other emission points). These are different from what's used for NATA (i.e., we have more current & detailed facility-specific info, where available). If you'd like more detail, I can reach out to our technical leads on the rule/emission data and the risk modeling.

Thanks,

Amy

Message

From: Hoffman, Kathy [KHoffman@soterahealth.com]
Sent: 1/4/2022 11:39:35 PM
To: tcr@vnf.com; Koerber, Mike [Koerber.Mike@epa.gov]
Subject: RE: Request for a Virtual Meeting

Thanks for the suggested dates and times.

For me, I can make the Thursday timeslot (1 to 2pm ET) and am also available on Friday from 10-11am and after noon ET.

Regards,
Kathy

From: Tom Roberts <tcr@vnf.com>
Sent: Tuesday, January 4, 2022 4:13 PM
To: Koerber, Mike <Koerber.Mike@epa.gov>
Cc: Hoffman, Kathy <KHoffman@soterahealth.com>
Subject: [EXTERNAL] Re: Request for a Virtual Meeting

CAUTION: This email originated from outside of the organization. **DO NOT CLICK** links or attachments unless you recognize the sender and know the content is safe.

Thanks, Mike. No worries on the delayed response.

I have conflicts for both time slots tomorrow (Wednesday) but 1:00 - 2:00 Eastern on Thursday works very well for me. I also am fairly flexible on Friday.

Kathy, what works best for you?

Thanks.

Tom Roberts | Partner

Van Ness Feldman, LLP

1050 Thomas Jefferson Street, NW

Washington, DC 20007

O: (202) 298-1930 | C: (202) 365-7750

tcr@vnf.com | vnf.com

Admitted to practice in Alaska and the District of Columbia

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From: Koerber, Mike <Koerber.Mike@epa.gov>
Sent: Tuesday, January 4, 2022 1:50 PM
To: Tom Roberts <tcr@vnf.com>
Cc: Hoffman, Kathy <KHoffman@soterahealth.com>
Subject: RE: Request for a Virtual Meeting

Caution: External Email.

Hi, Tom. Sorry not responding to your earlier note. Yes, happy to schedule some time. I'm open on Wednesday (2:00-2:30 and 3:00-4:00 pm EST), Thursday (1:00-2:00 pm EST) and Friday (almost all day). Just let me know what day/time work best for you.

Mike

Mike Koerber
o. 919-541-5557
c. 919-450-6478
he/him/his

From: Tom Roberts <tcr@vnf.com>
Sent: Tuesday, January 4, 2022 4:14 PM
To: Koerber, Mike <Koerber.Mike@epa.gov>
Cc: Hoffman, Kathy <KHoffman@soterahealth.com>
Subject: Re: Request for a Virtual Meeting
Importance: High

Mike - I hope you and your family had a relaxing and enjoyable holiday.

I am just following up on this request I sent a couple of weeks ago. It would be great if Kathy and I could get 30 minutes of your time in the next few days. As you may have heard, we expect our permit from Georgia EPD to be issued within the next couple of days. Similarly, we had a rather favorable ruling from the District Court in New Mexico regarding Sterigenics' Santa Teresa facility. We would like to update you on both.

Thanks, Mike.

Tom Roberts | Partner

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Washington, DC 20007

O: (202) 298-1930 | C: (202) 365-7750

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From: Tom Roberts <tcr@vnf.com>
Sent: Tuesday, December 21, 2021 9:46 AM
To: Koerber, Mike <Koerber.Mike@epa.gov>
Cc: Hoffman, Kathy <KHoffman@soterahealth.com>
Subject: Request for a Virtual Meeting

Mike - I hope you are able to get a little downtime with your family during the holidays. I expect things to be fairly hectic for you and your team after the first of the year.

In that regard, would you be available for a call with Kathy Hoffman and me sometime during the week of January 3-7 to catch up on our various ethylene oxide issues and matters?

Thanks Mike. Wishing you all the best for the holidays.

Tom Roberts | Partner

Van Ness Feldman, LLP

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Washington, DC 20007

O: (202) 298-1930 | C: (202) 365-7750

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Message

From: Tom Roberts [tcr@vnf.com]
Sent: 1/4/2022 10:13:07 PM
To: Koerber, Mike [Koerber.Mike@epa.gov]
CC: Hoffman, Kathy [KHoffman@soterahealth.com]
Subject: Re: Request for a Virtual Meeting

Thanks, Mike. No worries on the delayed response.

I have conflicts for both time slots tomorrow (Wednesday) but 1:00 - 2:00 Eastern on Thursday works very well for me. I also am fairly flexible on Friday.

Kathy, what works best for you?

Thanks.

Tom Roberts | Partner
Van Ness Feldman, LLP
1050 Thomas Jefferson Street, NW
Washington, DC 20007

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From: Koerber, Mike <Koerber.Mike@epa.gov>
Sent: Tuesday, January 4, 2022 1:50 PM
To: Tom Roberts <tcr@vnf.com>
Cc: Hoffman, Kathy <KHoffman@soterahealth.com>
Subject: RE: Request for a Virtual Meeting

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Mike

Mike Koerber
o. 919-541-5557
c. 919-450-6478
he/him/his

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Sent: Tuesday, January 4, 2022 4:14 PM
To: Koerber, Mike <Koerber.Mike@epa.gov>
Cc: Hoffman, Kathy <KHoffman@soterahealth.com>
Subject: Re: Request for a Virtual Meeting
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Thanks, Mike.

Tom Roberts | Partner
Van Ness Feldman, LLP
1050 Thomas Jefferson Street, NW
Washington, DC 20007

O: (202) 298-1930 | C: (202) 365-7750

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From: Tom Roberts <tcr@vnf.com>
Sent: Tuesday, December 21, 2021 9:46 AM
To: Koerber, Mike <Koerber.Mike@epa.gov>
Cc: Hoffman, Kathy <KHoffman@soterahealth.com>
Subject: Request for a Virtual Meeting

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Tom Roberts | Partner
Van Ness Feldman, LLP
1050 Thomas Jefferson Street, NW
Washington, DC 20007

O: (202) 298-1930 | C: (202) 365-7750

tcr@vnf.com | vnf.com

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Message

From: Vasu, Amy [Vasu.Amy@epa.gov]
Sent: 1/18/2022 11:05:41 PM
To: Ross, Aftin [Aftin.Ross@fda.hhs.gov]
CC: Koerber, Mike [Koerber.Mike@epa.gov]
Subject: Following up -- Sterigenics, Santa Teresa, NM
Attachments: 2022-01-07 Deft Sterigenics Rpt Re ITS Installation of the Negative Pressure System.pdf; 2021-12-22 Order on MTDs.pdf

Aftin,

As a follow-up to your request for updates regarding the Sterigenics, Santa Teresa, NM facility, attached is the order denying the defendants' motions to dismiss (December 2021) and their Report Concerning Its Installation of the Negative Pressure System (January 2022).

Regards,

Amy

Amy Vasu (*she/her*)
Air Toxics Assessment Group
U.S. EPA/OAQPS/HEID
Research Triangle Park, NC
919.541.0107

FILED
3rd JUDICIAL DISTRICT COURT
Dona Ana County
1/7/2022 3:31 PM
DAVID S. BORUNDA
CLERK OF THE COURT
Joseph Martinez

STATE OF NEW MEXICO
COUNTY OF DOÑA ANA
THIRD JUDICIAL DISTRICT COURT

THE STATE OF NEW MEXICO, EX REL. HECTOR BALDERAS, ATTORNEY GENERAL, Plaintiff, v. STERIGENICS U.S., LLC, SOTERA HEALTH HOLDINGS, LLC, SOTERA HEALTH LLC, AND SOTERA HEALTH COMPANY, Defendants.	)	No. D-307-CV-2020-02629

DEFENDANT STERIGENICS U.S., LLC'S REPORT CONCERNING ITS INSTALLATION OF THE NEGATIVE PRESSURE SYSTEM

Pursuant to the Court's December 20, 2021 Order, Defendant Sterigenics U.S., LLC ("Sterigenics U.S") hereby submits this report concerning the progress and status of the enhancements for the Negative Pressure System at its Santa Teresa sterilization facility (the "Facility"):

1. All areas of the Facility where ethylene oxide is present are currently under negative pressure, and the air in approximately 70% of the indoor areas of the Facility is presently routed through an internal recirculating emissions control system.
2. The New Mexico Environment Department issued the Air Quality Permit attached hereto as Exhibit A to approve the Negative Pressure System on June 11, 2021.
3. Doña Ana County issued Sterigenics U.S. a Building Permit to begin work on the enhancements for the Negative Pressure System on October 15, 2021.

ED_013218_00001724-00001

4. Subcontracts for the various work scopes necessary for the Negative Pressure System work have been awarded.
5. The additional blower fans, additional catalytic oxidizer emissions control system, and other major equipment for the Negative Pressure System are on order.
6. The new emissions stack for the Negative Pressure System is in transit to the Facility.
7. All additional drybeds previously ordered to increase the capacity of the Facility's indoor air drybed filtration system have been delivered to the Facility.
8. This week (the week of January 3) the Facility is not in operation, for a scheduled shutdown to continue work on the Negative Pressure System. That scheduled work includes structural reinforcement work to support emissions control enhancements infrastructure for the Negative Pressure System, and installation of ductwork for capturing and cleaning the indoor air of additional areas inside the Facility.

[signature on following page]

ED_013218_00001724-00002

Respectfully submitted this January 7, 2022.

MODRALL, SPERLING, ROEHL, HARRIS
& SISK, P.A.

By: */s/ Jeremy K. Harrison*
Alex C. Walker (awalker@modrall.com)
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WE HEREBY CERTIFY that a true and correct copy of the foregoing was submitted through the Odyssey Electronic Filing System for filing and service to all counsel of record this 7th day of January 7, 2022.

MODRALL, SPERLING, ROEHL, HARRIS
& SISK, P.A.

By: */s/ Jeremy K. Harrison*
Jeremy K. Harrison

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AIR QUALITY BUREAU
NEW SOURCE REVIEW PERMIT
Issued under 20.2.72 NMAC

Certified Mail No:

NSR Permit No:	0733-M15-R2
Facility Name:	Sterigenics – Santa Teresa Facility
Permittee Name:	Sterigenics US., LLC
Mailing Address:	2015 Spring Road, Suite 650 Oak Brook, Il 60523
TEMPO/IDEA ID No:	127-PRN20210001
AIRS No:	35-013-0007
Permitting Action:	Technical Permit Revision
Source Classification:	Synthetic Minor
Facility Location:	340,303 m E by 3,526,222 m N, Zone 13; Datum NAD83
County:	Doña Ana County
Air Quality Bureau Contact	Marvin Mascareñas
Main AQB Phone No.	(505) 476-4300

For Liz Bisbey-Kuehn
Bureau Chief
Air Quality Bureau

Date

Template version: 05/26/2021

EXHIBIT A

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PART A FACILITY SPECIFIC REQUIREMENTS

A100 Introduction

A. This permit, NSR 0733-M15-R2, supersedes all portions of Air Quality Permit NSR 0733-M15-R1, issued December 23, 2014, except portions requiring compliance tests. Compliance test conditions from previous permits, if not completed, are still in effect, in addition to compliance test requirements contained in this permit.

B. Fee Requirement: This permit is not effective until the Department receives the permit fee specified in the attached invoice. Pursuant to 20.2.75.12 NMAC, the permittee shall pay this invoice no later than thirty (30) days after the permit issue date (invoicing), unless the Department has granted an extension. The permit fee must be paid by this date regardless of the permittee's intended use or non-use of the permit or of the Department's cancellation of the permit. The permittee's failure to pay this fee when due will automatically void the permit and the Department may initiate enforcement action to collect the fee and assess a civil penalty for non-payment. The permittee shall not construct the equipment S-1 to S-13, BV13, CD4, DBPS 1 or DB1 in Table 104.A. before the date that the Department receives the permit fee in full. The Department may initiate enforcement action for injunctive relief and civil penalties for any construction or operation specified in Table 104., Units S-1 to S-13, BV13, CD4, DBPS 1 or DB1 if the permit fee is not paid by the due date.

A101 Permit Duration (expiration)

A. The term of this permit is permanent unless withdrawn or cancelled by the Department.

A102 Facility: Description

A. The function of the facility is to sterilize medical devices and food products by exposure to ethylene oxide and propylene oxide gases.

B. This facility is located approximately 2 miles northwest of Santa Teresa, New Mexico in Doña Ana County.

A. This modification consists of:

(1) Route the existing acid-water scrubber (CD 2) exhausts to a bank of dry bed control systems (DBPS 1) with a destruction efficiency of approximately 80% to further reduce vacuum pump emissions, and to redirect the outlet of this bank of dry beds to the existing catalytic oxidizer (CD 3) stack.

(2) Install an additional catalytic oxidizer (CD 4), equipped with a natural gas burner with an approximate rating of 4.7 MMBTU, with a control efficiency of at least 99%, or 1 ppm ethylene oxide or propylene oxide at the outlet. The site's control scheme will be modified so that the new oxidizer (CD 4) would control emissions from the facility's aeration rooms (AR 8 and AR 9) instead of the existing catalytic oxidizer (CD 3).

(3) The existing catalytic oxidizer (CD 3), and the new catalytic oxidizer (CD 4) will be installed with the capability of operating both units simultaneously during normal operation, and for either unit to provide continuing emission control for site operations during periods of maintenance or malfunction when one of the units may be down.

(4) A negative pressure and dry bed bank system (DB 1) is proposed to be installed to capture air internally from chamber rooms, work aisles, processed product storage, and shipping areas. With this system and other work, the facility will modify the flow of indoor air. Indoor air from the Chamber 1-7 area will be sent to the existing catalytic oxidizer (CD 3). Indoor air from the Chamber 8-14 area will be sent to the new bank of dry beds (DB 1) which will then exhaust to the stack of the new catalytic oxidizer (CD 4). When applied to treat indoor air, the dry bed system (DB 1) is expected to reduce ethylene oxide levels by approximately 80%, or 1 ppm at the outlet. CD 3 has a control efficiency of at least 99%, or 1 ppm at the outlet.

(5) Like-kind replacement of Chamber 1 with an equivalently sized chamber vessel, backvent (BV 1), and vacuum pump (S 1). The existing vacuum pump (S 1) will be replaced with a dry screw style vacuum. The dry screw style vacuum pump will provide the same sealing capability as the previous oil-seal pump. This will require a revision to permit condition A800 B. "Oil Seals" that requires all pumps in contact with EO or PO to have closed-loop oil seals.

(6) Improvements to the stacks of the facility's existing commercial natural gas-fired boilers (Boiler 1 and Boiler 2, collectively permitted as Bx) are also planned to be made. These changes to the site's two existing natural gas boilers (Bx) will increase dispersion of the boiler's combustion of natural gas by removing rain caps, installing rain drainage appurtenances, and velocity cones to both boiler stacks. The stack of the outside boiler (Boiler 1 - Bx) will also be extended to reach a minimum of 20 feet.

(7) Like-kind replacement of Chamber 5 and 7's existing vacuum pumps (S 5 and S 7) with new dry screw style vacuum pumps with a flow capacity restricted to existing permit levels using an orifice plate flow restrictor. These dry screw style pumps provide the same sealing capability of the existing wet-seal pumps. This will also require a revision to permit condition A800 B. "Oil Seals" that requires all pumps in contact with EO or PO to have closed-loop oil seals.

(8) Update permit information, model and serial numbers.

The description of this modification is for informational purposes only and is not enforceable.

B. Tables 102.A and Table 102.B show the total potential emission rates (PER) from this facility for information only. This is not an enforceable condition and excludes emissions from Minor NSR exempt activities per 20.2.72.202 NMAC.

Table 102.A: Total Potential Emission Rate (PER) from Entire Facility

Pollutant	Emissions (tons per year)
Nitrogen Oxides (NOx)	7.9
Carbon Monoxide (CO)	11.9
Volatile Organic Compounds (VOC)	2.6
Sulfur Dioxide (SO_2)	<1
Particulate Matter 10 microns or less (PM_{10})	<1

Table 102.B: Total Potential Emissions Rate (PER) for *Hazardous Air Pollutants (HAPs) that exceed 1.0 ton per year

Pollutant	Emissions (tons per year)
Ethylene Oxide	1.6
Propylene Oxide	
Total HAPs**	1.6

* HAP emissions are already included in the VOC emission total.

** The total HAP emissions may not agree with the sum of individual HAPs because only individual HAPs greater than 1.0 tons per year are listed here.

A103 Facility: Applicable Regulations

A. The permittee shall comply with all applicable sections of the requirements listed in Table 103.A.

Table 103.A: Applicable Requirements

Applicable Requirements	Federally Enforceable	Unit No.
20.2.1 NMAC General Provisions	X	Entire Facility
20.2.3 NMAC Ambient Air Quality Standards	X	Entire Facility
20.2.7 NMAC Excess Emissions	X	Entire Facility
20.2.61 NMAC Smoke and Visible Emissions	X	Bx, CD3 and CD4
20.2.72 NMAC Construction Permit	X	Entire Facility
20.2.73 NMAC Notice of Intent and Emissions Inventory Requirements	X	Entire Facility
20.2.75 NMAC Construction Permit Fees	X	Entire Facility

Table 103.A: Applicable Requirements

Applicable Requirements	Federally Enforceable	Unit No.
20.2.82 NMAC Maximum Achievable Control Technology Standards for Source Categories of HAPs	X	Sterilization Equipment
40 CFR 50 National Ambient Air Quality Standards	X	Sterilization Equipment
40 CFR 63, Subpart A, General Provisions	X	Entire Facility
40 CFR 63, Subpart O	X	Entire Facility

A104 Facility: Regulated Sources

A. Table 104.A lists the emission units authorized for this facility. Emission units identified as exempt activities (as defined in 20.2.72.202 NMAC) and/or equipment not regulated pursuant to the Act are not included.

Table 104.A: Regulated Sources List

Unit No.	Source Description	Make	Model	Serial No.	Construction/ Reconstruction Date	Manufacture Date	Manufacturer Rated Capacity /Permitted Capacity
S-1	Sterilizer #1 Vacuum Pump	TBD	TBD	TBD	TBD	TBD	TBD
S-2	Sterilizer #2 Vacuum Pump	Dekker	DV02516 DA2	050725G07	Not Reported	2006	250 cfm
S-3	Sterilizer # 3 Vacuum Pump	Dekker	DV0251B-DA3	060920G01	Not Reported	2014	250 cfm
S-4	Sterilizer #4 Vacuum Pump	Dekker	DV025OB DA2	12005	Not Reported	2014	250 cfm
S-5	Sterilizer #5 Vacuum Pump	TBD	TBD	TBD	TBD	TBD	TBD
S-6	Sterilizer #6 Vacuum Pump	Dekker	DV0251B-DA3	070129G03	Not Reported	2014	250 cfm
S-7	Sterilizer #1 Vacuum Pump	TBD	TBD	TBD	TBD	TBD	TBD
S-8	Sterilizer #8 Vacuum Pump	Dekker	PUMP A&B DV0550B-KA3	C02373602/ C02373601	Not Reported	2014	2 @ 550 cfm
S-9	Sterilizer #9 Vacuum Pump	Dekker	DV0550B-KA3/DV0550 B-KA2	060427G05/ C02373609	Not Reported	2014	2 @ 550 cfm
S-10	Sterilizer #10 Vacuum Pump	Dekker	DV0550B-KA2	071031G06	Not Reported	2014	550 cfm
S-11	Sterilizer #11 Vacuum Pump	Dekker	DV0550B-KA2	050628G02	Not Reported	2014	550 cfm
S-12	Sterilizer #12 Vacuum Pump	Sterling SIHI	LEHA 900 AB	BFK4SP	Not Reported	2006	550 cfm
S-13	Sterilizer #13 Vacuum Pump	TBD	TBD	TBD	TBD	TBD	TBD
S-14	Sterilizer #14 Vacuum Pump	TBD	TBD	TBD	TBD	TBD	TBD
AR 8	Aeration Room #8	Blower	Blower	-	Modified 2007	2006	9000 cfm

Table 104.A: Regulated Sources List

Unit No.	Source Description	Make	Model	Serial No.	Construction/ Reconstruction Date	Manufacture Date	Manufacturer Rated Capacity /Permitted Capacity
AR 9	Aeration Room #9	Blower	Blower	-	Modified 2013	2010	6000 cfm
BV 1	Back Vent Exhaust for Sterilizer 1	Captive Air	BI18CARM	455172	Not Reported	1986	3000 cfm
BV 2	Back Vent Exhaust for Sterilizer 2	Captive Air	BI18CARM	404418	Not Reported	1986	3000 cfm
BV 3	Back Vent Exhaust for Sterilizer 3	Dayton	UK	D2C799A	Not Reported	1986	1800 cfm
BV 4	Back Vent Exhaust for Sterilizer 4	Dayton	UK	2C799A	Not Reported	1986	1800 cfm
BV 5	Back Vent Exhaust for Sterilizer 5	Dayton	UK	13C074A	Not Reported	1986	1800 cfm
BV 6	Back Vent Exhaust for Sterilizer 6	Dayton	UK	D3C074A	Not Reported	1986	1800 cfm
BV 7	Back Vent Exhaust for Sterilizer 7	Dayton	UK	10C074A	Not Reported	1995	1800 cfm
BV 8	Back Vent Exhaust for Sterilizer 8	Greenheck	12-BISW-41-10-11	11865778 - 0909	Not Reported	2013	1800 cfm
BV 9	Back Vent Exhaust for Sterilizer 9	Greenheck	12-BISW-41-10-11	12327114 - 1102	Not Reported	2011	1800 cfm
BV 10	Back Vent Exhaust for Sterilizer 10	Greenheck	12-BISW-41-10-11	11872437 - 0909	Not Reported	2010	1800 cfm
BV 11	Back Vent Exhaust for Sterilizer 11	Greenheck	12-BISW-41-10-11	05L11546	Not Reported	2005	1800 cfm
BV 12	Back Vent Exhaust for Sterilizer 12	Greenheck	12-BISW-41-10-11	5647269-12982637	Not Reported	2007	2000 cfm
BV 13	Back Vent Exhaust for Sterilizer 13	TBD	TBD	TBD	TBD	TBD	TBD
BV 14	Back Vent Exhaust for Sterilizer 14	TBD	TBD	TBD	TBD	TBD	TBD
CD 2	Acid - Water Scrubber	Ceilcote	SPT-54-240	81318	Not Reported	2004	2,500 cfm
CD 3	Catalytic Oxidizer	Donaldson	20,000 AG EtO Abator	None	Not Reported	1991	20,000 cfm
CD 4	Catalytic Oxidizer	TBD	TBD	TBD	TBD	TBD	TBD
Bx	Any Combination of natural gas boilers with maximum combined	Various	Various	Various	Various	Not Reported	18.0 MMbtu/hr (Combined Max)
DBPS 1	Dry Bed Polishing System	AAT	-	-	TBD	Not Reported	2 Banks - 2000 cfm per bank
DB 1	Dry Bed	AAT	-	-	TBD	Not Reported	5 Banks - 2000 cfm per bank

1. All TBD (to be determined) units and like-kind engine replacements must be evaluated for applicability to NSPS and MACT requirements.

A105 Facility: Control Equipment

A. Table 105 lists all the pollution control equipment required for this facility. Each emission point is identified by the same number that was assigned to it in the permit application.

Table 105: Control Equipment List:

Control Equipment Unit No.	Control Description	Pollutant being controlled	Control for Unit Number(s)[1]
CD-2	Ceilcote Acid – Water Scrubber System	Ethylene Oxide / Propylene Oxide	S-1 – S-14
CD-3	Donaldson 20,000 AG EtO Abator – Catalytic Oxidizer	Ethylene Oxide / Propylene Oxide	BV 1 – BV 14
CD-4	Catalytic Oxidizer	Ethylene Oxide / Propylene Oxide	AR 8 & AR 9

1. Control for unit number refers to a unit number from the Regulated Equipment List

A106 Facility: Allowable Emissions

A. The following Section lists the emission units and their allowable emission limits. (40 CFR 50, 40 CFR 63, Subpart O, 20.2.72.210.A and B.1 NMAC).

Table 106.A: Allowable Emissions

Unit No.	NO_x[1] pph	NO_x[1] tpy	CO pph	CO tpy	VOC pph	VOC tpy	EO or PO pph	EO or PO tpy
CD 3 Stack[4]	<	1.6	<	1.4	<	1.3	0.3	1.2
CD 4 Stack[5]	<	<	<	3.8	<	<	0.1	0.3

1 Nitrogen dioxide emissions include all oxides of nitrogen expressed as NO_2
2 "-" indicates the application represented emissions of this pollutant are not expected.
"<" indicates that the application represented the uncontrolled mass emission rates are less than 1.0 pph or 1.0 tpy for this emissions unit and this air pollutant. The Department determined that allowable mass emission limits were not required for this unit and this pollutant
"*" indicates hourly emission limits are not appropriate for this operating situation.
3 To report excess emissions for sources with no pound per hour and/or ton per year emission limits, see condition B110F.
4 Emissions from S-1 to-S-14, CD 2, DBPS1, CD 3 Burner, BV1 to BV14, and fugitives are routed to the shared stack CD 3.
5 Emissions from CD 4 Burner, AR 8, AR9, DB1, and fugitives are routed to the shared stack CD 4.

A107 Facility: Allowable Startup, Shutdown, & Maintenance (SSM) and Malfunction Emissions

A. Separate allowable SSM emission limits are not required for this facility since the SSM emissions are predicted to be less than the limits established in Table 106A. The permittee shall maintain records in accordance with Condition B109.C.

A108 Facility: Allowable Operations

A. This facility is authorized for continuous operation. Monitoring, recordkeeping, and reporting are not required to demonstrate compliance with continuous hours of operation.

B. Propylene oxide (PO) may be substituted for ethylene oxide (EO), but the combined maximum charges are limited to the charge rate(s) specified in Condition A108.C and the PO emission shall be routed through the same control equipment as the EO emissions.

C. Ethylene Oxide and Propylene Oxide Charging Rates

Requirement: The combined maximum ethylene oxide gas charge rate(s) to the sterilizer chambers (Units S-1 to S-14) shall not exceed the following limits: (a) 1,790 lbs per hour, hourly average and averaged over a 24-hour period, (b) 1,692,000 lbs per 12-month period, calculated as a monthly rolling 12-month total.
Monitoring: Hourly, the permittee shall monitor the following: (1) EO or PO charge rates for each of the sterilization chambers (Units S-1 to S-14).
Recordkeeping: Records shall include: (1) Date; (2) EO or PO pounds per hour averaged over a 24 hour period; (3) EO or PO pounds per 12 month period, calculated as a monthly rolling 12-month total.
Reporting: The permittee shall report in accordance with Section B110.

A109 Facility: Reporting Schedules

A. The permittee shall report according to the Specific Conditions and General Conditions of this permit.

A110 Facility: Fuel and Fuel Sulfur Requirements

A. Fuel and Fuel Sulfur Requirements (Units CD3, CD4 and Bx)

Requirement: All combustion emission units shall combust only natural gas containing no more than 5 grains of total sulfur per 100 dry standard cubic feet.
Monitoring: No monitoring is required. Compliance is demonstrated through records.

Recordkeeping: The permittee shall demonstrate compliance with the natural gas or fuel oil limit on total sulfur content by maintaining records of a current, valid purchase contract, tariff sheet or transportation contract for the gaseous or liquid fuel, or fuel gas analysis, specifying the allowable limit or less.

Reporting: The permittee shall report in accordance with Section B110.

A111 Facility: 20.2.61 NMAC Opacity

A. 20.2.61 NMAC Opacity Limit (Units CD3, CD4 and Bx)

Requirement: Visible emissions from all stationary combustion emission stacks shall not equal or exceed an opacity of 20 percent in accordance with the requirements at 20.2.61.109 NMAC.

Monitoring:

(1) Use of natural gas fuel constitutes compliance with 20.2.61 NMAC unless opacity equals or exceeds 20% averaged over a 10-minute period. When any visible emissions are observed during operation other than during startup mode, opacity shall be measured over a 10-minute period, in accordance with the procedures at 40 CFR 60, Appendix A, Reference Method 9 (EPA Method 9) as required by 20.2.61.114 NMAC, or the operator will be allowed to shut down the equipment to perform maintenance/repair to eliminate the visible emissions. Following completion of equipment maintenance/repair, the operator shall conduct visible emission observations following startup in accordance with the following procedures:

(a) Visible emissions observations shall be conducted over a 10-minute period during operation after completion of startup mode in accordance with the procedures at 40 CFR 60, Appendix A, Reference Method 22 (EPA Method 22). If no visible emissions are observed, no further action is required.

(b) If any visible emissions are observed during completion of the EPA Method 22 observation, subsequent opacity observations shall be conducted over a 10-minute period, in accordance with the procedures at EPA Method 9 as required by 20.2.61.114 NMAC.

For the purposes of this condition, *Startup mode* is defined as the startup period that is described in the facility's startup plan.

Recordkeeping:

(1) If any visible emissions observations were conducted, the permittee shall keep records in accordance with the requirements of Section B109 and as follows:

(a) For any visible emissions observations conducted in accordance with EPA Method 22, record the information on the form referenced in EPA Method 22, Section 11.2.

(b) For any opacity observations conducted in accordance with the requirements of EPA Method 9, record the information on the form referenced in EPA Method 9, Sections

2.2 and 2.4.
Reporting: The permittee shall report in accordance with Section B110.

A112 Facility: Haul Roads – Not Applicable

A113 Facility: Initial Location Requirements – Not Applicable

A114 Facility: Relocation Requirements

A. This facility may not be relocated.

A115 Alternative Operating Scenario – Not Applicable

A116 Compliance Plan – Not Applicable

EQUIPMENT SPECIFIC REQUIREMENTS

A200 Oil and Gas Industry – Not Required

A300 Construction Industry – Aggregate – Not Required

A400 Construction Industry – Asphalt – Not Required

A500 Construction Industry – Concrete – Not Required

A600 Power Generation Industry – Not Required

A700 Solid Waste Disposal (Landfills) Industry – Not Required

STERILIZATION FACILITIES INTRODUCTION

A800 Sterilization Facilities Introduction

A. 40 CFR 63 Subpart O: Ethylene Oxide Emissions Standards for Sterilization Facilities

Requirement: This facility is subject to 40 CFR 63, Subparts A and O and shall comply with all applicable requirements of the regulation.
Monitoring: The permittee shall comply with all applicable monitoring requirements of 40 CFR 63, Subparts A and O.

Recordkeeping: The permittee shall comply with all applicable recordkeeping requirements of 40 CFR 63, Subparts A and O.
Reporting: The permittee shall comply with all applicable recordkeeping requirements of 40 CFR 63, Subparts A and O.

B. Oil Seals (Units S-2, S-3, S-4, S-6, S-8, S-9, S-10, S-11, S-12, S-13 and possibly S-14)

Requirement: All pumps in contact with EO or PO shall have closed-loop oil seals. All oil seals shall be maintained to ensure integrity. This condition does not apply to dry screw pumps.
Monitoring: The permittee shall inspect the oil seals weekly to ensure proper operations.
Recordkeeping: The permittee shall keep records of the required monitoring and any maintenance performed for EO or PO pump oil seals.
Reporting: The permittee shall report in accordance with Section B110.

C. This Specific Condition (A800.C) supersedes General Condition B111.C.4.:

During emissions tests, pollutant, O_2 concentration and fuel flow rate ***(if fuels are being combusted)*** shall be monitored and recorded. This information shall be included with the test report furnished to the Department.

A801 <u>Sterilization Chamber</u>

A. Sterilization Chambers (Units S1- S14)

Requirement: The permittee shall not operate any sterilization chambers unless their respective emission control equipment CD-2 is operated in accordance with manufacturer specifications.
Monitoring: To ensure that the control equipment is operating in accordance with manufacturer specifications, during each day that the sterilization chambers are in use, the permittee shall monitor: (1) The control equipment CD-2 is operating within the specified parameters in Condition A801.B.
Recordkeeping: The permittee shall maintain records of all daily inspections and record all of the parameters specified in Condition A801.B.
Reporting: The permittee shall report in accordance with Section B110.

B. Acid-Water Scrubber (Unit CD-2)

Requirement: All emissions from Units S-1 to S-14 shall be ducted to the acid-water scrubber CD-2. The permittee shall not operate the units S1 to S14 unless the unit CD-2 is operating within the specified parameters in this condition. Compliance with this condition demonstrates compliance with the emission limits in Table 106.A for Unit CD-2.
Monitoring: Each day, the permittee shall monitor the following parameters for each acid-water scrubber operated in any one calendar day. For CD-2, the permittee shall monitor:

(1) The gas flow rate shall not exceed 2500 SCFM @ 90 degrees Fahrenheit;

(2) The liquid temperature shall not exceed 120 degrees Fahrenheit;

(3) The liquid pH shall be ≤ 2; and

(4) Daily, the permittee shall monitor the scrubber spray atomizers to ensure that they are operating.

The permittee shall monitor the date, start time, and end time of any downtime and/or maintenance of the unit CD-2.

Recordkeeping: Daily, the permittee shall record:

For CD-2, the permittee shall record:

(1) The gas flow rate;

(2) The gas inlet temperature;

(3) The liquid temperature;

(4) The liquid pH; and

(5) The permittee shall record inspections of the scrubber spray atomizers and the results of the inspections.

The permittee shall record the date, start time, and end time of any downtime and/or maintenance of the unit CD-2.

Reporting: The permittee shall report in accordance with Section B110.

C. Interlock Systems for Acid-Water Scrubber (Unit CD-2)

Requirement: Unit CD-2 shall be equipped with an interlock system to prevent emission discharges to the atmosphere any time the scrubber system experiences a control parameter malfunction. Set points for the sterilization system interlock shall be specified by the control device CD-2 manufacturer and compliance test results (as applicable) for the unit. Upon request by Department personnel during an onsite inspection, the permittee shall demonstrate to the inspector that the interlock systems are operating within the set points.

Monitoring: The permittee shall monitor:
1. Daily, the permittee shall monitor for the parameters in Condition A 801.B to demonstrate that the interlock system is operating within the set points as specified by the control device CD-2.
2. The permittee shall monitor each time the Interlock System is used.

Recordkeeping:
1. Daily, the permittee shall record that the interlock system is operating within the set points

as specified in Condition A801.B for the control device CD-2. 2. The permittee shall record each time the Interlock System is used.
Reporting: The permittee shall report in accordance with Section B110.

D. Acid-Water Scrubber Shut down Alarm (Unit CD-2)

Requirement: The shutdown alarm on the acid-water scrubber shall be set to maintain at least a thirty (30) minute average residence time to ensure ethylene glycol formation during the scrubber operation.
Monitoring: The permittee shall monitor the alarm on the acid-water scrubber to ensure at least (30) minutes average residence time, each time the scrubber is operating.
Recordkeeping: The permittee shall record each time the average residence time fails to maintain at least 30 minutes average residence time.
Reporting: The permittee shall report in accordance with Section B110.

A802 Aerating Rooms, Backvents, and Catalytic Oxidizer

A. Operational and Control Requirements for Units AR 8, AR 9, and Units BV1 to BV14.

Requirement: A.) All emissions from aeration rooms AR 8 and AR 09 shall be ducted to the catalytic oxidizer (Unit CD-4 or CD-3). Emissions from Units BV1 to BV14 shall be vented to (Unit CD-3 or CD-4). B.) All untreated process emissions from the aeration rooms (AR 8 and AR 9) must be isolated and the chamber back vents (BV1 to BV14) must not operate whenever the catalytic oxidizers (CD-3 and CD-4) are not within operating temperatures. C.) The permittee shall ensure that a continuous strip chart recorder or data acquisition system for monitoring the catalytic bed temperature is continuously operated at all times the catalytic control system is in operation. E.) Compliance with this condition demonstrates compliance with the emission limits for Unit CD-3 and CD-4 in Table 106.A.
Monitoring: (1) The permittee shall continuously monitor the temperature at the outlet of the catalyst bed. (2) Monthly, the permittee shall monitor the pressure drop across the catalyst bed. (3) In the event of a malfunction of the continuous recorder, manual temperature recordings of the inlet temperature to the catalyst bed shall be taken hourly. The continuous temperature recorder shall be repaired within seven calendar days. (4) The permittee shall monitor the date, start time, and end time of any downtime and/or maintenance of the unit CD-3 and CD-4.

Recordkeeping: (1) The permittee shall keep a monthly record of the data from the continuous strip chart recorder or data acquisition system for monitoring the catalytic bed temperature. (2) Monthly, the permittee shall record the pressure drop across the catalyst bed. (3) The permittee shall record the date, start time, and end time of any downtime and/or maintenance of the unit CD-3 and CD-4.
Reporting: The permittee shall report in accordance with Section B110.

B. Interlock Systems for Catalytic Oxidizer (Units CD-3 and CD-4)

Requirement: Unit CD-3 and CD-4 shall be equipped with an interlock system to prevent emission discharges to the atmosphere any time the catalytic system experiences a control parameter malfunction. Set points for the sterilization system interlock shall be specified by the control device, CD-3 and CD-4, manufacturer and compliance test results (as appropriate) for the unit. Upon request by Department personnel during an onsite inspection, the permittee shall demonstrate to the inspector that the interlock systems are operating within the set points.
Monitoring: (1) Daily, the permittee shall monitor (CD-3 and CD-4) operating temperature to ensure it is operating within the temperature set points as specified for the control device (CD-3 and CD-4) from the manufacturer specification sheet and compliance test results (as appropriate). (2) Monthly, the permittee shall monitor the pressure drop across the catalyst bed of (CD-3 and CD-4) and ensure that it meets the manufacturer's specification. (3) The permittee shall monitor each time the Interlock System is used.
Recordkeeping: (1) Daily, the permittee shall record that the interlock system is operating within the temperature set points as specified by the manufacturer specifications and compliance test results (as appropriate) for the control device (CD-3 and CD-4). (2) Monthly, the permittee shall record the pressure drop across the catalyst bed of (CD-3 and CD-4). (3) The permittee shall record each time the Interlock System is used. (4) The permittee shall maintain a copy of the manufacturer specification sheet on the premises and provide it to the Department's inspector upon request.
Reporting: The permittee shall report in accordance with Section B110.

PART B GENERAL CONDITIONS (Attached)

PART C MISCELLANEOUS: Supporting On-Line Documents; Definitions; Acronyms (Attached)

AIR QUALITY BUREAU
NEW SOURCE REVIEW PERMIT
Issued under 20.2.72 NMAC

GENERAL CONDITIONS AND MISCELLANEOUS

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PART B GENERAL CONDITIONS

B100 Introduction

A. The Department has reviewed the permit application for the proposed construction/modification/revision and has determined that the provisions of the Act and ambient air quality standards will be met. Conditions have been imposed in this permit to assure continued compliance. 20.2.72.210.D NMAC, states that any term or condition imposed by the Department on a permit is enforceable to the same extent as a regulation of the Environmental Improvement Board.

B101 Legal

A. The contents of a permit application specifically identified by the Department shall become the terms and conditions of the permit or permit revision. Unless modified by conditions of this permit, the permittee shall construct or modify and operate the Facility in accordance with all representations of the application and supplemental submittals that the Department relied upon to determine compliance with applicable regulations and ambient air quality standards. If the Department relied on air quality modeling to issue this permit, any change in the parameters used for this modeling shall be submitted to the Department for review. Upon the Department's request, the permittee shall submit additional modeling for review by the Department. Results of that review may require a permit modification. (20.2.72.210.A NMAC)

B. Any future physical changes, changes in the method of operation or changes in restricted area may constitute a modification as defined by 20.2.72 NMAC, Construction Permits. Unless the source or activity is exempt under 20.2.72.202 NMAC, no modification shall begin prior to issuance of a permit. (20.2.72 NMAC Sections 200.A.2 and E, and 210.B.4)

C. Changes in plans, specifications, and other representations stated in the application documents shall not be made if they cause a change in the method of control of emissions or in the character of emissions, will increase the discharge of emissions or affect modeling results. Any such proposed changes shall be submitted as a revision or modification. (20.2.72 NMAC Sections 200.A.2 and E, and 210.B.4)

D. The permittee shall establish and maintain the property's Restricted Area as identified in plot plan submitted with the application. (20.2.72 NMAC Sections 200.A.2 and E, and 210.B.4)

E. Applications for permit revisions and modifications shall be submitted to:

Program Manager, Permits Section
New Mexico Environment Department

Air Quality Bureau
525 Camino de los Marquez, Suite 1
Santa Fe, NM 87505

F. The owner or operator of a source having an excess emission shall, to the extent practicable, operate the source, including associated air pollution control equipment, in a manner consistent with good air pollutant control practices for minimizing emissions. (20.2.7.109 NMAC). The establishment of allowable malfunction emission limits does not supersede this requirement.

B102 Authority

A. This permit is issued pursuant to the Air Quality Control Act (Act) and regulations adopted pursuant to the Act including Title 20, Chapter 2, Part 72 of the New Mexico Administrative Code (NMAC), (20.2.72 NMAC), Construction Permits and is enforceable pursuant to the Act and the air quality control regulations applicable to this source.

B. The Department is the Administrator for 40 CFR Parts 60, 61, and 63 pursuant to the delegation and exceptions of Section 10 of 20.2.77 NMAC (NSPS), 20.2.78 NMAC (NESHAP), and 20.2.82 NMAC (MACT).

B103 Annual Fee

A. The Department will assess an annual fee for this Facility. The regulation 20.2.75 NMAC set the fee amount at $1,500 through 2004 and requires it to be adjusted annually for the Consumer Price Index on January 1. The current fee amount is available by contacting the Department or can be found on the Department's website. The AQB will invoice the permittee for the annual fee amount at the beginning of each calendar year. This fee does not apply to sources which are assessed an annual fee in accordance with 20.2.71 NMAC. For sources that satisfy the definition of "small business" in 20.2.75.7.F NMAC, this annual fee will be divided by two. (20.2.75.11 NMAC)

B. All fees shall be remitted in the form of a corporate check, certified check, or money order made payable to the "NM Environment Department, AQB" mailed to the address shown on the invoice and shall be accompanied by the remittance slip attached to the invoice.

B104 Appeal Procedures

A. Any person who participated in a permitting action before the Department and who is adversely affected by such permitting action, may file a petition for hearing before the Environmental Improvement Board. The petition shall be made in writing to the

Environmental Improvement Board within thirty (30) days from the date notice is given of the Department's action and shall specify the portions of the permitting action to which the petitioner objects, certify that a copy of the petition has been mailed or hand-delivered and attach a copy of the permitting action for which review is sought. Unless a timely request for hearing is made, the decision of the Department shall be final. The petition shall be copied simultaneously to the Department upon receipt of the appeal notice. If the petitioner is not the applicant or permittee, the petitioner shall mail or hand-deliver a copy of the petition to the applicant or permittee. The Department shall certify the administrative record to the board. Petitions for a hearing shall be sent to: (20.2.72.207.F NMAC)

For Mailing:
Administrator, New Mexico Environmental Improvement Board
P.O. Box 5469
Santa Fe, NM 87502-5469

For Hand Delivery:
Administrator, New Mexico Environmental Improvement Board
1190 St. Francis Drive, Harold Runnels Bldg.
Santa Fe, New Mexico 87505

B105 Submittal of Reports and Certifications

A. Stack Test Protocols and Stack Test Reports shall be submitted electronically to Stacktest.AQB@state.nm.us or as directed by the Department.

B. Excess Emission Reports shall be submitted as directed by the Department. (20.2.7.110 NMAC)

C. Routine reports shall be submitted to the mailing address below, or as directed by the Department:

Manager, Compliance and Enforcement Section
New Mexico Environment Department
Air Quality Bureau
525 Camino de los Marquez, Suite 1
Santa Fe, NM 87505

B106 NSPS and/or MACT Startup, Shutdown, and Malfunction Operations

A. If a facility is subject to a NSPS standard in 40 CFR 60, each owner or operator that installs and operates a continuous monitoring device required by a NSPS regulation shall comply with the excess emissions reporting requirements in accordance with 40 CFR 60.7(c), unless specifically exempted in the applicable subpart.

B. If a facility is subject to a NSPS standard in 40 CFR 60, then in accordance with 40 CFR 60.8(c), emissions in excess of the level of the applicable emission limit during periods of startup, shutdown, and malfunction shall not be considered a violation of the applicable emission limit unless otherwise specified in the applicable standard.

C. If a facility is subject to a MACT standard in 40 CFR 63, then the facility is subject to the requirement for a Startup, Shutdown and Malfunction Plan (SSM) under 40 CFR 63.6(e)(3), unless specifically exempted in the applicable subpart.

B107 <u>Startup, Shutdown, and Maintenance Operations</u>

A. The establishment of permitted startup, shutdown, and maintenance (SSM) emission limits does not supersede the requirements of 20.2.7.14.A NMAC. Except for operations or equipment subject to Condition B106, the permittee shall establish and implement a plan to minimize emissions during routine or predictable start up, shut down, and scheduled maintenance (SSM work practice plan) and shall operate in accordance with the procedures set forth in the plan. (SSM work practice plan) (20.2.7.14.A NMAC)

B108 <u>General Monitoring Requirements</u>

A. These requirements do not supersede or relax requirements of federal regulations.

B. The following monitoring requirements shall be used to determine compliance with applicable requirements and emission limits. Any sampling, whether by portable analyzer or EPA reference method, that measures an emission rate over the applicable averaging period greater than an emission limit in this permit constitutes noncompliance with this permit. The Department may require, at its discretion, additional tests pursuant to EPA Reference Methods at any time, including when sampling by portable analyzer measures an emission rate greater than an emission limit in this permit; but such requirement shall not be construed as a determination that the sampling by portable analyzer does not establish noncompliance with this permit and shall not stay enforcement of such noncompliance based on the sampling by portable analyzer.

C. If the emission unit is shutdown at the time when periodic monitoring is due to be completed, the permittee is not required to restart the unit for the sole purpose of conducting the monitoring. Using electronic or written mail, the permittee shall notify the Department's Compliance and Enforcement Section of a delay in emission tests prior to the deadline for completing the tests. Upon recommencing operation, the permittee shall submit pre-test notification(s) to the Department's Compliance and Enforcement Section and shall complete the monitoring.

D. The requirement for monitoring during any monitoring period is based on the percentage of time that the unit has operated. However, to invoke the monitoring period exemption at B108.D(2), hours of operation shall be monitored and recorded.

(1) If the emission unit has operated for more than 25% of a monitoring period, then the permittee shall conduct monitoring during that period.

(2) If the emission unit has operated for 25% or less of a monitoring period then the monitoring is not required. After two successive periods without monitoring, the permittee shall conduct monitoring during the next period regardless of the time operated during that period, except that for any monitoring period in which a unit has operated for less than 10% of the monitoring period, the period will not be considered as one of the two successive periods.

(3) If invoking the monitoring **period** exemption in B108.D(2), the actual operating time of a unit shall not exceed the monitoring period required by this permit before the required monitoring is performed. For example, if the monitoring period is annual, the operating hours of the unit shall not exceed 8760 hours before monitoring is conducted. Regardless of the time that a unit actually operates, a minimum of one of each type of monitoring activity shall be conducted during any five-year period.

E. For all periodic monitoring events, except when a federal or state regulation is more stringent, three test runs shall be conducted at 90% or greater of the unit's capacity as stated in this permit, or in the permit application if not in the permit, and at additional loads when requested by the Department. If the 90% capacity cannot be achieved, the monitoring will be conducted at the maximum achievable load under prevailing operating conditions except when a federal or state regulation requires more restrictive test conditions. The load and the parameters used to calculate it shall be recorded to document operating conditions and shall be included with the monitoring report.

F. When requested by the Department, the permittee shall provide schedules of testing and monitoring activities. Compliance tests from previous NSR and Title V permits may be re-imposed if it is deemed necessary by the Department to determine whether the source is in compliance with applicable regulations or permit conditions.

G. If monitoring is new or is in addition to monitoring imposed by an existing applicable requirement, it shall become effective 120 days after the date of permit issuance. For emission units that have not commenced operation, the associated new or additional monitoring shall not apply until 120 days after the units commence operation. All pre-existing monitoring requirements incorporated in this permit shall continue to apply from the date of permit issuance.

H. Unless otherwise indicated by Specific Conditions or regulatory requirements, all instrumentation used for monitoring in accordance with applicable requirements including emission limits, to measure parameters including but not limited to flow, temperature, pressure and chemical composition, or used to continuously monitor

emission rates and/or other process operating parameters, shall be subject to the following requirements:

(1) The owner or operator shall install, calibrate, operate and maintain monitoring instrumentation (monitor) according to the manufacturer's procedures and specifications and the following requirements.

(a) The monitor shall be located in a position that provides a representative measurement of the parameter that is being monitored.

(b) At a minimum, the monitor shall complete one cycle of operation (sampling, analyzing, and data recording) for each successive 15-minute period.

(c) At a minimum, the monitor shall be spanned to measure the normal range +/- 5% of the parameter that is being monitored.

(d) At least semi-annually, perform a visual inspection of all components of the monitor for physical and operational integrity and all electrical connections for oxidation and galvanic corrosion.

(e) Recalibrate the monitor in accordance with the manufacturer's procedures and specifications at the frequency specified by the manufacturer, or every two years, whichever is less.

(2) Except for malfunctions, associated repairs, and required quality assurance or control activities (including calibration checks and required zero and span adjustments), the permittee shall operate and maintain all monitoring equipment at all times that the emissions unit or the associated process is operating.

(3) The monitor shall measure data for a minimum of 90 percent of the time that the emissions unit or the associated process is in operation, based on a calendar monthly average.

(4) The owner or operator shall maintain records in accordance with Section B109 to demonstrate compliance with the requirements in B108H (1)-(3) above, as applicable.

B109 General Recordkeeping Requirements

A. The permittee shall maintain records to assure and verify compliance with the terms and conditions of this permit and any other applicable requirements that become effective after permit issuance. The minimum information to be included in these records is as follows:

(1) Records required for testing and sampling:

(a) equipment identification (include make, model and serial number for all tested equipment and emission controls)

(b) date(s) and time(s) of sampling or measurements

(c) date(s) analyses were performed

(d) the qualified entity that performed the analyses

(e) analytical or test methods used

(f) results of analyses or tests

(g) operating conditions existing at the time of sampling or measurement

(2) Records required for equipment inspections and/or maintenance required by this permit:

(a) equipment identification number (including make, model and serial number)

(b) date(s) and time(s) of inspection, maintenance, and/or repair

(c) date(s) any subsequent analyses were performed (if applicable)

(d) name of the person or qualified entity conducting the inspection, maintenance, and/or repair

(e) copy of the equipment manufacturer's or the owner or operator's maintenance or repair recommendations (if required to demonstrate compliance with a permit condition)

(f) description of maintenance or repair activities conducted

(g) all results of any required parameter readings

(h) a description of the physical condition of the equipment as found during any required inspection

(i) results of required equipment inspections including a description of any condition which required adjustment to bring the equipment back into compliance and a description of the required adjustments

B. Except as provided in the Specific Conditions, records shall be maintained on-site or at the permittee's local business office for a minimum of two (2) years from the time of recording and shall be made available to Department personnel upon request. Sources subject to 20.2.70 NMAC "Operating Permits" shall maintain records on-site for a minimum of five (5) years from the time of recording.

C. Unless otherwise indicated by Specific Conditions, the permittee shall keep the following records for malfunction emissions and routine or predictable emissions during startup, shutdown, and scheduled maintenance (SSM):

(1) The owner or operator of a source subject to a permit shall establish and implement a plan to minimize emissions during routine or predictable startup, shutdown, and scheduled maintenance through work practice standards and good air pollution control practices. This requirement shall not apply to any affected facility defined in and subject to an emissions standard and an equivalent plan under 40 CFR Part 60 (NSPS), 40 CFR Part 63 (MACT), or an equivalent plan under 20.2.72 NMAC - Construction Permits, 20.2.70 NMAC - Operating Permits, 20.2.74 NMAC -

Permits - Prevention of Significant Deterioration (PSD), or 20.2.79 NMAC - Permits - Nonattainment Areas. The permittee shall keep records of all sources subject to the plan to minimize emissions during routine or predictable SSM and shall record if the source is subject to an alternative plan and therefore, not subject to the plan requirements under 20.2.7.14.A NMAC.

(2) If the facility has allowable SSM emission limits in this permit, the permittee shall record all SSM events, including the date, the start time, the end time, a description of the event, and a description of the cause of the event. This record also shall include a copy of the manufacturer's, or equivalent, documentation showing that any maintenance qualified as scheduled. Scheduled maintenance is an activity that occurs at an established frequency pursuant to a written protocol published by the manufacturer or other reliable source. The authorization of allowable SSM emissions does not supersede any applicable federal or state standard. The most stringent requirement applies.

(3) If the facility has allowable malfunction emission limits in this permit, the permittee shall record all malfunction events to be applied against these limits. The permittee shall also include the date, the start time, the end time, and a description of the event. **Malfunction means** any sudden and unavoidable failure of air pollution control equipment or process equipment beyond the control of the owner or operator, including malfunction during startup or shutdown. A failure that is caused entirely or in part by poor maintenance, careless operation, or any other preventable equipment breakdown shall not be considered a malfunction. (20.2.7.7.E NMAC) The authorization of allowable malfunction emissions does not supersede any applicable federal or state standard. The most stringent requirement applies. This authorization only allows the permittee to avoid submitting reports under 20.2.7 NMAC for total annual emissions that are below the authorized malfunction emission limit.

(4) The owner or operator of a source shall meet the operational plan defining the measures to be taken to mitigate source emissions during malfunction, startup or shutdown. (20.2.72.203.A(5) NMAC)

B110 <u>General Reporting Requirements</u>
(20.2.72 NMAC Sections 210 and 212)

A. Records and reports shall be maintained on-site or at the permittee's local business office unless specifically required to be submitted to the Department or EPA by another condition of this permit or by a state or federal regulation. Records for unmanned sites may be kept at the nearest business office.

B. The permittee shall notify the Department's Compliance Reporting Section using the current Submittal Form posted to NMED's Air Quality web site under Compliance and Enforcement/Submittal Forms in writing of, or provide the Department with (20.2.72.212.A and B):

(1) the anticipated date of initial startup of each new or modified source not less than thirty (30) days prior to the date. Notification may occur prior to issuance of the permit, but actual startup shall not occur earlier than the permit issuance date;

(2) after receiving authority to construct, the equipment serial number as provided by the manufacturer or permanently affixed if shop-built and the actual date of initial startup of each new or modified source within fifteen (15) days after the startup date; and

(3) the date when each new or modified emission source reaches the maximum production rate at which it will operate within fifteen (15) days after that date.

C. The permittee shall notify the Department's Permitting Program Manager, in writing of, or provide the Department with (20.2.72.212.C and D):

(1) any change of operators or any equipment substitutions within fifteen (15) days of such change;

(2) any necessary update or correction no more than sixty (60) days after the operator knows or should have known of the condition necessitating the update or correction of the permit.

D. Results of emission tests and monitoring for each pollutant (except opacity) shall be reported in pounds per hour (unless otherwise specified) and tons per year. Opacity shall be reported in percent. The number of significant figures corresponding to the full accuracy inherent in the testing instrument or Method test used to obtain the data shall be used to calculate and report test results in accordance with 20.2.1.116.B and C NMAC. Upon request by the Department, CEMS and other tabular data shall be submitted in editable, MS Excel format.

E. The permittee shall submit reports of excess emissions in accordance with 20.2.7.110.A NMAC.

F. Allowable Emission Limits for Excess Emissions Reporting for Flares and Other Regulated Sources with No Pound per Hour (pph) and/or Ton per Year (tpy) Emission Limits.

(1) When a flare has no allowable pph and/or tpy emission limits in Sections A106 and/or A107, the authorized allowable emissions include only the combustion of pilot and/or purge gas. Compliance is demonstrated by limiting the gas stream to the flare to only pilot and/or purge gas.

(2) For excess emissions reporting as required by 20.2.7 NMAC, the allowable emission limits are 1.0 pph and 1.0 tpy for each regulated air pollutant (except for H2S) emitted by that source as follows:

(a) For flares, when there are no allowable emission limits in Sections A106 and/or A107.

(b) For regulated sources with emission limits in Sections A106 or A107 represented by the less than sign ("<").

(c) For regulated sources that normally would not emit any regulated air pollutants, including but not limited to vents, pressure relief devices, connectors, etc.

(3) For excess emissions reporting as required by 20.2.7 NMAC for H2S, the allowable limits are 0.1 pph and 0.44 tpy for each applicable scenario addressed in paragraph (2) above.

B111 General Testing Requirements

Unless otherwise indicated by Specific Conditions or regulatory requirements, the permittee shall conduct testing in accordance with the requirements in Sections B111A, B, C, D and E, as applicable.

A. Initial Compliance Tests

The permittee shall conduct initial compliance tests in accordance with the following requirements:

(1) Initial compliance test requirements from previous permits (if any) are still in effect, unless the tests have been satisfactorily completed. Compliance tests may be re-imposed if it is deemed necessary by the Department to determine whether the source is in compliance with applicable regulations or permit conditions. (20.2.72 NMAC Sections 210.C and 213)

(2) Initial compliance tests shall be conducted within sixty (60) days after the unit(s) achieve the maximum normal production rate. If the maximum normal production rate does not occur within one hundred twenty (120) days of source startup, then the tests must be conducted no later than one hundred eighty (180) days after initial startup of the source.

(3) The default time period for each test run shall be **at least** 60 minutes and each performance test shall consist of three separate runs using the applicable test method. For the purpose of determining compliance with an applicable emission limit, the arithmetic mean of results of the three runs shall apply. In the event that a sample is accidentally lost or conditions occur in which one of the three runs must be discontinued because of forced shutdown, failure of an irreplaceable portion of the sample train, extreme meteorological conditions, or other circumstances, beyond the owner or operator's control, compliance may, upon the Department approval, be determined using the arithmetic mean of the results of the two other runs.

(4) Testing of emissions shall be conducted with the emissions unit operating at 90 to 100 percent of the maximum operating rate allowed by the permit. If it is not possible to test at that rate, the source may test at a lower operating rate

(5) Testing performed at less than 90 percent of permitted capacity will limit emission unit operation to 110 percent of the tested capacity until a new test is conducted.

(6) If conditions change such that unit operation above 110 percent of tested capacity is possible, the source must submit a protocol to the Department within 30 days of such change to conduct a new emissions test.

B. EPA Reference Method Tests

The test methods in Section B111.B(1) shall be used for all initial compliance tests and all Relative Accuracy Test Audits (RATAs), and shall be used if a permittee chooses to use EPA test methods for periodic monitoring. Test methods that are not listed in Section B111.B(1) may be used in accordance with the requirements at Section B111.B(2).

(1) All compliance tests required by this permit shall be conducted in accordance with the requirements of CFR Title 40, Part 60, Subpart A, General Provisions, and the following EPA Reference Methods as specified by CFR Title 40, Part 60, Appendix A:

(a) Methods 1 through 4 for stack gas flowrate

(b) Method 5 for particulate matter (PM)

(c) Method 6C SO_2

(d) Method 7E for NO_X (test results shall be expressed as nitrogen dioxide (NO_2) using a molecular weight of 46 lb/lb-mol in all calculations (each ppm of NO/NO_2 is equivalent to 1.194 x 10-7 lb/SCF)

(e) Method 9 for visual determination of opacity

(f) Method 10 for CO

(g) Method 19 for particulate, sulfur dioxide and nitrogen oxides emission rates. In addition, Method 19 may be used in lieu of Methods 1-4 for stack gas flowrate. The permittee shall provide a contemporaneous fuel gas analysis (preferably on the day of the test, but no earlier than three months prior to the test date) and a recent fuel flow meter calibration certificate (within the most recent quarter) with the final test report.

(h) Method 7E or 20 for Turbines per §60.335 or §60.4400

(i) Method 22 for visual determination of fugitive emissions from material sources and smoke emissions from flares

(j) Method 25A for VOC reduction efficiency

(k) Method 29 for Metals

(l) Method 30B for Mercury from Coal-Fired Combustion Sources Using Carbon Sorbent Traps

(m) Method 201A for filterable PM_{10} and $PM_{2.5}$

(n) Method 202 for condensable PM

(o) Method 320 for organic Hazardous Air Pollutants (HAPs)

(2) Permittees may propose test method(s) that are not listed in Section B111.B(1). These methods may be used if prior approval is received from the Department.

C. Periodic Monitoring and Portable Analyzer Requirements for the Determination of Nitrogen Oxides, Carbon Monoxide, and Oxygen Concentrations in Emissions from Reciprocating Engines, Combustion Turbines, Boilers, and Process Heaters

Periodic emissions tests (periodic monitoring) shall be conducted in accordance with the following requirements:

(1) Periodic emissions tests may be conducted in accordance with EPA Reference Methods or by utilizing a portable analyzer. Periodic monitoring utilizing a portable analyzer shall be conducted in accordance with the requirements of the current version of ASTM D 6522. However, if a facility has met a previously approved Department criterion for portable analyzers, the analyzer may be operated in accordance with that criterion until it is replaced.

(2) The default time period for each test run shall be **at least** 20 minutes.

Each performance test shall consist of three separate runs. The arithmetic mean of results of the three runs shall be used to determine compliance with the applicable emission limit.

(3) Testing of emissions shall be conducted in accordance with the requirements at Section B108.E.

(4) During emissions tests, pollutant and diluent concentration shall be monitored and recorded. Fuel flow rate shall be monitored and recorded if stack gas flow rate is determined utilizing Reference Method 19. This information shall be included with the test report furnished to the Department.

(5) Stack gas flow rate shall be calculated in accordance with Reference Method 19 utilizing fuel flow rate (scf) determined by a dedicated fuel flow meter and fuel heating value (Btu/scf). The permittee shall provide a contemporaneous fuel gas analysis (preferably on the day of the test, but no earlier than three months prior to the test date) and a recent fuel flow meter calibration certificate (within the most recent quarter) with the final test report. Alternatively, stack gas flow rate may be determined by using EPA Reference Methods 1-4.

(6) The permittee shall submit a notification and protocol for periodic emissions tests upon the request of the Department.

D. Initial Compliance Test and RATA Procedures

Permittees required to conduct initial compliance tests and/or RATAs shall comply with the following requirements:

(1) The permittee shall submit a notification and test protocol to the Department's Program Manager, Compliance and Enforcement Section, at least thirty (30) days before the test date and allow a representative of the Department to be present at the test. Proposals to use test method(s) that are not listed in Section B111.B(1) (if applicable) shall be included in this notification.

(2) Contents of test notifications, protocols and test reports shall conform to the format specified by the Department's Universal Test Notification, Protocol and Report Form and Instructions. Current forms and instructions are posted to NMED's Air Quality web site under Compliance and Enforcement Testing.

(3) The permittee shall provide (a) sampling ports adequate for the test methods applicable to the facility, (b) safe sampling platforms, (c) safe access to sampling platforms and (d) utilities for sampling and testing equipment.

(4) Where necessary to prevent cyclonic flow in the stack, flow straighteners shall be installed

E. General Compliance Test Procedures

The following requirements shall apply to all initial compliance and periodic emissions tests and all RATAs:

(1) Equipment shall be tested in the "as found" condition. Equipment may not be adjusted or tuned prior to any test for the purpose of lowering emissions, and then returned to previous settings or operating conditions after the test is complete.

(2) The stack shall be of sufficient height and diameter and the sample ports shall be located so that a representative test of the emissions can be performed in accordance with the requirements of EPA Reference Method 1 or the current version of ASTM D 6522, as applicable.

(3) Test reports shall be submitted to the Department no later than 30 days after completion of the test.

B112 Compliance

A. The Department shall be given the right to enter the facility at all reasonable times to verify the terms and conditions of this permit. Required records shall be organized by date and subject matter and shall at all times be readily available for inspection. The permittee, upon verbal or written request from an authorized representative of the Department who appears at the facility, shall immediately produce for inspection or copying any records required to be maintained at the facility. Upon written request at other times, the permittee shall deliver to the Department paper or electronic copies of any and all required records maintained on site or at an off-site location. Requested records shall be copied and delivered at the permittee's expense within three business days from receipt of request unless the Department allows additional time. Required records may include records required by permit and other information necessary to

demonstrate compliance with terms and conditions of this permit. (NMSA 1978, Section 74-2-13)

B. A copy of the most recent permit(s) issued by the Department shall be kept at the permitted facility or (for unmanned sites) at the nearest company office and shall be made available to Department personnel for inspection upon request. (20.2.72.210.B.4 NMAC)

C. Emissions limits associated with the energy input of a Unit, i.e. lb/MMBtu, shall apply at all times unless stated otherwise in a Specific Condition of this permit. The averaging time for each emissions limit, including those based on energy input of a Unit (i.e. lb/MMBtu) is one (1) hour unless stated otherwise in a Specific Condition of this permit or in the applicable requirement that establishes the limit.

B113 Permit Cancellation and Revocation

A. The Department may revoke this permit if the applicant or permittee has knowingly and willfully misrepresented a material fact in the application for the permit. Revocation will be made in writing, and an administrative appeal may be taken to the Secretary of the Department within thirty (30) days. Appeals will be handled in accordance with the Department's Rules Governing Appeals From Compliance Orders.

B. The Department shall automatically cancel any permit for any source which ceases operation for five (5) years or more, or permanently. Reactivation of any source after the five (5) year period shall require a new permit. (20.2.72 NMAC)

C. The Department may cancel a permit if the construction or modification is not commenced within two (2) years from the date of issuance or if, during the construction or modification, work is suspended for a total of one (1) year. (20.2.72 NMAC)

B114 Notification to Subsequent Owners

A. The permit and conditions apply in the event of any change in control or ownership of the Facility. No permit modification is required in such case. However, in the event of any such change in control or ownership, the permittee shall notify the succeeding owner of the permit and conditions and shall notify the Department's Program Manager, Permits Section of the change in ownership within fifteen (15) days of that change. (20.2.72.212.C NMAC)

B. Any new owner or operator shall notify the Department's Program Manager, Permits Section, within thirty (30) days of assuming ownership, of the new owner's or operator's name and address. (20.2.73.200.E.3 NMAC)

B115 Asbestos Demolition

A. Before any asbestos demolition or renovation work, the permittee shall determine whether 40 CFR 61 Subpart M, National Emissions Standards for Asbestos applies. If required, the permittee shall notify the Department's Program Manager, Compliance and Enforcement Section using forms furnished by the Department.

B116 Short Term Engine Replacement

A. The following Alternative Operating Scenario (AOS) addresses engine breakdown or periodic maintenance and repair, which requires the use of a short term replacement engine. The following requirements do not apply to engines that are exempt per 20.2.72.202.B(3) NMAC. Changes to exempt engines must be reported in accordance with 20.2.72.202.B NMAC. A short term replacement engine may be substituted for any engine allowed by this permit for no more than 120 days in any rolling twelve month period per permitted engine. The compliance demonstrations required as part of this AOS are in addition to any other compliance demonstrations required by this permit.

(1) The permittee may temporarily replace an existing engine that is subject to the emission limits set forth in this permit with another engine regardless of manufacturer, model, and horsepower without modifying this permit. The permittee shall submit written notification to the Department within 15 days of the date of engine substitution according to condition B110.C(1).

(a) The potential emission rates of the replacement engine shall be determined using the replacement engine's manufacturer specifications and shall comply with the existing engine's permitted emission limits.

(b) The direction of the exhaust stack for the replacement engine shall be either vertical or the same direction as for the existing engine. The replacement engine's stack height and flow parameters shall be at least as effective in the dispersion of air pollutants as the modeled stack height and flow parameters for the existing permitted engine. The following equation may be used to show that the replacement engine disperses pollutants as well as the existing engine. The value calculated for the replacement engine on the right side of the equation shall be equal to or greater than the value for the existing engine on the left side of the equation. The permitting page of the Air Quality Bureau website contains a spreadsheet that performs this calculation.

EXISTING ENGINE REPLACMENT ENGINE

$$\frac{[(g) \times (h1)] + [(v1)^2/2] + [(c) \times (T1)]}{q1} <= \frac{[(g) \times (h2)] + [(v2)^2/2] + [(c) \times (T2)]}{q2}$$

Where
g = gravitational constant = 32.2 ft/sec^2
h1 = existing stack height, feet
v1 = exhaust velocity, existing engine, feet per second
c = specific heat of exhaust, 0.28 BTU/lb-degree F
T1 = absolute temperature of exhaust, existing engine = degree F + 460
q1 = permitted allowable emission rate, existing engine, lbs/hour
h2 = replacement stack height, feet
v2 = exhaust velocity, replacement engine, feet per second
T2 = absolute temperature of exhaust, replacement engine = degree F + 460
q2 = manufacturer's potential emission rate, replacement engine, lbs/hour

The permittee shall keep records showing that the replacement engine is at least as effective in the dispersion of air pollutants as the existing engine.

(c) Test measurement of NOx and CO emissions from the temporary replacement engine shall be performed in accordance with Section B111 with the exception of Condition B111A(2) and B111B for EPA Reference Methods Tests or Section B111C for portable analyzer test measurements. Compliance test(s) shall be conducted within fifteen (15) days after the unit begins operation, and records of the results shall be kept according to section B109.B. This test shall be performed even if the engine is removed prior to 15 days on site.

i. These compliance tests are not required for an engine certified under 40CFR60, subparts IIII, or JJJJ, or 40CFR63, subpart ZZZZ if the permittee demonstrates that one of these requirements causes such engine to comply with all emission limits of this permit. The permittee shall submit this demonstration to the Department within 48 hours of placing the new unit into operation. This submittal shall include documentation that the engine is certified, that the engine is within its useful life, as defined and specified in the applicable requirement, and shall include calculations showing that the applicable emissions standards result in compliance with the permit limits.

ii. These compliance tests are not required if a test was conducted by portable analyzer or by EPA Method test (including any required by 40CFR60, subparts IIII and JJJJ and 40CFR63, subpart ZZZZ) within the last 12 months. These previous tests are valid only if conducted at the same or lower elevation as the existing engine location prior to commencing operation as a temporary replacement. A copy of the test results shall be kept according to section B109.B.

(d) Compliance tests for NOx and CO shall be conducted if requested by the Department in writing to determine whether the replacement engine is in compliance with applicable regulations or permit conditions.

(e) Upon determining that emissions data developed according to B116.A.1(c) fail to indicate compliance with either the NOx or CO emission limits, the permittee shall notify the Department within 48 hours. Also within that time, the permittee shall implement one of the following corrective actions:

i. The engine shall be adjusted to reduce NOx and CO emissions and tested per B116.A.1(c) to demonstrate compliance with permit limits.

ii. The engine shall discontinue operation or be replaced with a different unit.

(2) Short term replacement engines, whether of the same manufacturer, model, and horsepower, or of a different manufacturer, model, or horsepower, are subject to all federal and state applicable requirements, regardless of whether they are set forth in this permit (including monitoring and recordkeeping), and shall be subject to any shield afforded by this permit.

(3) The permittee shall maintain a contemporaneous record documenting the unit number, manufacturer, model number, horsepower, emission factors, emission test results, and serial number of any existing engine that is replaced, and the replacement engine. Additionally, the record shall document the replacement duration in days, and the beginning and end dates of the short term engine replacement.

(4) The permittee shall maintain records of a regulatory applicability determination for each replacement engine (including 40CFR60, subparts IIII and JJJJ and 40CFR63, subpart ZZZZ) and shall comply with all associated regulatory requirements.

B. Additional requirements for replacement of engines at sources that are major as defined in regulation 20.2.74 NMAC, Permits – Prevention of Significant Deterioration, section 7.AG. For sources that are major under PSD, the total cumulative operating hours of the replacement engine shall be limited using the following procedure:

(1) Daily, the actual emissions from the replacement engine(s) of each pollutant regulated by this permit for the existing engine shall be calculated and recorded.

(2) The sum of the total actual emissions since the commencement of operation of the replacement engine(s) shall not equal or exceed the significant emission rates in Table 2 of 20.2.74 NMAC, section 502 for the time that the replacement engine is located at the facility.

C. All records required by this section shall be kept according to section B109.

PART C MISCELLANEOUS

C100 Supporting On-Line Documents

A. Copies of the following documents can be downloaded from NMED's web site under Compliance and Enforcement or requested from the Bureau.

(1) Excess Emission Form (for reporting deviations and emergencies)

(2) Universal Stack Test Notification, Protocol and Report Form and Instructions

C101 Definitions

A. **"Daylight"** is defined as the time period between sunrise and sunset, as defined by the Astronomical Applications Department of the U.S. Naval Observatory. (Data for one day or a table of sunrise/sunset for an entire year can be obtained at http://aa.usno.navy.mil/. Alternatively, these times can be obtained from a Farmer's Almanac or from http://www.almanac.com/rise/).

B. **"Decommission"** and **"Decommissioning"** applies to units left on site (not removed) and is defined as the complete disconnecting of equipment, emission sources or activities from the process by disconnecting all connections necessary for operation (i.e. piping, electrical, controls, ductwork, etc.).

C. **"Exempt Sources"** and **"Exempt Activities"** is defined as those sources or activities that are exempted in accordance with 20.2.72.202 NMAC. Note; exemptions are only valid for most 20.2.72 NMAC permitting actions.

D. **"Fugitive Emission"** means those emissions which could not reasonably pass through a stack, chimney, vent, or other functionally equivalent opening.

E. **"Insignificant Activities"** means those activities which have been listed by the department and approved by the administrator as insignificant on the basis of size, emissions or production rate. Note; insignificant activities are only valid for 20.2.70 NMAC permitting actions.

F. **"Malfunction"** for the requirements under 20.2.7 NMAC, means any sudden and unavoidable failure of air pollution control equipment or process equipment beyond the control of the owner or operator, including malfunction during startup or shutdown. A failure that is caused entirely or in part by poor maintenance, careless operation, or any other preventable equipment breakdown shall not be considered a malfunction. (20.2.7.7.E NMAC)

G. **"Natural Gas"** is defined as a naturally occurring fluid mixture of hydrocarbons that contains 20.0 grains or less of total sulfur per 100 standard cubic feet (SCF) and is either composed of at least 70% methane by volume or has a gross calorific value of between 950 and 1100 Btu per standard cubic foot. (40 CFR 60.631)

H. **"Natural Gas Liquids"** means the hydrocarbons, such as ethane, propane, butane, and pentane, that are extracted from field gas. (40 CFR 60.631)

I. **"National Ambient air Quality Standards"** means, unless otherwise modified, the primary (health-related) and secondary (welfare-based) federal ambient air quality standards promulgated by the US EPA pursuant to Section 109 of the Federal Act.

J. **"Night"** is the time period between sunset and sunrise, as defined by the Astronomical Applications Department of the U.S. Naval Observatory. (Data for one day or a table of sunrise/sunset for an entire year can be obtained at http://aa.usno.navy.mil/. Alternatively, these times can be obtained from a Farmer's Almanac or from http://www.almanac.com/rise/).

K. **"Night Operation** or **Operation at Night"** is operating a source of emissions at night.

L. **"NO2"** or "Nitrogen dioxide" means the chemical compound containing one atom of nitrogen and two atoms of oxygen, for the purposes of ambient determinations. The term **"nitrogen dioxide,"** for the purposes of stack emissions monitoring, shall include nitrogen dioxide (the chemical compound containing one atom of nitrogen and two atoms of oxygen), nitric oxide (the chemical compound containing one atom of nitrogen and one atom of oxygen), and other oxides of nitrogen which may test as nitrogen dioxide and is sometimes referred to as NOx or NO_2. (20.2.2 NMAC)

M. "**NOx**" see NO_2

N. "**Paved Road**" is a road with a permanent solid surface that can be swept essentially free of dust or other material to reduce air re-entrainment of particulate matter. To the extent these surfaces remain solid and contiguous they qualify as paved roads: concrete, asphalt, chip seal, recycled asphalt and other surfaces approved by the Department in writing.

O. **"Potential Emission Rate"** means the emission rate of a source at its maximum capacity to emit a regulated air contaminant under its physical and operational design, provided any physical or operational limitation on the capacity of the source to emit a regulated air contaminant, including air pollution control equipment and restrictions on hours of operation or on the type or amount of material combusted, stored or processed, shall be treated as part of its physical and operational design only if the limitation or the effect it would have on emissions is enforceable by the department pursuant to the Air Quality Control Act or the federal Act.

P. "**Restricted Area**" is an area to which public entry is effectively precluded. Effective barriers include continuous fencing, continuous walls, or other continuous barriers approved by the Department, such as rugged physical terrain with a steep grade that would require special equipment to traverse. If a large property is completely enclosed by fencing, a restricted area within the property may be identified with signage only. Public roads cannot be part of a Restricted Area.

Q. **"Shutdown"** for requirements under 20.2.72 NMAC, means the cessation of operation of any air pollution control equipment, process equipment or process for any purpose, except routine phasing out of batch process units.

R. **"SSM"** for requirements under 20.2.7 NMAC, means routine or predictable startup, shutdown, or scheduled maintenance.

(1) **"Shutdown"** for requirements under 20.2.7 NMAC, means the cessation of operation of any air pollution control equipment or process equipment.

(2) **"Startup"** for requirements under 20.2.7 NMAC, means the setting into operation of any air pollution control equipment or process equipment.

S. **"Startup"** for requirements under 20.2.72 NMAC, means the setting into operation of any air pollution control equipment, process equipment or process for any purpose, except routine phasing in of batch process units.

C102 Acronyms

2SLB ..... 2-stroke lean burn
4SLB ..... 4-stroke lean burn
4SRB ..... 4-stroke rich burn
acfm ..... actual cubic feet per minute
AFR ..... air fuel ratio
AP-42 ..... EPA Air Pollutant Emission Factors
AQB ..... Air Quality Bureau
AQCR ..... Air Quality Control Region
ASTM ..... American Society for Testing and Materials
Btu ..... British thermal unit
CAA ..... Clean Air Act of 1970 and 1990 Amendments
CEM ..... continuous emissions monitoring
cfh ..... cubic feet per hour
cfm ..... cubic feet per minute
CFR ..... Code of Federal Regulation
CI ..... compression ignition
CO ..... carbon monoxides
COMS ..... continuous opacity monitoring system
EIB ..... Environmental Improvement Board
EPA ..... United States Environmental Protection Agency
gr/100 cf ..... grains per one hundred cubic feet
gr/dscf ..... grains per dry standard cubic foot
GRI ..... Gas Research Institute
HAP ..... hazardous air pollutant
hp ..... horsepower
H_2S ..... hydrogen sulfide
IC ..... internal combustion
KW/hr ..... kilowatts per hour

lb/hr ..... pounds per hour
lb/MMBtu ..... pounds per million British thermal unit
MACT ..... Maximum Achievable Control Technology
MMcf/hr ..... million cubic feet per hour
MMscf ..... million standard cubic feet
N/A ..... not applicable
NAAQS ..... National Ambient Air Quality Standards
NESHAP ..... National Emission Standards for Hazardous Air Pollutants
NG ..... natural gas
NGL ..... natural gas liquids
NMAAQS ..... New Mexico Ambient Air Quality Standards
NMAC ..... New Mexico Administrative Code
NMED ..... New Mexico Environment Department
NMSA ..... New Mexico Statues Annotated
NOx ..... nitrogen oxides
NSCR ..... non-selective catalytic reduction
NSPS ..... New Source Performance Standard
NSR ..... New Source Review
PEM ..... parametric emissions monitoring
PM ..... particulate matter (equivalent to TSP, total suspended particulate)
PM_{10} ..... particulate matter 10 microns and less in diameter
$PM_{2.5}$ ..... particulate matter 2.5 microns and less in diameter
pph ..... pounds per hour
ppmv ..... parts per million by volume
PSD ..... Prevention of Significant Deterioration
RATA ..... Relative Accuracy Test Assessment
RICE ..... reciprocating internal combustion engine
rpm ..... revolutions per minute
scfm ..... standard cubic feet per minute
SI ..... spark ignition
SO_2 ..... sulfur dioxide
SSM ..... Startup Shutdown Maintenance (see SSM definition)
TAP ..... Toxic Air Pollutant
TBD ..... to be determined
THC ..... total hydrocarbons
TSP ..... Total Suspended Particulates
tpy ..... tons per year
ULSD ..... ultra low sulfur diesel
USEPA ..... United States Environmental Protection Agency
UTM ..... Universal Transverse Mercator Coordinate system
UTMH ..... Universal Transverse Mercator Horizontal
UTMV ..... Universal Transverse Mercator Vertical
VHAP ..... volatile hazardous air pollutant
VOC ..... volatile organic compounds

FILED
3rd JUDICIAL DISTRICT COURT
Dona Ana County
12/22/2021 11:20 AM
DAVID S. BORUNDA
CLERK OF THE COURT
Bertha A Nevarrete

STATE OF NEW MEXICO
COUNTY OF DOÑA ANA
THIRD JUDICIAL DISTRICT COURT

THE STATE OF NEW MEXICO, ex rel. HECTOR BALDERAS, ATTORNEY GENERAL,	§	
Plaintiff,	§	**No.: D-307-CV-2020-02629**
v.	§	Hon. Marci Beyer
STERIGENICS U.S., LLC, SOTERA HEALTH HOLDINGS, LLC, SOTERA HEALTH LLC, and SOTERA HEALTH COMPANY,	§	
Defendants.	§	

ORDER ON MOTIONS TO DISMISS

THIS MATTER having come before the Court upon defendants Sterigenics U.S., LLC ("Sterigenics"), Sotera Health Holdings, LLC, Sotera Health LLC, and Sotera Health Company's (collectively "Sotera Defendants," and with Sterigenics, "Defendants") Motion to Dismiss Under Rule 1-012(B)(6) for failure to state a claim ("Rule 1-012(B)(6) Motion") and the Sotera Defendants' Motion to Dismiss Under 1-012(B)(2) for lack of personal jurisdiction ("Personal Jurisdiction Motion"), and the Court being fully advised of the issues and arguments presented therein, as well as the arguments presented by the parties during the October 28, 2021 motion hearing, the Court rules as follows:

1. The Sotera Defendants' Personal Jurisdictional Motion is held in abeyance while Plaintiff completes discovery from the Sotera Defendants concerning the jurisdictional issue.
2. Defendants' Rule 1-012(B)(6) Motion seeks dismissal of Plaintiff's request for public health monitoring remedies. *See, e.g.*, Complaint, ¶¶ 177, 201. The Court finds

Plaintiff's request for "an order requiring Defendants to fund a public health monitoring program designed to detect, assess, and treat medical disorders associated with EtO exposure, under State supervision" and "to abate the public nuisance" is adequately pleaded.

3. Defendants' Rule 1-012(B)(6) Motion seeks dismissal of Plaintiff's statutory and common law public nuisance claims (Counts I and II) for failure to state a claim upon which relief may be granted. The Court finds Plaintiff's statutory and common law public nuisance claims adequately pleaded.
4. Defendants' Rule 1-012(B)(6) Motion seeks dismissal of Plaintiff's strict liability claim (Count III) for failure to state a claim upon which relief may be granted. The Court finds Plaintiff's strict liability claim adequately pleaded.
5. Defendants' Rule 1-012(B)(6) Motion seeks dismissal of Plaintiff's claim for negligence (Count IV) for failure to state a claim upon which relief may be granted. The Court finds Plaintiff's negligence claim adequately pleaded.
6. Defendants' Rule 1-012(B)(6) Motion seeks dismissal of Plaintiff's claim under the Unfair Practices Act ("UPA") (Count VI). The Court finds Plaintiff's UPA claim adequately pleaded.

For these reasons, as well as the reasons set forth during the October 28, 2021 hearing, Defendants' Rule 1-012(B)(6) Motion is **DENIED**.

Defendant Sterigenics U.S., LLC shall answer the Complaint no later than 30 days from entry of this Order.

IT IS SO ORDERED.

Date: 12-20-2021

Mari E Beyer

ED_013218_00001725-00002

Marci Beyer, District Judge

Prepared by:

/s/ Jacqueline Ortiz
P. Cholla Khoury
Jacqueline Ortiz
Assistant Attorneys General
New Mexico Office of the Attorney General
P.O. Drawer 1508
Santa Fe, New Mexico 87504

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Approved as to form:

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Sara M. Warren *admitted pro hac vice
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1201 West Peachtree Street

ED_013218_00001725-00003

Atlanta, GA 30309

Attorneys for Defendants

ED_013218_00001725-00004

Message

From: Moeller, Njeri [Moeller.Njeri@epa.gov]
Sent: 3/8/2022 9:33:20 PM
To: Koerber, Mike [Koerber.Mike@epa.gov]
Subject: FW: Request for briefing materials -- for EtO briefing for Joe tomorrow
Attachments: EtO_2022_Risk_Results_Briefing_for JG 3 8 2022_.pptx

Hi Mike,

Here are the slides for the OAR Eto discussion for tomorrow. The slides look similar to the ones from last weeks briefing.

Njeri Moeller (she/her/hers)
U.S. Environmental Protection Agency
OAR/OAQPS IO Special Assistant – Detail
109 TW Alexander Drive
Research Triangle Park, NC 27711
Phone: 919-541-1380 |Email: Moeller.njeri@epa.gov

From: Vasu, Amy <Vasu.Amy@epa.gov>
Sent: Tuesday, March 8, 2022 4:22 PM
To: Moeller, Njeri <Moeller.Njeri@epa.gov>
Cc: Rimer, Kelly <Rimer.Kelly@epa.gov>; Michelsen-Correa, Stephani <michelsen-correa.stephani@epa.gov>
Subject: RE: Request for briefing materials -- for EtO briefing for Joe tomorrow

Hi Njeri,

Kelly asked me to send you the materials for tomorrow's briefing for Joe on **EtO Commercial Sterilizer Revised Risk Results** (attached).

Thank you,

Amy

From: Moeller, Njeri <Moeller.Njeri@epa.gov>
Sent: Tuesday, March 8, 2022 3:35 PM
To: Vasu, Amy <Vasu.Amy@epa.gov>; Rimer, Kelly <Rimer.Kelly@epa.gov>
Cc: Michelsen-Correa, Stephani <michelsen-correa.stephani@epa.gov>
Subject: RE: Request for briefing materials -- for EtO briefing for Joe tomorrow

Hello,

Just wanted to follow-up on this, please let know if there are briefing materials.

Thanks,

Njeri Moeller (she/her/hers)
U.S. Environmental Protection Agency
OAR/OAQPS IO Special Assistant – Detail
109 TW Alexander Drive
Research Triangle Park, NC 27711
Phone: 919-541-1380 |Email: Moeller.njeri@epa.gov

From: Vasu, Amy <Vasu.Amy@epa.gov>
Sent: Tuesday, March 8, 2022 11:33 AM
To: Rimer, Kelly <Rimer.Kelly@epa.gov>
Cc: Michelsen-Correa, Stephani <michelsen-correa.stephani@epa.gov>; Moeller, Njeri <Moeller.Njeri@epa.gov>
Subject: Request for briefing materials -- for EtO briefing for Joe tomorrow

Kelly,

Just passing on the OAQPS IO request for briefing materials for tomorrow's briefing for Joe on **EtO Commercial Sterilizer Revised Risk Results.**

Thanks,

Amy

From: Moeller, Njeri <Moeller.Njeri@epa.gov>
Sent: Tuesday, March 8, 2022 11:06 AM
To: Vasu, Amy <Vasu.Amy@epa.gov>
Subject: OAR Briefing - 3/9

Hi Amy,

Just wanted to check and see if there are any briefing materials for the **EtO Commercial Sterilizer Revised Risk Results** scheduled for tomorrow at 3pm?

Thanks,

Njeri Moeller (she/her/hers)
U.S. Environmental Protection Agency
OAR/OAQPS IO Special Assistant – Detail
109 TW Alexander Drive
Research Triangle Park, NC 27711
Phone: 919-541-1380 |Email: Moeller.njeri@epa.gov

Message

From: Ross, Aftin [Aftin.Ross@fda.hhs.gov]
Sent: 6/8/2022 8:43:37 PM
To: Koerber, Mike [Koerber.Mike@epa.gov]
Subject: RE: URGENT Request from FDA for a Meeting: [EXTERNAL] EtO sterilizer facility list and draft interagency EtO communications document

Good afternoon. Calling your cell now.

Best,

Aftin

Aftin Ross, Ph.D.
Senior Special Advisor for Emerging Initiatives
Office of Strategic Partnerships and Technology Innovation (OST)
Center for Devices and Radiological Health
U.S. Food and Drug Administration

WO 66, Room 5558
10903 New Hampshire Ave, Silver Spring, MD 20993
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aftin.ross@fda.hhs.gov
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U.S. FOOD & DRUG ADMINISTRATION

From: Koerber, Mike <Koerber.Mike@epa.gov>
Sent: Wednesday, June 8, 2022 4:40 PM
To: Ross, Aftin <Aftin.Ross@fda.hhs.gov>
Subject: RE: URGENT Request from FDA for a Meeting: [EXTERNAL] EtO sterilizer facility list and draft interagency EtO communications document

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Hi Aftin. Do you have a minute for a quick call? I'd like to follow up on this morning's conversation. Thanks.

Mike

Mike Koerber
o. 919-541-5557
c. 919-450-6478
he/him/his

From: Ross, Aftin <Aftin.Ross@fda.hhs.gov>
Sent: Wednesday, June 8, 2022 9:19 AM
To: Koerber, Mike <Koerber.Mike@epa.gov>; Vasu, Amy <Vasu.Amy@epa.gov>; Carbonell, Tomas <Carbonell.Tomas@epa.gov>; Goffman, Joseph <Goffman.Joseph@epa.gov>; Beal, Madeline <Beal.Madeline@epa.gov>; Noonan, Jenny <Noonan.Jenny@epa.gov>; Gillespie, Taylor <Gillespie.Taylor@epa.gov>
Cc: Schwartz, Suzanne <Suzanne.Schwartz@fda.hhs.gov>; Tarver, Michelle <Michelle.Tarver@fda.hhs.gov>; Ricci, Linda J <Linda.Ricci@fda.hhs.gov>; Beckham, Tammy <Tammy.Beckham@fda.hhs.gov>; Ellis, Nicole <Nicole.Ellis@fda.hhs.gov>
Subject: RE: URGENT Request from FDA for a Meeting: [EXTERNAL] EtO sterilizer facility list and draft interagency EtO communications document

Thank you very much. We will send an invite for 11am EST momentarily.

Best,

Aftin

Aftin Ross, Ph.D.
Senior Special Advisor for Emerging Initiatives
Office of Strategic Partnerships and Technology Innovation (OST)
Center for Devices and Radiological Health
U.S. Food and Drug Administration

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https://www.research.net/s/cdrhcustomerservice?ID=7011&S=E

U.S. FOOD & DRUG ADMINISTRATION

From: Koerber, Mike <Koerber.Mike@epa.gov>
Sent: Wednesday, June 8, 2022 9:12 AM
To: Ross, Aftin <Aftin.Ross@fda.hhs.gov>; Vasu, Amy <Vasu.Amy@epa.gov>; Carbonell, Tomas <Carbonell.Tomas@epa.gov>; Goffman, Joseph <Goffman.Joseph@epa.gov>; Beal, Madeline <Beal.Madeline@epa.gov>; Noonan, Jenny <Noonan.Jenny@epa.gov>; Gillespie, Taylor <Gillespie.Taylor@epa.gov>
Cc: Schwartz, Suzanne <Suzanne.Schwartz@fda.hhs.gov>; Tarver, Michelle <Michelle.Tarver@fda.hhs.gov>; Ricci, Linda J <Linda.Ricci@fda.hhs.gov>; Beckham, Tammy <Tammy.Beckham@fda.hhs.gov>; Ellis, Nicole <Nicole.Ellis@fda.hhs.gov>
Subject: RE: URGENT Request from FDA for a Meeting: [EXTERNAL] EtO sterilizer facility list and draft interagency EtO communications document

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Hi, Aftin. Let me know when you'd like to meet. We will be available.

Mike Koerber
o. 919-541-5557

c. 919-450-6478
he/him/his

From: Ross, Aftin <Aftin.Ross@fda.hhs.gov>
Sent: Wednesday, June 8, 2022 8:39 AM
To: Vasu, Amy <Vasu.Amy@epa.gov>; Koerber, Mike <Koerber.Mike@epa.gov>
Cc: Schwartz, Suzanne <Suzanne.Schwartz@fda.hhs.gov>; Tarver, Michelle <Michelle.Tarver@fda.hhs.gov>; Ricci, Linda J <Linda.Ricci@fda.hhs.gov>; Beckham, Tammy <Tammy.Beckham@fda.hhs.gov>; Ellis, Nicole <Nicole.Ellis@fda.hhs.gov>
Subject: URGENT Request from FDA for a Meeting: [EXTERNAL] EtO sterilizer facility list and draft interagency EtO communications document
Importance: High

Good morning. Thank you for sharing this information with us. We have shared this information with our leadership and they are very concerned about the timing and the framing of this list that you indicate is targeted for release next week. We would like to schedule a meeting with you as soon as possible to discuss our concerns.

Please let us know when you would be available and we will be flexible to accommodate.

Best,

Aftin

Aftin Ross, Ph.D.
Senior Special Advisor for Emerging Initiatives
Office of Strategic Partnerships and Technology Innovation (OST)
Center for Devices and Radiological Health
U.S. Food and Drug Administration

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10903 New Hampshire Ave, Silver Spring, MD 20993
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aftin.ross@fda.hhs.gov
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https://www.research.net/s/cdrhcustomerservice?ID=7011&S=E

U.S. FOOD & DRUG ADMINISTRATION

From: Vasu, Amy <Vasu.Amy@epa.gov>
Sent: Tuesday, June 7, 2022 4:49 PM
To: Ross, Aftin <Aftin.Ross@fda.hhs.gov>; Ricci, Linda J <Linda.Ricci@fda.hhs.gov>; Schwartz, Suzanne <Suzanne.Schwartz@fda.hhs.gov>; Breysse, Patrick N (CDC) <pjb7@cdc.gov>; Johnson, Mark D (ATSDR) <mki5@cdc.gov>; Li, Zheng (ATSDR) <kzl4@cdc.gov>; Hoadley, Mary L (ATSDR) <nrd2@cdc.gov>; ruskin.maureen@dol.gov; baughman.william@dol.gov
Cc: Koerber, Mike <Koerber.Mike@epa.gov>; Noonan, Jenny <Noonan.Jenny@epa.gov>; Beal, Madeline <Beal.Madeline@epa.gov>; Bremer, Kristen <Bremer.Kristen@epa.gov>; Rodan, Bruce <rodan.bruce@epa.gov>; Thayer, Kris <thayer.kris@epa.gov>; Pease, Anita <Pease.Anita@epa.gov>; Reaves, Elissa <Reaves.Elissa@epa.gov>; Bailey, Jessica <bailey.jessica@epa.gov>; Jennings, Susan <Jennings.Susan@epa.gov>; Yelverton, Tiffany

<Yelverton.Tiffany@epa.gov>; Sasser, Erika <Sasser.Erika@epa.gov>
Subject: [EXTERNAL] EtO sterilizer facility list and draft interagency EtO communications document

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear EtO Interagency Task Force members,

In advance of the June 13th special meeting of this group, we are sharing with you the list of 27 EtO commercial sterilizing facilities associated with elevated cancer risks in nearby communities (attached). This list has not yet been shared publicly, and we ask that you not share this outside of your agency/administration until after EPA posts the list of facilities and risk results. The plan is to post the facility-specific risk results for public viewing on an EPA website on June 14th, about a week prior to a national public webinar that EPA will be holding on June 22nd.

At our June 13th meeting, we will provide details on the risk assessment and results and describe plans for outreach to communities located near the 27 facilities with elevated cancer risks and 1 additional facility (Sterigenics, Santa Teresa, NM, which no longer has elevated risk).* We'd also like to discuss with you how best to coordinate moving forward and, with that in mind, have attached, for your consideration, a draft document that includes a set of key messages, likely questions that you will receive, and public-facing frequently asked questions that may be of interest to you.

If you receive any inquiries between now and June 22nd about EPA's risk analyses and results or other work in support of the commercial sterilizer rulemaking or EPA's plans for community outreach in the coming weeks, please direct those to Mike Koerber and Amy Vasu.

We look forward to meeting with you on Monday.

Amy

Amy Vasu (*she/her*)
Air Toxics Assessment Group
Office of Air Quality Planning and Standards
U.S. Environmental Protection Agency
vasu.amy@epa.gov
919.541.0107

*The Sterigenics, Santa Teresa, NM facility no longer has elevated risk; however, in the 2018 NATA, it was identified as having elevated risk. As part of the Office of the Inspector General (OIG) management alert, EPA has committed to outreach to the community near this facility.
Additional information is available at: https://www.epa.gov/hazardous-air-pollutants-ethylene-oxide/inspector-general-follow-ethylene-oxide-0

Message

From: Branning, Amy [Branning.Amy@epa.gov]
Sent: 6/2/2021 7:27:01 PM
To: Rimer, Kelly [Rimer.Kelly@epa.gov]
Subject: RE: If you are really busy right now

Excellent! Thank you so much!!

Amy Huang Branning
EPA Office of General Counsel
phone: (202) 564-1744
fax: (202) 564-5603 or (202) 564-0070

From: Rimer, Kelly <Rimer.Kelly@epa.gov>
Sent: Wednesday, June 02, 2021 3:26 PM
To: Branning, Amy <Branning.Amy@epa.gov>
Subject: RE: If you are really busy right now

Hi Amy,

There IS a users' guide for the NATA Map App. https://gispub.epa.gov/NATA/2014NATAmapappuserguide.pdf

I am filing this under, "things I should've known"

Kelly

From: Branning, Amy <Branning.Amy@epa.gov>
Sent: Wednesday, June 02, 2021 3:15 PM
To: Rimer, Kelly <Rimer.Kelly@epa.gov>
Subject: RE: If you are really busy right now

Thank you so much, Kelly.

Amy Huang Branning
EPA Office of General Counsel
phone: (202) 564-1744
fax: (202) 564-5603 or (202) 564-0070

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From: Rimer, Kelly <Rimer.Kelly@epa.gov>
Sent: Wednesday, June 02, 2021 3:13 PM
To: Branning, Amy <Branning.Amy@epa.gov>
Subject: RE: If you are really busy right now

Hi Amy, here is the information you requested.

NATA Website: https://www.epa.gov/national-air-toxics-assessment

I don't think there is any more detail about how to use the NATA map app than you can find on the NATA website here: https://www.epa.gov/national-air-toxics-assessment/2014-nata-map, and here https://gispub.epa.gov/NATA/

IRIS Website: https://www.epa.gov/iris

IRIS EtO document: https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=1025

And I attached the MON response to comments document.

Hope these items help --
Kelly

From: Branning, Amy <Branning.Amy@epa.gov>
Sent: Wednesday, June 02, 2021 2:42 PM
To: Rimer, Kelly <Rimer.Kelly@epa.gov>
Subject: RE: If you are really busy right now

Yes, right now. You available?

Amy Huang Branning
EPA Office of General Counsel
phone: (202) 564-1744
fax: (202) 564-5603 or (202) 564-0070

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From: Rimer, Kelly <Rimer.Kelly@epa.gov>
Sent: Wednesday, June 02, 2021 2:10 PM
To: Branning, Amy <Branning.Amy@epa.gov>
Subject: RE: If you are really busy right now

Do you have time for a quick chat via teams?

From: Branning, Amy <Branning.Amy@epa.gov>
Sent: Wednesday, June 02, 2021 2:02 PM
To: Rimer, Kelly <Rimer.Kelly@epa.gov>
Subject: If you are really busy right now

If you can first give us the citations of public sources on IRIS and NATA that DOJ should use to draft descriptions of IRIS and NATA (see 2 below) and also cite in the brief, that would be great.

Thank you in advance.

Amy Huang Branning
EPA Office of General Counsel
phone: (202) 564-1744
fax: (202) 564-5603 or (202) 564-0070

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From: Branning, Amy
Sent: Wednesday, June 02, 2021 1:58 PM
To: Rimer, Kelly <Rimer.Kelly@epa.gov>
Subject: FW: This may help

Ex. 5 AC/AWP/DP

Amy Huang Branning
EPA Office of General Counsel
phone: (202) 564-1744
fax: (202) 564-5603 or (202) 564-0070

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From: Branning, Amy
Sent: Wednesday, June 02, 2021 12:37 PM
To: Rimer, Kelly <Rimer.Kelly@epa.gov>
Subject: This may help

Hi Kelly:

Attached is my 2-page cheat sheet showing my first cut on what I think we should address in our amicus brief. Search your name and you will see 2 places, one on each of the briefs. Those are the areas that I most need your input.

Amy Huang Branning
EPA Office of General Counsel
phone: (202) 564-1744
fax: (202) 564-5603 or (202) 564-0070

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From: Branning, Amy
Sent: Wednesday, June 02, 2021 8:07 AM
To: Rimer, Kelly <Rimer.Kelly@epa.gov>
Subject: RE: New Mexico v. Sterigenics - next steps

Good morning Kelly.

Of course. Attached are the two documents with Jonathan's inputs. Ex. 5 AC/DP

Ex. 5 AC/DP

Amy Huang Branning
EPA Office of General Counsel
phone: (202) 564-1744
fax: (202) 564-5603 or (202) 564-0070

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From: Rimer, Kelly <Rimer.Kelly@epa.gov>
Sent: Wednesday, June 02, 2021 7:58 AM
To: Branning, Amy <Branning.Amy@epa.gov>
Subject: RE: New Mexico v. Sterigenics - next steps

Sorry,
Can you send the latest draft?

From: Branning, Amy <Branning.Amy@epa.gov>
Sent: Tuesday, June 01, 2021 5:16 PM
To: Rimer, Kelly <Rimer.Kelly@epa.gov>
Cc: Witt, Jon <Witt.Jon@epa.gov>; Anderson, Lea <anderson.lea@epa.gov>
Subject: RE: New Mexico v. Sterigenics - next steps

Hi Kelly:

Just checking in to see whether you had a chance to look at the factual statements I highlighted in the 2 briefs for this case.

Amy Huang Branning
EPA Office of General Counsel
phone: (202) 564-1744
fax: (202) 564-5603 or (202) 564-0070

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From: Rimer, Kelly <Rimer.Kelly@epa.gov>
Sent: Tuesday, May 25, 2021 12:39 PM
To: Branning, Amy <Branning.Amy@epa.gov>
Cc: Witt, Jon <Witt.Jon@epa.gov>; Anderson, Lea <anderson.lea@epa.gov>
Subject: RE: New Mexico v. Sterigenics - next steps

Sounds good. Thanks

From: Branning, Amy <Branning.Amy@epa.gov>
Sent: Tuesday, May 25, 2021 12:00 PM
To: Rimer, Kelly <Rimer.Kelly@epa.gov>
Cc: Witt, Jon <Witt.Jon@epa.gov>; Anderson, Lea <anderson.lea@epa.gov>
Subject: RE: New Mexico v. Sterigenics - next steps

Does not need to be today. How about later this week or by Friday?

Amy Huang Branning
EPA Office of General Counsel
phone: (202) 564-1744
fax: (202) 564-5603 or (202) 564-0070

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From: Rimer, Kelly <Rimer.Kelly@epa.gov>
Sent: Tuesday, May 25, 2021 11:47 AM
To: Branning, Amy <Branning.Amy@epa.gov>
Cc: Witt, Jon <Witt.Jon@epa.gov>; Anderson, Lea <anderson.lea@epa.gov>
Subject: Re: New Mexico v. Sterigenics - next steps

My day is packed. What is the deadline ?

On May 25, 2021, at 11:36 AM, Branning, Amy <Branning.Amy@epa.gov> wrote:

Ex. 5 AC/DP

Amy Huang Branning
EPA Office of General Counsel

phone: (202) 564-1744
fax: (202) 564-5603 or (202) 564-0070

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From: Witt, Jon <Witt.Jon@epa.gov>
Sent: Tuesday, May 25, 2021 9:46 AM
To: Rimer, Kelly <Rimer.Kelly@epa.gov>; Branning, Amy <Branning.Amy@epa.gov>
Cc: Anderson, Lea <anderson.lea@epa.gov>
Subject: RE: New Mexico v. Sterigenics - next steps

My comments on the company brief attached. This one had a lot on IRIS and NATA, so I didn't have a whole lot of feedback
Jonathan

From: Rimer, Kelly <Rimer.Kelly@epa.gov>
Sent: Tuesday, May 25, 2021 8:59 AM
To: Branning, Amy <Branning.Amy@epa.gov>; Witt, Jon <Witt.Jon@epa.gov>
Cc: Anderson, Lea <anderson.lea@epa.gov>
Subject: RE: New Mexico v. Sterigenics - next steps

Thanks Jonathan, I will take a look when you send it.

Ex. 5 AC/AWP

Kelly

From: Branning, Amy <Branning.Amy@epa.gov>
Sent: Tuesday, May 25, 2021 8:34 AM
To: Witt, Jon <Witt.Jon@epa.gov>; Rimer, Kelly <Rimer.Kelly@epa.gov>
Cc: Anderson, Lea <anderson.lea@epa.gov>
Subject: RE: New Mexico v. Sterigenics - next steps

Thank you so much, Jonathan.

Amy Huang Branning
EPA Office of General Counsel
phone: (202) 564-1744
fax: (202) 564-5603 or (202) 564-0070

From: Witt, Jon <Witt.Jon@epa.gov>
Sent: Tuesday, May 25, 2021 8:29 AM
To: Branning, Amy <Branning.Amy@epa.gov>; Rimer, Kelly <Rimer.Kelly@epa.gov>
Cc: Anderson, Lea <anderson.lea@epa.gov>
Subject: RE: New Mexico v. Sterigenics - next steps

Thanks Amy. Attaching what I have on the state motion to get the ball rolling. Will try to get the company brief out later this morning.
Jonathan

From: Branning, Amy <Branning.Amy@epa.gov>
Sent: Thursday, May 20, 2021 4:53 PM
To: Rimer, Kelly <Rimer.Kelly@epa.gov>; Witt, Jon <Witt.Jon@epa.gov>
Cc: Anderson, Lea <anderson.lea@epa.gov>
Subject: New Mexico v. Sterigenics - next steps

Ex. 5 AC/AWP/DP

Amy Huang Branning
EPA Office of General Counsel
phone: (202) 564-1744
fax: (202) 564-5603 or (202) 564-0070

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From: Branning, Amy
Sent: Thursday, May 20, 2021 4:16 PM
To: 'Oakes, Matthew (ENRD)' <Matthew.Oakes@usdoj.gov>
Subject: RE: New Mexico v. Sterigenics - next steps

Hi Matt:

Ex. 5 AC/AWP/DP

Amy Huang Branning
EPA Office of General Counsel

phone: (202) 564-1744
fax: (202) 564-5603 or (202) 564-0070

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From: Oakes, Matthew (ENRD) <Matthew.Oakes@usdoj.gov>
Sent: Thursday, May 20, 2021 12:28 PM
To: Srinivasan, Gautam <Srinivasan.Gautam@epa.gov>; Harvey, Judy (ENRD) <Judith.Harvey@usdoj.gov>; Branning, Amy <Branning.Amy@epa.gov>; Anderson, Lea <anderson.lea@epa.gov>; Witt, Jon <Witt.Jon@epa.gov>; Schoellkopf, Lynde <Schoellkopf.Lynde@epa.gov>; Puplampu, William <puplampu.william@epa.gov>
Subject: New Mexico v. Sterigenics - next steps

Ex. 5 AC/AWP/DP

Matt Oakes
Senior Counsel
United States Department of Justice
Environment and Natural Resources Division
Law and Policy Section
(202) 532-3129 (cell)

Message

From: Vasu, Amy [Vasu.Amy@epa.gov]
Sent: 10/7/2021 12:22:20 AM
To: Chow, Alice [chow.alice@epa.gov]
CC: Gross-Davis, CarolAnn [Gross-Davis.CarolAnn@epa.gov]; Nitsch, Chad [Nitsch.Chad@epa.gov]; Delgrosso, Karen [Delgrosso.Karen@epa.gov]; Rimer, Kelly [Rimer.Kelly@epa.gov]; Bremer, Kristen [Bremer.Kristen@epa.gov]
Subject: Response to citizen questions on EtO "cancer maps"

Hi Alice,

Here is our response to David Marsh's questions:

> In December 2016, EPA issued a final assessment of ethylene oxide (EtO) and found that EtO is much more toxic than we had previously thought. Prior to 2016, as part of the peer review and public review steps, the draft assessment was made available publicly (https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=329730).
>
> In August 2018, EPA released its 2014 National Air Toxics Assessment (NATA) (https://www.epa.gov/national-air-toxics-assessment/2014-nata-assessment-results), which includes maps, and identified a number of areas in the U.S. with potentially elevated risk from continuous exposure, over 70 years, to EtO in the outdoor air. NATA is a screening-level analysis that is intended to identify pollutants or areas for closer examination.
>
> The Sterigenics facility in Smyrna, GA, was identified in the NATA assessment, and actions have been taken at that facility to reduce EtO emissions (described in detail at https://www.epa.gov/sites/default/files/2021-01/documents/status_report._sterigenics_smyrna_ga_0.pdf). The EPA is taking a closer look at regulations to address ethylene oxide emissions and anticipates issuing a proposed rule for commercial sterilizers in 2022. Additional information on actions the EPA is taking to address EtO is provided at https://www.epa.gov/hazardous-air-pollutants-ethylene-oxide.

Thanks,

Amy

From: Chow, Alice <chow.alice@epa.gov>
Sent: Wednesday, October 6, 2021 9:14 AM
To: Vasu, Amy <Vasu.Amy@epa.gov>
Cc: Gross-Davis, CarolAnn <Gross-Davis.CarolAnn@epa.gov>; Nitsch, Chad <Nitsch.Chad@epa.gov>; Delgrosso, Karen <Delgrosso.Karen@epa.gov>
Subject: RE: RESPONSE: Cancer maps cover up

Yes, that would be fine.

Alice H. Chow
Chief, Air Quality Analysis Branch (3AD40)
Air & Radiation Division (14-130)
USEPA, Region 3
Phone: 215-814-2144
Cell: 215-817-4380
Email: chow.alice@epa.gov

From: Vasu, Amy <Vasu.Amy@epa.gov>
Sent: Wednesday, October 06, 2021 9:13 AM
To: Chow, Alice <chow.alice@epa.gov>
Cc: Gross-Davis, CarolAnn <Gross-Davis.CarolAnn@epa.gov>; Nitsch, Chad <Nitsch.Chad@epa.gov>; Delgrosso, Karen <Delgrosso.Karen@epa.gov>
Subject: RE: RESPONSE: Cancer maps cover up

Okay. Would it be better if I send you the response to send to David Marsh and to post?

From: Chow, Alice <chow.alice@epa.gov>
Sent: Wednesday, October 6, 2021 9:12 AM
To: Vasu, Amy <Vasu.Amy@epa.gov>
Cc: Gross-Davis, CarolAnn <Gross-Davis.CarolAnn@epa.gov>; Nitsch, Chad <Nitsch.Chad@epa.gov>; Delgrosso, Karen <Delgrosso.Karen@epa.gov>
Subject: RE: RESPONSE: Cancer maps cover up

We need to post the answer on our website.

Alice H. Chow
Chief, Air Quality Analysis Branch (3AD40)
Air & Radiation Division (14-130)
USEPA, Region 3
Phone: 215-814-2144
Cell: 215-817-4380
Email: chow.alice@epa.gov

From: Vasu, Amy <Vasu.Amy@epa.gov>
Sent: Wednesday, October 06, 2021 9:11 AM
To: Chow, Alice <chow.alice@epa.gov>
Cc: Gross-Davis, CarolAnn <Gross-Davis.CarolAnn@epa.gov>; Nitsch, Chad <Nitsch.Chad@epa.gov>; Delgrosso, Karen <Delgrosso.Karen@epa.gov>
Subject: RE: RESPONSE: Cancer maps cover up

Hi, Alice –

OAQPS will answer this one. We'll reply to David Marsh and forward the reply to the four of you so that you know it's been answered.

Thank you,

Amy

From: Chow, Alice <chow.alice@epa.gov>
Sent: Tuesday, October 5, 2021 11:30 AM
To: Vasu, Amy <Vasu.Amy@epa.gov>
Cc: Gross-Davis, CarolAnn <Gross-Davis.CarolAnn@epa.gov>; Nitsch, Chad <Nitsch.Chad@epa.gov>; Delgrosso, Karen <Delgrosso.Karen@epa.gov>
Subject: FW: RESPONSE: Cancer maps cover up
Importance: High

Amy: We just got this…not sure I know how to deal with this, it's more of a national issue.

Alice

Alice H. Chow
Chief, Air Quality Analysis Branch (3AD40)
Air & Radiation Division (14-130)
USEPA, Region 3
Phone: 215-814-2144
Cell: 215-817-4380
Email: chow.alice@epa.gov

From: Delgrosso, Karen <Delgrosso.Karen@epa.gov>
Sent: Tuesday, October 05, 2021 11:02 AM
To: Chow, Alice <chow.alice@epa.gov>; Gross-Davis, CarolAnn <Gross-Davis.CarolAnn@epa.gov>
Cc: Fernandez, Cristina <Fernandez.Cristina@epa.gov>; Febbo, Carol <febbo.carol@epa.gov>
Subject: RESPONSE: Cancer maps cover up
Importance: High

Hi Alice and CarolAnn,

Please see the below question that was found in the R3EthyleneOxide email box. (For some reason, I could not see messages in this email box, but it has since been corrected.)

Is this a question that you can address or is this one for WVDEP?

Thanks, Karen

From: Dave Mars <daveintrinidad2018@gmail.com>
Sent: Tuesday, September 21, 2021 8:25 PM
To: R3EthyleneOxide <R3EthyleneOxide@epa.gov>
Subject: Cancer maps cover up

My name is David Marsh, I was hired by the sterigenics corporation in 2012 as corporate ethylene oxide engineer. I was given several of the cancer maps and assigned to audit plant facilities and their equipment and apparatus as well as

maintenance practices in Smyrna Georgia Dallas Texas South Carolina Santa Teresa New Mexico, Grand island New York and others. I I provided the engineering manager I reported to, Brian Masch and the corporate vice president, John Gilbert documentation reporting the Dallas and Smyrna Plants were replete with leaks from poor maintenance practice and engineering short cuts, leaking chamber door seals as well as excessive cycle stops in Charleston. I was only six months into this effort, Ex. 6 Personal Privacy (PP) My question follows.
Why were the cancer maps that John Gilbert and Brian Masch corporate engineers, gave me as a work assignment to determine any equipment related causes for in 2012 not made public until 2018? Was the federal EPA aware of this cover up? And were any of the repair needs I brought to their attention ever repaired or do they continue to emit raw EO into these neighborhoods today? And how does all this compare to the tobacco cancer cover ups in the 1960s?
I plan to listen in on the phone on the 23rd.
Respectfully,
David Marsh
Former Sterigenics EO Engineer

Message

From: Branning, Amy [Branning.Amy@epa.gov]
Sent: 5/14/2021 9:14:46 PM
To: Witt, Jon [Witt.Jon@epa.gov]
Subject: Sterigenics (NM)
Attachments: Sterigenics.amicus.April22.pdf; 2021-04-14 Emergency Mtn ISO Request for TRO and Prelim Injunc.pdf; 2021-04-17 Sterigenics Brief in Opp to Pltf's Emergency Mtn for TRO and Prelim Injunc.pdf

Hi Jonathan:

For convenience, I have attached the Court's 4/22 order and the 2 briefs that the Court mentioned in her order (4/14 Emergency Motion and Sterigenic's 4/17 opposition).

Amy Huang Branning
EPA Office of General Counsel
phone: (202) 564-1744
fax: (202) 564-5603 or (202) 564-0070

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From: Branning, Amy
Sent: Thursday, May 13, 2021 3:09 PM
To: Witt, Jon <Witt.Jon@epa.gov>
Subject: Risk data on Sterigenics (NM)

Hi Jonathan:

Do we have risk data on this facility? If so, what does it show? Thank you.

Amy Huang Branning
EPA Office of General Counsel
phone: (202) 564-1744
fax: (202) 564-5603 or (202) 564-0070

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From: Anderson, Lea <anderson.lea@epa.gov>
Sent: Thursday, May 13, 2021 2:55 PM
To: Branning, Amy <Branning.Amy@epa.gov>
Subject: Sterigenics - State Nuisance Claim

Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

From: Srinivasan, Gautam <Srinivasan.Gautam@epa.gov>
Sent: Thursday, May 13, 2021 1:59 PM
To: Anderson, Lea <anderson.lea@epa.gov>
Subject: brief

Here's the brief I mentioned. Also attached is the order.

++++++++++++++++++++++++++++++
(202) 564-5647 (o)
(202) 695-6287 (c)

FILED
3rd JUDICIAL DISTRICT COURT
Dona Ana County
4/22/2021 4:36 PM
DAVID S. BORUNDA
CLERK OF THE COURT
Ashley Barreras

STATE OF NEW MEXICO
COUNTY OF DOÑA ANA
THIRD JUDICIAL DISTRICT COURT

THE STATE OF NEW MEXICO, EX REL. HECTOR BALDERAS, ATTORNEY GENERAL,

Plaintiff,

vs

STERIGENICS U.S., LLC, SOTERA HEALTH HOLDINGS, LLC, SOTERA HEALTH LLC, AND SOTERA HEALTH COMPANY,

Defendants.

No. D-307-CV-2020-2629
Judge Beyer

ORDER REQUESTING BRIEFS AMICUS CURIAE

THIS MATTER is before the Court on its own motion. The Court believes that amicus assistance from interested organizations would be helpful to it in rendering its decision.

NOW, THEREFORE, the Court orders the following.

The Court requests that the New Mexico Environment Department (NMED) and the U.S. Environmental Protection Agency (EPA) each submit an amicus brief within 45 days of the date of this Order. The amicus briefs should address the issues raised in Plaintiff's Emergency Motion for Temporary Restraining Order and Preliminary Injunction filed April 14, 2021 and Defendants' Brief in Opposition filed April 17, 2021, including the EPA and NMED's primary jurisdiction

IT IS SO ORDERED.

Marci Beyer, District Judge

ED_013218_00002873-00001

Certificate of Service

I hereby certify that a copy of this order was mailed or delivered to the following on this 22nd day of April 2021:

New Mexico Environmental Department
PO Box 5469
Santa Fe, NM 87502-5469
bruce.baizel@state.nm.us

Environmental Protection Agency Region 6
Office of Regional Counsel
1201 Elm Street, Suite 500
Dallas, Texas 75720

EPA Border Office
4050 Rio Bravo, Suite 100
El Paso, TX 77902

Jacqueline Ortiz
jortiz@nmag.gov

Marcus J. Rael
marcus@roblesrael.com

Tiffany L. Roach Martin
tlr@modrall.com

Alex C. Walker
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FILED
3rd JUDICIAL DISTRICT COURT
Dona Ana County
4/14/2021 5:30 PM
DAVID S. BORUNDA
CLERK OF THE COURT
Josephina Gomez

STATE OF NEW MEXICO
COUNTY OF DOÑA ANA
THIRTEENTH JUDICIAL DISTRICT COURT

THE STATE OF NEW MEXICO, ex rel.
HECTOR BALDERAS,
ATTORNEY GENERAL,

Plaintiff,

No.: D-307-CV-2020-02629

v.

Beyer, Marci

STERIGENICS U.S., LLC, SOTERA HEALTH HOLDINGS, LLC, SOTERA HEALTH LLC, and SOTERA HEALTH COMPANY,

Defendants.

EMERGENCY MOTION IN SUPPORT OF REQUEST FOR TEMPORARY RESTRAINING ORDER AND PRELIMINARY INJUNCTION

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I. INTRODUCTION

The State of New Mexico, by its Attorney General Hector Balderas ("Plaintiff" or "New Mexico" or the "State"), hereby moves the Court, pursuant to Rule 1-066 NMRA and other applicable law, if any, for a temporary restraining order and preliminary injunction to require the Defendants, as defined below, to do what is immediately necessary to protect the people of the State of New Mexico from the potentially devastating effects of exposure to elevated levels of the toxic chemical ethylene oxide ("EtO") known to be present at and emanating in uncontrolled fashion from Defendants' operations in Santa Teresa, Doña Ana County, New Mexico.

The State brought this civil action against Sterigenics U.S., LLC, Sotera Health Holdings, LLC, Sotera Health, LLC, and Sotera Health Company (collectively, "Defendants" or "Sterigenics") under New Mexico common and statutory law, including claims of public nuisance, to remedy, abate and end the imminent and substantial endangerment to human health resulting from Defendants' operations at their facility in Santa Teresa, Doña Ana County, New Mexico, at which industrial sterilization and fumigation processes have been and continue to be employed (the "Santa Teresa Plant" or the "Plant"). Since 1989, Defendants (or their predecessors) have used and continue to use substantial quantities of the highly toxic, carcinogenic air pollutant EtO in their industrial sterilization and fumigation processes at the Santa Teresa Plant, which is then released from Defendants' Plant into the surrounding atmosphere through both controlled and uncontrolled means. Once released into air, EtO can and does travel significant distances with air currents, and can remain in ambient air for over 200 days. As now understood by the State, based on its extensive presuit investigation and recent findings in the regulatory and academic communities, EtO emitted by Defendants from the Santa Teresa Plant has significantly

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deteriorated air quality in Santa Teresa and surrounding communities, and has materially contributed to increased health risks suffered by residents of such communities.

EtO is genotoxic (i.e., it damages DNA) and is known to cause cancer, including lymphoma, leukemia, stomach cancer, and breast cancer. The National Toxicology Program, a federal program, has recognized EtO as a known human carcinogen since 2000, and as a likely human carcinogen since 1985. Specifically, in 1990, the U.S. Environmental Protection Agency ("EPA") listed EtO as a hazardous air pollutant under the Clean Air Act, and categorized EtO as "probably carcinogenic to humans." EPA recognized EtO as a human carcinogen in 2016, following studies demonstrating that EtO is up to 30 times more toxic than EPA previously believed.

While the State does not yet know the full measure of current and historic EtO exposure levels in residential areas near the Santa Teresa Plant or in the local environment, it is clear that the Defendants' pollution—which as explained below results from both emissions passing through environmental control systems and emissions not passing through such systems—constitutes an actionable imminent and substantial endangerment under the law of public nuisance. Ongoing exposures to this toxic chemical will pose increasingly significant harms to public health and the State, accordingly, respectfully requests that the Court issue a temporary restraining order and preliminary injunction to force Defendants to immediately halt all uncontrolled emission of EtO from the Santa Teresa Plant, including but not limited to: leaving facility doors, shipping bays, or other means of egress open when not in use; leaving sterilization chamber doors, aeration room doors, and other interior doors open when not in use; allowing off-gassing associated with the storing, transporting, or handling of EtO prior to charging of sterilization chambers; allowing the off-gassing of EtO from under-controlled aeration rooms, from transfer of sterilized product from

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sterilizer chambers to aeration rooms, and from sterilized product removed from aeration rooms; and allowing any EtO to escape through pipes, equipment, vents, stacks, or other point sources prior to filtration or processing through fully functioning emission controls. To effectuate that relief and assure that continuing uncontrolled emissions of EtO do not occur at the Santa Teresa Plant, the State respectfully requests the Court to issue an order substantially in the form attached hereto as Exhibit A.

II. FACTS IN SUPPORT OF TEMPORARY RESTRAINING ORDER AND PRELIMINARY INJUNCTION

a. EtO is An Extremely Toxic Chemical

Even at very low levels, inhalation of EtO-contaminated air significantly increases the risk of developing cancer and other adverse health effects. In December 2016, the EPA's Integrated Risk Information System ("IRIS") program released an evaluation of EtO carcinogenicity (the "2016 IRIS Evaluation"), which characterized EtO as "carcinogenic to humans" and noted that EtO is a mutagenic carcinogen that causes cancer by damaging DNA in cells which is then duplicated when the cells divide. As outlined in the 2016 IRIS Evaluation, EtO exposure increases the cancer risk because DNA damage can take place with each and every exposure that is passed on to more cells, thereby increasing the number of mutated cells. Based on this concern, the 2016 IRIS Evaluation increased the EPA lifetime inhalation risk estimate by a factor of about 30.

The EPA's established inhalation unit risk ("IUR") estimates for exposure to EtO in ambient air was meant to provide an initial estimate of potential cancer risks posed by inhalation exposure to EtO. The EPA's unit risk estimates for cancer mortality and incidence were based on the human data from a National Institute for Occupational Safety and Health ("NIOSH") study. This study was selected for the derivation of risk estimates because it was deemed a "high-quality" study. The IUR established for EtO is .03 ug/m^3 (micrograms per cubic meter).

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b. Defendants Are Currently Emitting Dangerous Levels of EtO From Their Santa Teresa Plant.

Since 1989, Defendants have reported emitting several tons of EtO per year from the Santa Teresa Plant through controlled sources, including sterilizer vacuum pumps, acid-water scrubbers, catalytic oxidizers and back vent exhaust systems (controlled after 2014). However, Defendants have also caused substantial unreported, uncontrolled releases of EtO to the atmosphere from the Santa Teresa Plant as a result of their intentional or negligent subversion of environmental controls.

As revealed in the State's presuit investigation, due to Defendants' lax oversight in connection with sterilization operations—such as the practice of routinely leaving sterilization chamber doors ajar between sterilization cycles—EtO levels in the ambient indoor air at Defendants' Santa Teresa Plant were often elevated, as indicated by an air-quality monitoring system. To dissipate the elevated concentrations of EtO inside the Plant, Defendants caused shipping bays and large facility doors to be left open for hours, or entire days, releasing excess EtO into the atmosphere in an uncontrolled and unfiltered manner.

Further, during regular cleaning and maintenance operations, on an at least monthly basis, Defendants caused the removal of EtO and ethylene glycol residues that had been built up within the sterilization chambers by spraying the residues with a hose and then simply releasing the EtO and ethylene glycol residues through an ordinary drain.

The Santa Teresa Plant also assisted other Sterigenics facilities in performing sterilization operations, including aeration of sterilized products. For example, Sterigenics caused shipments of sterilized devices and equipment to be delivered to the Santa Teresa Plant from the company's San Diego facility on a near-weekly basis so that such devices and equipment could be aerated for 24 hours in the Santa Teresa Plant. As these shipments had been sterilized using EtO, but not aerated, they were off-gassing EtO during the shipping, receiving, and loading phases, including

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at the Santa Teresa Plant, further contributing to the uncontrolled release of EtO in the Santa Teresa region and the State more broadly.

c. Defendants' EtO Emissions Threaten to Irreparably Harm New Mexico and New Mexico Residents.

Defendants' EtO emissions have adversely affected local residents and air quality and will continue to do so unless Defendants' practices are enjoined. Indeed, in August 2018, the EPA published results from its 2014 National Air Toxics Assessment ("NATA") study. The study compiled evidence showing that, due to Defendants' *reported* emissions of EtO in 2014 alone, residents of Santa Teresa and surrounding locations are at a statistically significantly increased risk of developing cancer. The NATA study assessed the increased cancer risk due to EtO exposure in Doña Ana County based on 2014 emissions data reported by Sterigenics.

Notably, in 2014, Sterigenics had substantially decreased its reported EtO emissions as compared to prior years – indeed, from 1989 to 2013, Defendants reported emitting thousands more pounds of EtO as compared to 2014. From 2005 to 2013 alone, Defendants reportedly emitted at least 10,000 pounds of EtO per year. What is more, as revealed in the State's presuit investigation, Defendants have caused EtO emissions far in excess of the reported totals as a result of deficient environmental controls and intentional subversion of environmental controls. If anything, therefore, the NATA study greatly underestimates the historic and current impact of Defendants' EtO emissions, and the increased cancer risk in Doña Ana County.

The NATA data shows that, as of 2014, Doña Ana County residents in the census tract that likely suffered the most exposure to EtO have a cancer risk of 214.5543 per 1 million, which is far in excess of the national average (approximately 30 per 1 million), and that this increased risk is due to EtO exposure. The only source of EtO considered in the NATA study's evaluation of the Doña Ana County cancer risk assessment is the Santa Teresa Plant. For years prior to 2014, when

Defendants reported larger EtO emissions, the risk is considerably higher. The NATA data similarly shows that Doña Ana County residents in nearby census tracts suffer increased cancer risk due to EtO exposure. Because the Santa Teresa Plant is the only significant source of EtO in the region, and the only source considered in the study's assessment of Doña Ana County, this increased cancer risk is wholly or substantially attributable to Defendants' operations.

Beyond the cancer risk identified by the NATA data associated with the Santa Teresa Plant, the State's presuit investigation included sampling of ambient outdoor air within a four-mile radius of the Santa Teresa Plant for EtO. This investigation confirmed the substantial risk to New Mexico residents based on Defendants' EtO emissions. **Every one** of the air samples collected in the presuit investigation within a four-mile radius of the Santa Teresa Plant detected ambient airborne concentrations in excess of the EPA IUR of .03 ug/m^3, including one sample that was **96 times the EPA's cancer risk level** (measured at 2.88 ug/m^3). A map showing the exceedances of the EPA's IUR threshold appears below:

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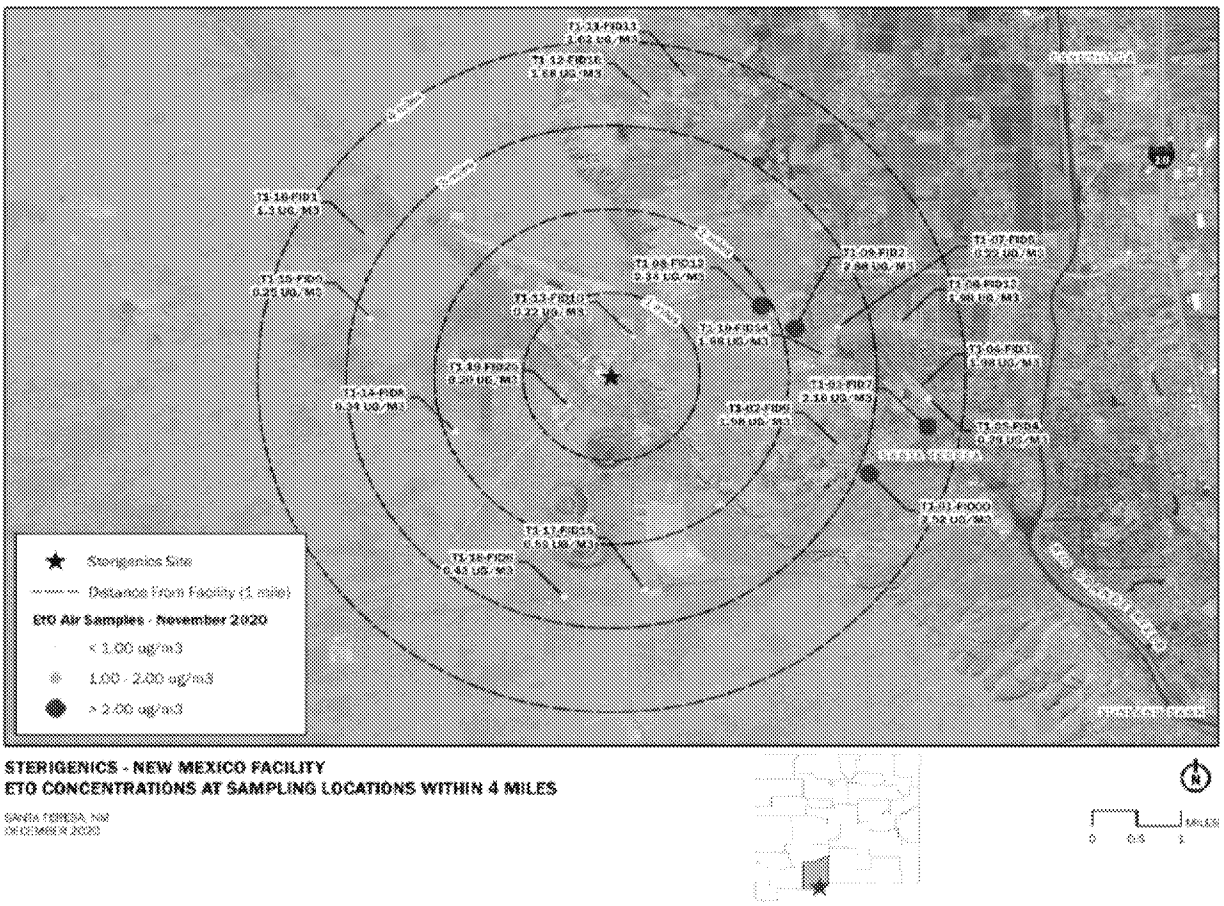

Although the State has and will continue to defend its regulatory and permitting authority, the instant action was necessitated by the Defendants' refusal to address the urgent crisis presented at the Santa Teresa Plant. While EtO contamination is known to be present on- and offsite at the Plant, and thus presents an imminent and substantial endangerment to the public, the full magnitude of the contamination is not yet known. The public continues to be exposed to this hazardous chemical at elevated levels due substantially to Defendants' uncontrolled emissions and the practices outlined above. Accordingly, the State requests a temporary restraining order and preliminary injunction requiring Defendants to suspend any and all uncontrolled emissions of EtO from the Plant under its authority to protect the public from an imminent and substantial endangerment, on an interim basis pending trial. The order sought will permit a comprehensive

delineation of the extent of EtO contamination resulting from Defendants' discharges at the Santa Teresa Plant and protect the public from adverse impacts associated with exposure to the same.

* * *

A temporary restraining order and preliminary injunction is an "extraordinary and drastic remedy," but this is an extraordinary case, and the State has satisfied the requirements for this emergency relief. Given the presence and extremely elevated levels of EtO contamination at and around the Santa Teresa Plant and the migration of that airborne contamination into public and residential areas that threaten the health and quality of the air in neighboring communities such as Santa Teresa, the State is able to prove that Defendants have created an imminent and substantial endangerment to human health. If the State is not granted the relief that it now seeks, irreparable harm will continue to occur in the form of increased health risks suffered by the New Mexico public (particularly in the Santa Teresa area) and impairment of air quality, as well as harms to local economies and small business owners that depend upon a clean, non-toxic atmosphere for their livelihoods. The threat of this continued injury far outweighs any prejudice that Defendants would face if a preliminary injunction is granted. Moreover, the requested order is not overly broad because it seeks only cessation of uncontrolled emissions of EtO from the Plant. If Defendants can operate the Plant without any uncontrolled EtO emission, they are free to do so.

Granting an immediate injunction to prevent continued exposure of the public to EtO is of great public interest, as it would serve to protect irreplaceable environmental, recreational, and economic resources, as well as the health of the citizens of the State. In the absence of the requested relief, there is an unacceptable risk of continued exposure and resulting harm to New Mexico and New Mexico residents. As such, a preliminary injunction is appropriate and this Court should grant the relief requested herein.

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III. AUTHORITY AND ARGUMENT

By allowing the continued uncontrolled emission and migration of EtO from the Santa Teresa Plant, Defendants are failing to protect the public and the environment from exposure to this toxic chemical. To prevent Defendants from causing further harm, the State respectfully requests that this Court grant a temporary restraining order and preliminary injunction based on the public nuisance Defendants have created and to require Defendants to halt all uncontrolled emission of EtO from the Santa Teresa Plant, including taking measures to assure that air emissions or exhausts that are not treated using environmental control technologies to remove EtO do not occur. At a minimum, such steps should include, but not are not limited to, prohibitions against: leaving facility doors, shipping bays, or other means of egress open when not in use; leaving sterilization chamber doors, aeration room doors, and other interior doors open when not in use; allowing off-gassing associated with the storing, transporting, or handling of EtO prior to charging of sterilization chambers; allowing the off-gassing of EtO from under-controlled aeration rooms, from transfer of sterilized product from sterilizer chambers to aeration rooms, and from sterilized product removed from aeration rooms; and allowing any EtO to escape through pipes, equipment, vents, stacks, or other point sources prior to filtration or processing through fully functioning emission controls. These measures are immediately necessary to protect the public health until the Court can issue a decision on the merits following trial.

A. Legal Standard for Obtaining a Temporary Restraining Order and Preliminary Injunction

Entry of a temporary restraining order is appropriate if: "(A) it clearly appears from specific facts shown by affidavit or by the verified complaint that immediate and irreparable injury or damage will result to the applicant before the adverse party or his attorney can be heard in opposition; and (B) the applicants' attorney certified to the court in writing the efforts, if any,

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which have been made to give notice and the reason supporting his claim that notice should not be required." Rule 1-066 NMRA. The Court should grant the State's request for a temporary restraining order and preliminary injunction under Rule 66 because, as demonstrated in the State's Verified Complaint, immediate and irreparable injury, loss and/or damage will result to the State and the residents of New Mexico if Defendants are allowed to continue to recklessly, negligently, or intentionally emit EtO through uncontrolled means from the Plant into the surrounding atmosphere.

To obtain a preliminary injunction, the moving party must demonstrate: "(1) the Plaintiff will suffer irreparable injury unless the injunction is granted; (2) the threatened injury outweighs any damage the injunction might cause the [D]efendant[s]; (3) issuance of the injunction will not be adverse to the public's interest; and (4) there is a substantial likelihood Plaintiff will prevail on the merits." *LaBalbo v. Hymes*, 115 N.M. 314, 318 (N.M. 1993) (citing *Tri-State v. Shoshone River Power, Inc.*, 805 F.2d 351 (10th Cir. 1986)) (acknowledging the similar elements of the test under state and federal law). These criteria are satisfied here, and thus, emergency relief is warranted.

B. The State is Likely to Prevail on the Merits of Its Case

The State will be able to make the required showing to succeed on its claim for a public nuisance. Under New Mexico law, a common law public nuisance is "an unreasonable interference with a right common to the general public." *New Mexico v. Gen. Elec. Co.*, 335 F. Supp. 2d 1185, 1236 (D.N.M. 2004) (citing *State of New Mexico ex rel. State ex rel. Vill. of Los Ranchos De Albuquerque v. City of Albuquerque*, 889 P. 2d 185, 198 (N.M. 1994)). Here, Defendants, with knowledge of EtO's toxicity to human and environmental health, knowingly allowed for its uncontrolled release into the atmosphere through intentional, reckless or negligent subversion of

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existing environmental controls and regulations, thereby substantially endangering the health of nearby residents and substantially contributing to increased health risks for these nearby communities.

That there is actual adverse impact on residents' health is already plain: the NATA study referenced above (published in 2018, based on 2014 data) shows that certain Doña Ana County residents located nearest to the Plant face a cancer risk of 214.5543 per 1 million due to EtO exposure. This is more than ***7 times*** the national average—and, as noted above, it is based on Defendants' self-reported emissions of EtO. The State's air quality sampling, conducted as part of its presuit investigation, has confirmed that the ambient EtO concentrations in Santa Teresa far exceed EPA's IUR threshold by several orders of magnitude. Defendants' continued conduct and the continued presence and uncontrolled release of EtO from the Plant thus annoys, injures, and endangers the comfort, repose, health, and safety of others and interferes with and obstructs the public's free use and comfortable enjoyment of New Mexico natural resources.

The seriousness of the risks created by this conduct further far outweighs any social utility of Defendants' conduct. The rights, interests, and inconvenience to New Mexico and the general public far outweighs the rights, interests, and inconvenience to Defendants, who profited significantly from the use of EtO for decades. On the other side, Defendants' conduct continues to harm the State and the health and welfare of its residents. Defendants knew their conduct in emitting, discharging, or otherwise releasing toxic EtO without adequate controls and indeed actively subverting those controls already in place would cause such injuries to the State and the New Mexico public. Accordingly, Defendants had a duty to cease such conduct, failed to do so, and are liable for creating a public nuisance endangering New Mexico's residents.

C. Irreparable Harm Is Likely in the Absence of Injunctive Relief

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To receive a preliminary injunction, the moving party must establish that it will suffer irreparable harm without the preliminary injunction—that is, that failing to grant the injunction will cause plaintiff to suffer an injury that is not "merely serious or substantial" but "certain, great, actual and not theoretical." *Vill. of Logan v. U.S. Dep't of Interior*, 577 Fed. Appx. 760, 766 (10th Cir. 2014) (quoting *Heideman v. S. Lake City*, 348 F.3d 1182, 1189 (10th Cir. 2003)).

New Mexicans live, work, and play in the area of the Santa Teresa Plant and breathe the air that will continue to be impaired by Defendants' conduct, resulting in a significantly increased risk of adverse health effects. As in *Valley Community Preservation Commission v. Mineta*, 373 F.3d 1078 (10th Cir. 2004), there is sufficient proximity to the harm to show that the ongoing, unmitigated presence of contamination will cause irreparable harm. Without immediate steps, unsafe levels of EtO will continue to accumulate in the Santa Teresa area as a result of Defendants' uncontrolled emissions from the Plant, thereby driving or sustaining the elevated cancer risk to the nearby residents and exposing countless people to harmful EtO. Exposure to EtO, even at low levels, has serious health implications. The public health will suffer, irreplaceable ecological resources will be lost, and local economies will suffer losses. Some of these injuries have already manifested, in that local residents face elevated cancer risks 7 times higher than that of the general public, according to conservative EPA estimates, and the air quality diminution has been documented. Further, the impacts associated with continued exposure to EtO associated with operations at the Santa Teresa Plant could be greater than currently expected, as the full extent of dangers associated with the chemicals are still yet to be discovered.

These present and future harms cannot be readily or expeditiously cured absent the relief sought. Thus, because the public health and the quality of the air have already been injured and

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will continue to be injured without immediate action, injunctive relief is needed to prevent potentially devastating impacts in the Santa Teresa area and beyond.

D. The Balance of Equities Tips in Favor of the State

The balance of equities in this case tilts strongly in favor of preventing continued harm to the public. As described above, the harms that have been and will continue to be suffered by the State and the residents of New Mexico are sufficiently likely, and thus, the balance of equities favors the issuance of an injunction. *Amoco Prod. Co. v. Vill. of Gambell, AK*, 480 U.S. 531, 545 (1987).

Any hardship Defendants may face as a result of this Court's issuance of a preliminary injunction would be temporary and monetary. Such hardships pale in comparison to the irreparable harm that the residents of the State will continue to face in the absence of any remedial action. When weighing temporary economic injury against "preventable human suffering," courts typically find that the balance of equities "'tips decidedly' in favor of the latter." *Golden Gate Rest. Ass'n v. City & Cty. of San Francisco*, 512 F.3d 1112, 1126 (9th Cir. 2008) (quoting *Lopez v. Heckler*, 713 F.2d 1432, 1437 (9th Cir. 1983)). Further, financial concerns alone generally do not outweigh environmental harm. *Valley Cmty. Pres. Comm'n*, 373 F.3d 1078.

There is no public interest served by allowing uncontrolled EtO contamination to continue to be pumped in the environment. The damages suffered by the State and the public by further delay on the part of Defendants are significant. As described above, the public health, economic resources, ecological resources, and recreational resources are all at risk of substantial, irreparable harm. Thus, the balancing of equities tips strongly in favor of the State.

E. Issuance of a Preliminary Injunction Is in the Public Interest

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The well-recognized and constitutionally grounded interest of protecting the public health and the environment weighs heavily in favor of a preliminary injunction in this case. Article XX, Section 21 of the New Mexico Constitution provides that "protection of the State's beautiful and healthful environment is . . . declared to be of fundamental interest to the public interest, health, safety and the general welfare." Allowing dangerous amounts of toxic chemicals to be regularly and carelessly (or intentionally) emitted without adequate controls into the atmosphere in the State, and allowing them to potentially poison more and more of the public and the environment for no reason other than to avoid the financial burden of full compliance with law, serves no public interest. Accordingly, the Court should promote the public interest and issue the temporary restraining order and preliminary injunction in favor of the State.

F. Notice of Requested Relief Under Civil Rule 1-066

Pursuant to Rule 1-066, a party seeking emergency injunctive relief must explain to the Court what efforts to provide notice were made or why such notice is not required. *See* Rule 1-066 NMRA (requiring that "the applicant's attorney certifies to the court in writing the efforts, if any, which have been made to give the notice and the reasons supporting his claim that notice should not be required"). Here, although notice to Defendants of the emergency relief sought is not necessary because Defendants' ongoing conduct has resulted in a significant risk to public health and in the creation of a dangerous public nuisance that requires immediate action to protect the public health, Defendants are on notice. Defendants' waived service of the Verified Complaint days after it was filed and removed this action to the United States District Court for the District of New Mexico before this Court could hear the earlier iteration of the present Motion. On April 13, 2021, the federal court granted the State's motion to remand this matter to this Court. Defendants are on notice of all proceedings in this matter.

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G. The State is not Required to Give Security

While the State is not required to give security for payment of such costs and damages as may be incurred or suffered by any party who is found to be wrongfully enjoined or restrained, pursuant to Rule 1-066(C),[1] out of an abundance of caution, the State requests the Court enter an order waiving any such security.

IV. CONCLUSION

The residents of New Mexico are being exposed to elevated levels of toxic chemicals as a result of Defendants' uncontrolled releases of EtO from their Santa Teresa Plant. Beyond the mere risk of harm, this exposure causes (and has caused) significant and potentially irreversible injuries. Without immediate relief, these harms will continue. The State has met its burden to show a likelihood of success on the merits at trial, irreparable harm in the absence of injunctive relief, and that both the balance of equities and the public interest favor an injunction.

WHEREFORE, the State respectfully requests this Court (i) to grant this Motion for a Temporary Restraining Order and Preliminary Injunction and enter an order substantially in the form attached hereto as **Exhibit A**, requiring Defendants to immediately halt all uncontrolled emission of EtO from the Santa Teresa Plant, (ii) to order that security, as set forth in Rule 1-066(C), is inapplicable to the State, or alternatively, to waive any such security, and (iii) for all other just and proper relief.

[1] *See*, for example, *Rhodes v. State ex rel. Bliss*, 1954-NMSC-085.

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Dated: April 14, 2021

Respectfully submitted:

HECTOR H. BALDERAS
ATTORNEY GENERAL OF NEW MEXICO

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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing was submitted through the Court's Electronic Filing System for filing and service to all counsel of record this 14th day of April, 2021.

/s/ Marcus J. Rael, Jr.
Marcus J. Rael, Jr.

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STATE OF NEW MEXICO
COUNTY OF DOÑA ANA
THIRTEENTH JUDICIAL DISTRICT COURT

THE STATE OF NEW MEXICO, ex rel. HECTOR BALDERAS, ATTORNEY GENERAL,

Plaintiff,

No.: D-307-CV-2020-02629

v.

Beyer, Marci

STERIGENICS U.S., LLC, SOTERA HEALTH HOLDINGS, LLC, SOTERA HEALTH LLC, and SOTERA HEALTH COMPANY,

Defendants.

TEMPORARY RESTRAINING ORDER

This matter came before the Court on the *Verified Complaint with Jury Demand and Request for Temporary Restraining Order and Preliminary Injunction* filed on December 21, 2020 (the "Complaint"), and an *Emergency Motion in Support of Request for Temporary Restraining Order and Preliminary Injunction* (the "Motion") filed on April 14, 2021, immediately following remand of this action to the Court. The Court, having reviewed and considered the Complaint and the Motion, hereby **FINDS**:

1. This Court has jurisdiction over this matter;

2. The Motion seeks a temporary restraining order and preliminary injunction under Rule 1-066 NMRA against the above captioned Defendants prohibiting the Defendants from the continued uncontrolled emission of ethylene oxide ("EtO") from the facility located at 2400 Airport Road, Santa Teresa, NM 88008 (the "Santa Teresa Plant");

3. Since 1989, Defendants (or their predecessors) have used and continue to use substantial quantities of EtO, a toxic, carcinogenic air pollutant, in their industrial sterilization and

EXHIBIT
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fumigation processes at the Santa Teresa Plant, which is then released from Defendants' Plant into the surrounding atmosphere through both controlled and uncontrolled means;

4. The uncontrolled emissions of EtO from the Santa Teresa Plant have resulted in significantly elevated levels of EtO in the atmosphere posing an imminent and substantial endangerment to the public health and welfare of residents in Santa Teresa and nearby communities, including a significant risk of cancer, and has resulted in substantial deterioration of air quality;

5. Irreparable injury, loss or damage may result to the State and its residents, which the State is empowered to protect, if the uncontrolled EtO emissions from the Santa Teresa Plant are allowed to continue;

6. A temporary restraining order should be issued;

7. Based on the evidence adduced in its Complaint, the Plaintiff is likely to succeed on its claims, including its claim for relief under the doctrine of public nuisance;

8. Any harm to the Defendants from issuance of the requested temporary restraining order is substantially outweighed by the substantial and irreparable harm occasioned by the continued uncontrolled emission of EtO from the Santa Teresa Plant, which is endangering the health and well-being of the State's residents;

9. The entry of this order will not harm any public interest;

10. There is no just reason to delay entry of this order.

IT IS HEREBY ORDERED, ADJUDGED AND DECREED:

A. The Defendants are hereby prohibited from causing, making, facilitating, or otherwise allowing any uncontrolled emission or release of EtO from the Santa Teresa Plant, including, but not limited to:

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i. Leaving facility doors, shipping bays, or other means of egress open when not in use;

ii. Leaving sterilization chamber doors, aeration room doors, and other interior doors open when not in use;

iii. Allowing off-gassing associated with the storing, transporting, or handling of EtO prior to charging of sterilization chambers;

iv. Allowing the off-gassing of EtO from under-controlled aeration rooms, from transfer of sterilized product from sterilizer chambers to aeration rooms, and from sterilized product removed from aeration rooms; and

v. Allowing any EtO to escape through pipes, equipment, vents, stacks, or other point sources prior to filtration or processing through fully functioning emission controls.

B. This Order will expire within 10 days of entry of this Order. This Order may be terminated by further order of the Court prior to that time. If a preliminary injunction is issued prior to the termination of this Order, the preliminary injunction will replace and supersede this Order.

C. A security for payment of such costs and damages as may be incurred or suffered by any party who is found to be wrongfully enjoined or restrained, pursuant to Rule 1-066(C), is inapplicable to Plaintiff.

D. The Court will set a hearing to consider the issuance of a preliminary injunction by separate notice.

_____
DISTRICT COURT JUDGE

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Submitted By:

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CLERK OF THE COURT
Amy Moncayo

STATE OF NEW MEXICO
COUNTY OF DOÑA ANA
THIRD JUDICIAL DISTRICT COURT

THE STATE OF NEW MEXICO, EX REL. HECTOR BALDERAS, ATTORNEY GENERAL,	)	
Plaintiff,	)	No. D-307-CV-2020-02629 Beyer, Marci
v.	)	
STERIGENICS U.S., LLC, SOTERA HEALTH HOLDINGS, LLC, SOTERA HEALTH LLC, AND SOTERA HEALTH COMPANY,	)	
Defendants.	)	

STERIGENICS U.S., LLC'S BRIEF IN OPPOSITION TO PLAINTIFF'S EMERGENCY MOTION FOR TEMPORARY RESTRAINING ORDER AND PRELIMINARY INJUNCTION

In the continuing COVID-19 pandemic, Plaintiff seeks an injunction to interfere with and, by judicial order, regulate Sterigenics U.S., LLC's ("Sterigenics U.S.") essential medical product sterilization operations at its Santa Teresa facility (the "Facility"). The Facility, which sterilizes over 2.5 million life-saving medical products each day, is under strict oversight by the U.S. Environmental Protection Agency ("EPA") and the New Mexico Environment Department ("NMED"), and is in full compliance with applicable air quality regulations. Those regulatory bodies—not the Attorney General—are charged with regulating the matters alleged in Plaintiff's Complaint and Emergency Motion for Temporary Restraining Order and Preliminary Injunction ("Motion").

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Nevertheless, Plaintiff's unsupported Motion (in this action that has been pending almost five months now) asks the Court to enjoin practices in which Sterigenics U.S. does not even engage. And Plaintiff's broad request that this Court immediately enjoin any escape of ethylene oxide ("EO") whatsoever from the Facility as a so-called "uncontrolled" emission (including but not limited to from an employee's entrance or exit of the Facility, a customer's necessary collection of its sterilized medical products for supply to medical providers, or otherwise) would impose requirements with which absolute compliance could be impracticable as evidenced by the fact that the EPA and the NMED—as the governing regulators of environmental matters at the Facility—do not require them. As expressed in the Motion, Plaintiff would use that requirement to dictate operations and regulate the Facility by Court order, arguing that only "[i]f Defendants[1] can operate the Plant without any uncontrolled EtO emission, [are they] free to do so." Motion at 9. To Plaintiff, the EPA and NMED are of no matter. Nor is the Facility's necessity for providing essential sterilizations of medical products for critical patient care.

Under established New Mexico law, the EPA and NMED have primary jurisdiction over the matters Plaintiff asks this Court to regulate in an injunction order. Accordingly, controlling law instructs that the Court should defer to those agencies' regulation of these matters and not grant the injunctive relief Plaintiff seeks. But even if it were appropriate to consider Plaintiff's injunction request, Plaintiff has not made the clear and unequivocal evidentiary showing required

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[1] Plaintiff has also sued Sterigenics U.S.'s parent company Sotera Health LLC, as well as Sotera Health Holdings, LLC and Sotera Health Company—foreign defendants which do not operate Sterigenics U.S.'s Facility and are not subject to the personal jurisdiction of the Court.

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to obtain the injunction it seeks. In fact, Plaintiff submitted no evidence at all with its Motion—relying entirely on the "verification" of its litigation counsel for factual support. And by Plaintiff's own admission, the requested injunction would not even redress the false harm it alleges in this case.

Also, underlying Plaintiff's baseless obtrusion is its reliance on an erroneous 2016 report of the EPA's Integrated Risk Information System, which drastically overestimated the risk of exposure to EO. Regulators have publicly recognized that drastic overestimation as "scientifically unsupportable," "biologically implausible and over-protective." And Plaintiff compounds its error with allegations concerning a derivative National Air Toxics Assessment that the EPA itself has explained is simply a "screening tool" with "inherent uncertainties" that should be used only to help assess whether further investigation is necessary. According to the EPA, that assessment does not estimate (much less evidence) whether a person or area is at an increased risk of disease and should not be used for that purpose. And the EPA has acknowledged that the Facility should not have been identified for further investigation in the assessment because of emissions control system enhancements Sterigenics U.S voluntarily made at the Facility approximately seven years ago.

Indeed, Sterigenics U.S. was already working cooperatively with the NMED toward additional voluntary enhancements at the Facility well before the Attorney General filed this unfounded lawsuit last year. And EPA was already (and still is) exercising its regulatory powers to further assess matters with respect to so-called "uncontrolled" emissions at sterilization facilities.

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In sum, without any supporting evidence, Plaintiff seeks an injunction to interfere with regulatory matters governed by the EPA and NMED based on misunderstandings and misapplications of federal agencies' ongoing evaluation and governance of such matters. That unfounded interference would be of great consequence to Sterigenics U.S., the medical products supply chain, and public health, particularly in the midst of the ongoing pandemic. The Court should deny the Motion.

FACTUAL AND PROCEDURAL BACKGROUND

I. The Facility Performs Essential Medical Products Sterilizations.

Sterigenics U.S. is a leading provider of medical product sterilizations in the United States. Decl. of Steve Ortiz ¶ 4 (**Exhibit A**). Since 1989, Sterigenics U.S. has operated its medical products sterilization Facility in Santa Teresa, New Mexico, which is registered with and regulated by the U.S. Food and Drug Administration (the "FDA"). *Id.* ¶¶3, 5.

The Facility performs essential EO sterilizations of approximately 2.5 million medical products each day according to specific processes validated by the FDA in order for healthcare providers to use them in critical patient medical procedures. *Id.* ¶¶6-7. Such products include custom surgical kits, preoperative skin preparation products, surgical drapes and gowns, cardiovascular tubing sets, internal powered surgical staplers, ophthalmic devices, Band-Aids, prefilled syringes, catheters, tubing for ear, nose, and throat, surgical diagnostic equipment, and tracheostomy-coiled-endotracheal tubes. *Id.*

The FDA has explained that "ethylene oxide is the most common method of sterilization of medical devices in the U.S. and is a well-established and scientifically-proven method of

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preventing harmful microorganisms from reproducing and causing infections. More than 20 billion devices sold in the U.S. every year are sterilized with ethylene oxide, accounting for approximately 50 percent of devices that require sterilization."[2] The FDA has emphasized, "It's important to note at this time there are no readily available processes or facilities that can serve as viable alternatives to those that use ethylene oxide to sterilize these devices. In short: this method is critical to our health care system and to the continued availability of safe, effective and high-quality medical devices."[3] The FDA has further recognized that "medical devices that are sterilized to remove potentially harmful germs and other microorganisms prior to use are critical to our health care system and a shortage—especially of life-saving, life-sustaining, or other critical devices—can be a detriment to public health."[4]

II. The Facility's Use and Emission of EO Are Governed and Permitted by Federal and State Environmental Regulations Administrated and Enforced by NMED.

A. The NMED governs and enforces environmental and EO air quality requirements for the Facility.

Under New Mexico's Environmental Improvement Act (the "Act"), the state has an Environmental Improvement Board (the "EIB") that is comprised of seven members appointed by the governor, by and with the advice and consent of the state senate. NMSA 1978 § 74-1-4(A). By statute, these members are comprised of "individuals who represent the public interest," *id.*,

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[2] *Statement on concerns with medical device availability due to certain sterilization facility closures*, FDA Statement (Oct. 25, 2019) (**Exhibit B**).

[3] *Id.*

[4] *Id.*

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and are responsible for promulgating rules and standards governing "air quality management as provided in the Air Quality Control Act," § 74-1-8(A)(4). The Act requires the EIB to adopt standards "consistent with the Air Quality Control Act [Chapter 74, Article 2 NMSA 1978] to attain and maintain national ambient air quality standards and prevent or abate air pollution." § 74-2-5(B)(1).

Under the Act, the legislature also created the NMED to:

> be responsible for environmental management and consumer protection in this state in order to ensure an environment that in the greatest possible measure will confer optimum health, safety, comfort and economic and social well-being on its inhabitants; [] protect this generation as well as those yet unborn from health threats posed by the environment; and [] maximize the economic and cultural benefits of a healthy people.

§§ 74-1-2, 74-1-3(B). The NMED "is the state air pollution control agency for all purposes under federal legislation relating to air pollution." *Id.* § 74-1-5.2. It is responsible for "serv[ing] as agent of the state in matters of environmental management" and enforcing the state's environmental rules and regulations, including the state's rules and standards governing "air quality management as provided in the Air Quality Control Act." *Id.* § 74-1-6(E), (F); *id.* § 74-1-7. It has the power to enforce those rules by civil penalties and "by appropriate action in courts of competent jurisdiction." *Id.* § 74-1-6(F), (G); *see also id.* § 74-1-5.1.B (the NMED shall "institute legal proceedings to compel compliance with the Air Quality Control Act or any regulation of the environmental improvement board or the local board"). Those powers and duties include issuing compliance orders and "commenc[ing] a civil action in district court for appropriate relief, including a temporary or permanent injunction," if "on the basis of any information, the secretary

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or the director determines that a person has violated or is violating a requirement or prohibition of the Air Quality Control Act, a regulation promulgated pursuant to that act or a condition of a permit issued under that act." *Id.* § 74-2-12(A).

A. Federal regulations expressly adopted by New Mexico specifically govern the use and emission of EO at the Facility.

The federal Clean Air Act governs the emission of hazardous air pollutants ("HAPs"), including EO, in the United States. *See* 42 U.S.C. § 7412. Under the Clean Air Act, the EPA sets national HAP emissions standards reflecting the maximum achievable control technology for emissions of each HAP as determined by the EPA, considering "the cost of achieving such emission reduction, and any non-air quality health and environmental impacts and energy requirements . . . through application of measures, processes, methods, systems or techniques . . . ." § 7412(d)(2). Those federal emissions standards are provided in the EPA's National Emission Standards for Hazardous Air Pollutants, 40 C.F.R. §§ 61 and 63 ("NESHAP").

Subpart O of NESHAP, titled, "Ethylene Oxide Emissions Standards for Sterilization Facilities," ("Subpart O") provides strict nationwide federal emissions standards governing the operation of medical product sterilization facilities using one or more tons of EO annually, which standards must be satisfied in order for such a facility to operate. §§ 63.360, 63.362. Those federal regulations govern the amount of EO that these facilities are allowed to emit for their operations. § 63.362. The regulations also set monitoring requirements for EO emissions, test methods and procedures, rules governing system malfunctions and maintenance, compliance and performance requirements, work practices, and reporting requirements for the operation of sterilization

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facilities. §§ 63.363, 63.364, 63.365, 63.366; *see also* §§ 63.6, 63.7, 63.8, 63.10, 63.11 (general NESHAP requirements applicable to EO sterilization facilities).

Subpart O is based on the EPA's consideration and weighing of the "nationwide impacts" the regulations present, including the reduction in "nationwide emissions of EO" from commercial EO sterilization facilities; the potential for the regulations to close sterilization facilities; the economic, financial and operational impacts on commercial EO sterilization operators; and the increased sterilization costs on medical device suppliers and other health-related manufacturers. 59 Fed. Reg. 10591 (Mar. 7, 1994).

The EPA has delegated the authority to implement and enforce Subpart O to the NMED, subject to "all of the conditions and limitations set forth in Federal law and regulations." 40 C.F.R. § 63.99(32). The NMED has adopted the NESHAP requirements in implementing its air quality program under New Mexico's Air Quality Act. NMAC ¶¶ 20.2.78.9; 20.2.82.8. The Facility operates under an Air Quality Permit issued by NMED pursuant to its delegated authority under NESHAP and its EPA-approved State Implementation Plan. Decl. of Steve Ortiz ¶ 9, Exhibit A (**Exhibit A**). That permit governs and expressly authorizes the Facility's operations and use and emission of EO in those operations. *Id.*

III. Plaintiff's "Public Nuisance" Claims.

A. Plaintiff claims that the Facility's permitted emission of EO is a public nuisance.

Plaintiff alleges that the Facility's permitted use and emission of EO—a naturally occurring chemical—constitutes a "public nuisance" under New Mexico law. *E.g.*, Compl. ¶¶159-202. Plaintiff alleges that "[t]here is no safe amount of EtO in air or other environmental media," "each

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and every exposure" to EO "increases the cancer risk," and "[e]ven at very low levels, inhalation of EtO-contaminated air significantly increase the risk of developing cancer and other adverse health effectives." *Id.* ¶¶9, 11, 63.

B. Plaintiff presents no evidence that the Facility's emissions are harming the public.

Plaintiff's public nuisance claims are based solely on alleged risks associated with EO claimed in the Complaint, unidentified or vaguely referenced animal studies and occupational studies of workers in sterilization facilities, and allegations of partial statements by certain agencies or organizations. *E.g., id.* ¶¶67, 70, 73-78, 98. Plaintiff's Motion presents no actual evidence that the Facility's emissions are harming the public.

To be sure, Plaintiff's Complaint includes allegations concerning a risk estimate for EO in a 2016 report from the EPA's Integrated Risk Information System ("IRIS"). Not only are those allegations not evidence, the referenced IRIS risk estimate drastically overestimates the risk from EO exposure. The IRIS erroneously states that an EO concentration as low as .0002 micrograms per cubic meter (the equivalent of 0.1 parts per trillion) poses a one-in-a-million lifetime cancer risk to someone exposed to that concentration continuously (24 hours per day) over 70 years.[5] That miniscule concentration is orders of magnitude below the endogenous EO levels produced

[5] Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide, Executive Summary, In Support of Summary Information on the Integrated Risk Information System (IRIS) at p. 5, *available at* https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/1025_summary.pdf.

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within the human body.[6] It is also orders of magnitude below the concentrations of EO in everyday ambient air, which the EPA has reported range from 0.185 to 0.397 micrograms per cubic meter of air (103 to 220 parts per trillion), with an average of 0.297 micrograms per cubic meter of air (164 parts per trillion).[7] It is millions of times below the concentrations emitted by a single lawnmower or a single backyard charcoal grill,[8] and is exponentially lower than the exposure level the U.S. Occupational Safety and Health Administration ("OSHA") has determined is safe for employees working inside sterilization facilities.[9] Also, global occupational EO exposure limits, including those in much of the European Union, range from 5 million to 50 million times higher than the IRIS level.[10] As the Texas Commission on Environmental Quality ("TCEQ") has

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[6] *See* C. Kirman, *et al.* Ethylene oxide review: characterization of total exposure via endogenous and exogenous pathways and their implications to risk assessment and risk management, 24 J. of Toxicol. & Envt'l Health Pt. B, No. 1, 1, 5 (2021) (**Exhibit C**) (finding that the mean air concentration equivalent to the endogenous concentration in nonsmokers is 2.9 parts per billion); Sheehan PJ, et al., Ethylene Oxide Exposure in U.S. Populations Residing Near Sterilization and Other Industrial Facilities: Context Based on Endogenous and Total Equivalent Concentration Exposures, Int. J. Environ. Res. Public Health, 18(2):607 (2021) (**Exhibit D**) (reporting endogenous metabolic concentrations of 1.1-5.5 parts per billion).

[7] Ethylene Oxide Data Summ. from Nat'l Air Toxics Trends Stations and Urban Air Toxics Mon. Prog. sites, *available at* https://www.epa.gov/hazardous-air-pollutants-ethylene-oxide/ethylene-oxide-data-summary-national-air-toxics-trends (**Exhibit E**).

[8] Proton Transfer Reaction/Time of Flight Mass Spectrometry (PTR-TOF-MS) Measurements of "Everyday Sources" for Ethylene Oxide, Montrose Air Quality Services (Oct. 16, 2019) (**Exhibit F**).

[9] OSHA Fact Sheet, *available at* https://www.osha.gov/sites/default/files/publications/ethylene-oxide-factsheet.pdf (**Exhibit G**).

[10] Comments in Response to HCL RTR Request for Comments on Use of 2016 IRIS Assessment for Regulatory Purposes at pp. 4-6 (**Exhibit H**) (collecting and citing exposure limits therein).

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explained, the IRIS risk value for EO cited by Plaintiff is "scientifically unsupportable," "biologically implausible and over-protective."[11]

Plaintiff also alleges (again without evidence) that the EPA's National Air Toxics Assessment update released in August 2018 ("NATA") shows that "residents of Santa Teresa and surrounding locations are at a statistically significantly increased risk of cancer" because of the Facility. Compl. ¶¶21, 24-27, 127-29, 134. This is demonstrably incorrect. The EPA has explained that NATA is a "screening tool" intended only to help determine if "areas, pollutants or types of pollution sources need to be examined further to better understand risks to public health."[12] The EPA also has acknowledged that this screening tool is "largely driven" by the IRIS risk value[13] for EO, which, as demonstrated above, drastically overestimates the risk from EO exposure. And, according to the EPA, NATA has "inherent uncertainties," and "additional work is necessary to more fully understand th[e] potential risks and the emissions from facilities that contribute to them."[14] The EPA has advised that "this follow-up work must be conducted prior to significant

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[11] TCEQ Resp. to Pub. Comm. Rec'd on the 2019 EO Draft Dev. Supp. Doc., CAS Registry No: 75-21-8, at pp. 4, 23 (Jan. 31, 2020), *available at* https://www.tceq.texas.gov/assets/public/implementation/tox/dsd/comments/rtc_rev_eto.pdf. (**Exhibit I**).

[12] 2014 NATA Assessment: Fact Sheet, *available at* https://www.epa.gov/sites/production/files/2018-08/documents/2014_nata_overview_fact_sheet.pdf ("NATA Fact Sheet") (**Exhibit J**).

[13] *Id.*

[14] EPA Resp. to Management Alert: Prompt Action Needed to Inform Residents Living Near Ethylene Oxide-Emitting Facilities About Health Concerns and Actions to Address Those Concerns Report No. 20-N-0128, *available at* https://www.epa.gov/sites/production/files/2021-01/documents/_epaoig_20-n-0128_agency_response_december_2.pdf (**Exhibit K**).

public outreach," and "[p]ublic engagement based on outdated, preliminary, uncertain information is irresponsible . . . ."[15] Contrary to Plaintiff's claims in this case, the EPA has explained that NATA "does not estimate any person's individual risk" of cancer and should not be used "as a definitive means to specify risk values within a census tract" or "to compare risks at local levels (such as between neighborhoods) or between states."[16]

In fact, while Plaintiff's claims about the Facility rely heavily on NATA, the EPA has said that the Facility was "erroneously" identified in NATA as a priority site for further investigation. Compl. ¶¶ 21-27, 127-34; Motion at 6-7, 12. The EPA has explained that NATA was based on 2014 emissions data and, "[p]rior to releasing NATA, EPA learned that the facility had installed a control device that reduced ethylene oxide emissions by 83 percent between 2014 and 2016, which would be expected to reduce risk."[17] The EPA noted that the Facility's emissions data had "changed since the EPA completed the modeling step of the NATA analysis."[18]

IV. Plaintiff's Motion Asks the Court to Enjoin All "Uncontrolled" EO Emissions at the Facility and Practices that Are Not Occurring.

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[15] *Id.*

[16] **Exhibit J**.

[17] Ethylene Oxide: Tech. Review and Outreach to Potentially Affected Communities, Status Report for Sterigenics – Santa Teresa, NM, *available at* https://www.epa.gov/sites/production/files/2021-01/documents/status_report._sterigenics_nm.pdf (**Exhibit L**).

[18] 2014 NATA Emissions Updates (as of July 28, 2020), *available at* https://www.epa.gov/sites/production/files/2018-08/documents/2014_nata_updates_to_emissions.pdf (**Exhibit M**).

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Plaintiff claims that two types of EO emissions at the Facility are causing the same alleged public nuisance: "controlled emissions" and "uncontrolled emissions." *E.g.*, Compl. ¶¶ 9, 17, 18, 19, 62, 125-26, 161, 164-65, 185, 188-89. Plaintiff alleges that "controlled" emissions are those "passing through environmental control systems" at the Facility. Motion at 3; Compl. ¶18. Plaintiff alleges that "uncontrolled" emissions are those "not passing through such systems" and resulting from the Facility's "routine operational and maintenance practices." Motion at 3; Compl. ¶¶19(c), 115.[19]

Plaintiff's Motion does not seek to enjoin any controlled EO emissions at the Facility. Rather, it seeks an injunction against "all uncontrolled emission of EtO from the" Facility, "including, but not limited to" those allegedly caused by:

> leaving facility doors, shipping bays, or other means of egress open when not in use; leaving sterilization chamber doors, aeration room doors, and other interior doors open when not in use; allowing off-gassing associated with the storing, transporting, or handling of EtO prior to charging of sterilization chambers; allowing the off-gassing of EtO from under-controlled aeration rooms, from transfer of sterilized product from sterilizer chambers to aeration rooms, and from sterilized product removed from aeration rooms; and allowing any EtO to escape through pipes, equipment, vents, stacks, or other point sources prior to filtration or processing through fully functioning emission controls.

Motion at 3-4, 8.

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[19] Plaintiff's allegations of what constitutes an "uncontrolled" emission varies from emissions allegedly caused by opening of doors at the Facility and the loading of sterilized medical products for customers' receipt in the Facility's shipping area, to alleged "under-controlled" aeration rooms and emissions "without adequate controls." Compl. ¶¶121, 125, Prayer for Relief; Motion at 10, 15.

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Plaintiff presents no evidence that these practices are even occurring at the Facility.[20] Nor does Plaintiff present any evidence that these alleged practices or any other alleged "uncontrolled" EO emission at the Facility are harming anyone in the community.

Contrary to Plaintiffs' allegations, Compl. ¶119, Sterigenics U.S. does not leave Facility doors, shipping bays or other means of egress open when not in use, much less for hours or days. Decl. of Steve Ortiz ¶13(b) (**Exhibit A**). Nor does it leave sterilization chamber doors, aeration room doors, and other interior doors open when not in use. *Id.* ¶13(f). And when chamber doors are open, the chamber back vent fans are running to route any EO in the chamber to the Facility's emissions control system. *Id.* ¶13(h). Sterigenics U.S. does not allow off-gassing of EO in the storage, transportation or handling of EO prior to charging of sterilization chambers at the Facility.

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[20] While this case was pending in federal court, Plaintiff submitted a reply to Stergenics U.S.'s opposition to Plaintiff's Motion, attaching declarations of three former Sterigenics U.S. employees apparently as purported evidence of these alleged practices. Those declarations are no such evidence. The Declaration of Michael Lucero stated he last worked at the Facility almost a decade ago, "from October 2008 to February 2012." His declaration stated what he purportedly "recall[ed]" and "believe[d]" occurred at the Facility on occasions at that time. Mr. Lucero worked in shipping and receiving while employed at the Facility and was not trained or certified at the Facility. **Exhibit A** ¶¶10–11. His knowledge of operations, process controls, emissions control systems, and sterilization chamber interlocks would have been limited. *Id.* ¶11. Not only are his alleged beliefs and recollections from more than nine years ago incorrect, they are not evidence of such activities occurring at the Facility today for the purpose of an injunction. The declarations of Patrick John Sullivan and Christopher Giardini submitted by Plaintiff are even more attenuated. Mr. Sullivan's declaration says he last worked at an entirely different Sterigenics U.S. facility, over 1,200 miles away in Illinois eighteen years ago, and Mr. Giardini's declaration states that he last worked at that facility in Illinois, as a temporary employee, for five months more than four years ago. None of those declarations are evidence of the practices Plaintiff alleges at Sterigenics U.S.'s Facility in Santa Teresa, much less today, for the purpose of the injunction Plaintiff seeks.

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Id. ¶ 13(i). It does not allow ethylene oxide to off-gas from "under-controlled aeration rooms" at the Facility. *Id.* ¶ 13(j). Rather, the Facility's aeration rooms are designed to be under constant negative pressure to keep air from escaping the aeration rooms so that it is captured and cleaned by the Facility's emissions control system. *Id.* Sterigenics U.S. also has work practices designed to minimize the time any sterilized medical products are not in sterilization chambers or aeration rooms. *Id.* ¶ 14. It also has design, engineering and work practices in place to minimize any EO emissions from pipes, equipment and vents, and has emission control systems at the Facility to minimize EO emissions from stacks and point sources well below permitted levels. *Id.* ¶ 15.[21] In all of these respects, all emission of EO are controlled at the Facility.

ARGUMENT AND CITATION OF AUTHORITY

I. The Court Should Defer to the NMED's and EPA's Primary Jurisdiction.

The Court should deny Plaintiff's request for injunctive relief under the established doctrine of primary jurisdiction. The doctrine "is concerned with preserving the relationship between courts and administrative agencies." *Valdez v. State*, 2002-NMSC-028, ¶6, 132 N.M. 667. It applies where "a claim is originally cognizable in the courts . . . [but] enforcement of the claim requires the resolution of issues which, under a regulatory scheme, have been placed within the special competence of an administrative body." *State ex rel. Norvell v. Ariz. Pub. Serv. Co.*,

[21] Contrary to Plaintiff's allegations, Sterigenics U.S. also does not bring in sterilized products from other facilities to aerate at the Facility, cause EO residue to build up inside Facility sterilization chambers to be cleaned out using a hose, have "lax oversight in connection with sterilization operations," or leave shipping bays and "large doors" open to allow EO to escape or to "return" EO monitors within the Facility to "green" status. *Id.* ¶ 13(a), (c), (d) and (e).

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1973-NMSC-051, ¶ 31, 85 N.M. 165 (quoting *United States v. W. Pac. R.R.*, 352 U.S. 59 (1956)). In such a case, "the judicial process is suspended" while the issues are referred to the proper administrative body. *Id.* Particularly in matters of equity, courts should avoid the exercise of "jurisdiction to interfere with the comprehensive programs designed to solve a complex social, economic and technological problem," such as environmental regulation. *Schwartzman, Inc. v. Atchison, T& S.F. Ry.*, 857 F. Supp. 838, 844 (D.N.M. 1994) (quoting *Norvell*, 1973-NMSC-051). The doctrine "is 'specifically applicable to claims properly cognizable in court that contain some issue within the special competence of an administrative agency.'" *W. Ref. Sw., Inc. v. 3.7820 Acres of Land in McKinley Cty.*, No. 14-cv-804-KG-KK, 2015 U.S. Dist. LEXIS 193642, at *6 n.1 (D.N.M. May 21, 2015).

The New Mexico Supreme Court and other New Mexico courts have recognized the EPA's and NMED's primary jurisdiction over issues concerning regulated environmental matters where a plaintiff seeks injunctive relief to force actions by a company to reduce alleged pollution. *New Mexico v. Gen. Elec. Co.*, 335 F. Supp. 2d 1185, 1244 (D.N.M. 2004); *New Mexico v. Gen. Elec. Co.*, No. CIV-99-1118 BSJ-KBM, 2004 U.S. Dist. LEXIS 18932, at *83-84 (D.N.M. June 23, 2004); *Norvell*, 1973-NMSC-051; *Schwartzman*, 857 F. Supp. at 841-43. As the courts have recognized, "the legislature has created the agency in order to afford a systematic method of factfinding . . . and the agency's jurisdiction should be given priority in the absence of a valid reason for judicial intervention." *Schwartzman*, 857 F. Supp. at 841 (quoting *Norvell*, 1973-NMSC-051).

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The NMED's primary jurisdiction is explained in the Supreme Court's *Norvell* decision. In *Norvell*, the New Mexico Attorney General sought an injunction to abate emissions of particulate matter, sulphur oxides, nitrogen oxides and mercury from a power plant allegedly creating a public nuisance, and to require certain operational practices and equipment at the facility for that abatement. *See* 1973-NMSC-051, ¶¶1-2. The Court reversed the trial court's refusal to dismiss the complaint on primary jurisdiction grounds, holding that the doctrine applied to preclude the claim. *Id.* ¶¶43-45.

The Court explained that the purpose of the state's Environmental Improvement Act "'is to create an agency which will be responsible for environmental management in this state.'" *Id.* ¶14 (quoting § 12-19-2 of the Act (1971)). The Court found that the Act "empowers the [Agency] to 'serve as agent of the State of New Mexico in matters of environmental management' and 'to enforce the rules regulations and orders promulgated by the board and environmental management . . . laws for which the agency is responsible by appropriate action in courts of competent jurisdiction." *Id.* ¶15 (quoting § 12-19-9 of the Act (1971)) (ellipses in original). The Act also "placed with the Agency the responsibility for environmental management and imposed upon it the duty to maintain and enforce rules, regulations and standards in certain environmental areas," and declared that "air quality management, nuisance abatement and environmental injury prevention are 'to the extent that these programs are not expressly delegated by law to another agency or political subdivision . . . now or hereafter made the responsibility of the agency by law.'" *Id.* ¶16 (quoting § 12-19-10 of the Act (1971)) (ellipses in original). The Court further recognized

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that the EIB "may also exercise federal enforcement powers under federal air quality legislation," including the Clean Air Act. *Id.* ¶19.

The Court explained, "'The doctrine of primary jurisdiction . . . is concerned with promoting proper relationships between the courts and administrative agencies charged with particular regulatory duties." *Id.* ¶31. Accordingly, the doctrine applies "whenever enforcement of the claim requires the resolution of issues which, under a regulatory scheme, have been placed within the special competence of an administrative body . . . ." *Id.*

In holding that the doctrine applied in *Norvell*, the Court stated, "the basic issue" is whether the public nuisance claim "requires the resolution of issues which have been placed within the special competence of an administrative agency." *Id.* The Court reasoned, "It is obvious that the administrative scheme of the state, as evidenced by the acts to which we have referred, operates in exactly the same field as that in which plaintiffs would have the trial court function," "[t]here is little, if anything before us to indicate that the Agency has wanted for diligence or efficiency," and "[n]othing indicates to us that the district court is likely to formulate better regulations." *Id.* ¶36. The Court further explained, "All of the plaintiffs' claims involve areas in which the Agency is active," *id.* ¶42, and "'[i]t would be improper for this Court to exercise its equitable jurisdiction to interfere with the comprehensive programs designed to solve a complex social, economic and technological problem,'" *id.* (quoting *City of Chicago v. General Motors Corp.*, 332 F. Supp. 285 (N.D. Ill. 1971)). The Court concluded, "The legislature has clearly intended that the Agency should have primary jurisdiction over pollution control." *Id.* ¶43.

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Here, just as in *Norvell*, the primary jurisdiction doctrine applies to Plaintiff's public nuisance claim. As expressly recognized in *Norvell*, the legislature committed the air quality matters at issue in the Complaint to the expertise of NMED environmental regulators. Indeed, the EPA's NESHAP regulations (which the NMED has adopted) specifically govern "Ethylene Oxide Emissions Standards for Sterilization Facilities," based on the EPA's consideration and weighing of the "nationwide impacts" the regulations present, including the reduction in "nationwide emissions of EO" from commercial EO sterilization facilities; the potential for the regulations to close sterilization facilities; the economic, financial and operational impacts on commercial EO sterilization operators; and the increased sterilization costs on medical device suppliers and other health-related manufacturers. 59 Fed. Reg. 10591 (Mar. 7, 1994). Moreover, the Court's determination of such issues and those concerning technical, medical and scientific matters concerning EO; medical sterilization facility operations; air sampling, dispersion and quality issues; and other issues "would represent a serious drain of judicial resources and would largely duplicate the present efforts of the EPA and the NMED." *Schwartzman,* 857 F. Supp. at 842.

In fact, the EPA is currently considering proposed revisions to its regulations on the issue of so-called "uncontrolled" or "fugitive" emissions as part of its recent advanced notice of proposed rulemaking for potential revisions to Subpart O. 84 Fed. Reg. 67889 (Dec. 12, 2019). In making that regulatory determination, it is considering, *inter alia*, data "quantify[ing] facility-wide and area/room-specific fugitive emissions from commercial EtO sterilizers (e.g., internal and ambient air monitoring data), along with relevant monitoring characteristics such as monitoring collection equipment and techniques, averaging time, equipment detection limits, equipment

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quality assurance, and quality control procedures employed." *Id.* at 67894. The EPA also has been:

> investigating these issues through discussions with stakeholders, reviews of operating permits, and research. As part of the information gathering to date, the EPA has consulted with the EtO sterilization industry, including companies, trade associations, and control technology vendors, to better understand the current state of controls for EtO emission sources. The EPA held teleconferences and meetings with 12 different EtO trade associations, air pollution control device (APCD) manufacturers, industry representatives, and other government agencies to better understand sterilization processes, emissions (including measurement and monitoring), current control techniques, and how widely such techniques are used, as well as how control efficiencies are determined and guaranteed by manufacturers. The discussions have focused on common operational practices, including practices used by EtO commercial sterilization facilities to determine EtO concentration at various emissions points in the process.

Id.

For these reasons, the Court should deny Plaintiff's Motion based on the clear application of the primary jurisdiction doctrine.

II. Plaintiff Has Not Established a Right to Interlocutory Injunctive Relief.

In addition, Plaintiff has not shown a need for or entitlement to the requested injunction. Injunctions are "harsh and drastic remedies" that should issue only in "extreme cases of pressing necessity." *Insure N.M., LLC v. McGonigle*, 2000 NMCA-018, ¶7, 128 N.M. 611. To obtain a temporary restraining order or preliminary injunction, it is the moving party's burden to show "that: (1) [the movant] will suffer irreparable injury unless the injunction is granted; (2) the threatened injury outweighs any damage the [proposed] injunction might cause the [opposing party]; (3) issuance of the injunction will not be adverse to the public's interest; and (4) there is a substantial likelihood [of success] on the merits." *Labalbo v. Hymes*, 1993-NMCA-010, ¶ 11, 115

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N.M. 314.

The object of preliminary injunctive relief "is to preserve the status quo pending the litigation of the merits." *Insure*, 2000 NMCA-018, ¶9. Where the plaintiff seeks a change to the status quo—as is the case here—its request for a temporary restraining order and preliminary injunction is held to a "heightened burden of proof." *Grisham v. Romero*, 2021-NMSC-009, ¶ 20. The movant must show that the factors "weigh heavily and compellingly" in its favor. *Id.* ¶22. Also, "[a]n injunction can issue only after the plaintiff has established that . . . the defendant, if not enjoined, will engage in such conduct." *United Transp. Union v. State Bar of Mich.*, 401 U.S. 576, 584 (1971); *Mountain Med. Equip., Inc. v. Healthdyne, Inc.*, 582 F. Supp. 846, 849 (D. Colo. 1984) ("In a preliminary injunction setting, the burden is on the movant to establish that the defendant will engage in the conduct sought to be proscribed unless the injunction issues.").

A. Plaintiff fails to show that the Facility engages in the practices it seeks to enjoin.

Plaintiff asks the Court to enjoin certain alleged practices at the Facility it claims are causing "uncontrolled" emissions of EO. Motion at 3-4, 7. But Plaintiff has presented no evidence that Sterigenics U.S. is engaging in those practices at the Facility. In fact, the only evidence is that Sterigenics U.S. does not engage in these alleged practices. Decl. of Steve Ortiz ¶ 13 (**Exhibit A**). Plaintiff's request that the Court enjoin those alleged practices therefore should be denied for this initial reason. *United Transp. Union*, 401 U.S. at 584.

B. Plaintiff fails to show the injunction is needed to prevent irreparable harm.

To establish irreparable harm, the movant must show both "an actual and substantial" injury, or the "affirmative prospect" of such an injury, and that there is no adequate remedy at law.

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State v. City of Sunland Park, 2000-NMCA-044, ¶19, 129 N.M. 151. The movant must do more than merely claim irreparable harm; it must "come forth with evidence of the irreparability of his harm or inadequacy of any remedy." *Id.* The movant must also show that "the alleged harm will directly result from the action which the movant seeks to enjoin," *Wisc. Gas Co. v. FERC*, 758 F.2d 669, 674 (D.C. Cir. 1985), and that the injunction sought would actually prevent the alleged harm. *Sierra Club v. U.S. Dep't of Energy*, 825 F. Supp. 2d. 142, 153 (D.D.C. 2011) ("It would make little sense for a court to conclude that a plaintiff has shown irreparable harm when the relief sought would not actually remedy that harm.").

Plaintiff comes nowhere close to proving irreparable harm; it offers no evidence that the alleged "uncontrolled" EO emissions are harming the State, much less imminently or irreparably. Plaintiff's request for injunctive relief consists of its Motion and Complaint (that was "verified" by its lawyer). Nothing else. Moreover, as discussed above, Plaintiff's allegations concerning the IRIS and NATA are unfounded and do not show that the Facility's EO emissions are harming anyone. *Supra* at 9-12.

Also, the notion that the state does not have an adequate remedy at law to preclude "uncontrolled" emissions at the Facility is false. As discussed above, the NMED regulates the Facility's use and emission of EO and ensures the Facility's compliance with its Air Quality Permit. To be clear, Sterigenics U.S. operates lawfully under its permit, and in accordance with all permit requirements and all applicable state and federal regulations. But the state—through the NMED—clearly has the authority to take action against an alleged violation of the applicable environmental regulations or the Facility's Air Quality Permit. *See* NMSA § 74-2-5.1. Tellingly,

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the NMED has not taken any such action, because the Facility is in compliance with all applicable air quality requirements governing its use and emission of EO.

Indeed, Plaintiff's own actions illustrate there is no emergency here. IRIS was released in 2016 and NATA was released in 2018, and Plaintiff did not file this action until years later during the week of Christmas 2020. Also, Plaintiff filed this case almost five months ago, failed to sign the Motion by which it seeks the injunctive relief requested, and chose to engage in jurisdictional and procedural fights in the federal court rather than prioritize the injunction it seeks.

Moreover, the requested injunction would not prevent the false harm Plaintiff alleges. Plaintiff asks the Court to enjoin only the Facility's "uncontrolled" emissions. Motion at 16; *see* Compl. ¶¶ 29, 64, 116-17. But Plaintiff claims that the Facility's "controlled" emissions, which it does not seek to enjoin, are causing the same alleged harm as the "uncontrolled" emissions. Compl. ¶¶18, 125, 127-34, 149, 219; Motion at 3. In fact, Plaintiff's only ground for claiming the Facility's EO emissions "have caused a statistically significant increase in cancer risk for Santa Teresa residents" is based on the Facility's "controlled" emissions. *See* Compl. ¶¶126-34 (claiming NATA allegedly showing that the statistical increase in cancer risk considered only the Facility's "controlled" emissions). Indeed, Plaintiff alleges that "[t]here is no safe amount of EtO in air or other environmental media," "each and every exposure" to EO "increases the cancer risk," and "[e]ven at very low levels, inhalation of EtO-contaminated air significantly increase the risk of developing cancer and other adverse health effectives." *Id.* ¶¶9, 11, 63. Thus, the false harm Plaintiff alleges the Facility's "uncontrolled" emissions are causing the public would still allegedly occur if the injunction were granted. Consequently, the injunction would not redress the alleged

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harm Plaintiff allegedly seeks to prevent, and Plaintiff fails to show that it will suffer irreparable injury "unless the injunction issues." *Heideman v. S. Salt Lake City*, 348 F.3d 1182, 1188 (10th Cir. 2003); *Sierra Club*, 825 F. Supp. 2d at 153 ("the irreparable harm considered by the court must be caused by the conduct in dispute and remedied by the relief sought. . . . If the relief requested does little, if anything, to alleviate the alleged injuries, it is difficult to comprehend how the refusal to grant that relief could cause irreparable harm") (citations omitted).

C. An injunction is adverse to the public interest.

The Facility performs essential EO sterilizations of approximately 2.5 million medical products each day for healthcare providers to use in critical patient medical procedures. Decl. of Steve Ortiz ¶¶6-7 (**Exhibit A**). Such products include custom surgical kits, preoperative skin preparation products, surgical drapes and gowns, cardiovascular tubing sets, internal powered surgical staplers, ophthalmic devices, Band-Aids, prefilled syringes, catheters, tubing for ear, nose, and throat, surgical diagnostic equipment, and tracheostomy-coiled-endotracheal tubes. *Id.*

In the United States, more than 50 percent of all medical products are sterilized with EO, and for many of those products, EO sterilization is the only option.[22] EO sterilization facilities in the United States are already operating at capacity; any disruption to the Facility's operations could cause shortages of critical medical devices.[23]

The FDA has emphasized:

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[22] *Statement on concerns with medical device availability due to certain sterilization facility closures*, FDA Statement (Oct. 25, 2019) (**Exhibit B**).

[23] *See id.*

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> Without adequate availability of ethylene oxide sterilization, we anticipate a national shortage of these devices and other critical devices including feeding tube devices used in neonatal intensive care units, drug-eluting cardiac stents, catheters, shunts and other implantable devices. It's important to note at this time there are no readily available processes or facilities that can serve as viable alternatives to those that use ethylene oxide to sterilize these devices. In short: this method is critical to our health care system and to the continued availability of safe, effective and high-quality medical devices.[24]

The FDA further emphasized that the impact of closing EO sterilization facilities would "be difficult to reverse, and ultimately could result in years of spot or nationwide shortages of critical medical devices, which could compromise patient care.[25]

Plaintiff's broad request that this Court immediately enjoin any escape of EO whatsoever from the Facility as a so-called "uncontrolled" emission (including but not limited to from an employee's entrance or exit of the Facility, a customer's necessary collection of its sterilized medical products for supply to medical providers, or otherwise) would impose requirements with which absolute compliance could be impracticable, as evidenced by the fact that the EPA and the NMED—as the governing regulators of environmental matters at the Facility—do not require them. As expressed in the Motion, Plaintiff would use the injunction to dictate operations and regulate the Facility by Court order, arguing that only "[i]f Defendants can operate the Plant without any uncontrolled EtO emission, [are they] free to do so." Motion at 9.

Courts have recognized that the public interest is "especially significant when health and safety concerns are implicated." *Conopco, Inc. v. Campbell Soup Co.*, 95 F.3d 187, 194 (2d Cir.

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[24] *Id.*

[25] *Id.*

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1996). Here, particularly considering the complete lack of evidence of any harm or wrongdoing, the Facility's necessity for providing essential sterilizations of medical products for critical patient care demonstrates that the requested injunction interfering in the Facility's operations would be adverse to the public interest.

D. Plaintiff has not shown a substantial likelihood of success on the merits.

Plaintiff has not shown that it is substantially likely to succeed on the merits of its public nuisance claims for multiple reasons. Among those reasons are: (1) the Facility's operations and EO emissions are authorized by law and therefore do not constitute a public nuisance under New Mexico law; and (2) Plaintiff has presented no evidence showing a substantial likelihood it will prevail on its claim that the Facility's EO emissions are harming the public.

i. Plaintiff has not presented evidence that it is likely to succeed in showing that the Facility's alleged emissions were without lawful authority.

An essential element of a public nuisance claim under New Mexico law is that the defendant's acts allegedly constituting the public nuisance must have been taken "without lawful authority." Section 30-8-1, NMSA 1978 states, "A public nuisance consists of knowingly creating, performing or maintaining anything affecting any number of citizens <u>without lawful authority</u> which is either: **A**. injurious to public health, safety, morals or welfare; or **B**. interferes with the exercise and enjoyment of public rights, including the right to use public property." *See also* Compl. ¶182 (quoting Section 30-8-1), *and, State v. Cabezuela*, 2011-NMSC-041, ¶38, 150 N.M. 654 ("The language of a statute determines the essential elements of an offense."); *State ex rel. Smith v. Riley*, 1997-NMCA-063, ¶12, 123 N.M. 453 (affirming dismissal of public nuisance claim for failure to allege defendants' lack of lawful authority); *Citizens for Alternatives to Radioactive*

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Dumping v. Cast Transp. Inc., No. CIV 99-321 MCA/ACT, 2004 U.S. Dist. LEXIS 34843, at *87 (D.N.M. Sept. 30, 2004) ("without lawful authority" is an "essential [e]lement" of a public nuisance claim under NMSA § 30-8-1). This essential element is equally applicable to common law and statutory public nuisance claims. *Albuquerque v. State ex rel. Vill. of Los Ranchos de Albuquerque*, 1991-NMCA-015, ¶15, 111 N.M. 608 (neither cause of action will exist for an activity authorized by law).

Sterigenics U.S. has an Air Quality Permit for the Facility from the NMED under New Mexico's Air Quality Act, pursuant to NMED's delegated authority under NESHAP and its EPA-approved State Implementation Plan. *See* Decl. of Steve Ortiz ¶9 and Exh. A (**Exhibit A**). That permit authorizes the Facility's continuous operation and sets the Facility's allowable EO emissions under 40 C.F.R. § 63, Subparts A and O. *Id.* Thus, to succeed on its public nuisance claims, Plaintiff must show that the Facility's emissions are violating the Facility's Air Quality Permit and applicable regulations to establish that they were not legally authorized. Plaintiff has not presented any such evidence in support of its Motion, much less evidence showing a substantial likelihood that it will prevail in establishing such a violation.

ii. Plaintiff has not shown a substantial likelihood it will establish that the Facility's alleged "uncontrolled" emissions are harming the public as claimed.

Plaintiff has presented no evidence that the Facility's "uncontrolled" EO emissions are injuring anyone in the public or interfering with any public right. Again, Plaintiff's allegations concerning IRIS and NATA are unfounded and not such evidence. *Supra* at 9-12. And IRIS and

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NATA do not show that the Facility's EO emissions are putting anyone at risk of harm. *Id.* Notably, also, the Facility's EO emissions are permitted by governing federal and state regulations.

Moreover, the actual scientific evidence in this case will show that the Facility's emissions are not harming anyone and that Plaintiff's claims are wrong. *See, e.g.*, *supra* 10-11 nn.6-8, 11.[26] Plaintiff simply has not shown a substantial likelihood that it will succeed on these issues of proof to prevail in this case.

E. The balance of harms weighs substantially against the injunction.

The Facility is responsible for sterilizing over 2.5 million life-saving medical products each day and is under strict oversight by the EPA and NMED; critical factors when considering the balance of harms. On top of that, Plaintiff—who must meet a "heightened" burden in seeking an injunction and must show that the factors "weigh heavily and compellingly" in its favor—has not presented any evidence that the Facility's alleged "uncontrolled" emissions are harming the public. Particularly given these considerations, the balance of harms clearly weighs against an injunction that would essentially have the Court dictate the operations at the Facility and could interfere with the Facility's ability to operate, satisfy its customer obligations and, most importantly, sterilize essential medical products for use in critical patient care.

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[26] *See also, e.g.*, Vincent MJ, Ethylene Oxide: Cancer Evidence Integration and Dose–Response Implications, Dose-Response: An International Journal, 2019:1-17 (2019) (**Exhibit N**); Valdez-Flores C, et al., Quantitative cancer risk assessment based on NIOSH and UCC epidemiological data for workers exposed to ethylene oxide, Reg. Toxicol. Pharmacol., 56(3):312-20 (2009) (**Exhibit O**); Marsh GM, et al., Ethylene oxide and risk of lympho-hematopoietic cancer and breast cancer: a systematic literature review and meta-analysis, 92, 919-939 (2019) (**Exhibit P**).

CONCLUSION

The Court should defer to the NMED's and EPA's specialized competence and regulatory governance of the matters the Motion improperly seeks to enjoin. In addition, Plaintiff has not made the evidentiary and legal showings required to obtain the injunctive relief – including that the relief sought would even redress the false harm claimed in this case. And to grant the injunction could disrupt and jeopardize the supply of essential medical products needed for critical patient care. In all respects, Plaintiff's Motion is unfounded and improper, and it should be denied.

Respectfully submitted,

MODRALL, SPERLING, ROEHL, HARRIS
& SISK, P.A.

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WE FURTHER CERTIFY that a true and correct copy of the foregoing was submitted through the Odyssey Electronic Filing System for filing and service to all counsel of record and served all counsel of record this 17th day of April, 2021.

MODRALL, SPERLING, ROEHL, HARRIS & SISK, P.A.

By: /s/Jeremy K. Harrison
Jeremy K. Harrison

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Exhibit A

STATE OF NEW MEXICO
COUNTY OF DOÑA ANA
THIRD JUDICIAL DISTRICT COURT

THE STATE OF NEW MEXICO, EX REL. HECTOR BALDERAS, ATTORNEY GENERAL, Plaintiff, v. STERIGENICS U.S., LLC, SOTERA HEALTH HOLDINGS, LLC, SOTERA HEALTH LLC, AND SOTERA HEALTH COMPANY, Defendants.	)	No. D-307-CV-2020-02629

DECLARATION OF STEVE ORTIZ

I, Steve Ortiz, declare as follows:

1. I have been the General Manager of the Sterigenics U.S., LLC ("Sterigenics U.S.") medical product sterilization facility in Santa Teresa, Doña Ana County, New Mexico (the "Facility") since 1996. I am over 18 years of age, of sound mind, and under no legal disability.

2. The facts set forth herein are based upon my personal knowledge, including my familiarity with Sterigenics U.S.'s history, policies, and practices, and my review of Sterigenics U.S.'s business records made by or with information from persons with knowledge of the events described therein, at or near the time of the events described in the ordinary course of such persons' and Sterigenics U.S.'s

regularly conducted business activity. If called to testify about those facts, I could and would do so competently and under oath.

3. Sterigenics U.S. is a medical product sterilization company whose facilities are registered with and regulated by the U.S. Food and Drug Administration (the "FDA").

4. Sterigenics U.S. is a leading provider of medical product sterilizations in the United States.

5. Sterigenics U.S.—formerly known as Griffith Micro Science, Inc.—has operated the Facility since 1989.

6. The Facility is responsible for performing essential sterilizations for over 2.5 million medical products each day, including: custom surgical kits, preoperative skin preparation products, surgical drapes and gowns, cardiovascular tubing sets, internal powered surgical staplers, ophthalmic devices, Band-Aids, prefilled syringes, catheters, tubing for ear, nose, and throat, surgical diagnostic equipment, and tracheostomy-coiled-endotracheal tubes.

7. The Facility sterilizes medical products using ethylene oxide according to specific processes validated by the FDA, in order for the products to be used by healthcare providers in critical patient medical procedures.

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8. Sterigenics U.S.'s use of ethylene oxide to sterilize essential medical products is mandated by specifically defined, FDA-validated sterilization processes for each product.

9. A true and correct copy of Sterigenics U.S.'s current Air Quality Permit for the Facility is attached to this Declaration as **Exhibit A**.

10. Mr. Michael Lucero worked in shipping and receiving while he was employed at the Facility more than nine years ago. His primary responsibilities were to load and unload trucks while he was employed at the Facility.

11. Mr. Lucero was not a trained or certified operator at the Facility. His knowledge of operations, process controls, emission control systems, and sterilization chamber interlocks would have been limited.

12. Mr. Lucero's employment at the Facility was terminated because he severely damaged a forklift by hitting a steel pole while driving the forklift, and he failed to disclose the accident after Facility supervisors asked him about the damage to the forklift. Mr. Lucero did not leave employment at the Facility on good terms.

13. Sterigenics U.S. is not engaging in the following practices at the Facility that the Plaintiff's lawsuit alleges:

a. Sterigenics U.S. does not have "lax oversight in connection with sterilization operations" at the Facility.

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b. Sterigenics U.S. does not leave Facility doors, shipping bays or other means of egress open when not in use, much less frequently or for hours or days.

c. Sterigenics U.S. does not leave shipping bays and "large doors" at the Facility open to allow ethylene oxide to escape or to "return" ethylene oxide air quality monitors within the Facility to "green" status.

d. Sterigenics U.S. does not cause ethylene oxide residue to build up inside Facility sterilization chambers to be cleaned out using a hose.

e. Sterigenics U.S. does not bring in sterilized products from other facilities to aerate at the Facility.

f. Sterigenics U.S. does not leave Facility sterilization chamber doors, aeration room doors, and other interior doors open when not in use.

g. A door interlock system monitors end-of-cycle conditions of the chambers to prevent opening of chamber doors if there are levels of EO present. There is a manual bypass for emergency situations, but the bypass requires several steps and high-level password controls to operate.

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h. In addition, when chamber doors are open, the chamber back vent fans are running to route any ethylene oxide in the chamber to the Facility's emissions control system.

i. Sterigenics U.S. does not allow off-gassing of EO in the storage, transportation or handling of EO prior to charging of sterilization chambers at the Facility.

j. Sterigenics U.S. does not allow ethylene oxide to off-gas from "under-controlled aeration rooms" at the Facility. The Facility's aeration rooms are designed to be under constant negative pressure to keep air from escaping the aeration rooms so that it is captured and cleaned by the Facility's emissions control system.

14. Sterigenics U.S. also has work practices designed to minimize the time any sterilized medical products are not in sterilization chambers or aeration rooms.

15. Sterigenics U.S. also has design, engineering and work practices in place to minimize any ethylene oxide emissions from pipes, equipment and vents, and has emission control systems at the Facility to minimize EO emissions from stacks and point sources well below permitted levels.

I verify under penalty of perjury under the laws of the State of New Mexico and United States of America that the foregoing is true and correct.

Executed on April 16, 2021.

Steve Ortiz

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Exhibit A to Declaration of Steve Ortiz

New Mexico
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CABINET SECRETARY

BUTCH TONGATE
DEPUTY SECRETARY

AIR QUALITY BUREAU
NEW SOURCE REVIEW PERMIT
Issued under 20.2.72 NMAC

Certified Mail No: 7005 1820 0001 5773 4411
Return Receipt Requested

NSR Permit No:	0733-M15-R1
Facility Name:	Sterigenics-Santa Teresa, NM
Permittee Name:	Sterigenics US., LLC
Mailing Address:	2015 Spring Road, Suite 650 Oak Brook, IL 60523
TEMPO/IDEA ID No:	127-PRN20140001
AIRS No:	35-013-0007
Permitting Action:	Technical Permit Revision
Source Classification:	HAP and VOC Synthetic Minor
Facility Location:	31°51'38" N and 106°41'17" W
County:	Dona Ana
Air Quality Bureau Contact	Rhonda Trujillo
Main AQB Phone No.	(505) 476-4300

Richard L. Goodyear, PE
Bureau Chief
Air Quality Bureau

DEC 23 2014
Date

Template version: 10/30/14

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PART A FACILITY SPECIFIC REQUIREMENTS

A100 Introduction

A. This permit, NSR 0733-M15-R1, supersedes all portions of Air Quality Permit 0733-M15, issued June 13, 2013, except the portion requiring compliance tests. Compliance test conditions from previous permits, if not completed, are still in effect, in addition to compliance test requirements contained in this permit.

B. Fee Requirement: This permit is not effective until the Department receives the permit fee specified in the attached invoice. Pursuant to 20.2.75.12 NMAC, the permittee shall pay this invoice no later than thirty (30) days after the permit issue date (invoicing), unless the Department has granted an extension. The permit fee must be paid by this date regardless of the permittee's intended use or non-use of the permit or of the Department's cancellation of the permit. The permittee's failure to pay this fee when due will automatically void the permit and the Department may initiate enforcement action to collect the fee and assess a civil penalty for non-payment. The permittee shall not construct the new equipment in Table 104 before the date that the Department receives the permit fee in full. The Department may initiate enforcement action for injunctive relief and civil penalties for any construction or operation specified in this technical revision, 0733M15R1, if the permit fee is not paid by the due date.

A101 Permit Duration (expiration)

A. The term of this permit is permanent unless withdrawn or cancelled by the Department.

A102 Facility: Description

A. The function of the facility is to sterilize medical devices and food products by exposure to ethylene oxide and propylene oxide gases.

B. This facility is located approximately 2 miles northwest of Santa Teresa, New Mexico in Dona Ana County.

C. This modification consists of:

(1) Installation of a new 30-pallet sterilization chamber (Chamber 14), including associated process emissions from a new vacuum pump and chamber back vent. The vacuum pump is rated at 550 cfm and will exhaust process emissions from the new chamber directly to the facility's existing Ceilcote scrubber system. The Ceilcote system control efficiency for the new vacuum pump will be ≥ 99.3%. The chamber backvent consists of residual Ethylene Oxide (EO) or Propylene Oxide (PO) process emissions produced at the conclusion of each chamber sterilization cycle. The new Chamber 14 backvent will exhaust to the facility's existing Donaldson catalytic oxidizer system via an existing inlet duct. The Donaldson system control efficiency for the Chamber 14 backvent will be ≥ 99%.

(2) Increasing the facility's cap on the usage of EO or PO by 20% to accommodate the new chamber mentioned above. The 20% increase will revise the EO/PO usage caps to: 1,692,000 lbs/year and 1,790 lbs/hour.

(3) Rerouting the facility's remaining nine (9) backvent emissions which currently are uncontrolled, to the existing Donaldson catalytic oxidizer for emissions treatment. (Note: The backvents for Chambers 8, 9, 10 and 13 were re-routed to the Donaldson system in 2013. This request entails rerouting backvents for Chambers 1, 2, 3, 4, 5, 6, 7, 11 and 12.) This change will result in all chamber backvents receiving emissions treatment to a minimum control efficiency of 99%.

(4) Updating equipment descriptions in the current permit (shown in Table 104) for several listed emission sources. These revisions pertain only to "like-for-like" equipment replacements made in recent years. The new equipment has the same capacity and/or level of emissions as the replaced equipment.

D. Table 102.A and Table 102.B show the total potential emissions from this facility for information only, not an enforceable condition, excluding exempt sources or activities.

Table 102.A: Total Potential Pollutant Emissions from Entire Facility

Pollutant	Emissions (tons per year)
Nitrogen Oxides (NOx)	9.6
Carbon Monoxide (CO)	8.0
Volatile Organic Compounds (VOC) *	6.6
Sulfur Dioxide (SO_2)	<1
Particulate Matter less than 10 microns (PM_{10})	<1

Table 102.B: Total Potential HAP Emissions from Entire Facility

Pollutant	Emissions (tons per year)
Ethylene Oxide	6.1
Propylene Oxide	
Total HAPs**	6.1

* HAP emissions are already included in the VOC emission total.

** The total HAP emissions may not agree with the sum of individual HAPs because only individual HAPs greater than 1.0 tons per year are listed here.

A103 Facility: Applicable Regulations

A. The permittee shall comply with all applicable sections of the requirements listed in Table 103.A.

Table 103.A: Applicable Requirements

Applicable Requirements	Federally Enforceable	Unit No.
20.2.1 NMAC General Provisions	X	Entire Facility
20.2.3 NMAC Ambient Air Quality Standards	X	Entire Facility
20.2.7 NMAC Excess Emissions	X	Entire Facility
20.2.61 NMAC Smoke and Visible Emissions	X	Bx and CD3
20.2.72 NMAC Construction Permit	X	Entire Facility
20.2.73 NMAC Notice of Intent and Emissions Inventory Requirements	X	Entire Facility
20.2.75 NMAC Construction Permit Fees	X	Entire Facility
20.2.82 NMAC MACT Standards for Source Categories of HAPS	X	Entire Facility
40 CFR 50 National Ambient Air Quality Standards	X	Entire Facility
40 CFR 63, Subpart A, General Provisions	X	Sterilization Equipment
40 CFR 63, Subpart O Ethylene Oxide Emissions Standards for Sterilization Facilities	X	Sterilization Equipment

A104 Facility: Regulated Sources

A. Table 104 lists the emission units authorized for this facility. Emission units identified as exempt activities (as defined in 20.2.72.202 NMAC) and/or equipment not regulated pursuant to the Act are not included.

Table 104: Regulated Sources List

Unit No.	Source Description	Make & Model No.	Serial No.	Capacity	Mfr. Date	Status	Controls
S-1	Sterilizer #1 Vacuum Pump	Dekker DV02516 DA2	050926G03	250 cfm	2006	Existing	Controlled by Acid-Water Scrubber (Unit CD-2 or CD-1) at 99.3% reduction efficiency
S-2	Sterilizer #2 Vacuum Pump	Dekker DV02516 DA2	050725G07	250 cfm	2006	Existing	
S-3	Sterilizer #3 Vacuum Pump	Dekker DV0251B DA3	060920G01	250 cfm	TBD	Replacement Unit	
S-4	Sterilizer #4 Vacuum Pump	Dekker DV025OB DA2	12005	250 cfm	TBD	Replacement Unit	
S-5	Sterilizer #5 Vacuum Pump	Dekker DV0251B DA2	060610G03	250 cfm	TBD	Replacement Unit	
S-6	Sterilizer #6 Vacuum Pump	Dekker DV0251B DA3	070129G03	250 cfm	TBD	Replacement Unit	
S-7	Sterilizer #7 Vacuum Pump	Dekker DV0550B KA2	070323G11	550 cfm	TBD	Replacement Unit	
S-8	Sterilizer #8 Vacuum Pumps for 30 Pallet Chamber	Dekker PUMP A&B DV0550B KA3	C02373602/C 02373601	2 @ 550 cfm	TBD	Replacement Unit	
S-9	Sterilizer #9 Vacuum Pumps for 30 Pallet Chamber	Dekker DV0550B KA3/ DV0550B-KA2	060427G05/ C02373609	2 @ 550 cfm	TBD	Replacement Unit	
S-10	Sterilizer #10 Vacuum Pumps for 30 Pallet Chamber	Dekker DVB0550B KA2	071031G06	550 cfm	TBD	Replacement Unit	
S-11	Sterilizer #11 Vacuum Pump for 15 pallet chamber	Dekker DV0550B KA2	050628G02	550 cfm	TBD	Replacement Unit	
S-12	Sterilizer #12 Vacuum Pump for 30 pallet chamber	Sterling SIHI LEHA 900 AB	BFK4SP	550 cfm	2006	Existing	
S-13	Sterilizer #13 Vacuum Pump for 30 Pallet Chamber	Dekker DVO550-KA2	O61031G10	550 cfm	2007	New 2007	

Unit No.	Source Description	Make & Model No.	Serial No.	Capacity	Mfr. Date	Status	Controls
S-14	Sterilizer #14 Vacuum Pump for 30 Pallet Chamber	TBD	TBD	TBD	TBD	TBD	Controlled by Catalytic Oxidizer (Unit CD-3) at 99% reduction efficiency.
AR 8	Aeration Room 8	Blower	--	9000 cfm	2006	Modified 2007	
AR09	Aeration Room 9	Blower	--	6000 cfm	2010	Modified 2013	
BV-1	Back Vent Exhaust for S-1	Captive Air BI18CARM	455172	3,000 cfm	1986	To be Modified	
BV-2	Back Vent Exhaust for S-2	Captive Air BI18CARM	404418	3,000 cfm	1986	To be Modified	
BV-3	Back Vent Exhaust for S-3	Dayton UK	D2C799A	1,800 cfm	1986	To be Modified	
BV-4	Back Vent Exhaust for S-4	Dayton UK	2C799A	1,800 cfm	1986	To be Modified	
BV-5	Back Vent Exhaust for S-5	Dayton UK	13C074A	1,800 cfm	1986	To be Modified	
BV-6	Back Vent Exhaust for S-6	Dayton UK	D3C074A	1,800 cfm	1986	To be Modified	
BV-7	Back Vent Exhaust for S-7	Dayton UK	10C074A	1,800 cfm	1995	To be Modified	
BV-11	Back Vent Exhaust for S-11	Greenheck 12-BISW-41-10-11	05L11546	1,800 cfm	2005	To be Modified	
BV-12	Back Vent Exhaust for S-12	Greenheck 12-BISW-41-10-11	5647269-12982637	2,000 cfm	3/28/07	To be Modified	
BV-8	Back Vent Exhaust for S-8	Greenheck 12-BISW41-X-10-11	118657780909	1800 cfm	3/16/10	New 2013	
BV-9	Back Vent Exhaust for S-9	Greenheck 12-BISW41-10-11	123271141102	1800 cfm	3/08/11	New 2013	
BV-10	Back Vent Exhaust for S-10	Greenheck 12-BISW41-X-10-11	118724370909	1800 cfm	2/17/10	New 2013	
BV-13	Back Vent Exhaust for S-13	Greenheck 12-BISW-41	07B02982	1,800 cfm	8/13/07	New 2013	
BV-14	Back Vent Exhaust for S-14	TBD	TBD	TBD	TBD	TBD	

Unit No.	Source Description	Make & Model No.	Serial No.	Capacity	Mfr. Date	Status	Controls
CD-1	Acid-Water Scrubber	Deoxx 88-485	None	600 cfm	1989	Existing	Back-up for CD-2
CD-2	Acid-Water Scrubber	Ceilcote SPT-54-240	81318	2500 cfm	2004	Existing	Controls S-1 to S-14
CD-3	Catalytic Oxidizer	Donaldson 20,000 AG EtO Abator	None	20,000 cfm	1991	Existing	Controls AR 08, AR 09, BV 1-14
Bx	Any combination of natural gas boilers not to exceed a manufactures energy input rating of 18 MM Btu/hr	Various	Various	18 MM Btu/hr (Combined Max)	N/A	N/A	N/A

1. All TBD (to be determined) units and like-kind engine replacements must be evaluated for applicability to NSPS and NESHAP requirements.

A105 Facility: Control Equipment

A. Table 105 lists all the pollution control equipment required for this facility. Each emission point is identified by the same number that was assigned to it in the permit application.

Table 105: Control Equipment List:

Control Equipment Unit No.	Control Description	Pollutant being controlled	Control for Unit Number(s)[1]
CD-1	Deoxx Acid-Water Scrubber System	Ethylene Oxide, Propylene Oxide	S-1 – S-14, (Back-up to CD-2)
CD-2	Ceilcote Acid-Water Scrubber System	Ethylene Oxide, Propylene Oxide	S-1- S-14
CD-3	Donaldson 20,000 AG EtO Abator	Ethylene Oxide, Propylene Oxide	AR-08, AR-09, BV-1 – BV-14

1. Control for unit number refers to a unit number from the Regulated Equipment List

A106 Facility: Allowable Emissions

A. The following Section lists the emission units and their allowable emission limits. (40 CFR 50, 40 CFR 63, Subparts A and O, 20.2.72.210.A and B.1 NMAC).

Table 106.A: Allowable Emissions

Unit No.	NO_x[1] pph	NO_x[1] tpy	CO pph	CO tpy	VOC pph	VOC tpy	EO or PO pph	EO or PO tpy
CD-1 or CD-2	-	-	-	-	*	5.7	*	5.7
CD-3	<	1.7	<	1.4	<	<	0.9	0.4

1 Nitrogen dioxide emissions include all oxides of nitrogen expressed as NO_2
2 "-" indicates the application represented emissions of this pollutant are not expected.
"<" indicates the application represented uncontrolled emissions are less than 1.0 pph or 1.0 tpy for this pollutant. Allowable limits are not imposed on this level of emissions, except for flares and pollutants with controls.
"*" indicates hourly emission limits are not appropriate for this operating situation.

A107 Facility: Allowable Startup, Shutdown, & Maintenance (SSM) and Malfunction Emissions

A. Separate allowable SSM emission limits are not required for this facility since the SSM emissions are predicted to be less than the limits established in Table 106A. The permittee shall maintain records in accordance with Condition B109.C.

A108 Facility: Allowable Operations

A. This facility is authorized for continuous operation. Monitoring, recordkeeping, and reporting are not required to demonstrate compliance with continuous hours of operation

B. Propylene oxide (PO) may be substituted for ethylene oxide (EO), but the combined maximum charges are limited to the charge rate(s) specified in Condition A108.C and the PO emission shall be routed through the same control equipment as the EO emissions.

C. Ethylene Oxide and Propylene Oxide Charging Rates

Requirement:
The combined maximum ethylene oxide gas charge rate(s) to the sterilizer chambers (Units S-1 to S-14) shall not exceed the following limits:

(a) 1,790 lbs per hour, hourly average and averaged over a 24-hour period,
(b) 1,692,000 lbs per 12 month period, calculated as a monthly rolling 12-month total.

Monitoring:
Hourly, the permittee shall monitor the following:

(1) EO or PO charge rates for each of the sterilization chambers (Units S-1 to S-14).

Recordkeeping: Records shall include:

(1) Date; (2) EO or PO pounds per hour averaged over a 24 hour period; (3) EO or PO pounds per 12 month period, calculated as a monthly rolling 12-month total.
Reporting: The permittee shall report in accordance with Section B110.

A109 Facility: Reporting Schedules – Not Applicable

A110 Facility: Fuel Sulfur Requirements

A. Fuel and Fuel Sulfur Requirements (CD3 and Bx)

Requirement: All combustion emission units shall combust only natural gas containing no more than 5.0 grains of total sulfur per 100 dry standard cubic feet
Monitoring: None
Recordkeeping: The permittee shall demonstrate compliance with the natural gas or fuel oil limit on total sulfur content by maintaining records of a current, valid purchase contract, tariff sheet or transportation contract for the gaseous or liquid fuel, or fuel gas analysis, specifying the allowable limit or less.
Reporting: The permittee shall report in accordance with Section B110.

A111 Facility: 20.2.61 NMAC Opacity

A. 20.2.61 NMAC Opacity Limit (Units CD3 and Bx)

Requirement: Visible emissions from all stationary combustion emission stacks shall not equal or exceed an opacity of 20 percent.
Monitoring: Use of natural gas fuel constitutes compliance with 20.2.61 NMAC unless opacity equals or exceeds 20% averaged over a 10-minute period. When any visible emissions are observed at or above 20% opacity, during steady state operation, opacity shall be measured over a 10-minute period, in accordance with the procedures at 40 CFR 60, Appendix A, Method 9 as required by 20.2.61.114 NMAC
Recordkeeping: The permittee shall record the opacity measures with the corresponding opacity readings in accordance with Method 9 in 40 CFR 60, Appendix A.
Reporting: The permittee shall report in accordance with Section B110.

A112 Facility: Haul Roads – Not Applicable

A113 Facility: Initial Location Requirements – Not Applicable

A114 Facility: Relocation Requirements

A. This facility may not be relocated.

A115 Alternative Operating Scenario – Not required

A116 Compliance Plan – Not Required

A117 Reducing Facility Emissions

A. Within 60 days of permit issuance, the permittee shall come into compliance with the emissions limits in this permit NSR (0733M15R1) by permanently ducting the remaining back vents (BV 1-7, 11, 12, and 14) to the Donaldson catalytic oxidizer.

A200 Oil and Gas Industry – Not Required

A300 Construction Industry – Aggregate – Not Required

A400 Construction Industry – Asphalt – Not Required

A500 Construction Industry – Concrete

A600 Power Generation Industry – Not Required

A700 Solid Waste Disposal (Landfills) Industry– Not Required

STERILIZATION FACILITIES INTRODUCTION

A800 Sterilization Facilities Introduction

A. 40 CFR 63 Subpart O: Ethylene Oxide Emissions Standards for Sterilization Facilities

Requirement: This facility is subject to 40 CFR 63, Subparts A and O and shall comply with all applicable requirements of the regulation.
Monitoring: The permittee shall comply with all applicable monitoring requirements of 40

CFR 63, Subparts A and O.
Recordkeeping: The permittee shall comply with all applicable recordkeeping requirements of 40 CFR 63, Subparts A and O.
Reporting: The permittee shall comply with all applicable recordkeeping requirements of 40 CFR 63, Subparts A and O.

B. Oil Seals

Requirement: All pumps in contact with EO or PO shall have closed-loop oil seals. All oil seals shall be maintained to ensure integrity.
Monitoring: The permittee shall inspect the oil seals weekly to ensure proper operations.
Recordkeeping: The permittee shall keep records of the required monitoring and any maintenance performed for EO or PO pump oil seals.
Reporting: The permittee shall report in accordance with Section B110.

C. This Specific Condition (A800.C) supersedes General Condition B111.C.4.:

During emissions tests, pollutant, O_2 concentration and fuel flow rate ***(if fuels are being combusted)*** shall be monitored and recorded. This information shall be included with the test report furnished to the Department.

A801 <u>Sterilization Chamber</u>

A. Sterilization Chambers (S1- S14)

Requirement: The permittee shall not operate any sterilization chambers unless their respective emission control equipment (CD-1 or CD-2) is operated in accordance with manufacturer specifications.
Monitoring: To ensure that the control equipment is operating in accordance with manufacturer specifications, during each day that the sterilization chambers are in use, the permittee shall monitor: (1) The control equipment (CD-1 or CD-2) is operating within the specified parameters in Condition A801.B.
Recordkeeping: The permittee shall maintain records of all daily inspections and record all of the parameters specified in Condition A801.B.
Reporting: The permittee shall report in accordance with Section B110.

B. Acid-Water Scrubber (Unit CD-1 and CD-2)

Requirement: All emissions from Units S-1 – S-14 shall be ducted to the acid-water scrubber CD-1 or CD-2. The permittee shall not operate the units S1- S14 unless the units CD-1 or CD-2 are operating within the specified parameters in this condition. Unit CD-1 may be used as a back-up for Unit CD-2 only when Unit CD-1 has minimum emission reduction efficiency equal to or greater than Unit CD-2. Compliance with this condition demonstrates compliance with the emission limits in Table

106.A for Units CD-1 and CD-2.
Monitoring: Each day, the permittee shall monitor the following parameters for each acid-water scrubber operated in any one calendar day. A) For CD-1, the permittee shall monitor: (1) The gas flow rate shall not exceed 600 ACFM @ 90 degrees Fahrenheit; (2) The liquid temperature shall not exceed 100 degrees Fahrenheit; (3) The liquid pH shall be ≤ 1; and (4) The permittee shall monitor the scrubber spray atomizers and ensure that they are operating. B) For CD-2, the permittee shall monitor: (1) The gas flow rate shall not exceed 2500 SCFM @ 90 degrees Fahrenheit; (2) The liquid temperature shall not exceed 120 degrees Fahrenheit; (3) The liquid pH shall be ≤ 2; and (4) Daily, the permittee shall monitor the scrubber spray atomizers to ensure that they are operating. The permittee shall monitor the date, start time, and end time of any downtime and/or maintenance of the units CD-1 and CD-2.
Recordkeeping: Daily, the permittee shall record: For CD-1 and CD-2, the permittee shall record: (1) The gas flow rate; (2) The gas inlet temperature; (3) The liquid temperature; (4) The liquid pH; and (5) The permittee shall record inspections of the scrubber spray atomizers and the results of the inspections. The permittee shall record the date, start time, and end time of any downtime and/or maintenance of the units CD-1 and CD-2.

Reporting: The permittee shall report in accordance with Section B110.

C. Interlock Systems for Acid-Water Scrubber (Unit CD-1 and CD-2)

Requirement: Units CD-1 and CD-2 shall be equipped with an interlock system to prevent emission discharges to the atmosphere any time the scrubber system experiences a control parameter malfunction. Set points for the sterilization system interlock shall be specified by the control device (CD-1 or CD-2) manufacturer and compliance test results (as applicable) for the unit. Upon request by Department personnel during an onsite inspection, the permittee shall demonstrate to the inspector that the interlock systems are operating within the set points.
Monitoring: The permittee shall monitor: 1. Daily, the permittee shall monitor for the parameters in Condition A 801.B to demonstrate that the interlock system is operating within the set points as specified by the control device (CD-1 or CD-2). 2. The permittee shall monitor each time the Interlock System is used.
Recordkeeping: 1. Daily, the permittee shall record that the interlock system is operating within the set points as specified in Condition A801.B for the control device (CD-1 or CD-2). 2. The permittee shall record each time the Interlock System is used.
Reporting: The permittee shall report in accordance with Section B110.

D. Acid-Water Scrubber Shut down Alarm (Unit CD-1 and CD-2)

Requirement: The shutdown alarm on the acid-water scrubber shall be set to maintain at least a thirty (30) minute average residence time to ensure ethylene glycol formation during the scrubber operation.
Monitoring: The permittee shall monitor the alarm on the acid-water scrubber to ensure at least (30) minutes average residence time, each time the scrubber is operating.
Recordkeeping: The permittee shall record each time the average residence time fails to maintain at least 30 minutes average residence time.
Reporting: The permittee shall report in accordance with Section B110.

A802 Aerating Rooms, Backvents, and Catalytic Oxidizer

A. Operational and Control Requirements for Units AR-08, AR-09, and Units BV1-BV14)

Requirement: A.) All emissions from aeration rooms AR-08 and AR-09 shall be ducted to the catalytic oxidizer (Unit CD-3). Emissions from Units BV1- BV14 shall be vented to (Unit CD-3). B.) All untreated process emissions from the aeration rooms (AR-08 and AR-09) must be isolated and the chamber back vents (BV1- BV14) must not operate whenever the catalytic oxidizer (CD-3) is not within operating temperatures. C.) In the event that the catalytic oxidizer is not operating, the permittee shall ensure that any

emissions from the aeration rooms (AR-08 and AR-09) are isolated and remain in the aeration rooms until such time that the catalytic oxidizer is operating. D.) The permittee shall ensure that a continuous strip chart recorder or data acquisition system for monitoring the catalytic bed temperature is continuously operated at all times the catalytic control system is in operation. E.) Compliance with this condition demonstrates compliance with the emission limits for Unit CD-3 in Table 106.A.
Monitoring: (1) The permittee shall continuously monitor the temperature at the outlet of the catalyst bed. (2) Monthly, the permittee shall monitor the pressure drop across the catalyst bed. (3) In the event of a malfunction of the continuous recorder, manual temperature recordings of the inlet temperature to the catalyst bed shall be taken hourly. The continuous temperature recorder shall be repaired within seven calendar days. (4) The permittee shall monitor the date, start time, and end time of any downtime and/or maintenance of the unit CD-3.
Recordkeeping: (1) The permittee shall keep a monthly record of the data from the continuous strip chart recorder or data acquisition system for monitoring the catalytic bed temperature. (2) Monthly, the permittee shall record the pressure drop across the catalyst bed. (3) The permittee shall record the date, start time, and end time of any downtime and/or maintenance of the unit CD-3.
Reporting: The permittee shall report in accordance with Section B110.

B. Interlock Systems for Catalytic Oxidizer (Unit CD-3)

Requirement: Unit CD-3 shall be equipped with an interlock system to prevent emission discharges to the atmosphere any time the catalytic system experiences a control parameter malfunction. Set points for the sterilization system interlock shall be specified by the control device, CD-3, manufacturer and compliance test results (as appropriate) for the unit. Upon request by Department personnel during an onsite inspection, the permittee shall demonstrate to the inspector that the interlock systems are operating within the set points.
Monitoring: (1) Daily, the permittee shall monitor (CD-3) operating temperature to ensure it is operating within the temperature set points as specified for the control device (CD-3) from the manufacturer specification sheet and compliance test results (as appropriate). (2) Monthly, the permittee shall monitor the pressure drop across the catalyst bed of (CD-3) and ensure that it meets the manufacturer's specification.

(3) The permittee shall monitor each time the Interlock System is used.
Recordkeeping: (1) Daily, the permittee shall record that the interlock system is operating within the temperature set points as specified by the manufacturer specifications and compliance test results (as appropriate) for the control device (CD-3). (2) Monthly, the permittee shall record the pressure drop across the catalyst bed of (CD-3). (3) The permittee shall record each time the Interlock System is used. (4) The permittee shall maintain a copy of the manufacturer specification sheet on the premises and provide it to the Department's inspector upon request.
Reporting: The permittee shall report in accordance with Section B110.

PART B GENERAL CONDITIONS

B100 Introduction

A. The Department has reviewed the permit application for the proposed construction/modification/revision and has determined that the provisions of the Act and ambient air quality standards will be met. Conditions have been imposed in this permit to assure continued compliance. 20.2.72.210.D NMAC, states that any term or condition imposed by the Department on a permit is enforceable to the same extent as a regulation of the Environmental Improvement Board.

B101 Legal

A. The contents of a permit application specifically identified by the Department shall become the terms and conditions of the permit or permit revision. Unless modified by conditions of this permit, the permittee shall construct or modify and operate the Facility in accordance with all representations of the application and supplemental submittals that the Department relied upon to determine compliance with applicable regulations and ambient air quality standards. If the Department relied on air quality modeling to issue this permit, any change in the parameters used for this modeling shall be submitted to the Department for review. Upon the Department's request, the permittee shall submit additional modeling for review by the Department. Results of that review may require a permit modification. (20.2.72.210.A NMAC)

B. Any future physical changes, changes in the method of operation or changes in restricted area may constitute a modification as defined by 20.2.72 NMAC, Construction Permits. Unless the source or activity is exempt under 20.2.72.202 NMAC, no modification shall begin prior to issuance of a permit. (20.2.72 NMAC Sections 200.A.2 and E, and 210.B.4)

C. Changes in plans, specifications, and other representations stated in the application documents shall not be made if they cause a change in the method of control of

emissions or in the character of emissions, will increase the discharge of emissions or affect modeling results. Any such proposed changes shall be submitted as a revision or modification. (20.2.72 NMAC Sections 200.A.2 and E, and 210.B.4)

D. The permittee shall establish and maintain the property's Restricted Area as identified in plot plan submitted with the application. (20.2.72 NMAC Sections 200.A.2 and E, and 210.B.4)

E. Applications for permit revisions and modifications shall be submitted to:

Program Manager, Permits Section
New Mexico Environment Department
Air Quality Bureau
525 Camino de los Marquez, Suite 1
Santa Fe, NM 87505

F. The owner or operator of a source having an excess emission shall, to the extent practicable, operate the source, including associated air pollution control equipment, in a manner consistent with good air pollutant control practices for minimizing emissions. (20.2.7.109 NMAC). The establishment of allowable malfunction emission limits does not supersede this requirement.

B102 Authority

A. This permit is issued pursuant to the Air Quality Control Act (Act) and regulations adopted pursuant to the Act including Title 20, Chapter 2, Part 72 of the New Mexico Administrative Code (NMAC), (20.2.72 NMAC), Construction Permits and is enforceable pursuant to the Act and the air quality control regulations applicable to this source.

B. The Department is the Administrator for 40 CFR Parts 60, 61, and 63 pursuant to the delegation and exceptions of Section 10 of 20.2.77 NMAC (NSPS), 20.2.78 NMAC (NESHAP), and 20.2.82 NMAC (MACT).

B103 Annual Fee

A. The Department will assess an annual fee for this Facility. The regulation 20.2.75 NMAC set the fee amount at $1,500 through 2004 and requires it to be adjusted annually for the Consumer Price Index on January 1. The current fee amount is available by contacting the Department or can be found on the Department's website. The AQB will invoice the permittee for the annual fee amount at the beginning of each calendar year. This fee does not apply to sources which are assessed an annual fee in accordance with 20.2.71 NMAC. For sources that satisfy the definition of

"small business" in 20.2.75.7.F NMAC, this annual fee will be divided by two. (20.2.75.11 NMAC)

B. All fees shall be remitted in the form of a corporate check, certified check, or money order made payable to the "NM Environment Department, AQB" mailed to the address shown on the invoice and shall be accompanied by the remittance slip attached to the invoice.

B104 Appeal Procedures

A. Any person who participated in a permitting action before the Department and who is adversely affected by such permitting action, may file a petition for hearing before the Environmental Improvement Board. The petition shall be made in writing to the Environmental Improvement Board within thirty (30) days from the date notice is given of the Department's action and shall specify the portions of the permitting action to which the petitioner objects, certify that a copy of the petition has been mailed or hand-delivered and attach a copy of the permitting action for which review is sought. Unless a timely request for hearing is made, the decision of the Department shall be final. The petition shall be copied simultaneously to the Department upon receipt of the appeal notice. If the petitioner is not the applicant or permittee, the petitioner shall mail or hand-deliver a copy of the petition to the applicant or permittee. The Department shall certify the administrative record to the board. Petitions for a hearing shall be sent to: (20.2.72.207.F NMAC)

Secretary, New Mexico Environmental Improvement Board
1190 St. Francis Drive, Runnels Bldg. Rm. N2153
Santa Fe, New Mexico 87502

B105 Submittal of Reports and Certifications

A. Stack Test Protocols and Stack Test Reports shall be submitted electronically to Stacktest.AQB@state.nm.us or as directed by the Department.

B. Excess Emission Reports shall be submitted as directed by the Department. (20.2.7.110 NMAC)

C. Routine reports shall be submitted to the mailing address below, or as directed by the Department:

Manager, Compliance and Enforcement Section
New Mexico Environment Department
Air Quality Bureau
525 Camino de los Marquez, Suite 1
Santa Fe, NM 87505

B106 NSPS and/or MACT Startup, Shutdown, and Malfunction Operations

A. If a facility is subject to a NSPS standard in 40 CFR 60, each owner or operator that installs and operates a continuous monitoring device required by a NSPS regulation shall comply with the excess emissions reporting requirements in accordance with 40 CFR 60.7(c), unless specifically exempted in the applicable subpart.

B. If a facility is subject to a NSPS standard in 40 CFR 60, then in accordance with 40 CFR 60.8(c), emissions in excess of the level of the applicable emission limit during periods of startup, shutdown, and malfunction shall not be considered a violation of the applicable emission limit unless otherwise specified in the applicable standard.

C. If a facility is subject to a MACT standard in 40 CFR 63, then the facility is subject to the requirement for a Startup, Shutdown and Malfunction Plan (SSM) under 40 CFR 63.6(e)(3), unless specifically exempted in the applicable subpart.

B107 Startup, Shutdown, and Maintenance Operations

A. The establishment of permitted startup, shutdown, and maintenance (SSM) emission limits does not supersede the requirements of 20.2.7.14.A NMAC. Except for operations or equipment subject to Condition B106, the permittee shall establish and implement a plan to minimize emissions during routine or predictable start up, shut down, and scheduled maintenance (SSM work practice plan) and shall operate in accordance with the procedures set forth in the plan. (SSM work practice plan) (20.2.7.14.A NMAC)

B108 General Monitoring Requirements

A. These requirements do not supersede or relax requirements of federal regulations.

B. The following monitoring requirements shall be used to determine compliance with applicable requirements and emission limits. Any sampling, whether by portable analyzer or EPA reference method, that measures an emission rate over the applicable averaging period greater than an emission limit in this permit constitutes noncompliance with this permit. The Department may require, at its discretion, additional tests pursuant to EPA Reference Methods at any time, including when sampling by portable analyzer measures an emission rate greater than an emission limit in this permit; but such requirement shall not be construed as a determination that the sampling by portable analyzer does not establish noncompliance with this permit and shall not stay enforcement of such noncompliance based on the sampling by portable analyzer.

C. If the emission unit is shutdown at the time when periodic monitoring is due to be accomplished, the permittee is not required to restart the unit for the sole purpose of

performing the monitoring. Using electronic or written mail, the permittee shall notify the Department's Compliance and Enforcement Section of a delay in emission tests prior to the deadline for accomplishing the tests. Upon recommencing operation, the permittee shall submit any pertinent pre-test notification requirements set forth in the current version of the Department's Standard Operating Procedures For Use Of Portable Analyzers in Performance Test, and shall accomplish the monitoring.

D. The requirement for monitoring during any monitoring period is based on the percentage of time that the unit has operated. However, to invoke the monitoring period exemption at B108.D(2), hours of operation shall be monitored and recorded.

(1) If the emission unit has operated for more than 25% of a monitoring period, then the permittee shall conduct monitoring during that period.

(2) If the emission unit has operated for 25% or less of a monitoring period then the monitoring is not required. After two successive periods without monitoring, the permittee shall conduct monitoring during the next period regardless of the time operated during that period, except that for any monitoring period in which a unit has operated for less than 10% of the monitoring period, the period will not be considered as one of the two successive periods.

(3) If invoking the monitoring **period** exemption in B108.D(2), the actual operating time of a unit shall not exceed the monitoring period required by this permit before the required monitoring is performed. For example, if the monitoring period is annual, the operating hours of the unit shall not exceed 8760 hours before monitoring is conducted. Regardless of the time that a unit actually operates, a minimum of one of each type of monitoring activity shall be conducted during any five-year period.

E. For all periodic monitoring events, except when a federal or state regulation is more stringent, three test runs shall be conducted at 90% or greater of the unit's capacity as stated in this permit, or in the permit application if not in the permit, and at additional loads when requested by the Department. If the 90% capacity cannot be achieved, the monitoring will be conducted at the maximum achievable load under prevailing operating conditions except when a federal or state regulation requires more restrictive test conditions. The load and the parameters used to calculate it shall be recorded to document operating conditions and shall be included with the monitoring report.

F. When requested by the Department, the permittee shall provide schedules of testing and monitoring activities. Compliance tests from previous NSR and Title V permits may be re-imposed if it is deemed necessary by the Department to determine whether the source is in compliance with applicable regulations or permit conditions.

G. If monitoring is new or is in addition to monitoring imposed by an existing applicable requirement, it shall become effective 120 days after the date of permit issuance. For emission units that have not commenced operation, the associated new or additional

monitoring shall not apply until 120 days after the units commence operation. All pre-existing monitoring requirements incorporated in this permit shall continue to apply from the date of permit issuance.

B109 General Recordkeeping Requirements

A. The permittee shall maintain records to assure and verify compliance with the terms and conditions of this permit and any other applicable requirements that become effective after permit issuance. The minimum information to be included in these records is:

(1) equipment identification (include make, model and serial number for all tested equipment and emission controls);

(2) date(s) and time(s) of sampling or measurements;

(3) date(s) analyses were performed;

(4) the qualified entity that performed the analyses;

(5) analytical or test methods used;

(6) results of analyses or tests; and

(7) operating conditions existing at the time of sampling or measurement.

B. Except as provided in the Specific Conditions, records shall be maintained on-site or at the permittee's local business office for a minimum of two (2) years from the time of recording and shall be made available to Department personnel upon request. Sources subject to 20.2.70 NMAC "Operating Permits" shall maintain records on-site for a minimum of five (5) years from the time of recording.

C. Unless otherwise indicated by Specific Conditions, the permittee shall keep the following records for malfunction emissions and routine or predictable emissions during startup, shutdown, and scheduled maintenance (SSM):

(1) The owner or operator of a source subject to a permit shall establish and implement a plan to minimize emissions during routine or predictable startup, shutdown, and scheduled maintenance through work practice standards and good air pollution control practices. This requirement shall not apply to any affected facility defined in and subject to an emissions standard and an equivalent plan under 40 CFR Part 60 (NSPS), 40 CFR Part 63 (MACT), or an equivalent plan under 20.2.72 NMAC - Construction Permits, 20.2.70 NMAC - Operating Permits, 20.2.74 NMAC - Permits - Prevention of Significant Deterioration (PSD), or 20.2.79 NMAC - Permits - Nonattainment Areas. The permittee shall keep records of all sources subject to the plan to minimize emissions during routine or predictable SSM and shall record if the source is subject to an alternative plan and therefore, not subject to the plan requirements under 20.2.7.14.A NMAC.

(2) If the facility has allowable SSM emission limits in this permit, the permittee shall record all SSM events, including the date, the start time, the end time, a description of the event, and a description of the cause of the event. This record also shall include a copy of the manufacturer's, or equivalent, documentation showing that any maintenance qualified as scheduled. Scheduled maintenance is an activity that occurs at an established frequency pursuant to a written protocol published by the manufacturer or other reliable source. The authorization of allowable SSM emissions does not supersede any applicable federal or state standard. The most stringent requirement applies.

(3) If the facility has allowable malfunction emission limits in this permit, the permittee shall record all malfunction events to be applied against these limits. The permittee shall also include the date, the start time, the end time, and a description of the event. **Malfunction means** any sudden and unavoidable failure of air pollution control equipment or process equipment beyond the control of the owner or operator, including malfunction during startup or shutdown. A failure that is caused entirely or in part by poor maintenance, careless operation, or any other preventable equipment breakdown shall not be considered a malfunction. (20.2.7.7.E NMAC) The authorization of allowable malfunction emissions does not supersede any applicable federal or state standard. The most stringent requirement applies. This authorization only allows the permittee to avoid submitting reports under 20.2.7 NMAC for total annual emissions that are below the authorized malfunction emission limit.

(4) The owner or operator of a source shall meet the operational plan defining the measures to be taken to mitigate source emissions during malfunction, startup or shutdown. (20.2.72.203.A(5) NMAC)

B110 <u>General Reporting Requirements</u>
(20.2.72 NMAC Sections 210 and 212)

A. Records and reports shall be maintained on-site or at the permittee's local business office unless specifically required to be submitted to the Department or EPA by another condition of this permit or by a state or federal regulation. Records for unmanned sites may be kept at the nearest business office.

B. The permittee shall notify the Department's Compliance Reporting Section using the current Submittal Form posted to NMED's Air Quality web site under Compliance and Enforcement/Submittal Forms in writing of, or provide the Department with (20.2.72.212.A and B):

(1) the anticipated date of initial startup of each new or modified source not less than thirty (30) days prior to the date. Notification may occur prior to issuance of the permit, but actual startup shall not occur earlier than the permit issuance date;

(2) after receiving authority to construct, the equipment serial number as provided by the manufacturer or permanently affixed if shop-built and the actual date of initial startup of each new or modified source within fifteen (15) days after the startup date; and

(3) the date when each new or modified emission source reaches the maximum production rate at which it will operate within fifteen (15) days after that date.

C. The permittee shall notify the Department's Permitting Program Manager, in writing of, or provide the Department with (20.2.72.212.C and D):

(1) any change of operators or any equipment substitutions within fifteen (15) days of such change;

(2) any necessary update or correction no more than sixty (60) days after the operator knows or should have known of the condition necessitating the update or correction of the permit.

D. Results of emission tests and monitoring for each pollutant (except opacity) shall be reported in pounds per hour (unless otherwise specified) and tons per year. Opacity shall be reported in percent. The number of significant figures corresponding to the full accuracy inherent in the testing instrument or Method test used to obtain the data shall be used to calculate and report test results in accordance with 20.2.1.116.B and C NMAC. Upon request by the Department, CEMS and other tabular data shall be submitted in editable, MS Excel format.

E. The permittee shall submit reports of excess emissions in accordance with 20.2.7.110.A NMAC.

B111 <u>General Testing Requirements</u>

A. Compliance Tests

(1) Compliance test requirements from previous permits (if any) are still in effect, unless the tests have been satisfactorily completed. Compliance tests may be re-imposed if it is deemed necessary by the Department to determine whether the source is in compliance with applicable regulations or permit conditions. (20.2.72 NMAC Sections 210.C and 213)

(2) Compliance tests shall be conducted within sixty (60) days after the unit(s) achieve the maximum normal production rate. If the maximum normal production rate does not occur within one hundred twenty (120) days of source startup, then the tests must be conducted no later than one hundred eighty (180) days after initial startup of the source.

(3) Unless otherwise indicated by Specific Conditions or regulatory requirements, the default time period for each test run shall be **at least** 60 minutes and each

performance test shall consist of three separate runs using the applicable test method. For the purpose of determining compliance with an applicable emission limit, the arithmetic mean of results of the three runs shall apply. In the event that a sample is accidentally lost or conditions occur in which one of the three runs must be discontinued because of forced shutdown, failure of an irreplaceable portion of the sample train, extreme meteorological conditions, or other circumstances, beyond the owner or operator's control, compliance may, upon the Department approval, be determined using the arithmetic mean of the results of the two other runs.

(4) Testing of emissions shall be conducted with the emissions unit operating at 90 to 100 percent of the maximum operating rate allowed by the permit. If it is not possible to test at that rate, the source may test at a lower operating rate, subject to the approval of the Department.

(5) Testing performed at less than 90 percent of permitted capacity will limit emission unit operation to 110 percent of the tested capacity until a new test is conducted.

(6) If conditions change such that unit operation above 110 percent of tested capacity is possible, the source must submit a protocol to the Department within 30 days of such change to conduct a new emissions test.

B. EPA Reference Method Tests

(1) All compliance tests required by this permit, unless otherwise specified by Specific Conditions of this permit, shall be conducted in accordance with the requirements of CFR Title 40, Part 60, Subpart A, General Provisions, and the following EPA Reference Methods as specified by CFR Title 40, Part 60, Appendix A:

(a) Methods 1 through 4 for stack gas flowrate

(b) Method 5 for TSP

(c) Method 6C and 19 for SO_2

(d) Method 7E for NO_X (test results shall be expressed as nitrogen dioxide (NO_2) using a molecular weight of 46 lb/lb-mol in all calculations (each ppm of NO/NO_2 is equivalent to 1.194 x 10-7 lb/SCF)

(e) Method 9 for opacity

(f) Method 10 for CO

(g) Method 19 may be used in lieu of Methods 1-4 for stack gas flowrate upon approval of the Department. A justification for this proposal must be provided along with a contemporaneous fuel gas analysis (preferably on the day of the test) and a recent fuel flow meter calibration certificate (within the most recent quarter).

(h) Method 7E or 20 for Turbines per 60.335 or 60.4400

(i) Method 29 for Metals

(j) Method 201A for filterable PM_{10} and $PM_{2.5}$

(k) Method 202 for condensable PM

(l) Method 320 for organic Hazardous Air Pollutants (HAPs)

(m) Method 25A for VOC reduction efficiency

(n) Method 30B for Mercury

(2) Alternative test method(s) may be used if the Department approves the change

C. Periodic Monitoring and Portable Analyzer Requirements

(1) Periodic emissions tests (periodic monitoring) may be conducted in accordance with EPA Reference Methods or by utilizing a portable analyzer. Periodic monitoring utilizing a portable analyzer shall be conducted in accordance with the requirements of ASTM D 6522-00. However, if a facility has met a previously approved Department criterion for portable analyzers, the analyzer may be operated in accordance with that criterion until it is replaced.

(2) Unless otherwise indicated by Specific Conditions or regulatory requirements, the default time period for each test run shall be **at least** 20 minutes.

Each performance test shall consist of three separate runs. The arithmetic mean of results of the three runs shall be used to determine compliance with the applicable emission limit.

(3) Testing of emissions shall be conducted in accordance with the requirements at Section B108.E.

(4) During emissions tests, pollutant, O_2 concentration and fuel flow rate shall be monitored and recorded. This information shall be included with the test report furnished to the Department.

(5) Pollutant emission rate shall be calculated in accordance with 40 CFR 60, Appendix A, Method 19 utilizing fuel flow rate (scf) and fuel heating value (Btu/scf) obtained during the test.

D. Test Procedures:

(1) The permittee shall notify the Department's Program Manager, Compliance and Enforcement Section at least thirty (30) days before the test date and allow a representative of the Department to be present at the test.

(2) Equipment shall be tested in the "as found" condition. Equipment may not be adjusted or tuned prior to any test for the purpose of lowering emissions, and then returned to previous settings or operating conditions after the test is complete.

(3) Contents of test notifications, protocols and test reports shall conform to the format specified by the Department's Universal Test Notification, Protocol and Report Form and Instructions. Current forms and instructions are posted to NMED's Air Quality web site under Compliance and Enforcement Testing.

(4) The permittee shall provide (a) sampling ports adequate for the test methods applicable to the facility, (b) safe sampling platforms, (c) safe access to sampling platforms and (d) utilities for sampling and testing equipment.

(5) The stack shall be of sufficient height and diameter and the sample ports shall be located so that a representative test of the emissions can be performed in accordance with the requirements of EPA Method 1 or ASTM D 6522-00 as applicable.

(6) Where necessary to prevent cyclonic flow in the stack, flow straighteners shall be installed

(7) Unless otherwise indicated by Specific Conditions or regulatory requirements, test reports shall be submitted to the Department no later than 30 days after completion of the test.

B112 <u>Compliance</u>

A. The Department shall be given the right to enter the facility at all reasonable times to verify the terms and conditions of this permit. Required records shall be organized by date and subject matter and shall at all times be readily available for inspection. The permittee, upon verbal or written request from an authorized representative of the Department who appears at the facility, shall immediately produce for inspection or copying any records required to be maintained at the facility. Upon written request at other times, the permittee shall deliver to the Department paper or electronic copies of any and all required records maintained on site or at an off-site location. Requested records shall be copied and delivered at the permittee's expense within three business days from receipt of request unless the Department allows additional time. Required records may include records required by permit and other information necessary to demonstrate compliance with terms and conditions of this permit. (NMSA 1978, Section 74-2-13)

B. A copy of the most recent permit(s) issued by the Department shall be kept at the permitted facility or (for unmanned sites) at the nearest company office and shall be made available to Department personnel for inspection upon request. (20.2.72.210.B.4 NMAC)

C. Emissions limits associated with the energy input of a Unit, i.e. lb/MMBtu, shall apply at all times unless stated otherwise in a Specific Condition of this permit. The averaging time for each emissions limit, including those based on energy input of a

Unit (i.e. lb/MMBtu) is one (1) hour unless stated otherwise in a Specific Condition of this permit or in the applicable requirement that establishes the limit.

B113 Permit Cancellation and Revocation

A. The Department may revoke this permit if the applicant or permittee has knowingly and willfully misrepresented a material fact in the application for the permit. Revocation will be made in writing, and an administrative appeal may be taken to the Secretary of the Department within thirty (30) days. Appeals will be handled in accordance with the Department's Rules Governing Appeals From Compliance Orders.

B. The Department shall automatically cancel any permit for any source which ceases operation for five (5) years or more, or permanently. Reactivation of any source after the five (5) year period shall require a new permit. (20.2.72 NMAC)

C. The Department may cancel a permit if the construction or modification is not commenced within two (2) years from the date of issuance or if, during the construction or modification, work is suspended for a total of one (1) year. (20.2.72 NMAC)

B114 Notification to Subsequent Owners

A. The permit and conditions apply in the event of any change in control or ownership of the Facility. No permit modification is required in such case. However, in the event of any such change in control or ownership, the permittee shall notify the succeeding owner of the permit and conditions and shall notify the Department's Program Manager, Permits Section of the change in ownership within fifteen (15) days of that change. (20.2.72.212.C NMAC)

B. Any new owner or operator shall notify the Department's Program Manager, Permits Section, within thirty (30) days of assuming ownership, of the new owner's or operator's name and address. (20.2.73.200.E.3 NMAC)

B115 Asbestos Demolition

A. Before any asbestos demolition or renovation work, the permittee shall determine whether 40 CFR 61 Subpart M, National Emissions Standards for Asbestos applies. If required, the permittee shall notify the Department's Program Manager, Compliance and Enforcement Section using forms furnished by the Department.

B116 Short Term Engine Replacement

A. The following Alternative Operating Scenario (AOS) addresses engine breakdown or periodic maintenance and repair, which requires the use of a short term replacement engine. The following requirements do not apply to engines that are exempt per 20.2.72.202.B(3) NMAC. Changes to exempt engines must be reported in accordance with 20.2.72.202.B NMAC. A short term replacement engine may be substituted for any engine allowed by this permit for no more than 120 days in any rolling twelve month period per permitted engine. The compliance demonstrations required as part of this AOS are in addition to any other compliance demonstrations required by this permit.

(1) The permittee may temporarily replace an existing engine that is subject to the emission limits set forth in this permit with another engine regardless of manufacturer, model, and horsepower without modifying this permit. The permittee shall submit written notification to the Department within 15 days of the date of engine substitution according to condition B110.C(1).

(a) The potential emission rates of the replacement engine shall be determined using the replacement engine's manufacturer specifications and shall comply with the existing engine's permitted emission limits.

(b) The direction of the exhaust stack for the replacement engine shall be either vertical or the same direction as for the existing engine. The replacement engine's stack height and flow parameters shall be at least as effective in the dispersion of air pollutants as the modeled stack height and flow parameters for the existing permitted engine. The following equation may be used to show that the replacement engine disperses pollutants as well as the existing engine. The value calculated for the replacement engine on the right side of the equation shall be equal to or greater than the value for the existing engine on the left side of the equation. The permitting page of the Air Quality Bureau website contains a spreadsheet that performs this calculation.

EXISTING ENGINE REPLACMENT ENGINE

$$\frac{[(g) \times (h1)] + [(v1)^2/2] + [(c) \times (T1)]}{q1} <= \frac{[(g) \times (h2)] + [(v2)^2/2] + [(c) \times (T2)]}{q2}$$

Where
g = gravitational constant = 32.2 ft/sec^2
h1 = existing stack height, feet
v1 = exhaust velocity, existing engine, feet per second
c = specific heat of exhaust, 0.28 BTU/lb-degree F
T1 = absolute temperature of exhaust, existing engine = degree F + 460

q1 = permitted allowable emission rate, existing engine, lbs/hour
h2 = replacement stack height, feet
v2 = exhaust velocity, replacement engine, feet per second
T2 = absolute temperature of exhaust, replacement engine = degree F + 460
q2 = manufacturer's potential emission rate, replacement engine, lbs/hour

The permittee shall keep records showing that the replacement engine is at least as effective in the dispersion of air pollutants as the existing engine.

(c) Test measurement of NOx and CO emissions from the temporary replacement engine shall be performed in accordance with Section B111 with the exception of Condition B111A(2) and B111B for EPA Reference Methods Tests or Section B111C for portable analyzer test measurements. Compliance test(s) shall be conducted within fifteen (15) days after the unit begins operation, and records of the results shall be kept according to section B109.B. This test shall be performed even if the engine is removed prior to 15 days on site.

i. These compliance tests are not required for an engine certified under 40CFR60, subparts IIII, or JJJJ, or 40CFR63, subpart ZZZZ if the permittee demonstrates that one of these requirements causes such engine to comply with all emission limits of this permit. The permittee shall submit this demonstration to the Department within 48 hours of placing the new unit into operation. This submittal shall include documentation that the engine is certified, that the engine is within its useful life, as defined and specified in the applicable requirement, and shall include calculations showing that the applicable emissions standards result in compliance with the permit limits.

ii. These compliance tests are not required if a test was conducted by portable analyzer or by EPA Method test (including any required by 40CFR60, subparts IIII and JJJJ and 40CFR63, subpart ZZZZ) within the last 12 months. These previous tests are valid only if conducted at the same or lower elevation as the existing engine location prior to commencing operation as a temporary replacement. A copy of the test results shall be kept according to section B109.B.

(d) Compliance tests for NOx and CO shall be conducted if requested by the Department in writing to determine whether the replacement engine is in compliance with applicable regulations or permit conditions.

(e) Upon determining that emissions data developed according to B116.A.1(c) fail to indicate compliance with either the NOx or CO emission limits, the

permittee shall notify the Department within 48 hours. Also within that time, the permittee shall implement one of the following corrective actions:

i. The engine shall be adjusted to reduce NOx and CO emissions and tested per B116.A.1(c) to demonstrate compliance with permit limits.

ii. The engine shall discontinue operation or be replaced with a different unit.

(2) Short term replacement engines, whether of the same manufacturer, model, and horsepower, or of a different manufacturer, model, or horsepower, are subject to all federal and state applicable requirements, regardless of whether they are set forth in this permit (including monitoring and recordkeeping), and shall be subject to any shield afforded by this permit.

(3) The permittee shall maintain a contemporaneous record documenting the unit number, manufacturer, model number, horsepower, emission factors, emission test results, and serial number of any existing engine that is replaced, and the replacement engine. Additionally, the record shall document the replacement duration in days, and the beginning and end dates of the short term engine replacement.

(4) The permittee shall maintain records of a regulatory applicability determination for each replacement engine (including 40CFR60, subparts IIII and JJJJ and 40CFR63, subpart ZZZZ) and shall comply with all associated regulatory requirements.

B. Additional requirements for replacement of engines at sources that are major as defined in regulation 20.2.74 NMAC, Permits – Prevention of Significant Deterioration, section 7.AG. For sources that are major under PSD, the total cumulative operating hours of the replacement engine shall be limited using the following procedure:

(1) Daily, the actual emissions from the replacement engine(s) of each pollutant regulated by this permit for the existing engine shall be calculated and recorded.

(2) The sum of the total actual emissions since the commencement of operation of the replacement engine(s) shall not equal or exceed the significant emission rates in Table 2 of 20.2.74 NMAC, section 502 for the time that the replacement engine is located at the facility.

C. All records required by this section shall be kept according to section B109.

PART C MISCELLANEOUS

C100 Supporting On-Line Documents

A. Copies of the following documents can be downloaded from NMED's web site under Compliance and Enforcement or requested from the Bureau.

(1) Excess Emission Form (for reporting deviations and emergencies)

(2) Universal Stack Test Notification, Protocol and Report Form and Instructions

(3) SOP for Use of Portable Analyzers in Performance Tests

C101 Definitions

A. **"Daylight"** is defined as the time period between sunrise and sunset, as defined by the Astronomical Applications Department of the U.S. Naval Observatory. (Data for one day or a table of sunrise/sunset for an entire year can be obtained at http://aa.usno.navy.mil/. Alternatively, these times can be obtained from a Farmer's Almanac or from http://www.almanac.com/rise/).

B. **"Exempt Sources"** and **"Exempt Activities"** is defined as those sources or activities that are exempted in accordance with 20.2.72.202 NMAC. Note; exemptions are only valid for most 20.2.72 NMAC permitting actions.

C. **"Fugitive Emission"** means those emissions which could not reasonably pass through a stack, chimney, vent, or other functionally equivalent opening.

D. **"Insignificant Activities"** means those activities which have been listed by the department and approved by the administrator as insignificant on the basis of size, emissions or production rate. Note; insignificant activities are only valid for 20.2.70 NMAC permitting actions.

E. **"Malfunction"** for the requirements under 20.2.7 NMAC, means any sudden and unavoidable failure of air pollution control equipment or process equipment beyond the control of the owner or operator, including malfunction during startup or shutdown. A failure that is caused entirely or in part by poor maintenance, careless operation, or any other preventable equipment breakdown shall not be considered a malfunction. (20.2.7.7.E NMAC)

F. **"Natural Gas"** is defined as a naturally occurring fluid mixture of hydrocarbons that contains 20.0 grains or less of total sulfur per 100 standard cubic feet (SCF) and is either composed of at least 70% methane by volume or has a gross calorific value of between 950 and 1100 Btu per standard cubic foot. (40 CFR 60.631)

G. **"Natural Gas Liquids"** means the hydrocarbons, such as ethane, propane, butane, and pentane, that are extracted from field gas. (40 CFR 60.631)

H. **"National Ambient air Quality Standards"** means, unless otherwise modified, the primary (health-related) and secondary (welfare-based) federal ambient air quality standards promulgated by the US EPA pursuant to Section 109 of the Federal Act.

I. **"Night"** is the time period between sunset and sunrise, as defined by the Astronomical Applications Department of the U.S. Naval Observatory. (Data for one day or a table of sunrise/sunset for an entire year can be obtained at http://aa.usno.navy.mil/. Alternatively, these times can be obtained from a Farmer's Almanac or from http://www.almanac.com/rise/).

J. **"Night Operation** or **Operation at Night"** is operating a source of emissions at night.

K. **"NO2"** or "Nitrogen dioxide" means the chemical compound containing one atom of nitrogen and two atoms of oxygen, for the purposes of ambient determinations. The term **"nitrogen dioxide,"** for the purposes of stack emissions monitoring, shall include nitrogen dioxide (the chemical compound containing one atom of nitrogen and two atoms of oxygen), nitric oxide (the chemical compound containing one atom of nitrogen and one atom of oxygen), and other oxides of nitrogen which may test as nitrogen dioxide and is sometimes referred to as NOx or NO_2. (20.2.2 NMAC)

L. **"NOx"** see NO_2

M. **"Paved Road"** is a road with a permanent solid surface that can be swept essentially free of dust or other material to reduce air re-entrainment of particulate matter. To the extent these surfaces remain solid and contiguous they qualify as paved roads: concrete, asphalt, chip seal, recycled asphalt and other surfaces approved by the Department in writing.

N. **"Potential Emission Rate"** means the emission rate of a source at its maximum capacity to emit a regulated air contaminant under its physical and operational design, provided any physical or operational limitation on the capacity of the source to emit a regulated air contaminant, including air pollution control equipment and restrictions on hours of operation or on the type or amount of material combusted, stored or processed, shall be treated as part of its physical and operational design only if the limitation or the effect it would have on emissions is enforceable by the department pursuant to the Air Quality Control Act or the federal Act.

O. **"Restricted Area"** is an area to which public entry is effectively precluded. Effective barriers include continuous fencing, continuous walls, or other continuous barriers approved by the Department, such as rugged physical terrain with a steep grade that would require special equipment to traverse. If a large property is completely

enclosed by fencing, a restricted area within the property may be identified with signage only. Public roads cannot be part of a Restricted Area.

P. **"Shutdown"** for requirements under 20.2.72 NMAC, means the cessation of operation of any air pollution control equipment, process equipment or process for any purpose, except routine phasing out of batch process units.

Q. **"SSM"** for requirements under 20.2.7 NMAC, means routine or predictable startup, shutdown, or scheduled maintenance.

(1) **"Shutdown"** for requirements under 20.2.7 NMAC, means the cessation of operation of any air pollution control equipment or process equipment.

(2) **"Startup"** for requirements under 20.2.7 NMAC, means the setting into operation of any air pollution control equipment or process equipment.

R. **"Startup"** for requirements under 20.2.72 NMAC, means the setting into operation of any air pollution control equipment, process equipment or process for any purpose, except routine phasing in of batch process units.

C102 Acronyms

2SLB ..... 2-stroke lean burn
4SLB ..... 4-stroke lean burn
4SRB ..... 4-stroke rich burn
acfm ..... actual cubic feet per minute
AFR ..... air fuel ratio
AP-42 ..... EPA Air Pollutant Emission Factors
AQB ..... Air Quality Bureau
AQCR ..... Air Quality Control Region
ASTM ..... American Society for Testing and Materials
Btu ..... British thermal unit
CAA ..... Clean Air Act of 1970 and 1990 Amendments
CEM ..... continuous emissions monitoring
cfh ..... cubic feet per hour
cfm ..... cubic feet per minute
CFR ..... Code of Federal Regulation
CI ..... compression ignition
CO ..... carbon monoxides
COMS ..... continuous opacity monitoring system
EIB ..... Environmental Improvement Board
EPA ..... United States Environmental Protection Agency
gr/100 cf ..... grains per one hundred cubic feet
gr/dscf ..... grains per dry standard cubic foot
GRI ..... Gas Research Institute

HAP ..... hazardous air pollutant
hp ..... horsepower
H_2S ..... hydrogen sulfide
IC ..... internal combustion
KW/hr ..... kilowatts per hour
lb/hr ..... pounds per hour
lb/MMBtu ..... pounds per million British thermal unit
MACT ..... Maximum Achievable Control Technology
MMcf/hr ..... million cubic feet per hour
MMscf ..... million standard cubic feet
N/A ..... not applicable
NAAQS ..... National Ambient Air Quality Standards
NESHAP ..... National Emission Standards for Hazardous Air Pollutants
NG ..... natural gas
NGL ..... natural gas liquids
NMAAQS ..... New Mexico Ambient Air Quality Standards
NMAC ..... New Mexico Administrative Code
NMED ..... New Mexico Environment Department
NMSA ..... New Mexico Statues Annotated
NOx ..... nitrogen oxides
NSCR ..... non-selective catalytic reduction
NSPS ..... New Source Performance Standard
NSR ..... New Source Review
PEM ..... parametric emissions monitoring
PM ..... particulate matter (equivalent to TSP, total suspended particulate)
PM_{10} ..... particulate matter 10 microns and less in diameter
$PM_{2.5}$ ..... particulate matter 2.5 microns and less in diameter
pph ..... pounds per hour
ppmv ..... parts per million by volume
PSD ..... Prevention of Significant Deterioration
RATA ..... Relative Accuracy Test Assessment
RICE ..... reciprocating internal combustion engine
rpm ..... revolutions per minute
scfm ..... standard cubic feet per minute
SI ..... spark ignition
SO_2 ..... sulfur dioxide
SSM ..... Startup Shutdown Maintenance (see SSM definition)
TAP ..... Toxic Air Pollutant
TBD ..... to be determined
THC ..... total hydrocarbons
TSP ..... Total Suspended Particulates
tpy ..... tons per year
ULSD ..... ultra low sulfur diesel
USEPA ..... United States Environmental Protection Agency

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Exhibit B

FDA STATEMENT

Statement on concerns with medical device availability due to certain sterilization facility closures

For Immediate Release:

October 25, 2019

Statement From:

Norman E. "Ned" Sharpless MD

As the agency responsible for ensuring the safety and effectiveness of all medical devices, the U.S. Food and Drug Administration has been closely monitoring the supply chain effects of closures and potential closures of certain large-scale sterilization facilities that use a gas called ethylene oxide (/medical-devices/general-hospital-devices-and-supplies/ethylene-oxide-sterilization-medical-devices) to sterilize medical devices prior to their use. The recent closure of a Sterigenics ethylene oxide sterilization facility in Illinois, the temporary closure of another Sterigenics facility in Georgia, and the potential closure of a large Becton Dickinson sterilization facility in Georgia could affect the availability of some sterile medical devices used by health care delivery organizations and patients. We have been working diligently with impacted device manufacturers and health care delivery organizations to ensure that they are aware of these developments and preparing to minimize adverse effects on patients whose care could be negatively affected if medical devices sterilized at these large facilities were not accessible. Medical devices that are sterilized to remove potentially harmful germs and other microorganisms prior to use are critical to our health care system and a shortage—especially of life-saving, life-sustaining, or other critical devices—can be a detriment to public health. In light of the possibility of continued ethylene oxide sterilization facility closures, we are again alerting the public to growing concerns about the future availability of sterile medical devices and impending medical device shortages.

Although medical devices can be sterilized by several methods, ethylene oxide is the most common method of sterilization of medical devices in the U.S. and is a well-established and scientifically-proven method of preventing harmful microorganisms from reproducing and causing infections. More than 20 billion devices sold in the U.S. every year are sterilized with ethylene oxide, accounting for approximately 50 percent of devices that require sterilization.

Medical devices made from certain polymers (such as plastic or resin), metals, or glass—or devices that have multiple layers of packaging or hard-to-reach crevices—are likely to be sterilized with ethylene oxide to avoid product damage during the process. These include surgical kits used in emergency procedures such as emergency Caesarean sections ("C-sections") and in routine procedures such as cardiac surgery and hip or knee replacement surgeries. Without adequate availability of ethylene oxide sterilization, we anticipate a national shortage of these devices and

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other critical devices including feeding tube devices used in neonatal intensive care units, drug-eluting cardiac stents, catheters, shunts and other implantable devices. It's important to note at this time there are no readily available processes or facilities that can serve as viable alternatives to those that use ethylene oxide to sterilize these devices. In short: this method is critical to our health care system and to the continued availability of safe, effective and high-quality medical devices.

The FDA recognizes that there are concerns associated with release of ethylene oxide into the environment if emissions were to occur at unsafe levels. Concerns about ethylene oxide emissions have resulted in certain state actions against sterilization facilities that are currently impacting manufacturers' ability to use the ethylene oxide process to sterilize their medical devices. In February, the FDA became aware that the Illinois Environmental Protection Agency (EPA) issued a state EPA Order (https://www2.illinois.gov/Pages/news-item.aspx?ReleaseID=19717) to stop Sterigenics from sterilizing medical products and other products with ethylene oxide at their Willowbrook, Illinois, facility. The state EPA order was due to the presence of levels of ethylene oxide higher than the EPA found to be acceptable in the air around the facility. This closure caused a temporary shortage (/news-events/press-announcements/statement-jeff-shuren-md-director-center-devices-and-radiological-health-agency-efforts-mitigate) of pediatric breathing tubes.

Another Sterigenics contract sterilization facility, in Atlanta, Georgia, has been closed since August while it undergoes construction to reduce ethylene oxide emissions. In October, the Sterigenics Willowbrook, Illinois, facility announced they would not reopen. As a consequence of these two large sterilization facilities being unavailable, the FDA continues to coordinate with multiple stakeholders on any impacts to medical device availability and to communicate with Sterigenics and medical device companies that may be affected. Because the number of ethylene oxide contract sterilization facilities in the U.S. is limited, we are very concerned that additional facility closures could severely impact the supply of sterile medical devices to health care delivery organizations that depend on those devices to take care of patients. The impact resulting from closure of these and perhaps more facilities will be difficult to reverse, and ultimately could result in years of spot or nationwide shortages of critical medical devices, which could compromise patient care.

This is why today we are urging medical device manufacturers that use ethylene oxide facilities to assess their inventory for any potential downstream impacts of sterilization facility closures on their product distribution. We are committed to working with manufacturers to look for alternative sterilization options. When manufacturers keep the FDA apprised of progress and obstacles encountered, it helps ensure that everyone's best efforts are being made to mitigate any shortages and prevent potential shortages. When U.S. manufacturers are not able to resolve a shortage and it involves a critical device needed for U.S. patients, the FDA may look for a firm that is willing and able to redirect safe and effective product into the U.S. market to address a shortage.

We also encourage health care facilities to perform similar inventory assessments of critical medical supplies that undergo contract terminal sterilization via ethylene oxide prior to shipping and reach out to the FDA so we can assist in any way we can to help identify sources of potential substitute devices. Hospitals and other health care delivery organizations should also work with their

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purchasing departments, group purchasing organizations and distributors, as appropriate, to help obtain product needed for patient care. So as to not exacerbate anticipated product availability concerns, we urge facilities to work together and not hoard product or attempt to purchase larger quantities of devices beyond their normal purchase volume.

We also encourage device manufacturers and health care providers to provide (/vaccines-blood-biologics/safety-availability-biologics/how-report-product-shortage-or-supply-issue-fda) us with information on potential supply issues. We have a device shortages mailbox (mailto:deviceshortages@fda.hhs.gov) so that any user, patient, manufacturer, or organization within the supply chain that is aware of a delay in distribution of new product, and/or anticipates a shortage, can notify us. It's never too early to contact us – the sooner we are aware of a potential shortage, the better we can assist in proactively developing a plan to mitigate its effects on patient care.

Since we first became aware of this issue earlier this year, we have continued to focus intently on addressing the immediate impacts of these closures and potential closures to help ensure patients can have access to the safe, effective, and high-quality medical devices they need today. We continue to communicate directly with manufacturers and monitor the supply of devices sterilized in facilities that have closed or that may close, paying special attention to life-saving, life-sustaining, and other critical devices. For instance, in the case of Smiths Medical's Bivona tracheostomy breathing tubes that were processed at the now-closed Sterigenics facility in Illinois, we helped mitigate that shortage by helping the manufacturer get a timely site change that kept supply interruptions to a minimum.

We share the public's objective to reduce over-reliance on ethylene oxide for medical device sterilization. And therefore, in addition to our shortage mitigation efforts, we have also been addressing the broader need for innovation and improvements to medical device sterilization techniques in general. For example, earlier this year we announced two new innovation challenges (/news-events/fda-voices-perspectives-fda-leadership-and-experts/preventing-medical-device-shortages-ensuring-safe-and-effective-sterilization-manufacturing) to encourage ideas from stakeholders, academics, industry and others about novel solutions for improving sterilization processes. This includes a call to identify new or alternative sterilization methods and technologies that are alternatives to those that use ethylene oxide, and another to develop new strategies to reduce ethylene oxide emissions.

In addition, we've previously announced we're holding a public advisory committee meeting (/advisory-committees/advisory-committee-calendar/november-6-7-2019-general-hospital-and-personal-use-devices-panel-medical-devices-advisory-committee) on November 6 and 7, 2019, dedicated to discussing how best to encourage innovation in medical device sterilization. We also continue to collaborate with the U.S. EPA, the entity responsible for reviewing and enforcing Clean Air Act regulations for sterilization facilities that emit ethylene oxide to ensure that facilities protect the public from significant risks, providing the U.S. EPA with updates on FDA activities in this area. And we'll continue to update stakeholders and the public as new information becomes available.

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We want to be clear that we understand that there are very real consequences that medical device shortages have on patients, and we're committed to doing everything in our authority to help mitigate the adverse patient impact these sterilization facility closures are expected to have. We're also calling on all stakeholders—manufacturers, contract sterilizers, government agencies and other public health advocates—to join us and do your part to avert new device shortages and ensure patients have access to important and life-saving medical devices.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

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Related Information

- FDA: Ethylene Oxide Sterilization for Medical Devices (/medical-devices/general-hospital-devices-and-supplies/ethylene-oxide-sterilization-medical-devices)
- FDA: Ethylene Oxide Sterilization Facility Updates (/medical-devices/general-hospital-devices-and-supplies/ethylene-oxide-sterilization-facility-updates)

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Exhibit C

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Ethylene oxide review: characterization of total exposure via endogenous and exogenous pathways and their implications to risk assessment and risk management

CR Kirman , AA Li , PJ Sheehan , JS Bus , RC Lewis & SM Hays

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Ethylene oxide review: characterization of total exposure via endogenous and exogenous pathways and their implications to risk assessment and risk management

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ABSTRACT
This review is intended to provide risk assessors and risk managers with a better understanding of issues associated with total exposures of human populations to ethylene oxide from endogenous and exogenous pathways. Biomonitoring of human populations and lab animals exposed to ethylene oxide has relied upon the detection of hemoglobin adducts such as 2-hydroxyethylvaline (HEV), which provides a useful measure of total exposure to ethylene oxide from all pathways. Recent biomonitoring data from CDC provide an excellent characterization of total exposure to ethylene oxide to the general U.S. population by demographic factors such as age, gender, and race as well as smoking habit, which might be comparable to previous measurements reported for humans and lab animals. The biochemical pathways including gastrointestinal (production by bacteria) and systemic (enzymatic production) pathways by which endogenous ethylene is generated and converted to ethylene oxide are described. The relative importance of endogenous pathways and exogenous pathways via ambient air or tobacco smoke was quantified based upon available data to characterize their relative importance to total exposure. Considerable variation was noted for HEV measurements in human populations, and important sources of variation for all pathways are discussed. Issues related to risk assessment and risk management of human populations exposed to ethylene oxide are provided within the context of characterizing total exposure, and data needs for supporting future risk assessment identified.

KEYWORDS
Biomarkers; Risk Assessment; Hemoglobin Adducts; Endogenous Exposure

Introduction

Ethylene oxide is a reactive epoxide that is used in the manufacture of chemicals including ethylene glycol, glycol ethers, ethanolamines, ethoxylates and acrylonitrile and in the sterilization of materials such as foods, spices, and medical equipment. For decades, ethylene oxide was recognized as an animal carcinogen based upon observations of increased tumor rates in highly exposed mice and rats (Lynch et al. 1984; NTP, 1987; Snellings, Weil, and Maronpot 1984). The results of epidemiology studies, however, have been inconclusive. Increases in certain types of cancers were reported in a large study of sterilant workers (2004; Steenland et al. 2003); but these elevations were not seen consistently in other studies, including in a more heavily exposed cohort of chemical workers, followed over an extended time period (Marsh et al. 2019; Swaen et al. 2009). USEPA (2016) reassessed the cancer potency of ethylene oxide on its IRIS database resulting in the derivation of a unit risk value (a quantitative estimate of cancer potency) that is approximately 50-fold higher (i.e. more potent) than its preceding value. This large change in cancer potency estimated for ethylene oxide has initiated changes in its regulation such as the amount that can be released from facilities that produce or use ethylene oxide and the level of exposure considered acceptable. This has also resulted in enhanced public attention and concern over the potential adverse health effects associated with exposures at or near facilities that use ethylene oxide (Hogue 2019; Olaguer et al. 2019).

There are multiple ways in which individuals might be exposed to ethylene oxide. First, ethylene oxide is produced in the body from endogenous ethylene via multiple pathways such as bacterial production in the gastrointestinal tract or systemic formation in the liver. For this reason, all individuals have some exposure to ethylene oxide regardless of their exogenous exposures to ethylene oxide in air (Swenberg et al. 2011; Thier and Bolt, 2000). Second, ethylene oxide is metabolically generated in the body following exposures to exogenous

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ethylene from a variety of sources including incomplete combustion of cigarette smoke and vehicle fossil fuels, and natural processes including forest fires, ripening of fruits and vegetables and volcanoes (Artati 2010; Fennell et al. 2004; Filser and Klein 2018; Morgott 2015; Health Canada 2016). Third, ethylene oxide and ethylene are components of tobacco smoke, and therefore smokers and nonsmokers have different exposure profiles to ethylene oxide (Törnqvist et al. 1986a; Tates et al. 1991; Tavares et al. 1994; Farmer, Cordero, and Autrup 1996a; 1996b; Müller et al. 1998; Bono et al. 1999, 2002; Fennell et al. 2000; Wu et al. 2004; Baren et al. 2004; CDC, 2019). Fourth, some workers are exposed to elevated concentrations of ethylene oxide in workplace air (Angerer, Bader, and Krämer 1998; Boogaard, Rocchi, and van Sittert 1999; Tates et al. 1991; van Sittert et al. 1993; Yong et al. 2001). Fifth, some populations near industrial or sterilization facilities are also exposed to elevated levels of ethylene oxide in air as a result of emissions (Olaguer et al. 2019). Finally, additional pathways such as dietary exposures to ethylene (a plant hormone) present in fruits, vegetables, and grains are also possible (Larsen 2015; Yin et al. 2017; Iqbal et al. 2013; Morgott 2015; Health Canada 2016). All of these pathways contribute to total exposure to ethylene oxide, but their relative importance to human populations and to individuals is both variable and uncertain.

The measurement of hemoglobin adducts, specifically 2-hydroxyethylvaline (HEV), serves as a useful biomarker for characterizing total exposure to ethylene oxide from all exposure pathway(s) including exogenous ethylene oxide, exogenous ethylene, endogenous ethylene oxide (Bailey, Farmer, and Shuker 1987; Boogaard, Rocchi, and van Sittert 1999; Kirman and Hays 2017; Swenberg et al. 2011; Yong et al. 2001). Because hemoglobin adducts are stable and cumulative, HEV measurements reflect exposures to ethylene oxide from all pathways over several months preceding sample collection/measurement. Since the potential risks of ethylene oxide are expected to be proportionate to total exposure (i.e. aggregated across all pathways), characterization of total exposure is important to risk assessment and risk management decisions.

The goals of this review are the following to:

(1) provide a characterization of total ethylene oxide exposure (exogenous + endogenous) in human populations;

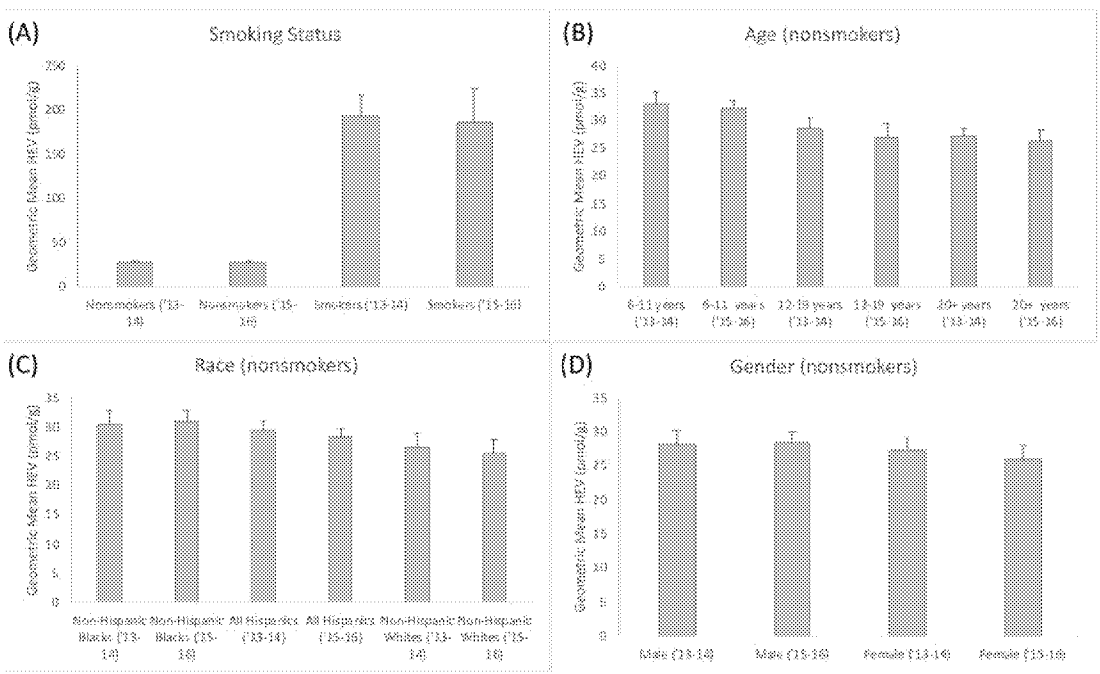

Figure 1. HEV Levels (pmol/g hemoglobin) in the U.S. Population (n = 4,777) by Demographic Strata for Two Sampling Periods (2013–4, 2015–6; Center for Disease Control (CDC) 2019): (a) Smoking Status; (b) Age (nonsmokers only); (c) Race (nonsmokers only); and (d) Gender (nonsmokers only). Columns indicate the geometric mean values as calculated by Center for Disease Control (CDC) (2019), error bars indicate standard deviations.

Table 1. Summary of HEV levels (Arithmetic mean values) reported in human populations.

				HEV Levels (pmol/g Hb)		Endogenous Equivalent Concentration in Air (ppb, continuous) [b]	
Source	Year	Population	Sample Size	Mean[a]	SD (CV)	Mean[a]	SD
Kirman and Hays (2017)	1986–2012	Nonsmokers	661	21.1	14.6 (69%)	1.9	1.3
		Smokers	379	205.4	193.3 (94%)	18.8	17.7
CDC NHANES (2019)	Combined 2013–2016	Nonsmokers[c]	3,841	31.4	24.8 (79%)	2.9	2.3
		Smokers[c]	936	236	220 (93%)	21.7	20.2
		Combined	4,777	75.7	131 (173%)	6.9	12.0

[a]Arithmetic mean values, based on weighted data, are presented here rather than the geometric mean values calculated by CDC in Figure 1, since arithmetic means are typically used to quantify exposures in human health risk assessment.
[b]Calculated using *Eq.1* (see text).
[c]Defined using serum cotinine: nonsmokers≤10 ng/mL; smokers>10 ng/mL.

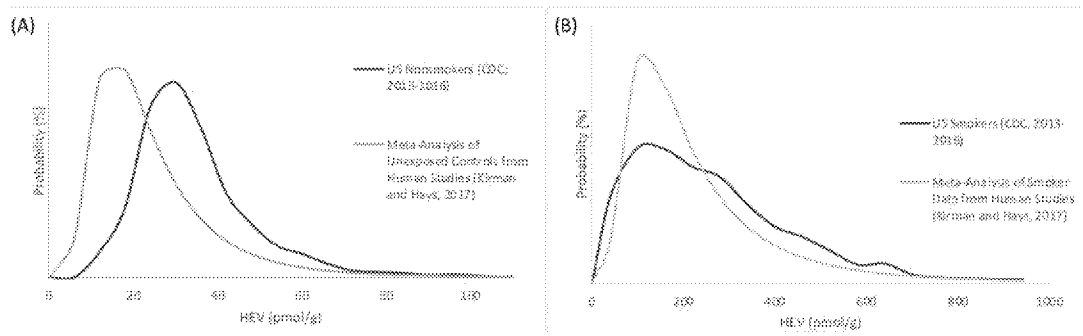

Figure 2. Distribution of HEV Levels in Human Populations: (a) Nonsmokers; (b) Smokers.

(2) summarize the biochemical pathways that contribute to endogenous exposures;
(3) identify and characterize sources of variation in measured HEV levels in human populations;
(4) identify and address key questions pertaining to the potential risks associated with ethylene oxide exposures;
(5) update the estimates of endogenous action levels derived previously for ethylene oxide (Kirman and Hays 2017) and evaluate their utility in interpreting general population exposures to ethylene oxide; and
(6) identify potential data needs for future risk assessment/risk management of ethylene oxide.

Characterization of HEV levels in humans and lab animals

HEV levels in human populations

The Centers for Disease Control (Center for Disease Control (CDC) 2019) recently released biomonitoring data for HEV concentrations in the general U.S. population collected over two sampling periods (2013–14, 2015–16) (Figure 1). These data demonstrated there are differences in HEV levels (and therefore total ethylene oxide exposure), depending upon smoking status (Figure 1a), age, and gender. Among nonsmokers, a decreasing trend with age is observed across age groups (Figure 1b), and non-significant differences were noted across race (Figure 1c) and gender (Figure 1d). There are known genetic polymorphisms and differences in ontogenesis for enzyme systems that contribute to ethylene oxide formation (cytochrome P450 2E1) and metabolic clearance (glutathione-S-transferases, epoxide hydrolase) that may help explain some of the differences in HEV levels in demographic subgroups (London, Smart, and Daly 2000; Saghir, Khan, and McCoy 2012; Worhhoudt et al., 1999; Yoshikawa et al. 2000).

For comparison purposes, Kirman and Hays (2017) conducted a meta-analysis of data from the published literature for HEV in human populations (exposed and unexposed samples). As a result of this analysis, a distribution for HEV burden was characterized assuming a lognormal distribution from a total sample of 661 nonsmokers and 379 smokers (Table 1). Similar to the findings of Kirman and Hays (2017), HEV levels reported by CDC (2019) are nearly an order of

Table 2. Summary of HEV levels reported in laboratory animal control groups.

Species	Strain	n	Mean (pmol/g Hb)[a]	SD (pmol/g Hb)(CV)	Reference
Rat	F344	5	42	18 (43%)	Walker et al. (1993)
	F344	7	50	10 (20%)	Walker et al. (2000)
	F344	21	440[b]	458[b]	Rusyn et al. (2005)
	SD	3–8	25	3 (12%)	Eide et al. (1995)
	Lewis	3	45	8 (18%)	Van Sittert et al. (2000)
Mouse	B6C3F1	5	58	22 (38%)	Walker et al. (1993)
	B6C3F1	7	100	10 (10%)	Walker et al. (2000)
	CBA	5 (pooled samples)	29	6.8[c]	Tornqvist et al. (1989)
	CBA	Unspecified (pooled samples)	8.3–8.7	0.2–0.4[c]	Kautiainen et al. (1991)
	CBA	5 (pooled samples)	21.7	1.4[c]	Kautiainen et al. (1993)

[a]Arithmetic mean
[b]Values appear elevated compared to other data sets collected for the same species/strain, and were excluded from the pooled data set. CV not calculated.
[c]Use of pooled samples is expected to underestimate interindividual variation. CV not calculated.

magnitude higher in smokers compared to nonsmokers (Table 1).

A comparison of the distribution of HEV levels in unexposed control subjects (Kirman and Hays 2017) and in the U.S. nonsmokers from the Center for Disease Control (CDC) (2019) data is provided in Table 1 and Figure 2a. This comparison shows the HEV distribution described by Kirman and Hays (2017) based upon pooled control data tended to underestimate the distribution in the U.S. as characterized by Center for Disease Control (CDC) (2019). The arithmetic mean HEV level reported by Kirman and Hays (2017) was approximately 70% of that calculated for the combined Center for Disease Control (CDC) (2019) periods. However, the coefficients of variation (CV) for Kirman and Hays (2017) and Center for Disease Control (CDC) (2019) are both large and similar (70% and 80% respectively) indicating moderately high variability in HEV levels in nonsmokers. The difference in the two distributions may be explained in part by variations in demographics, which is expected to exhibit a greater degree of variation with respect to age, race, and gender in

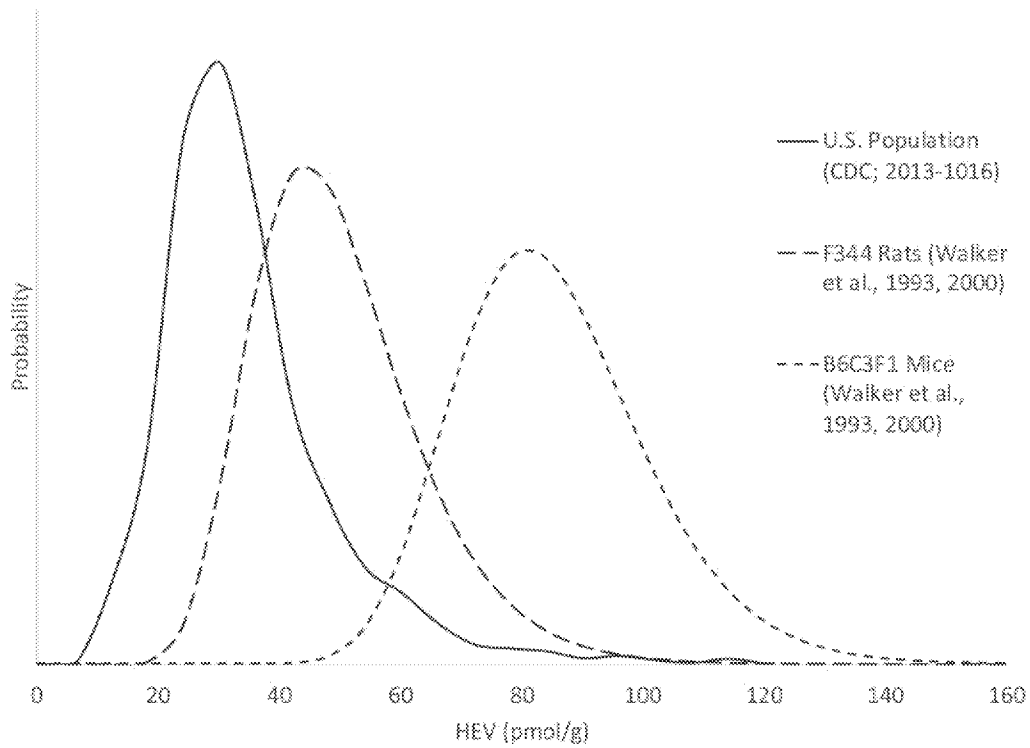

Figure 3. Comparison of Background HEV Distributions in Humans (Center for Disease Control (CDC) 2019), F344 Rats, and B6C3F1 Mice (Walker et al. 1993, 2000).

the more diverse CDC dataset. Geographical difference may also play a role in the observed differences, as the majority of studies used by Kirman and Hays (2017) measured adducts in subjects outside the U.S. (primarily Europe), whereas the Center for Disease Control (CDC) (2019) data are exclusively from within the U.S. In addition, some difference may be attributable to differences in analytical methods, which primarily relied upon GC-MS (using EI or NCI ionization mode) in the studies analyzed by Kirman and Hays (2017), whereas Center for Disease Control (CDC) (2019) relied upon HPLC-MS/MS (using APCI, positive ion mode). The CDC measurements rely on one analytical method performed by a single lab, whereas the Kirman and Hays (2017) distribution reflects data from publications from different investigators using differing analytical methods. In contrast, the distributions defined for smokers are fairly similar between the pooled data of Kirman and Hays (2017) and the U.S. population as characterized by Center for Disease Control (CDC) (2019) (Table 1 and Figure 2b), with the former dataset exhibiting greater kurtosis than the latter. Both datasets demonstrate differences in HEV levels between smokers and nonsmokers by approximately an order of magnitude.

From this point forward, the Center for Disease Control (CDC) (2019) dataset for HEV from both sampling periods combined (Table 1) are considered to be the best representative dataset for characterizing HEV levels in the U.S. general population, and are used to support additional comparisons and analyses below. These HEV levels in human blood may be converted to endogenous equivalent (EE) levels of ethylene oxide based upon the following equation between HEV adduct levels and measured occupational exposures to ethylene oxide adjusted to general population exposures (Kirman and Hays 2017).

$$HEV(pmol/gHb) = 10.9 * [EO, ppb\ continuous] \quad (1)$$

Using this linear relationship, the arithmetic mean HEV level calculated for the U.S. general population from the Center for Disease Control (CDC) (2019) data (31.4 pmol/g Hb) corresponds to an equivalent air concentration of 2.9 ppb (Table 1). Other datasets are also available for characterizing the relationship between occupational exposures to ethylene oxide in air and HEV level (Boogaard, Rocchi, and van Sittert 1999; Brugnone et al. 1986; Duus et al. 1989; Hagmar et al. 1991; Norpoth and Bolt 1995; Törnqvist et al. 1986a), and are generally consistent with the correlation defined in Equation (1), within a factor of approximately 2. As discussed in greater detail below, although the HEV levels in blood are expressed as equivalent levels of exogenous ethylene oxide, these HEV levels in

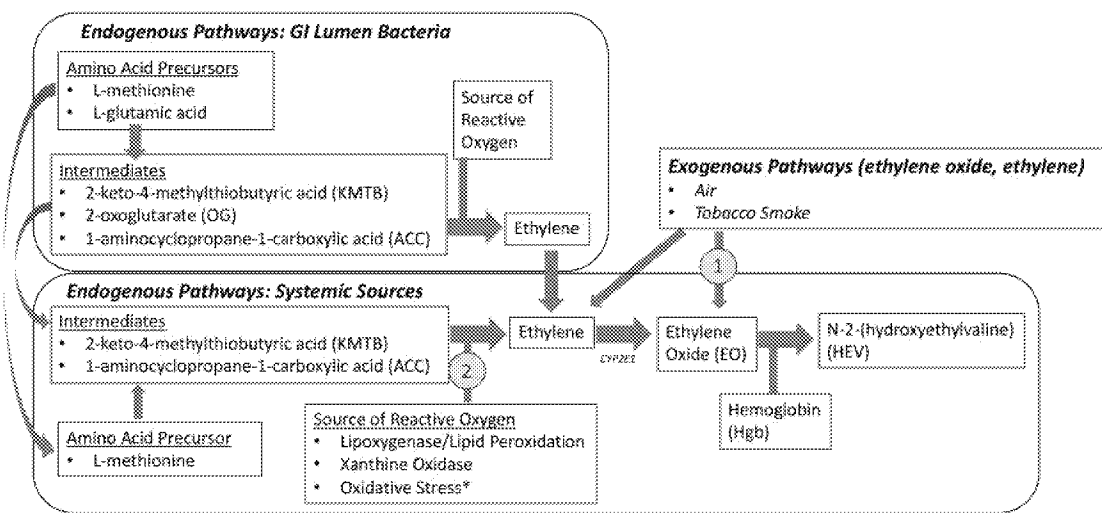

Figure 4. Endogenous and Exogenous Pathways of Ethylene/Ethylene Oxide Exposure. *Exogenous chemical exposures, including exposures to ethylene oxide (pathway 1), are also capable of increasing endogenous production of ethylene and ethylene oxide indirectly via oxidative stress (pathway 2; see discussion of Marsden et al. 2009).

nonsmokers are predominately attributed to endogenous levels (see pathway contribution discussion).

HEV levels in lab animals

The levels of HEV in unexposed lab animals have been fairly well characterized in the published literature (Table 2). In control rats, mean levels of HEV were reported to range from 25 to 50 pmol/g Hb, excluding the unexpectedly high value reported by Rusyn et al. (2005), with some evidence to support the observation of strain differences (Sprague-Dawley<Lewis~F344). In control mice, mean levels of HEV were noted to range from 8.3 to 100 pmol/g Hb, with evidence of differences across strain (CBA<B6C3F1).

For the purposes of comparing HEV levels across species, focus is placed here on the data collected in F344 rats and B6C3F1 mice by Walker et al. (1993); Walker et al. (2000), since these strains are typically used in studies to support human health risk assessment (i.e. bases for unit risk derivation), and these investigators characterized variation across individual animals, rather than relied upon pooled samples. Based on these data, pooled means and standard deviations for F344 rats and B6C3F1 mice were calculated to be 46.7 ± 13.7 (approximate CV 29%) pmol/g Hb and 82.5 ± 16.1 (approximate CV 20%) pmol/g Hb, respectively. Assuming HEV concentrations in control rats and mice are lognormally distributed, a graphical comparison of these distributions across species is provided in Figure 3.

Table 3. Bacterial species in the human gastrointestinal tract.

Bacterium in Human Large Intestines (Todar 2012)	Detection Frequency (%)	Ethylene Production Reported in Bacteria Species (Fukuda, Ogawa, and Tanase 1993; Mansouri and Bunch 1989)
Bacteroides fragilis	100	–
Bacteroides melaninogenicus	100	–
Bacteroides oralis	100	–
Lactobacillus	20–60	–
Clostridium perfringens	25–35	–
Clostridium septicum	5–25	–
Clostridium tetani	1–35	–
Bifidobacterium bifidum	30–70	–
Staphylococcus aureus	30–50	Y
Enterococcus faecalis	100	–
Escherichia coli	100	Y
Salmonella enteritidis	3–7	–
Klebsiella sp.	40–80	Y
Enterobacter sp.	40–80	Y
Proteus mirabilis	5–55	–
Pseudomonas aeruginosa	3–11	Y
Peptostreptococcus sp.	Common	–
Peptococcus sp.	Common	–

" – " = no data were located in the published literature for this strain.

Table 4. HEV levels in control and germ-free CBA mice (Törnqvist et al., 1986a)*.

HEV (pmol/g Hb)		
Control Animals	Germ-Free Animals	Difference
36	28	−22%
41	31	−24%
43	28	−35%
29	22	−24%
26	20	−23%
29	19	−34%
28	15	−46%
23	12	−48%
26	13	−50%
20	17	−15%
25	14	−44%
23	14	−39%
25	14	−44%
25	14	−44%
Mean Values		
29 ± 6.8	19 ± 6.3	−35 ± 11%

*Each row reflects a different replication, derivation, and/or analytical occasion based on pooled samples as reported by the study authors.

Because of species differences in erythrocyte lifetimes (humans approximate 120 days vs. rodents approximate 60 days), the difference in estimated circulating blood levels of ethylene oxide across species is even greater than depicted in Figure 3 for HEV levels (i.e. distribution for ethylene oxide in blood of humans would be shifted further to the left when compared to distribution for ethylene oxide in blood of rodents). The pattern observed across species for background HEV levels is consistent with known biological and biochemical processes (see discussion of pathways below). For example, the volume of gastrointestinal tract expressed as a fraction of body weight, which is expected to be proportionate to microbial contributions to HEV levels, is consistent with the observed pattern across species where gastrointestinal lumen volume in rodents > gastrointestinal lumen volume in humans when expressed as a fraction of body volume (Kirman et al. 2013, 2012). There is greater variety in the major taxa of bacteria present in the human gastrointestinal tract when compared to rats and mice (Hillman et al. 2017). With respect to systemic factors, the rate of oxidative metabolism of ethylene to ethylene oxide is consistent with this observed pattern (Vmax/Km in rodents > Vmax/Km in humans) (Filser and Klein 2018). Species differences in metabolic clearance of ethylene oxide are also apparent for both the epoxide hydrolase pathway (Vmax/Km in

Table 5. HEV levels in CBA mice fed diets with a differing fatty acid composition (Tornqvist et al., 1989)*.

HEV (pmol/g Hb)		
Sunflower Oil (~90% unsaturated FAs)	Lard (~60% unsaturated FAs)	Coconut Oil (~8% unsaturated FAs)
32	17	15
27	12	6
–	–	6
28	23	–
21	14	12
23	6	5
31	13	9
Mean Values (pmol/g Hb)		
27 ± 4.3	14 ± 5.6	8.8 ± 4.0

Each row reflects a different replication and/or derivation, pooled from 2–4 animals. "–" = samples were not analyzed or were contaminated.

humans > Vmax/Km in rodents) and for glutathione conjugation pathway (Vmax/Km in rodents > Vmax/Km in humans) (Filser and Klein 2018).

The moderately higher variability for HEV levels in humans (approximate CV 79%) reflects data collected from a genetically heterogenous population sample with different diets, health conditions, and potential exposures to ethylene oxide in air. In contrast, less variation for HEV levels in rodents (approximate CV 19–29%) reflects data from a genetically homogenous population sample consuming the same diet, where exogenous sources of ethylene and ethylene oxide are expected to be negligible under controlled lab conditions.

Pathways contributing to measured HEV levels

The HEV levels detected in blood discussed above serve as measures of total exposure, which reflect combined contributions of endogenous and exogenous exposures pathways for ethylene oxide and ethylene. These pathways are depicted in Figure 4 and discussed below.

Endogenous pathways for ethylene oxide production

Endogenous production of ethylene and ethylene oxide in lab animals and humans includes pathways originating from gastrointestinal lumen (bacterial pathways) and systemic pathways.

Table 6. Summary of ambient air monitoring for ethylene oxide (U.S. Environmental Protection Agency (USEPA) 2019a).

			Site Mean	
City, State	Setting	State	ug/m^3	ppb
Smithland, KY	Rural	KY	0.31	0.17
Chester, NJ	Rural	NJ	0.36	0.20
East Brunswick, NJ	Rural	NJ	0.30	0.17
Grayson lake, KY	Rural	KY	0.19	0.10
Rural Mean±SD			*0.29 ± 0.07*	*0.16 ± 0.04*
Chicago, IL	Suburban	IL	0.37	0.20
Ashland, KY	Suburban	KY	0.29	0.16
Calvert City, KY	Suburban	KY	0.36	0.20
Dearborn, MI	Suburban	MI	0.24	0.13
Elizabeth, NJ	Suburban	NJ	0.31	0.17
Bountiful, UT	Suburban	UT	0.34	0.19
Lacey, WA	Suburban	WA	0.19	0.11
Suburban Mean±SD			*0.30 ± 0.06*	*0.17 ± 0.04*
Phoenix, AZ	Urban	AZ	0.40	0.22
Phoenix, AZ	Urban	AZ	0.35	0.19
Northbrook, IL	Urban	IL	0.29	0.16
St. Louis, MO	Urban	MO	0.27	0.15
Camden, NJ	Urban	NJ	0.35	0.19
Seattle, WA	Urban	WA	0.19	0.10
Grand Junction, CO	Urban	CO	0.26	0.14
Urban Mean±SD			*0.30 ± 0.07*	*0.17 ± 0.04*
Overall Mean±SD			***0.30 ± 0.06***	***0.16 ± 0.04***

Gastrointestinal lumen pathways (Bacterial)

Under normal conditions, bacteria are able to produce ethylene from amino acids (methionine, glutamic acid) and their metabolites (2-keto-4-methylthiobutyric acid or KMTB, 2-oxoglutarate or OG, 1-aminocyclopropane-1-carboxylic acid or ACC) (Fukuda, Ogawa, and Tanase 1993). The ability to produce ethylene from methionine or KMTB was assessed in 14 species of bacteria (Mansouri and Bunch 1989). Most bacterial species were able to generate ethylene from KMTB, while only two (*E. coli SPAO, C. violaceum*) were able to synthesize ethylene from methionine. Production was also dependent on the carbon/nitrogen source used in the growth medium (glutamate, glucose+ammonia). A survey of 757 bacterial species from soil found that 229 species (approximately 30%) were capable of producing ethylene (Nagahama et al. 1992). Most of the producing strains (225/229) were categorized as synthesizing ethylene from methionine (via KMTB). A smaller fraction of the producing species did so from other source material. These include one species generating ethylene from oxoglutarate, three species producing ethylene from meat extract, and two species whose source was not characterized. Induction of oxidative stress in bacteria (via menadione and paraquat

addition) increased ethylene synthesis by cells, but not by cell-free extracts of *E. coli* (Mansouri and Bunch 1989). One additional species (*P. aeruginosa*) was able to produce ethylene from KMTB only when co-incubated with menadione or paraquat.

Some ethylene-producing bacteria are typically found in the human gastrointestinal tract (Table 3), although data were not located in the published literature for a majority of the species present. Ethylene produced in the gastrointestinal lumen via bacterial pathways might be absorbed from the intestinal tract into the body. Once absorbed, systemic ethylene may be metabolized to ethylene oxide in tissues via enzymatic oxidation where it might bind to hemoglobin to form HEV (Figure 4).

The gastrointestinal pathway has been well characterized in lab animals. In a series of experiments Tornqvist et al. (1989) studied the levels of HEV in both control and germ-free CBA mice. Germ-free animals were found to exhibit HEV levels that were on average approximately 35% lower than detected in corresponding controls (Table 4), suggesting that bacteria in the gastrointestinal lumen might serve as a major contributing pathway to endogenous HEV levels.

Systemic pathways

Fu, Zic, and Ozimy (1979) characterized the enzymatic production of ethylene from methionine and KMTB by Wistar rat liver extracts. Ethylene production by the extracts was reported to be oxygen dependent, and inhibited by sulfhydryl agents. In addition, ethylene production was age-dependent, peaking at an age of approximately 50 days. Lawrence and Cohen (1985) characterized the synthesis of ethylene from KMTB in Swiss-Webster mice. Injection of 1000 mg/kg KMTB resulted in an 8.6-fold rise in ethylene production above normal endogenous levels reported in controls. Induction of lipid peroxidation (via carbon tetrachloride dosing) prior to KMTB produced a 13.9-fold elevation over endogenous levels or approximately 1.6-fold increase over that observed for KMTB alone. Pretreatment of mice in this study with vitamin E (an inhibitor of lipid peroxidation) or metyrapone (inhibitor of mixed function oxidase activity) did not alter ethylene production by KMTB alone or in combination with carbon tetrachloride. For this reason, Lawrence and Cohen (1985) concluded that ethylene production from KMTB did not appear to derive from free radicals generated during lipid peroxidation. *In vitro* studies showed that oxidation of erythrocyte membranes resulted in the generation of ethylene (Clemens and Remmer 1982; Einsele, Clemens, and Remmer 1987).

Ethylene produced by these systemic pathways might be metabolized to ethylene oxide in tissues via enzymatic oxidation, and then bound to hemoglobin to form HEV (Figure 4). Törnqvist et al. (1989a) examined the formation of HEV in CBA mice fed diets differing in lipid source (sunflower oil, lard, or coconut oil), which varied in their fatty acid composition and carbon chain length. In mice fed diets with sunflower oil (high in unsaturated fatty acids) HEV levels were significantly higher (approximately 2- to 3-fold) than in animals fed diets with either lard or coconut oil (low in unsaturated fatty acids) (Table 5). These data indicated

Table 7. Estimates of historical HEV means for U.S. population based on smoking pattern trends.

	Smoking Intensity (% U.S. smokers)[a]				Estimated Mean HEV (pmol/g Hb)	
Year	>24 cigarettes/day	15–24 cigarettes/day	<15 cigarettes/day	Smoking Prevalence (% U.S. population)[a]	U.S. Smokers[b]	U.S. Population (smokers and nonsmokers combined)[c]
1975	25.9	43	31.2	37.1	196–237	92–108
1980	29.1	42.1	28.2	33.2	201–243	88–102
1985	26.6	41.8	31.6	30.1	196–237	81–93
1990	22.9	42.6	34.5	25.5	190–229	72–82
1995	20.1	39	40.9	24.7	180–217	68–77
2000	15.4	38.8	45.8	23.3	171–205	64–72
2005	11.7	36.6	51.7	20.9	161–193	58–65
2010	7.4	33.7	58.9	19.3	149–179	54–60
2015	6.4	29.7	63.9	15.1	143–171	48–52

[a]ALA (2020)
[b]HEV burden in smokers estimated from smoking intensity patterns, and an HEV added burden of 8.8–11 pmol/g Hb per cigarette/day (Bader, Lewalter, and Angerer 1995; Wu et al. 2004).
[c]Calculated as the weighted arithmetic mean for smokers and nonsmokers combined, based on historical prevalence of smoking, along with a mean HEV level of 31.4 pmol/g Hb for nonsmokers (endogenous and ambient air contributions assumed constant over time).

that dietary fatty acids, presumably via their systemic metabolism, are an important contributor to endogenous HEV levels.

Studies in which HEV levels have been characterized in animals after induction of lipid peroxidation may be used to assess the relative importance of cellular macromolecule oxidation to background HEV burden. HEV levels in animals administered agents to induce lipid peroxidation (phenobarbital, carbon tetrachloride, buthionine sulphoximine; alone or in combination) were found to be modestly higher (4–14%) than HEV burdens in corresponding controls (Kautiainen et al. 1991). Increased systemic inflammation and associated lipid peroxidation were identified as endogenous sources of ethylene production in humans (Paardekooper et al. 2017). These data suggest that induction of oxidative stress via chemical exposures and/or disease states might increase HEV levels. This represents an important aspect of the mode of action for ethylene oxide, since data in rats indicate that exogenous ethylene oxide exposure (Pathway 1 in Figure 4) enhances production via the endogenous pathways (Pathway 2 in Figure 4). This rise in endogenous production might occur via an oxidative stress mechanism, and perhaps surprisingly, the latter pathway might predominate over the former pathway in its relative contribution to total exposure in exposed rats (see discussion of Marsden et al. 2009).

Exogenous pathways

The levels of HEV detected in human populations may be influenced by exogenous sources of exposure, including (1) ethylene oxide in ambient air; (2) ethylene in ambient air; and (3) other potential pathways. Each of these pathways is discussed below.

Ethylene Oxide in Ambient Air

U.S. Environmental Protection Agency (USEPA) (2019a) summarized recent monitoring efforts ethylene oxide in ambient air at rural, suburban, and urban locations across the U.S. (Table 6). With arithmetic mean values consistently at or near 0.16 ppb, there appears to be no meaningful difference among ambient air concentrations of ethylene oxide measured in rural, suburban, or urban settings. Higher concentrations of ethylene oxide in air may be detected near emission sources. For example, recent data collected for ethylene oxide concentrations air at multiple locations over a 6-month period near two facilities that use or make ethylene oxide reported weighted mean concentrations of 0.33 ± 0.76 ppb (CV = 230%) (Medline Industries Inc. sterilization facility in Waukegan, IL) and 0.20 ± 0.55 ppb (CV = 270%) (Vantage Specialty Chemicals Inc. facility in Gurnee) (Lake County, 2020; raw data provided in **Attachment 1**). Mean concentrations for both sites are 1.3–2.1-fold higher than national ambient air concentrations (0.16 ppb, Table 6). Ninety-five percent upper confidence limits of the mean were calculated to be 0.43 ppb and 0.22 ppb, respectively, assuming a lognormal distribution (ProUCL 5.1).

Non-point sources of ethylene oxide releases to air have not been well characterized, but may include both anthropogenic and natural sources. Ethylene oxide was identified as a combustion product of hydrocarbons, particularly from n-pentane as a fuel source (Barnard and Lee 1972). For this reason, ethylene oxide may be released in automotive exhaust, as well as in exhaust from stationary sources of hydrocarbon combustion. High concentrations of ethylene oxide (25–75 ppm) were determined in an approximate 60–80 ml headspace gas phase of a 100 ml flask following the frying of approximately 20 g of foods in 10–20 of soybean oil (Lin et al. 2007). Although specific emission factors are not available for ethylene oxide release from wildfires as they are for ethylene (Urbanski, Hao, and Baker 2009), the presence of both ethylene in tobacco smoke (Baren et al. 2004) and ethylene oxide in tobacco smoke (based on increased HEV levels; Figure 1) suggests wildfires may serve as a source of ethylene oxide emissions.

Ethylene in ambient air

As discussed above, ethylene is produced by bacteria present in soil (Nagahama et al. 1992), and as a plant hormone that signals leaf senescence and fruit ripening, ethylene is also generated by plants (Schaller 2012). Sawada and Totsuka (1986) estimated that 74% of global ethylene was released from natural sources (terrestrial and aquatic

ecosystems), and 26% was released from the anthropogenic sources (biomass burning, combustion of fossil fuels). Wildfires were identified as a significant source of ethylene emissions (Morgott 2015; Urbanski, Hao, and Baker 2009). Health Canada (2016) recently characterized ambient levels of ethylene in rural air and urban air as displaying mean concentrations of 0.46 ug/m^3 (0.40 ppb) and 1.7 ug/m^3 (1.5 ppb), respectively. Morgott (2015) reported that continuous personal monitoring at the community level, which is expected to reflect exposures to both indoor and outdoor air, to typically range from 3 to 4 ppb.

Other potential pathways

Two important sources of elevated exogenous exposure to ethylene oxide in air (i.e. above ambient levels) include (1) occupational exposures and (2) tobacco smoke. Occupational exposures to ethylene oxide are associated with specific industries including hospital workers (Haufroid et al. 2007), sterilization workers (Bogen et al. 2019), chemical manufacturing workers (Swaen et al. 2009; Teta, Benson, and Vitale 1993), and fruit store workers exposed to plant-produced ethylene (Tornqvist et al., 1989). An exposure reconstruction of sterilization operators exposed to ethylene oxide was recently conducted (Bogen et al. 2019). Estimated historical exposures to ethylene oxide by sterilization operators are many orders of magnitude higher than those encountered today. These reconstructed exposures suggest a strong decreasing trend in ethylene oxide concentrations in air over time. Similarly, Teta, Benson, and Vitale (1993) and Swaen et al. (2009) estimated exposures to be approximately 70,000 ppb for the highest exposed workers in 1925–1939, but 1 ppb for the highest exposed workers in 1974–1988 at a chemical manufacturing plant for ethylene oxide. A diminishing trend in occupational exposures to ethylene oxide is also suggested more generally, based upon historical changes in occupational exposure limits for ethylene oxide, which have fallen from 100,000 ppb (ACGIH TLV-TWA in the 1940s-50s) to 1,000 ppb (current OSHA PEL) over the past 70 years.

As noted above, tobacco smoke contains both ethylene and ethylene oxide. Consistent with the Center for Disease Control (CDC) (2019) data for HEV levels in the U.S. population, tobacco smoke is identified as the single largest source of ethylene oxide exposure to the general population. In the U.S., based on trends in smoking intensity and prevalence, along with estimates of HEV level increases per cigarette (Bader, Lewalter, and Angerer 1995; Wu et al. 2004), tobacco-related exposures to ethylene oxide have been decreasing over time, as estimated in Table 7. The levels of HEV estimated for smokers in this table are generally consistent with the levels reported in NHANES for collections around 2015 (i.e. estimated arithmetic mean HEV of 48–52 pmol/g Hb falls between the arithmetic of 72.9 pmol/g Hb and the geometric mean of 38.3 pmol/g Hb based upon measured HEV data for 2014–5; CDC 2019).

With respect to dietary exposures to ethylene oxide, although plant vegetation is an important source of ethylene, particularly during fruit ripening, Health Canada (2016) concluded that dietary doses of ethylene from consumption of plant materials are negligible.

Sources of variation in HEV measurements

Based on the CDC data (Center for Disease Control (CDC) 2019), the coefficient of variation (CV calculated as the standard deviation divided by the arithmetic mean) for nonsmokers was estimated to be 79%, which is similar to the CV reported from the meta-analysis of nonsmoker control subjects across multiple human studies (69%) (Kirman and Hays 2017) (Table 1). There are multiple sources of variation that may contribute to differences in HEV measurements in human populations. These include both general sources and pathway-specific sources of variation, as described below.

General sources of variation include intra-individual and inter-lab variation. Although HEV is a stable cumulative biomarker of exposure to ethylene oxide, which reflects exposures over several months (based upon erythrocyte half-life), it does exhibit variation over time. In a single individual with no known exposure to ethylene oxide who was repeatedly sampled over a 15-month period, the HEV burden was observed to vary with a mean and standard deviation of 22.4 and 3.6

pmol/g Hb, respectively (Tornqvist and Kautiainen, 1993), suggesting that temporal (intra-individual) variation is relatively small (CV = 16%). In a study that examined the results of four different labs in analyzing eight human hemoglobin samples (Törnqvist et al. 1992), data demonstrated a strong correlation, but with systematic differences across labs contributing moderate variation (CV = 28%). Erythrocyte lifespans may also vary across individuals (e.g. mean = 126 days, SD = 26 days (CV = 21%); Zhang et al. 2018), and contribute to variation in measured HEV levels in humans.

Several pathway-specific sources of variation were identified for HEV formation. Gut microflora is highly variable in humans and affected by diet (e.g. probiotics, food consumption), geographic location, medication (e.g. antibiotic use), disease states, and other factors (e.g. age, gender, race). As summarized in Table 3, although some ethylene-producing bacteria are frequently found in humans (e.g. *E. coli*), others are detected less frequently (e.g. *S. aureus, Klebsiella, Enterobacter, P. aeruginosa*). In addition, because bacterial production of ethylene is dependent on the availability of precursor and intermediate molecules (e.g. methionine, KMTB), dietary variation in precursors might contribute to HEV variation, for example, meats, eggs, and fish are excellent sources of methionine, and KMTB is found in a number of food items such as leeks, hickory nuts, brussel sprouts, and giant butterbur (*Petasites japonicus*) (FOODB 2020).

Several sources of variation were identified for endogenous, systemic pathways of HEV formation. Ethylene oxide is detoxified in part by conjugation with glutathione. Investigators noted that genetic polymorphisms for the GST-T1 enzyme might affect HEV burden (Fennell et al. 2000; Müller et al. 1998; Thier et al. 1999; Yong et al. 2001). In a sample of 21 people (5 GST-T1-, 16 GST-T1+), mean and SD values for HEV burden were calculated to be 116 ± 53 pmol/g Hb, 45 ± 11 pmol/g Hb, and 62 ± 40 pmol/g Hb, for the GST-T1- subgroup, GST-T1+ subgroup, and for the total sample combined,

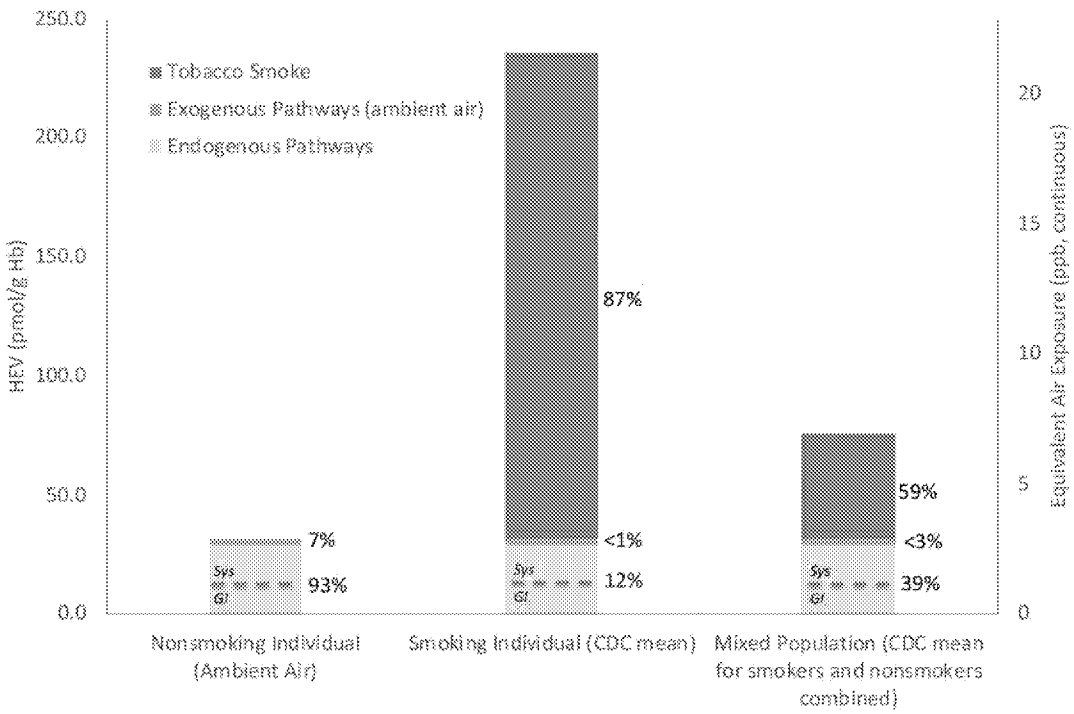

Figure 5. Estimated Pathway Contribution to HEV Burden in the U.S. Population Via Endogenous and Exogenous (Ambient Air, Smoking) Pathways. Equivalent air concentration for 2nd y-axis are based on the correlation described in Eq.1. Sys = systemic production; GI = gastrointestinal production.

respectively. These data indicate that GST-T1 polymorphism may contribute markedly to variation in HEV burden in human populations. Because humans rely primarily on epoxide hydrolase for ethylene oxide clearance, Filser and Klein (2018) concluded that it seems doubtful the elevated HEV levels resulted from differences in ethylene oxide glutathione-mediated metabolism alone. Alternatively, because GST-T1 polymorphism is also associated with changes in lipid biomarkers (Block et al. 2011; Maciel et al. 2009), it remains possible that lipid metabolism or other endogenous pathway factors indirectly affecting HEV formation are impacted by GST-T1 polymorphism.

In addition to genetic factors, based upon studies in mice, dietary lipid composition (i.e. consumption of unsaturated vs. saturated fatty acids) might exert a strong effect on HEV burden (Table 5; Tornqvist et al., 1989). Fatty acid intake in the U.S. population is highly variable (CV>100%), with average values reported as follows: total saturated fat = 27 ± 28 g/day; total mono-unsaturated fat = 30 ± 37 g/day; and total polyunsaturated fat = 16 ± 19 g/day (for all ages, both genders based on NHANES, 1999–2000; CDC, 2004). For these reasons, variation in dietary lipid consumption is expected to contribute significantly to differences in HEV measurements in human populations.

With respect to sources of variation for exogenous pathways, ambient air concentrations of ethylene oxide and ethylene in air are expected to exhibit some temporal and spatial variation in the U.S (Table 6), with higher concentrations and differences associated with locations near emission sources. Spatial variation across sample locations not associated with specific ethylene oxide point sources exhibits a CV of approximately 20% (Table 6). Higher variation (CV>200%) might occur near emission sources (example IL site data in **Attachment 1**). However, ambient air concentrations of ethylene oxide are not expected to be a major contributor to variability in measured HEV levels for most individuals since mean ambient levels of ethylene in air represent only a small % of total exposure (see Section 4.1).

Overall, given the number of sources of variation and their relative magnitudes, the variation in HEV values reported for nonsmokers based upon the

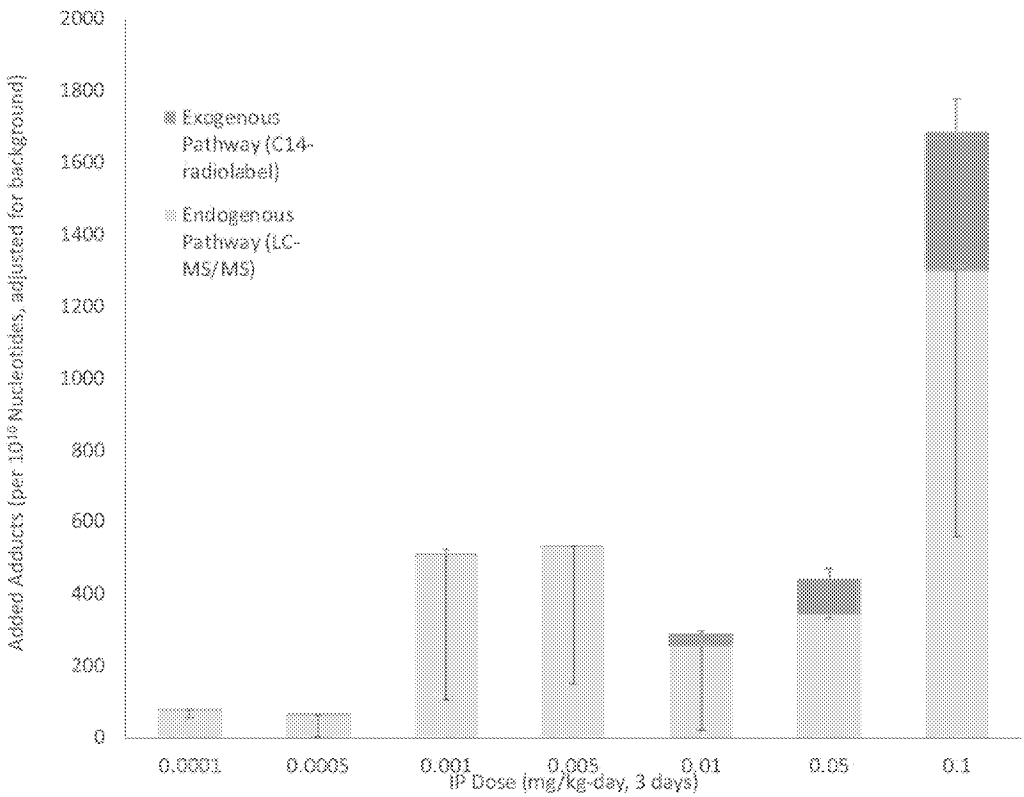

Figure 6. Liver DNA Adducts Produced by Endogenous and Exogenous Pathways in Rats Exposed to Ethylene Oxide via i.p. Injection. Columns indicate the mean value (n = 3), error bars indicate SE (adapted from Marsden et al. 2009).

Center for Disease Control (CDC) (2019) data (CV = 79%; Figure 2), and noted for pooled, control subjects in Kirman and Hays (2017; CV = 69%) is generally consistent with expectations. Variation of HEV levels in smokers is numerically higher (93--94%; Table 1) than for nonsmokers, which is consistent with consideration of contributions from variation in smoking habits (e.g. intensity, frequency) and content of tobacco products.

Risk assessment and risk management of ethylene oxide

Risk assessment for carcinogenic chemicals such as ethylene oxide relies on quantitative estimates of cancer potency such as unit risk values, which reflect the slope of the dose–response relationship at low exposure levels where a high unit risk value indicates a steep slope indicative of a potent carcinogen. Recently, at least two regulatory agencies conducted quantitative dose–response assessments on the same cohort of exposed workers (NIOSH; Steenland, Stayner, and Deddens 2004) to derive the cancer unit risk values for ethylene oxide, with values that differ by several orders of magnitude ranging from 0.0000041 per ppb (TCEQ, 2020) to 0.0091 per ppb (USEPA 2016, 2019b). Briefly, USEPA's unit risk value for ethylene oxide is based upon elevated incidence/mortality for two cancer types in exposed workers: (1) mortality data for lymphoid cancer (a special category combining non-Hodgkin lymphoma, myeloma, and lymphocytic leukemia); and (2) incidence data for breast cancer (USEPA, 2016). U.S. Environmental Protection Agency (USEPA) (2016) selected a 2-slope model with an initial steep slope at low exposures followed by a shallow slope at higher exposures. U.S. Environmental Protection Agency (USEPA) (2019b) also considered a range of possible regulatory values based upon different dose–response models. TCEQ (2020) also considered the 2-slope model but ultimately selected the more commonly used log-linear Cox-proportional hazards model for lymphoid cancer mortality,

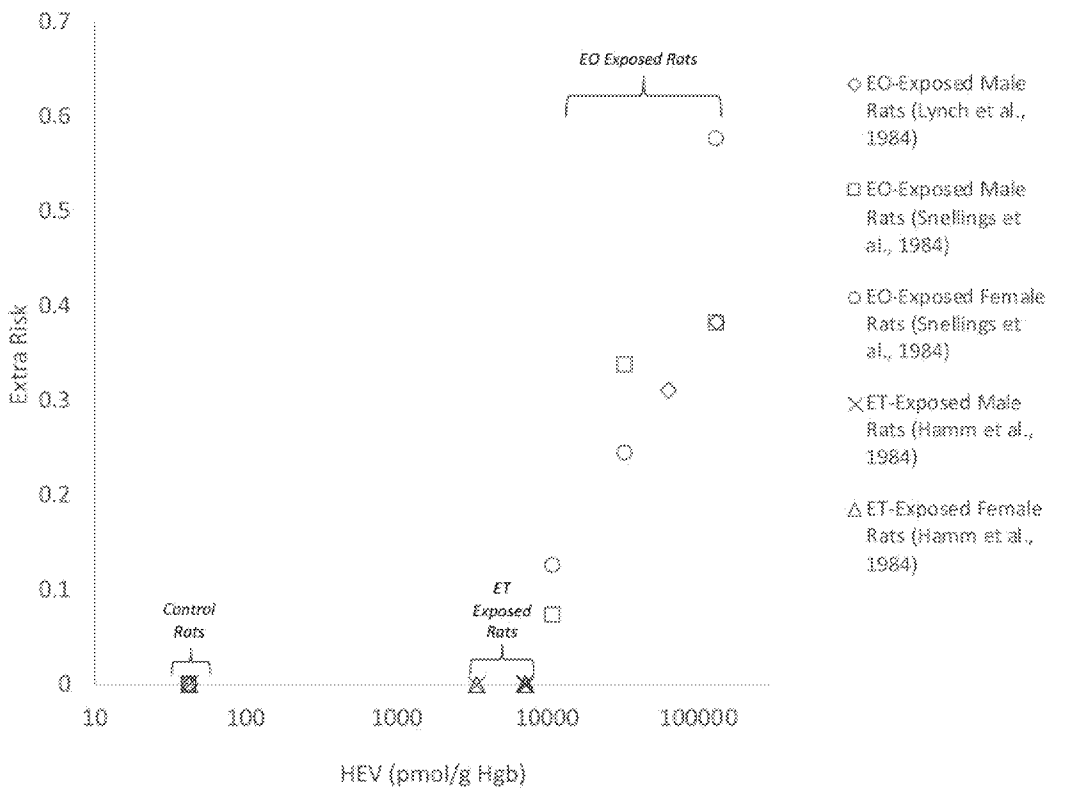

Figure 7. Total Extra Risk vs. Total Ethylene Oxide Internal Dose (HEV, pmol/g Hb) in Rats Exposed to Ethylene or Ethylene Oxide. X-axis displayed on log-scale to clear depict the broad range of internal doses (4 orders of magnitude), and not to accentuate a nonlinear dose-response relationship.

which results in a shallower linear slope at the lower exposures of interest than the 2-slope model.

Selecting an appropriate model to extrapolate from the occupationally exposed workers to the general population is especially challenging because the upper percentiles of the NIOSH cohort were exposed to high concentrations of ethylene oxide. Exposures measured between 1979 and 1985 in the NIOSH cohort ranged from 2,200 to 4,600 ppb (Hornung et al. 1994), which is 4 orders of magnitude higher than ambient concentrations recently measured by USEPA (Table 6). Although a regression model was developed to estimate exposures between 1938 and 1978, historical exposure reconstruction predictions are inevitably uncertain. The NIOSH regression model for exposure, validated only with data collected after 1978 (i.e. pre-1978 measurements are not available), predicted that exposures were lowest in 1938 and rose to peak levels in 1978. A recent analysis by Bogen et al. (2019) yielded an exposure model that better accounts for engineering/industrial hygiene factors (E/IH). The E/IH-based model of Bogen et al. (2019) was developed using historical data on ethylene oxide kill concentrations, residue levels in sterilized materials, post-wash concentrations in a sterilization chamber, and information on sterilizer operator practices prior to 1978. The E/IH exposure more predicts a trend in ethylene oxide exposures for the most highly exposed workers (e.g. sterilizer operators) that are substantially higher pre-1978 compared to post-1978. This prediction is more realistic and consistent with the observation made by NIOSH study authors that exposures to ethylene oxide "*were likely to have been higher . . . .before installation of engineering controls, when the OSHA standard was 50 ppm*" (Steenland et al. 1991). Consequently, the USEPA calculations of the unit risk value based upon NIOSH study have a high level of uncertainty and potential for underestimating pre-1978 exposures, which subsequently results in an overestimation of cancer potency for ethylene oxide.

Determining the magnitude of the unit risk value (i.e. steepness of the slope for the dose–response relationship) and the nature of the dose–response relationship (i.e. linear vs. nonlinear models) for low exposures to ethylene oxide is complex and uncertain. Ultimately, addressing these uncertainties requires a full consideration of the evidence for ethylene oxide within a mode of action framework, which is beyond the scope of this review. This section of the review examines how endogenous levels together with other biological data and evidence may inform the shape of the dose–response curve at lower exposure levels relevant to the general population within the context of total exposure to ethylene oxide. A number of important questions arise when assessing and/or managing the potential extra risks of ethylene oxide exposures, including the following: *What are the contributions of endogenous and exogenous ethylene oxide production to total exposure? How does exogenous exposure to ethylene oxide affect total exposure? What are the risks associated with endogenous and low-level exogenous exposures? How can endogenous levels (considering mean and variability) inform selection of regulatory values for extra risk to the general population? What are the benefits of ethylene oxide use? How should risks associated with total exposure be managed?* Information to address these important questions is discussed below.

Contribution of endogenous and exogenous pathways to total ethylene oxide exposure

Characterization of the relative importance of exogenous and endogenous pathways in contributing to background HEV burden measured in human populations is key to understanding the health significance of exogenous exposure and risk management of ethylene oxide. The mean levels of ethylene observed in personal community air samples of approximately 3.5 ppb (Morgott 2015), while considering a metabolic conversion rate of approximately 1.25% (based upon PBPK simulations for ethylene concentrations <1 ppm using the model of Filser and Klein 2018) correspond to equivalent concentrations of ethylene oxide in air of approximately 0.04 ppb. Combined with the mean ambient air concentration of 0.16 ppb in the U.S. (Table 6), total ethylene oxide equivalents for ambient air in the U.S. is estimated to be approximately 0.2 ppb (0.16 ppb + 0.04 ppb). Using the correlation defined in Equation (1) this air concentration corresponds to an HEV level of 2.2 pmol/g Hb.

For nonsmoking individuals, these results suggest that only a small % (2.2 out of 31.4 pmol/g Hb, or approximately 7%) is associated with exogenous pathways for ethylene and ethylene oxide, leaving a majority (29.2 out of 31.4 pmol/g Hb, or approximately 93%) associated with endogenous pathways (Figure 5). Similarly for smoking individuals in the U.S., ambient air contributes a small % of total exposures (approximately 0.9% of mean HEV of 236 pmol/g Hb), while a moderate approximate 12% is associated with endogenous production, and the vast majority of HEV adduct burden approximately 87% is correlated with smoking (Figure 5). At the population level (i.e. considering US population as mix of smokers and nonsmokers), ambient air contributes a small approximately 2.9% of weighted mean HEV of 75.7 pmol/g Hb exposure (Table 1), while a moderate approximate 39% is associated with endogenous production, and the majority of HEV adduct burden approximately 59% is correlated with smoking (Figure 5).

Table 8. Endogenous equivalent values for ethylene oxide calculated using HEV levels in nonsmokers (based on data from Center for Disease Control (CDC) 2019).

Basis	Multiplier or Percentile	Hemoglobin Adduct Level (HEV pmol/g Hb) Unadjusted	Adjusted*	Endogenous Equivalent Concentration in Air (ppb, Continuous**
Multiples of Adjusted Mean (29.2 pmol/g Hb)	0.1	3.14	2.95	0.27
	0.25	7.85	7.37	0.68
	0.5	15.7	14.7	1.4
	1	31.4	29.5	2.7
	2	62.8	58.9	5.4
	3	94.2	88.4	8.1
Multiples of SD (unadjusted; 24.8 pmol/g Hb)	0.1	2.48	2.48	0.23
	0.25	6.20	6.20	0.57
	0.5	12.4	12.4	1.1
	1	24.8	24.8	2.3
	2	49.6	49.6	4.6
	3	74.4	74.4	6.8
Adjusted Percentiles for Population Sample	0.01	9.12	7.18	0.66
	0.05	13.4	11.5	1.1
	0.1	16.0	14.1	1.3
	0.25	20.8	18.9	1.7
	0.5	27.0	25.1	2.3
	0.75	35.1	33.2	3.0
	0.9	47.5	45.6	4.2
	0.95	60.1	58.2	5.3
	0.99	123	121	11

*To estimate HEV levels due to endogenous production, mean (31.4 pmol/g Hb, **Table 1**) and percentile values for U.S. background HEV levels were adjusted for the estimated contribution from exogenous pathway (~2.2 pmol/g Hb, see Section 4.1). No adjustments were made to multiples of SD.
**Calculated using Eq.1, values rounded to two significant figures.

With respect to characterizing the relative importance of the gastrointestinal tract and systemic pathway to endogenous pathways, no apparent data were located to address this issue specifically in humans. However, in lab animals, there appears to be sufficient information to provide an initial characterization of their relative importance. Based upon measurements of HEV in germ-free vs. control mice (Table 4), approximately 35% of endogenous HEV production is associated with gastrointestinal pathways, leaving the remainder approximately 65% of total endogenous production correlated with systemic pathways. Assuming these relative contributions also reflect ethylene oxide production in humans, estimates of the relative contribution of endogenous and exogenous pathways in U.S. nonsmokers and smokers are illustrated in Figure 5 (dashed line dividing the light gray region in each column).

Effects of exogenous ethylene oxide exposure on total exposure

While the direct effects of ethylene oxide on the exogenous pathway for HEV formation are expected, evidence in rats suggests that these exposures also indirectly affect endogenous production pathways. Marsden et al. (2009) exposed rats to a broad range of C^{14}-radiolabeled ethylene oxide doses (0.0001–0.1 mg/kg, via single i.p. injections/day for 3 days) and measured the formation of DNA adducts [i.e. N7-(2-hydroxyethyl)guanine or N7-HEG] in several tissues by two different methods: (1) ^{14}C-radiolabeled adducts (via liquid scintillation), which reflect those formed by the exogenous pathway (pathway 1 in Figure 4); and (2) unlabeled adducts (via LC-MS/MS), which reflect those formed by the endogenous pathway (i.e. systemic formation; pathway 2 in Figure 4). To put these i.p. doses in perspective, the dose range used in this study corresponds to equivalent inhalation exposures of approximately 0.-27–270 ppb in rats exposed for 6 hr/day [assuming BW = 0.18 kg (USEPA, 1988), an inhalation rate of 0.2 m^3/24 hr day (U.S. Environmental Protection Agency (USEPA) 1988), and an inhalation absorption fraction of 0.75 (Brugnone et al. 1986)]. Data for liver adducts in exposed animals (adjusted for background) are presented in Figure 6.

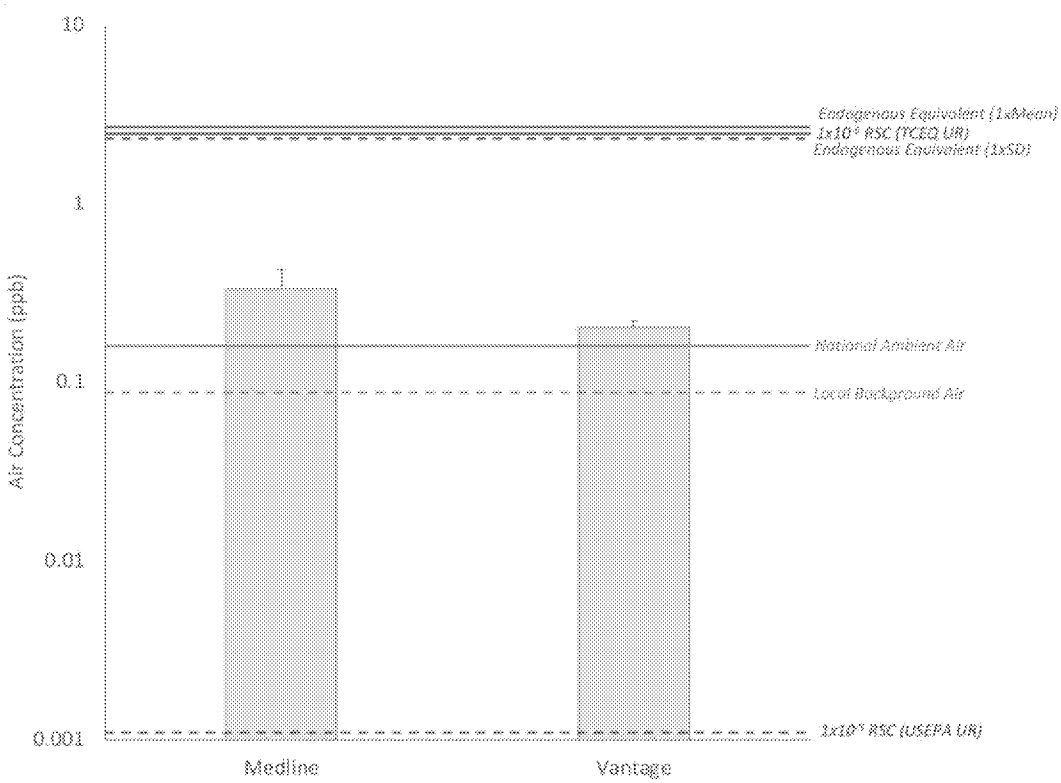

Figure 8. Example Comparison of Site Concentrations (gray columns = mean; error bars = 95% UCL, assuming a lognormal distribution, ProUCL 5.1) to Background Concentrations (green lines; solid = national, dashed = local), 1×10^{-5} Risk-Specific Concentrations (red lines; solid = TCEQ unit risk basis, dashed = USEPA unit risk basis), and Endogenous Equivalent Levels (blue lines; solid = 1xCDC Mean, dashed = 1xCDC SD). RSC = Risk-Specific Concentration, UR = Unit Risk.

Table 9. Unit risk values derived for ethylene oxide using epidemiology data.

	Unit Risk			$1x10^{-5}$ Risk Specific Concentration (RSC)		
Agency	per ug/m^3	per ppb	Basis	Air (ppb)	Fraction of Mean Endogenous Exposure[a]	Fraction of Standard Deviation for Endogenous Exposure[b]
U.S. Environmental Protection Agency (USEPA) (2016)	0.005	0.0091	NIOSH workers (lymphoid and breast cancer in male and female workers)	0.0011	0.00041	0.00048
TCEQ (2020)	0.0000023	0.0000041	NIOSH workers (lymphoid cancer in males)	2.4	0.91	1.1

[a]Mean endogenous exposure estimated to be 29.2 pmol/g Hb, equivalent to 2.7 ppb ethylene oxide in air (Table 8), based on CDC HEV arithmetic mean (31.4 pmol/g Hb; Table 1), adjusted for exogenous ambient air exposure (2.2 pmol/g Hb; Section 4.1)
[b]SD for endogenous exposure assumed to be equivalent to SD for CDC HEV data (24.8 pmol/g Hb, Table 1), equivalent to 2.4 ppb ethylene oxide in air (Table 8).

There are several conclusions that might be supported by these data. First, DNA adducts are increased in a treatment-related manner, becoming significant for adducts produced by the exogenous pathway at doses of 0.005 mg/kg and higher, and for adducts synthesized by the endogenous pathway at doses of 0.05 mg/kg and higher. Second, the treatment-related effects of ethylene oxide on adduct formation are far greater for the endogenous pathway when compared to the exogenous pathway (i.e. pathway 2 in Figure 4 ≫ pathway 1 in Figure 4). Because the route of exposure (i.p. injection) used in this study effectively bypasses ethylene oxide production via the gastrointestinal tract, the elevated adduct number generated by the endogenous pathway reflects modulation of endogenous, systemic processes by ethylene oxide, possibly by increasing the source of reactive oxygen

species (ROS) via oxidative stress, as proposed by Marsden et al. (2009). Finally, the relative importance of the exogenous pathway rises as a function of dose (<1% at the treatment group corresponding to approximate 0.27 ppb, increasing to 23% at the highest treatment corresponding to approximately 270 ppb), a trend that is presumed to continue up to the tumorigenic exposure range in rats (10,000--100,000 ppb)(Lynch et al. 1984; Snellings, Weil, and Maronpot 1984). Depending upon the nature of this trend at higher doses, adduct formation via the exogenous pathway may predominate at tumorigenic exposure levels.

Contribution of endogenous and low-level exogenous ethylene oxide exposures to risk

In determining the magnitude of the unit risk value for ethylene oxide (i.e. the steepness of the dose–response slope) used to predict cancer risk in the general population (e.g. at exposures well below those experienced in the NIOSH cohort), it is important to understand how observations at higher occupational concentrations need to be extrapolated to lower exposures. Inferences for low-exposure risk from available animal and human datasets are discussed below.

Inference from animal data sets

Two hypotheses that relate to the precautionary assumption of low-dose linearity adopted for endogenously produced chemicals such as ethylene oxide are as follows: (1) endogenous levels of ethylene oxide contribute to background cancer risk; and (2) low-level exposures to ethylene oxide (e.g. endogenous plus ambient exogenous exposures well below the tumorigenic point of departure) result in increased risk of cancer. HEV values, as a measure of total ethylene oxide exposure, might be used to assess these hypotheses by examining the data on the carcinogenicity of ethylene oxide in rats, along with data on the carcinogenicity of ethylene in rats. Cancer bioassay data collected in rats exposed to 10,000--100,000 ppb ethylene oxide showed significant elevation in several cancer types, including mononuclear

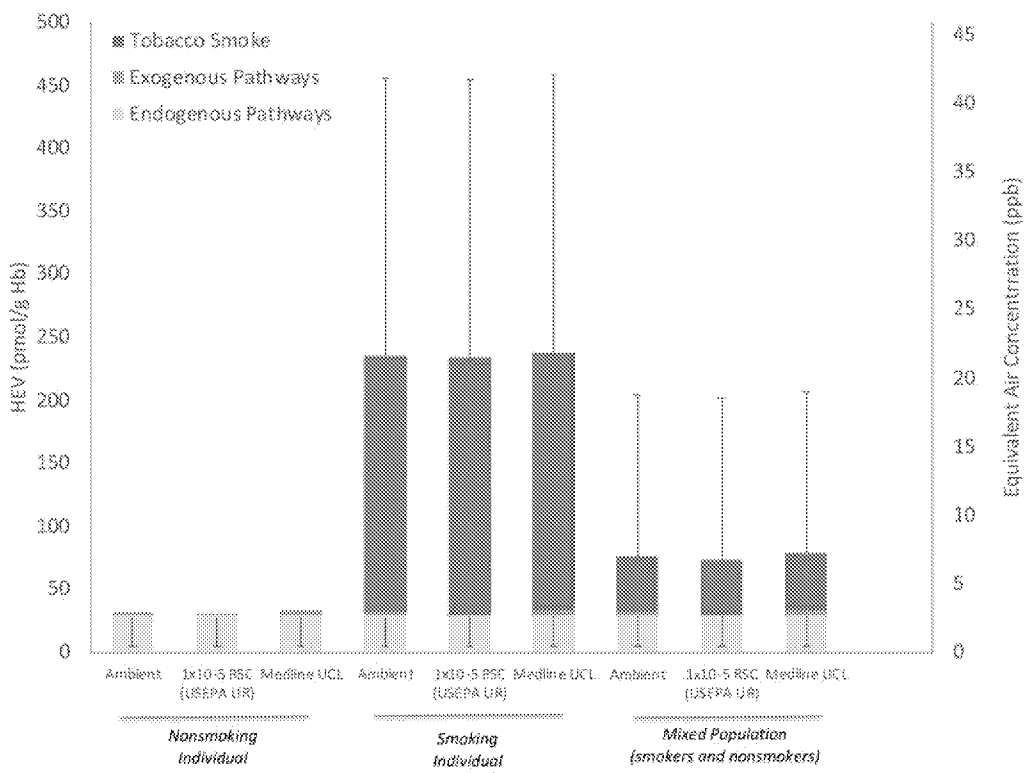

Figure 9. Comparison of Ambient Background, 1×10^{-5} RSC, and Site-Related Air Concentrations to Total Exposure to Ethylene Oxide. RSC = Risk-Specific Concentration, UR = Unit Risk, UCL = Upper Confidence Limit.

cell leukemia, testicular peritoneal mesothelioma, and brain tumors (Lynch et al. 1984; Snellings, Weil, and Maronpot 1984). In contrast, cancer bioassay data collected in rats for ethylene at 300, 1,000, and 3,000 ppm demonstrated no marked change in tumors of any kind (Hamm, Guest, and Dent 1984). Levels of HEV, which reflect total exposure to ethylene oxide (via all pathways) were measured for rats exposed to ethylene oxide or to ethylene under conditions similar to those corresponding to the rat cancer bioassays (Filser et al. 2013), as well as in unexposed control animals (Walker et al. 1993, 2000).

Take together these data may be assembled to characterize the dose–response relationship for ethylene oxide assessed in terms of HEV levels and extra risk (summed across the three cancer types observed in rats) (Figure 7). Combined, these data appear inconsistent with an assumption of low-dose linearity below a 10% point of departure, but cannot differentiate between alternative nonlinear dose–response relationships (i.e. one with a decreasing slope with diminishing dose vs. one with a threshold). Evidence of low-dose nonlinearity in the cancer dose–response relationship for ethylene oxide is supported by data collected for ethylene. HEV levels measured in rats resulting from ethylene exposure under conditions of the cancer bioassay (Hamm, Guest, and Dent 1984) (300–3,000 ppm) are well above background levels in rats (i.e. approximately 50- to 160-fold higher than endogenous levels based on HEV data of Walker et al. 2000), and yet these enhanced systemic exposures did not result in an increased incidence of tumors. The lack of an elevated tumor response in ethylene-exposed animals (Hamm, Guest, and Dent 1984) is particularly robust given the study design (testing of 120 rats of each gender per treatment group, which is more than twice the number of animals typically used in cancer bioassays studies). If either of the low-dose linear hypotheses described above were valid, then a rise in risk would be observable in rats under conditions of the ethylene cancer bioassay (which increased ethylene oxide exposure by more than two orders of magnitude). Because an elevation in tumor incidence was not detected under these conditions, and thus neither hypothesis is supported.

While it is recognized that these data characterize the dose–response relationship of ethylene oxide in rats rather than humans, there is no mechanistic rationale to suggest that the dose–response relationship in Figure 7 is unique to rats. Although some species differences in toxicokinetic factors are noted, PBPK modeling indicating ethylene oxide blood concentrations in rats, mice, and humans are expected to be equivalent up to 200 ppm ethylene oxide exposures (Fennell and Brown 2001). Further, as an alkylating agent, the mode of action for ethylene oxide was proposed to involve genetic damage via adduction to DNA, resulting in gene mutation and chromosomal aberration (U.S. Environmental Protection Agency (USEPA) 2016), processes that are expected to be generally applicable across species.

Inference on risk at low concentrations of ethylene oxide in humans

As noted above, ethylene oxide exposures in smokers are significantly higher than in nonsmokers (Figure 1, Table 1), but are also lower than occupational exposures to workers in the upper percentiles of the NIOSH cohort. Thus, as representative of intermediate exposures to ethylene oxide human data from smoking populations may inform the shape of the dose–response curve (i.e. steepness of the slope) and provide some insight on potential risks of lymphohematopoietic and breast cancer from low-level exposures to ethylene oxide.

Neither the Surgeon General's Report (2014) nor the American Cancer Association (2020) correlated any of the lymphoid cancers (non-Hodgkin's lymphoma, myeloma, lymphocytic leukemia) with smoking. These findings reflect the weight of evidence collected over 50 years since the 1st Surgeon General's report on smoking, and stand in contrast to findings for cancer types in which the weight of evidence for a causal relationship with smoking is sufficient (e.g. lung, liver, colorectal cancers). In addition, there is no clear relationship with breast cancer based on the General's (2014), which concludes "*evidence is suggestive but not sufficient to infer a causal relationship between tobacco smoke and breast cancer.*" These data suggest that the cancer potency for ethylene oxide for lymphoid and breast cancers at lower exposures is low, and does not support the use of a steep exposure–response model at lower exposures. In a recent example, a cross-sectional study of Jain (2020) relied upon NHANES/CDC data to assess the potential associations between ethylene oxide (i.e. using the same

HEV depicted in Figure 1) and prevalence of self-reported physician diagnosis of cancers in general (n = 3,593), and of breast cancer for females (n = 1,919). These data reported in Jain (2020) are collected across the range of ethylene oxide exposures for smokers and nonsmokers. Jain (2020) concluded that for the general US population, levels of ethylene oxide were not found to be associated with cancers including breast cancer in females (*p*-values for regression slopes: 0.34 for males and females combined; 0.52 for females only). The results of this limited study suggest that ethylene oxide exposures as measured by HEV levels in nonsmokers and smokers are not associated with an observable increase in self-reported cancer prevalence, including for cancer types used to estimate the cancer potency of ethylene oxide by USEPA.

Assuming a genotoxic mode of action for ethylene oxide, the magnitude of the unit risk value for ethylene oxide (i.e. steepness of the slope at low exposures) is dependent upon the type of genetic damage produced by exposure, and may be moderated at low exposures by overlapping biological defenses. A thorough review of the mechanistic data within a mode of action framework is beyond the scope of this review, but there are some mechanistic data available that lend support to a nonlinear dose–response relationship for ethylene oxide, and include the following observations: (1) evidence showing that ethylene oxide-induced DNA damage is readily repairable in humans (Tates et al. 1995); (2) consideration that for cancer endpoints dependent on the reciprocal translocations by chemical alkylators (e.g. leukemia), cancer response is expected to be proportionate to the square of the dose (Preston et al. 1995); and (3) evidence in human cells exposed to ethylene oxide that a certain level of promutagenic adducts must be attained before mutations become detectable above background (Tompkins et al. 2009). Empirically, there are two pieces of evidence that are important to understanding low-dose risk: (1) absence of clear association for cancers of interest in smokers exposed to up to an order of magnitude higher ethylene oxide exposures than endogenous levels; and (2) positive results for some cancers in only the highest exposed workers (Steenland, Stayner, and Deddens 2004) whose exposures are up to many orders of magnitude higher than endogenous levels. Taken together combined evidence provides a dose–response pattern for humans that appears consistent with that observed in ethylene- and ethylene oxide-exposed rats in Figure 7.

Managing ethylene oxide risks

Information regarding endogenous equivalent values (Kirman and Hays 2017; as updated with the NHANES HEV data), risk-specific concentrations (using unit risk values from USEPA and TCEQ), potential health benefits, and their application to an example site-specific data for ethylene oxide are discussed below.

Endogenous equivalent levels

Kirman and Hays (2017) proposed endogenous equivalent concentrations in air (action levels) for ethylene oxide based on a consideration of its endogenous production. Endogenous action levels reflect air concentrations of ethylene oxide that are equivalent to the levels that are produced endogenously. The endogenous action levels are recalculated here for ethylene oxide in Table 8, with two important changes: (1) mean HEV values from CDC for nonsmokers in the U.S. (31.4 pmol/g Hb; Table 1) were used as the basis, instead of relying upon pooled data for unexposed control subjects used in Kirman and Hays (2017); and (2) background levels of HEV were adjusted for contributions from exogenous exposure pathways (2.2 pmol/g Hb), instead of assuming that contributions from exogenous exposures were negligible. By analogy to characterizations of background metals in soil (USEPA, 2002), there are several options for identifying what concentration constitutes a "*substantial difference*" from background to warrant additional attention/action. These options include (1) multiples of the mean background (exogenous) level; (2) multiples of the standard deviation for background levels; and (3) percentiles for the distribution of background levels (Table 8). These endogenous equivalent values are intended to help risk managers in search of a more pragmatic, science-based approach to managing the potential risks from ethylene oxide exposure. For example, the mean and SD endogenous equivalent levels are used as a basis of comparing to site-specific data below (see Figure 8).

Risk-specific concentrations

As described previously, state and federal agencies within the U.S. have conducted assessments to estimate the cancer potency of ethylene oxide (Table 9). Although both assessments are derived from the same epidemiology study, their values differ by several orders of magnitude owing to different approaches and decisions made at multiple steps in the derivation process, with the primary difference being the selection of different dose–response models. Using USEPA's and TCEQ's inhalation unit risk value, air concentrations corresponding to 1×10^{-5} extra cancer risk can be calculated as 0.0011 and 2.4 ppb, respectively, with the former being three orders of magnitude below ambient concentrations of ethylene oxide in air (Table 6), and the latter nearly equivalent to ambient air concentrations.

Public health benefits considerations

Health care-associated infections (i.e. infections resulting from treatment for another condition; HAIs) are of great importance to public health. A survey of 199 hospitals reported the prevalence of HAIs in 2015 to be approximately 3.2%, which was lower than the 4% noted from a similar survey conducted in 2011 (Magill et al., 2018). Sterilization of medical equipment and health-care products is essential to ensuring that the prevalence of HAIs remains as low as possible. Ethylene oxide is used to sterilize health-care products (e.g. drapes, gowns), implantable medical devices (e.g. bare metal stents, heart valves, vessel closure devices, etc.), and materials used during implantation procedures (e.g. catheters, guidewires, etc.) (Lambert et al., 2011). Ethylene oxide is an effective sterilizing agent against a wide variety of bacteria (e.g. *E. coli, E. faecalis, P. aeruginosa, M.* chelonei, *B. stearothermophilus, B. subtilis, B. circulans, S. aureus, M. terrae, B. atrophaeus, G. stearothermophilus, C. difficile*), viruses (herpes, vaccinia, parainfluenza, polio), and fungi (e.g. *A. flavus, A. niger, A. fumigatus, A. versicolor, N. fischeri, E. chevalieri, P. chrysogenum, C. globosum, Ulocladium*) (Ries et al., 1996; Alfa et al., 1996; Rakotonirainy et al., 2003; Rutala et al., 2020; Shintani, et al., 2017).

Ethylene oxide is particularly useful for sterilizing devices made from materials that are sensitive to heat, moisture, and/or radiolytic stress, for which alternative sterilization methods (e.g. autoclave, radiation) are incompatible (Shintani et al., 2017). Because ethylene oxide is compatible with a wide variety of materials, it is used to sterilize combination products where devices, drugs, and/or biologics are contained within a single product/packet (Lambert et al., 2011). Careful aeration of sterilized devices is needed to ensure that residual ethylene oxide concentrations are safe for use (Shintani et al., 2017).

Changes in ethylene oxide regulation due to the approximate 50-fold change in cancer potency estimate (USEPA, 2019) have affected operations at sterilization facilities in the U.S., which in turn affect the supply of medical devices. Shortages of sterilized medical devices might pose a threat to public health by delaying or disrupting critical care for patients, and is of even greater importance given the sterilization demands of hospitals as they manage the Covid-19 pandemic.

Example application to site-specific data for ethylene oxide

Considering the exogenous pathway in isolation, a comparison of site-specific air concentrations, using the data for the Illinois sites mentioned above (Medline, Vantage; **Attachment 1**), to background levels (local and national), 1×10^{-5} risk-specific concentrations (RSCs based on USEPA and TCEQ unit risk values), and endogenous equivalent levels is provided in Figure 8. For both sites, mean concentrations of ethylene oxide in air in the vicinity of the facility are within a factor of 2 to background national ambient air concentrations. Mean concentrations of ethylene oxide in air at both sites are below the 1×10^{-5} RSC calculated using TCEQ's unit risk value, but are well above the corresponding RSC calculated using USEPA's unit risk value (which is also the case for local and national background concentrations). Both site mean concentrations fall approximately an order of magnitude below the endogenous equivalent concentrations based upon either the mean or SD for HEV levels in the U.S. population or that experienced by the 50th percentile of the U.S. nonsmoking population.

Based upon the comparison in Figure 8 and on the information provided in this paper, the authors suggest that a risk manager might opt to use endogenous equivalent levels in at least two possible ways: (1) conclude that site-related exposures to ethylene oxide are negligible when compared to the magnitude and variation of endogenous exposures, and therefore no action is required to reduce site-related exposures; or (2) determine that site-related exposures to ethylene oxide are better managed using the unit risk from TCEQ (shallow linear slope assumption) rather than the unit risk from USEPA (steep linear slope assumption), since its predictions of risk fall within a more biologically plausible range when compared to magnitude and variation of endogenous exposures.

Potential risks from ethylene oxide are expected to be related to total exposure (i.e. from exogenous and endogenous pathways combined). When the exposures via the exogenous pathway are viewed within the context of total exposure to ethylene oxide in nonsmoking individuals, smoking individuals, and to a mixed population of smokers and nonsmokers (medium gray region of the columns in Figure 9), it may be concluded that the exogenous exposure pathway in the vicinity of these facilities is not an important contributor. Comparison of the total exposures for different exogenous exposures (ambient levels, 1×10^{-5} RSCs, site-related concentrations based on Medline IL site) in Figure 9 might be used to support a conclusion that site-related exposures do not contribute to a "*substantial difference*" from background total exposure that would warrant additional attention/action. That is, the column heights for each of the three exogenous exposure options are essentially the same, particularly when the variation in the endogenous and tobacco smoke pathways (error bars = SD in Figure 9) are taken into consideration. Since the increased prevalence of cancer was not observed with the elevated exposures to ethylene oxide from smoking (dark gray regions in Figure 9) (Jain 2020), and since the exogenous pathway (medium gray regions in Figure 9) is not an important contributor to total exposure in most cases, managing the potential risks from the exogenous pathway by investing resources to reduce ambient or site-related air concentrations of ethylene oxide to 1×10^{-5} RSC levels are not expected to result in a meaningful change to public health for nonsmoking individuals, smoking individuals, or a mixed population of smokers and nonsmokers.

Discussion and conclusions

This review is intended to provide a better understanding of issues associated with total exposures to ethylene oxide from endogenous and exogenous pathways. Based upon information available in the published literature, a number of general conclusions may be supported for ethylene oxide.

(1) HEV is a useful biomarker exposure that reflects total exposure to ethylene oxide from all pathways (endogenous and exogenous combined) for the several months prior to sampling.
(2) HEV is detectable in nearly all samples collected in the U.S. population (Center for Disease Control (CDC) 2019), indicating that all individuals have some level of exposure to ethylene oxide via endogenous and/or exogenous pathways.
(3) For nonsmokers, endogenous exposures to ethylene oxide serve as the largest contributor to total exposure:
    - Endogenous exposures to ethylene oxide result from multiple pathways, including those associated with the gastrointestinal lumen (bacterial) and systemic production.
    - There is considerable variation in measured HEV levels in the U.S. population, and this variation is generally consistent with the current understanding of variation in underlying factors and pathways for endogenous production.
    - Species differences in endogenous exposures to ethylene oxide are observed, with humans generally experiencing lower endogenous exposures than experienced by laboratory animals (with some species and strain differences noted).
(4) Some human populations (e.g. workers in specific industries, smokers) experience elevated exposures to ethylene oxide compared to the general population of nonsmokers. However, exposure trends in workers have

been decreasing over time in the U.S. due to better industry hygiene, engineering controls, and changes in occupational exposure limits. Similarly, tobacco-related exposures to ethylene oxide have also been decreasing over time due to changes in smoking habits in the U.S.

- Although diminishing over time, smoking remains the largest single source of ethylene oxide exposure to smoking individuals, and to the U.S. population considered as a whole (mix of smokers and nonsmokers).

(5) Exogenous exposure to ethylene oxide also indirectly affects endogenous production pathways possibly via an oxidative stress mechanism, and the latter pathway might be more important than the former pathway in contributing to total exposure.

(6) Risk associated with low-level environmental exposures (i.e. well below the point of departure estimated from dose–response modeling for cancer effects) is highly uncertain, and may be considerably lower than that estimated using USEPA's unit risk value (steep linear slope assumption), based on data collected in rats, on human experience with smoking, and on the unit risk for ethylene oxide derived by TCEQ (shallow linear slope assumption).

(7) Risk management of ethylene oxide exposures is challenging, and has important public health implications.

- RSC values based on USEPA's unit risk value (U.S. Environmental Protection Agency (USEPA) 2016) are negligible compared to endogenous production and its variation in contributing to total exposure.
- Ambient air concentrations of ethylene oxide are generally small compared to endogenous production in their contribution to total exposure.
- Use of ethylene oxide as a sterilizing agent provides a benefit to public health in reducing HAIs.

(8) Endogenous equivalent action levels provide a means for risk management decisions to be considered within the context of total exposure to ethylene oxide, so that the health impact of exogenous exposure pathways can be considered.

Although ethylene oxide is a well-studied chemical, substantial sources of uncertainty remain with respect to assessing potential risk to exposed human populations. Data needs for improving our understanding of ethylene oxide exposures and potential risks are identified below.

- *Endogenous Exposure Pathways* – The bacteria present in the human gastrointestinal tract has been characterized (Table 3), but data on the ethylene production status of many of these strains were not located. A more complete characterization of ethylene production by human gut bacteria is needed. In addition, a better understanding of the relative contribution of gastrointestinal tract vs. systemic endogenous pathways in humans would be useful (e.g. studies of HEV levels measured in humans following long-term antibiotic use, total parenteral nutrition).
- *Exogenous Exposure Pathways* – Recent monitoring efforts suggest ethylene oxide levels in air are widespread, and are generally consistent across rural, sub-urban, and urban locations (Table 6; U.S. Environmental Protection Agency (USEPA) 2019a). Better information is needed to understand the sources of ethylene oxide detected in ambient air, as well as for characterizing temporal and spatial variation in measured concentrations.
- *Mode of Action* – Although low-dose linearity is assumed for genotoxic agents as a matter of policy, there exists some empirical and mechanistic evidence for ethylene oxide that lends support for nonlinear dose–response relationship. In addition, data in rats (Marsden et al. 2009) indicate that exogenous exposure to ethylene oxide increases its production by endogenous pathways. Full consideration of the available evidence within a mode of action framework would be useful to support low-dose extrapolation assumptions. Additional mechanistic studies are needed to help inform low-dose extrapolations assumptions (e.g. characterization of the dose–

response relationship for key events in the proposed mode of action and relative contribution of endogenous and exogenous pathways following inhalation exposures to ethylene and ethylene oxide in B6C3F1 mice and F334 rats).

- *Cancer Potency Estimate* – USEPA recently derived unit risk value for ethylene oxide is approximately 50-fold higher than the previous derived unit risk value. This unit risk value could be reconciled with a number of data sets and analyses.
  1. Recent exposure reconstruction efforts which indicate that historical worker exposures may have been considerably higher than estimated for USEPA unit risk values (Bogen et al. 2019). In addition, the unit risk value should be assessed in terms of total exposures to workers, rather than relying solely on the characterization of the exogenous pathway, and include three components: (A) endogenous production; (B) exogenous occupational exposure; and (C) exogenous exposures from smoking, for which historical exposures are expected to be larger than current exposures due to changes in smoking habits (Table 7);
  2. The combined concentration-response data for ethylene and ethylene oxide (Figure 9) indicate that the default assumption of low-dose linearity may be invalid for this chemical;
  3. Epidemiology data for smokers, as a subset of the population with moderate exposure levels to ethylene oxide, provide an independent dataset which should be used to inform USEPA's unit risk value and its low-dose assumptions.
- *Risk-Benefit Analysis* – Because the use of ethylene oxide as a sterilizing agent provides a benefit to public health in reducing HAIs, a risk-benefit analysis would be useful in quantifying the net effects of any changes ethylene oxide use and release as a result of the USEPA's revised unit risk value. A draft case study of the "*health-risk tradeoff*" associated with managing ethylene oxides public health benefits and risks has been developed (ARA, 2020; Frasier 2020), serves as a good starting point for such an analysis.

From a public health standpoint, the potential health effects of ethylene oxide are best managed by carefully considering total exposures to human populations, and the relative contributions of underlying pathways. With smoking identified as the single largest source of ethylene oxide exposure to the U.S. population (Figure 5), efforts to reduce total exposures to ethylene oxide are best focused on maintaining the decreasing trends for tobacco use in the U.S. population (Table 7). Although dietary factors such as fatty acid consumption may exert a significant effect on total exposure to ethylene oxide, changes in fatty acid intakes cannot be recommended since the health benefits of consuming unsaturated fats over saturated fats are well recognized (USDA, 2010), and far outweigh any theoretical risks associated with increased endogenous ethylene oxide production. Similarly, attempts to reduce endogenous ethylene oxide production via management of gastrointestinal bacteria populations (e.g. reduction of ethylene-generating strains) is strongly not advised given the potential unforeseen consequences of gut biome manipulation and the potential impact this can have on human health. Exogenous ethylene oxide/ethylene exposure is identified as a relatively small contributor to total exposure. Because exogenous exposures represent only a small component of total exposure to ethylene, risk management efforts that rely on risk-based concentrations using USEPA's unit risk value are not expected to produce a meaningful impact on total exposure. For this reason, such approaches are not expected to produce a meaningful benefit to public health (i.e. reduced cancer risk). In contrast, to the extent that reliance on risk-specific concentrations for ethylene oxide results in reduced availability of sterilized medical equipment, this practice has the potential to cause a net detriment to public health (e.g. increased rate of HAIs). The updated endogenous equivalent levels for ethylene oxide provided herein enables risk managers to place decisions within the context of total exposure, so that risk management decisions are informed.

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Exhibit D

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Ethylene Oxide Exposure in U.S. Populations Residing Near Sterilization and Other Industrial Facilities: Context Based on Endogenous and Total Equivalent Concentration Exposures

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Abstract: Given ubiquitous human exposure to ethylene oxide (EO), regardless of occupation or geography, the current risk-specific concentrations (RSCs: 0.0001–0.01 ppb) from the U.S. Environmental Protection Agency (EPA) cancer risk assessment for EO are not useful metrics for managing EO exposures to the general U.S. population. The magnitude of the RSCs for EO are so low, relative to typical endogenous equivalent metabolic concentrations (1.1–5.5 ppb) that contribute ~93% of total exposure, that the RSCs provide little utility in identifying excess environmental exposures that might increase cancer risk. EO monitoring data collected in the vicinity of eight EO-emitting facilities and corresponding background locations were used to characterize potential excess exogenous concentrations. Both 50th and 90th percentile exogenous exposure concentrations were combined with the 50th percentile endogenous exposure concentration for the nonsmoking population, and then compared to percentiles of total equivalent concentration for this population. No potential total exposure concentration for these local populations exceeded the normal total equivalent concentration 95th percentile, indicating that excess facility-related exposures are unlikely to require additional management to protect public health.

Keywords: ethylene oxide; exposure metrics; endogenous equivalent concentration; total equivalent concentration; exposure contextualization; exposure science

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1. Introduction

In 2016, the U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS) assessment of ethylene oxide (EO) estimated risk-specific concentrations (RSCs) of 0.0001 to 0.01 parts per billion by volume (ppb), associated with a 10^{-6} to 10^{-4} increase in inhalation cancer risk, respectively [1]. As everyone is exposed to single-digit, parts per billion (ppb) equivalent levels of endogenous, metabolically-produced EO and fractions of ppb levels from inhalation of ambient air, regardless of their occupation or location of residence [2–5], these exceedingly low RSCs relative to endogenous levels and variability raise questions as to their practical utility in risk management of public exogenous EO exposure, as well as their scientific merit. In contrast, the Texas Commission on Environmental Quality (TCEQ) using the same cohort data as EPA IRIS, but a different dose-response model, estimated 10^{-6} to 10^{-4} RSCs of 0.24 to 24 ppb, respectively [6]. We note that neither the EPA nor TCEQ addressed the assumption of low exposure concentrations for early sterilization workers, which was shown to be invalid [7]. The EPA assessment short comings left a gap in our ability to interpret the health significance of general population exogenous EO background exposures from non-industrial and natural EO sources, and,

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perhaps more importantly, local general population exposures from point source industrial emissions. Kirman and Hays [2] and Kirman et al. [3] proposed an endogenous exposure metric, endogenous equivalent concentration, to provide context to exogenous exposures for decision-making by risk managers. This study proposes and evaluates the utility of a total exposure metric (total equivalent concentration) incorporating both background endogenous and exogenous EO exposures to help inform the health significance of excess ambient air exposures to EO.

As background, the primary limitation with the EPA RSCs for EO is that they are so low relative to the amount and variability in typical background endogenous and exogenous general population exposures that they have limited utility of distinguishing a health-significant increase in environmental exposure for risk managers. In addition, these RSCs are below the capabilities of current technology to measure these EO concentrations in ambient air (current method limit of detection (LOD) ~0.025–0.040 ppb). These RSCs are also more than two orders of magnitude below the EO ambient air concentrations, which are not associated with industrial emission sources (mean of 0.13 ppb based on recent EPA monitoring [5]). More importantly, these RSCs are more than three orders of magnitude below airborne concentrations equivalent to endogenously produced EO, in the general nonsmoking population (mean concentrations of ~1.9 and 2.9 ppb) based on data evaluated by Kirman and Hays [2], based on data from published unexposed control subjects [8–17] and Kirman et al. [3], and based on data from nonsmoking U.S. individuals [4], respectively. For additional perspective, as described by Bogen et al. [7], these RSCs are up to seven orders of magnitude below the levels of EO to which 1930s–1970s sterilization operators and other highly exposed sterilization workers in the National Institute for Occupational Safety and Health (NIOSH) cohort used by EPA in its risk assessment were exposed (50,000 to >100,000 ppb). Based on these comparisons, it is obvious that the EPA RSCs are incapable of providing useful benchmarks to evaluate the health significance of such low general population EO exposures. In addition, regulatory use of these RSCs inadvertently led to substantial confusion on the health significance of exogenous EO exposures among emitting facility management and locally exposed populations, resulting in public fear and closure of key medical supply sterilization operations [18,19], during the COVID-19 pandemic.

Total EO exposures in humans were characterized using hemoglobin adducts, specifically 2-hydroxyethylvaline (HEV), which serves as a useful biomarker of exposure, regardless of the exposure pathway. A summary of HEV levels in non-smokers and smoker populations and the relatively high variability in adduct levels in these population is provided in Kirman and Hays [2] and Kirman et al. [3]. The distribution of HEV levels for the non-smoking general population, therefore, describes the expected range of adducts from background exposure from endogenous and exogenous sources to which everyone is exposed in their daily lives. Kirman et al. [3] describe the three primary pathways of EO exposure to the non-occupational general population in the U.S.—(1) EO is produced endogenously in the body via multiple pathways, including ethylene from bacterial pathways in the gastrointestinal lumen and systemic enzymatic production from methionine and 2-keto-4-methylthiobutyric acid, (2) exogenous ethylene inhaled from ambient air and converted metabolically to EO, and (3) exogenous EO inhaled from ambient air from sources other than industrial emissions. To compare the contribution of these sources to total background EO exposure, HEV levels were converted to endogenous equivalent air concentrations (i.e., the amounts of exogenous EO exposures necessary to result in the measured endogenous HEV adduct concentrations, regardless of the three potential sources). Based on data collected between 1986 and 2012, a mean and standard deviation (SD) endogenous equivalent concentration were calculated (1.9 ± 1.3 ppb) [2]. More recently, Kirman et al. [3] recalculated equivalent levels incorporating two important changes—(1) HEV values for non-smokers in the U.S. population between 2013 and 2016 were used as the basis, instead of relying upon pooled data for unexposed experimental control subjects in the previous analysis, and (2) background levels of HEV were adjusted for contributions from exogenous exposure pathways (via ambient air), instead of assuming

that the contributions from exogenous exposures were negligible. The new endogenous equivalent mean was higher than that previously calculated (2.9 ± 2.3 ppb).

Thus, the endogenous pathway is a major source of the total EO exposure among the general population, however, everyone also receives a small exogenous exposure from ambient air. As described by Kirman et al. [3], the specific contributions of all sources to the mean total EO exposure concentration, as measured by the HEV adducts among the non-smoking general population (2.9 ppb; background EO exposure), were estimated as follows: (1) endogenous metabolism, 2.7 ppb (~93.1%); (2) exogenous ethylene inhalation and metabolism, 0.04 ppb (~1.4%); and (3) exogenous EO inhalation, 0.16 ppb (~5.5%). The contribution from ethylene metabolism from endogenous and exogenous sources (~94.5%) clearly indicates that exogenous EO exposure is a minor contributor to total background exposure among individuals in the non-smoking general population. As such, it is reasonable to conclude that EO exposure concentrations among the non-smoking local population near emitting facilities could be compared to the general population endogenous equivalent concentrations (based only on the endogenous contribution) [2,3] or perhaps more representatively, total equivalent concentrations (background endogenous and exogenous EO contributions), as exposure metrics to provide context for EO risk management. An example of this approach was shown in Kirman et al. [3]. This practical alternative risk management approach is based on the premise that increased exogenous exposure does not necessarily pose a significant increase in the risk of disease if the total exposure does not exceed the upper bound of the non-smoking total background exposure concentration range. This approach is equivalent to the medical interpretation of risk, based on the comparison of the level of a clinical measure to the normal population range (i.e., if the measured clinical value of interest is in the normal population range, such a value is not interpreted as an indicator of a treatment-required disease state).

The goal of this paper is to assess the utility of the normal nonsmoking population total equivalent exposure range to provide context for the EO exposures for local populations residing in the vicinity of sterilization and other EO emitting industrial facilities. To evaluate the utility of this exposure metric to inform risk management decisions, this study included the following:

- Development of distribution of percentiles of the nonsmoking general population endogenous equivalent concentrations and total equivalent concentrations.
- Characterization of recently measured ambient EO concentrations in the vicinity of sterilization and other EO emitting facilities and at corresponding representative background sites to assess exogenous exposure concentration above background levels.
- Assessment of the relative importance of excess EO concentrations in the vicinity of emitting facilities by comparing a central tendency or upper bound ambient air EO concentration added to the general population 50th percentile endogenous equivalent concentration, measures of total exposure, to the normal percentile range of nonsmoking general population total equivalent concentrations.

2. Materials and Methods

This section identifies the data and method used to characterize endogenous equivalent and total equivalent exposure concentrations, and EO concentrations in ambient air in the vicinity of emitting facilities and associated background locations.

2.1. Equivalent Exposure Concentrations

Recently, the Centers for Disease Control and Prevention (CDC) released biomonitoring data for HEV concentrations in the general U.S. population collected over two sampling periods (2013–14, 2015–16) for non-smokers (3841 persons) and smokers (93 persons) [4]. These data, which reflect a larger and more diverse population than assessed in Kirman and Hays [2], demonstrate that there are differences in HEV levels (and therefore in the total ethylene oxide exposure), depending on smoking status, age, and gender. These HEV levels in human blood can be converted to endogenous equivalent levels of ethylene oxide,

based on the following equation between HEV adduct levels and measured occupational exposures to ethylene oxide, adjusted to general population exposures [2].

$$\text{HEV (pmol/g Hb)} = 10.9 * [\text{EO, ppb continuous}] \quad (1)$$

Endogenous equivalent levels reflect air concentrations of ethylene oxide that are equivalent to the levels that are produced endogenously. The endogenous equivalent levels are calculated here for ethylene oxide, based on (1) HEV values from CDC for non-smokers in the U.S. [4], and (2) background levels of HEV adjusted for contributions from exogenous EO exposure pathway (via ambient air [5]). This process produces two exposure metrics—(1) endogenous equivalent concentrations that represent continuous exposure levels produced metabolically from endogenous ethylene, and (2) total equivalent concentrations that represent continuous exposure produced both metabolically and from inhaled ambient air. Distributions of these metrics were developed to describe the percentile concentrations of non-smoking general population normal exposure.

2.2. EO Concentrations in Ambient Air Near Emitting U.S. Facilities and Associated Background Locations

Ambient air samples were collected at selected locations, in the vicinity of emitting U.S. facilities, to characterize EO concentrations for local populations. To date (as of 19 October 2020), we are aware of publicly available data concerning monitoring programs associated with seven sterilization facilities (Medline, Sterigenics-Illinois, Sterigenics-Georgia, Becton-Dickinson, Sterilization Services, Terumo, and Viant) and one specialty chemical facility (Vantage). With each monitoring programs, samples were also collected at various distances from the facility to characterize the reference ambient air EO concentrations from non-industrial sources (background concentrations), which, in turn, would help inform what fraction of the EO in air in the vicinity of a facility might be related to facility emissions.

2.2.1. Available Data

The EO monitoring programs for the eight facilities providing data that were evaluated in this manuscript are described in Table 1; the raw data can be found in Supplementary Material S1. All samples were long-term (24 h and, to a much lesser extent, 12 h) and were collected at multiple locations, generally within 2000 m of the facility and over multiple days per month and months per year. None of the monitoring represented samples collected over an entire year, although several programs likely captured most seasonal differences in wind direction. The one exception was the Viant facility for which there was very limited temporal data collected. Samples at the Medline and Terumo facilities were unique because they were collected before and after installation of additional EO emissions control technology. Facility monitoring programs collected local background/reference samples at locations between 2000 and 10,000 m from the facility location. Again, the exception was Viant, where no reference samples were identified, so four location >2100 m from the facility were selected as the background reference locations. In addition, the background locations for the three Georgia facilities (Coffee Park and South DeKalb, Atlanta, GA, USA) were more state than local background locations and were located at substantial distances from these facilities (>22,500 to >45,000 m for the closest background location).

Additionally, there were national ambient EO monitoring data collected under the EPA National Air Toxics Trends Stations (NATTS) and Urban Air Toxics (UAT) monitoring Programs. The goals of these monitoring program were to identify and reduce air toxics of greatest potential concern, for contribution to the general population risk.

Table 1. Summary of publicly-available datasets concerning ambient EO concentrations in the vicinity of seven sterilization and one other EO-emitting industrial facility [1] and at corresponding representative background locations.

Facility	Location	Year	Season [1]	*n* (sites) [2,3]	Dist. [4]	Dur. [5]
Medline [6] [20]	Waukegan, IL	19/20	A, B, C	174 (5)	~190–1660	24
Vantage [20]	Gurnee, IL	19/20	A, B, C	250 (5)	~260–1130	24
Background [20]	Gurnee, IL	19/20	A, B, C, D	98 (2)	>2440	24
Sterigenics [21]	Willowbrook, IL	18/19	C, D	237 (8)	~100–1700	24
Background [22]	Chicago, IL area	18/19	C	28 (14)	>9600	12
Sterigenics [23]	Smyrna, GA	19/20	A, B, C, D	211 (7)	~280–1970	24
BD [7] [24]	Covington, GA	19/20	A, B, C, D	267 (8)	~60–1980	24
SS [8] [25]	Atlanta, GA	19/20	A, B, D	64 (3)	~150–840	24
Background [26]	General Coffee, GA	19/20	A, B, C, D	25 (1)	>290,000	24
Background [27]	South DeKalb, GA	19/20	A, B, C, D	58 (2)	>22,500	24
Viant [28]	Grand Rapids, MI	18/19	A, B, C, D	20 (12)	~80–1520	24
Background [28]	Grand Rapids, MI	19	A	4 (4)	>2100	24
Terumo [29]	Lakewood, CO	18	B, C	84 (8)	~40–1570	24
Background [29]	Denver, CO area	18	C	18 (4)	>4500	24

[1] Season in which samples were collected: A, spring (Mar.–May); B, summer (Jun.–Aug.); C, fall (Sept.–Nov.); D, winter (Dec.–Feb.); [2] total number of samples (total number of sampling sites); [3] excludes facility data during temporary shutdown or after permanent shutdown; [4] distance of sample sites from facility in meters; [5] duration of samples in hours; [6] did not include measurement data during which the facility was temporarily shut down; [7] BD, Becton Dickinson; and [8] SSG, Sterilization Services.

2.2.2. EO Collection and Analytical Methods Applied to EO Monitoring

Concentrations of EO from national monitoring program samples and facility monitoring samples were determined by the protocols in EPA Compendium Method TO-15 and its recent update TO-15A, both of which were incorporated into the NATTS Technical Assistance Document (TAD) [30]. The NATTS method used Method TO-15 as its foundation—(1) sample collection of ambient air usually for a 24-h period into an evacuated summa or silica-coated canister; (2) pre-concentration of an aliquot to remove permanent gases and carbon dioxide; (3) moisture management techniques to remove interfering water; (4) injection of the sample into a gas chromatograph for separation of individual species; and (5) detection by mass spectrometry, either by full scan or (mostly) the selected ion mode. The current method was based on refinements of the NATTS TAD specifications undertaken throughout the period in which these samples were collected. Sensitivity was determined by EPA's contract laboratory on three separate systems, using 7 spiked canisters at 0.1 ppb (by volume), resulting in method detection limits from 0.025 to 0.061 ppb [31].

2.2.3. Statistical Methods

Non-detect data were assigned a value of limit of detection divided by 2, and the collocated samples were averaged and treated as a single sample in subsequent analyses. Exploratory analyses were performed, examining not only the EO concentration by location over time, but also the distribution by facility and location, to investigate skewness and potential outliers. Two unusually high concentration samples were removed from the Georgia background data set, but no potential outliers were removed from other background data sets or any facility area data sets. The EO concentration of each sub-group was tested for normality or lognormality. For each facility and location, the mean and SD were calculated, along with the 50th and 90th percentiles, based on the lognormal distribution.

2.3. Comparing EO Exposure Concentrations to Endogenous Equivalent Concentration Benchmarks

Three exposure comparisons were proposed to provide context for interpreting the health implication of exposure concentrations near emitting facilities—(1) compare the facility mean concentration to local background mean concentration (i.e., increase above background), (2) compare the facility mean concentration to the endogenous equivalent mean concentration (i.e., fraction of endogenous equivalent), and (3) add the facility 50th

and 90th percentile concentration to the 50th percentile endogenous equivalent concentration, and compare this total exposure metric to the non-smoking population percentile total equivalent concentration.

3. Results

3.1. Total Equivalent and Endogenous Equivalent Concentrations

Kirman and Hays [2] initially proposed endogenous equivalent concentrations in air for EO (termed action levels), considering it endogenous HEV production. These endogenous equivalent concentrations were recalculated for EO, based on the mean HEV values from CDC for nonsmokers in the U.S. [4] and levels of HEV were adjusted for contributions from exogenous exposure pathways, instead of assuming that contributions from exogenous exposures were negligible [3]. Table 2 summarizes the percentiles of the distribution of the nonsmoking U.S. population for the total equivalent concentration metric, the focus of this evaluation, as well as the endogenous equivalent concentration metric. The total equivalent concentrations were about 0.2 ppb greater than the endogenous concentrations, as exogenous background concentrations constitute a small fraction of total exposure.

Table 2. Total equivalent and endogenous equivalent EO air concentrations (ppb) using HEV levels (pmol/g Hb) in percentiles of nonsmoker population in the United States, as originally reported by Kirman et al. [3], based on CDC [4] data.

Percentile	HEV_{unadj} [1]	Total Eq. [2]	HEV_{adj} [3]	Endog. Eq. [4]
	pmol/g Hb	ppb	pmol/g Hb	ppb
P5	13.4	1.3	11.2	1.0
P10	16.0	1.5	13.8	1.3
P25	20.8	1.9	18.6	1.7
P50	27.0	2.5	24.8	2.3
P75	35.1	3.2	32.9	3.0
P90	47.5	4.4	45.3	4.2
P95	60.1	5.5	57.9	5.3

[1] HEV_{unadj}, HEV level from exogenous + endogenous sources; [2] total equivalent EO concentration from endogenous and background exogenous source; [3] HEV_{adj}, HEV level from endogenous sources only; and [4] endogenous equivalent EO concentration from individual metabolism.

3.2. Facility Vicinity and Background EO Concentrations

Figure 1 shows the distribution of EO concentrations in the vicinity of the eight facilities and at corresponding representative background locations. It is clear that the concentrations were positively skewed, especially near these facilities, indicating that the median was a more representative measure of central tendency than the mean. Except for Terumo (pre-additional EO emission controls), median concentrations in the vicinity of the facilities were less than 0.5 ppb. Peak EO concentrations at Terumo and Medline were greatly reduced with implementation of additional emission controls.

As shown in Table 3, these EO concentrations were separately fit to the lognormal distributions, from which the selected percentiles were estimated. For facility vicinity EO concentrations, Vantage had the lowest 50th percentile (0.09 ppb) and 90th percentile (0.43 ppb), whereas Terumo (pre-additional emission controls) had the highest 50th percentile (0.87 ppb) and 90th percentile (3.1 ppb); the majority had a 50th percentile less than about 0.20 ppb and a 90th percentile less than about 0.90 ppb. The 50th percentile (0.07 to 0.13 ppb) and 90th percentile (0.12 to 0.56 ppb) for the background locations were comparatively less variable. These metrics provide further support for characterizing ambient air EO distributions as positively skewed.

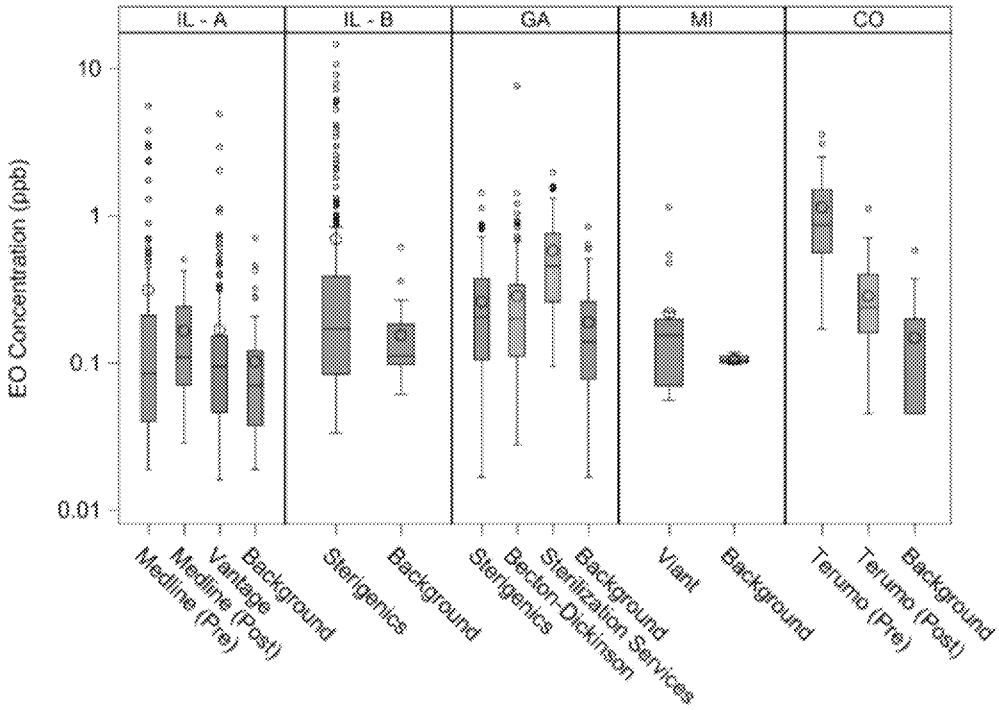

Figure 1. Distribution of ambient air EO concentrations in the vicinity of eight EO-emitting industrial facilities and at corresponding representative background locations. Length of box = interquartile range (IQR or P75–P25); horizontal line = P50; large circle = mean; lower whisker = P25 – (1.5 × IQR); upper whisker = P75 + (1.5 × IQR); small circle = potential outlier.

Table 3. Statistical characterization of EO concentrations (ppb) in ambient air in the vicinity of eight EO-emitting industrial facilities and at corresponding representative background locations.

Facility (Controls [1])	Mean ± SD	P50 [2]	P90 [3]
Medline (pre)	0.31 ± 0.74	0.11	0.86
Medline (post)	0.17 ± 0.12	0.13	0.43
Vantage	0.17 ± 0.40	0.09	0.43
Background	0.10 ± 0.11	0.07	0.26
Sterigenics [4]	0.70 ± 1.72	0.22	1.92
Background	0.15 ± 0.11	0.13	0.31
Sterigenics [5]	0.26 ± 0.21	0.19	0.77
Becton Dickinson	0.28 ± 0.50	0.20	0.73
Sterilization Services	0.58 ± 0.42	0.46	1.45
Background	0.19 ± 0.16	0.13	0.56
Viant	0.22 ± 0.26	0.15	0.57
Background	0.11 ± 0.01	0.11	0.12
Terumo (pre)	1.14 ± 0.87	0.87	3.10
Terumo (post)	0.29 ± 0.21	0.21	0.89
Background	0.15 ± 0.15	0.10	0.44

[1] Pre- or post-installation of additional EO emissions controls; [2] P50, lognormal estimate of the 50th percentile; [3] P90, lognormal estimate of the 90th percentile; [4] Sterigenics in Willowbrook, IL; and [5] Sterigenics in Smyrna, GA.

3.3. National Background and Local Background EO Concentrations

Background EO concentrations in ambient air represent EO emissions from natural and anthropogenic sources, excluding point source industrial emissions. Background sources include EO released from microbial processes in soil and exhaust from automobiles and stationary sources of hydrocarbon combustion [32]. An overall mean background EO concentration in ambient air was nationally (0.13 ppb) calculated for EO monitoring

at 27 monitoring locations, as part of the EPA's NATTS and UAT monitoring program stations, sampled between October 2018 and September 2019 [5]. The overall mean for EO concentration for local background EO concentration (0.14 ppb) for the eight industrial facilities evaluated herein was calculated for 27 individual locations sampled at various times between September 2018 and August 2020 (Table 4). The national and local background monitoring programs thus contained the same number of monitoring locations, were sampled in overlapping time-periods and provided equivalent results.

Table 4. Ambient air EO concentrations (ppb) at the NATTS and UAT locations (as reported by EPA in 2020 and summarized by ATSDR [5]) and at representative background locations associated with the eight EO-emitting industrial facilities.

NATTS / UAT Background		Facility Background	
Location	**ppb**	**Location**	**ppb** [1]
Phoenix, AZ	0.22	Denver, CO area	0.18
Phoenix, AZ	0.12	Denver, CO area	0.07
Grand Junction, CO	0.17	Denver, CO area	0.25
Pinellas Park, FL	0.08	Denver, CO area	0.08
St. Petersburg, FL	0.08	General Coffee, GA	0.20
Valrico, FL	0.08	South DeKalb, GA	0.19
Northbrook, IL	0.15	South DeKalb, GA	0.15
Schiller Park, IL	0.19	Chicago, IL area	0.18
Ashland, KY	0.16	Chicago, IL area	0.15
Calvert City, KY	0.16	Chicago, IL area	0.09
Grayson, KY	0.14	Chicago, IL area	0.14
Smithland, KY	0.17	Chicago, IL area	0.17
Albany, NY	0.10	Chicago, IL area	0.10
Bronx, NY	0.09	Chicago, IL area	0.11
Bronx, NY	0.08	Chicago, IL area	0.10
Camden, NJ	0.19	Chicago, IL area	0.10
Chester, NJ	0.19	Chicago, IL area	0.10
E. Brunswick, NJ	0.17	Chicago, IL area	0.49
Elizabeth, NJ	0.16	Chicago, IL area	0.15
Pinnacle, NY	0.10	Chicago, IL area	0.27
Queens, NY	0.08	Chicago, IL area	0.11
Rochester, NY	0.10	Gurnee, IL	0.11
Dearborn, MI	0.13	Gurnee, IL	0.09
St. Louis, MO	0.15	Grand Rapids, MI	0.10
Bountiful, UT	0.14	Grand Rapids, MI	0.10
Lacey, WA	0.11	Grand Rapids, MI	0.12
Seattle, WA	0.09	Grand Rapids, MI	0.10
Overall mean ± SD	0.13 ± 0.04	Overall mean ± SD	0.14 ± 0.14

[1] All values are means of multiple measurements at a single sampling site over time, except for those in Grand Rapids, MI and one location in Chicago, IL, which are single measurements.

As shown in Figure 2, the national ambient air monitoring sites mean background EO concentration and the local facility-related monitoring sites mean background EO concentration were comparable (0.13–0.14 ppb); a Wilcoxon statistical comparison of these means showed no statistically significant difference. The overall national mean calculated here (0.13 ppb) was slightly lower than the mean calculated from an earlier data set (0.16 ppb) [3].

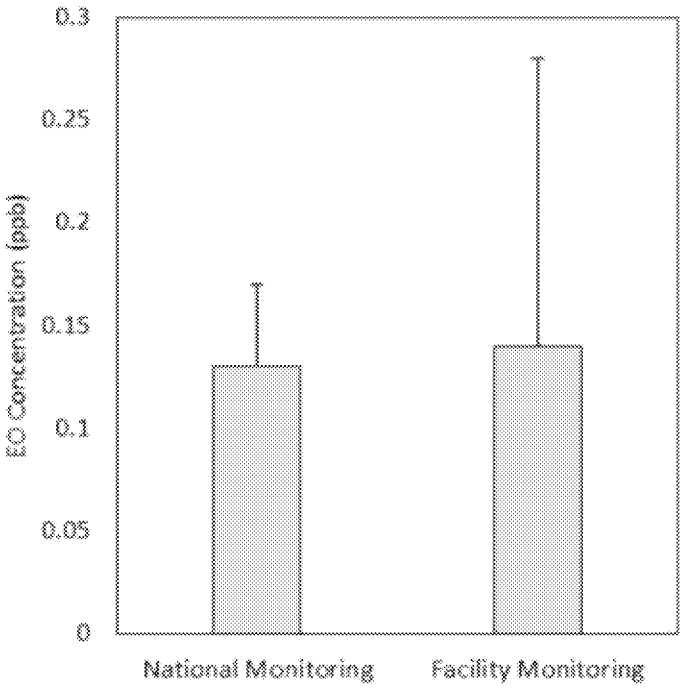

Figure 2. Overall mean (top of box) and SD (whisker) of ambient air EO concentrations across 27 national monitoring locations and across the 27 individual locations aggregated into five background locations for the facilities characterized in this manuscript.

3.4. Risk Management Context for Near Facility Potential Population Exposure Concentrations

Figures3 and 4 summarize the values for exposure metrics that provide context for interpreting the health significance of potential EO exposure concentrations in the vicinity of the eight emitting facilities evaluated in this study. In all cases, the mean concentration in the vicinity of the facility was no greater than eight times the mean background concentration for the facility and in a substantial majority of the cases, was greater by two or less (Figure3). Thus, the facility mean concentrations were not substantially elevated above the related background mean concentrations. Similarly, the facility mean concentration composed a small fraction of the endogenous equivalent mean concentration, generally 0.1 or less. This finding was consistent with previously reported analyses that exogenous concentrations constitute a small fraction of endogenous EO exposure concentrations [3]. More importantly, the final two metrics that evaluate the significance of adding the exogenous facility area 50th and 90th percentile EO concentration to nonsmoking population 50th percentile endogenous concentration, showed that these total exposure concentrations were within the normal population range of total equivalent exposure concentrations experienced by nonsmoking populations in the United States (Figure4). For the 50th percentile exogenous addition, all total concentration values were within the 75th percentile total equivalent concentration and the vast majority were approximately equal to 50th percentile total equivalent concentration. For the 90th percentile addition, all total concentration values were within the 95th percentile total equivalent concentration and the vast majority were equal to or less than the 75th percentile total equivalent concentration.

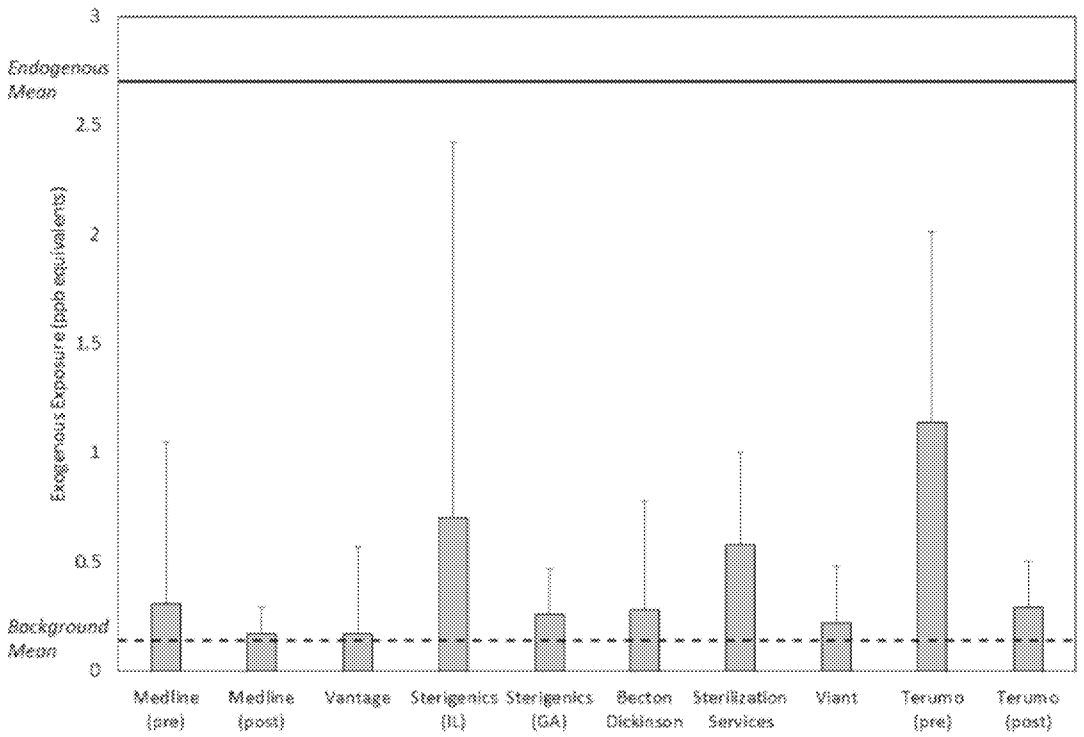

Figure 3. Mean (top of box) and SD (whisker) of ambient air EO concentrations in the vicinity of eight sterilization and other EO-emitting industrial facilities, relative to overall facility-specific background mean EO concentration (0.14 ppb) and endogenous mean EO concentration for the non-smoking U.S. population (2.7 ppb).

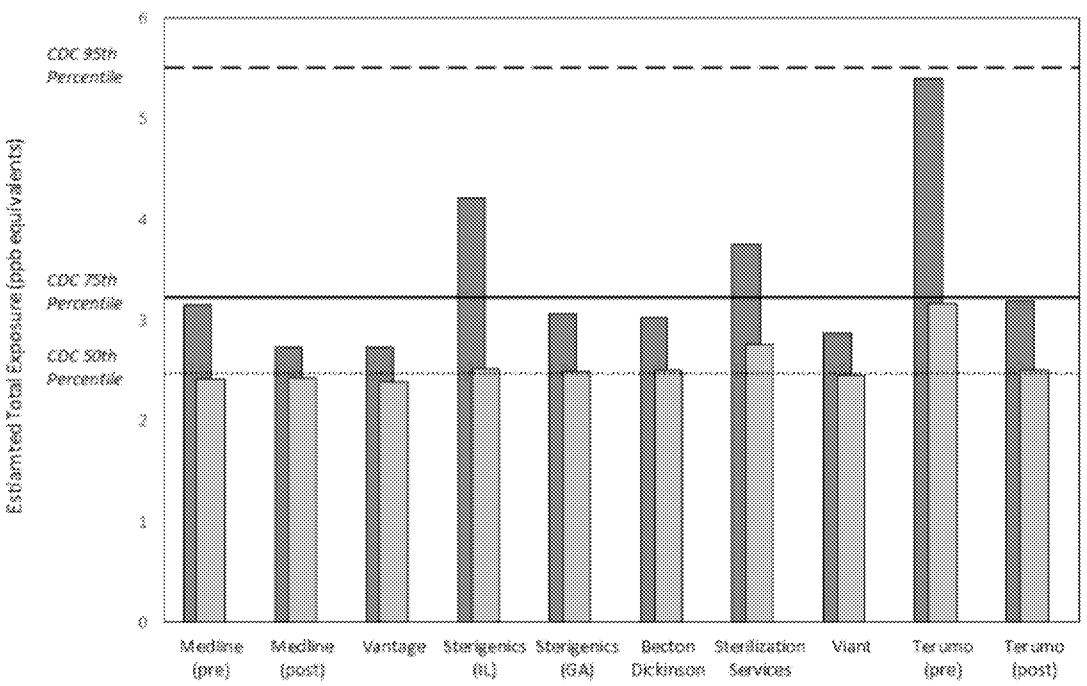

Figure 4. Estimated total equivalent exposure to EO in the vicinity of eight sterilization and other EO-emitting industrial facilities relative to that of the 50th, 75th, and 95th percentiles of the non-smoking U.S. population (2.5, 3.2, and 5.5 ppb, respectively). Light gray = [50th percentile endogenous equivalent for the non-smoking U.S. population, or 2.3 ppb] + [50th percentile EO concentration for the facility area from Table3]. Dark gray = same as light gray, except using 90th percentile EO concentration for the facility area from Table3 .

4. Discussion

The limitations in the utility of the EPA IRIS cancer risk assessment for EO left a serious gap in confidence in interpreting the health significance of general population EO exposure, and of particular interest, managing exposure risk for local populations in the vicinity of EO emitting sterilization and other industrial facilities. As everyone is exposed to EO and endogenous exposure from ethylene metabolism is the predominant pathway, Kirman and Hays [2] and Kirman et al. [3] calculated endogenous equivalent concentration values for nonsmokers to help risk managers in search of a pragmatic science-based approach to informing management potential EO risk for exposed general populations. The evaluations herein provide an additional nonsmoker population exposure metric, total equivalent concentration, focused specifically on providing context to the health significance of EO exposures for populations in the vicinity of sterilization facilities and other industrial emitting facilities, as these population receive an additional exogenous EO exposure beyond the general population background exposure. Both the endogenous equivalent concentration and total equivalent concentration metrics are based on the premise that exposure concentrations within the normal ranges of these metrics should not significantly increase risk. This premise is consistent with clinical metrics for which the risk of disease does not increase significantly until the values are above the healthy population normal range defined by individual variability within the population.

The health significance of facility area concentrations in this analysis was defined as a continuous total exposure concentration (50th percentile endogenous concentration + facility area exogenous concentration) greater than the 95th percentile total equivalent EO concentration, a statistical upper bound of the normal nonsmoking population range. The analyses summarized in Table 4 above show that the facility mean concentrations were not substantially above the representative mean background concentrations (frequently <2 fold) and compose a small fraction of the mean endogenous equivalent concentration (generally <0.1). More importantly, this analysis showed that the excess exogenous concentrations experienced near facilities did not contribute substantially to the nonsmoking population total EO exposure. This was indicated by the total equivalent concentration percentile comparisons, which showed that all total concentration values were within the 95th percentile total equivalent concentration for background populations not exposed to industry emission sources, and the vast majority were equal to or less than the 75th percentile total equivalent concentration.

Kirman et al. [3] also evaluated exogenous EO exposures from populations of smoking individuals as well as non-smoking individuals. Since increased prevalence of EO-associated cancer (lymphoid and breast) was not observed with the elevated exposures to EO from smoking where endogenous production levels were up to an order of magnitude higher than for non-smokers [33], endogenous equivalent and total equivalent concentrations for nonsmokers in the general population should be considered to be conservative metrics in informing risk management decisions for locally exposed populations.

The endogenous equivalent and total equivalent concentration risk management metrics are believed to be health conservative, supported by current HEV data for U.S. populations [4], and the science of EO metabolic production is easy to interpret. Thus, these should provide additional risk management tools to contextualize general population exogenous EO exposures during this period of uncertainty in EO cancer risk assessment. An additional benefit of the HEV data is that they can be informative for contextualizing individual adduct measures from populations residing near EO emitting facilities.

5. Conclusions

Total equivalent concentration, derived from adduct data for nonsmokers in the U.S., provides an exposure metric to inform risk management decisions for individuals and populations in the vicinity of emitting industrial facilities, accounting for their total EO exposure. Without useful RSCs, this total exposure metric can provide important context

as to whether the increased general population EO exposures resulting from industrial emissions are sufficient to pose an increased risk of cancer.

Supplementary Materials: The following are available online at https://www.mdpi.com/1660-4601/18/2/607/s1. S1: Publicly available datasets (as of 19 October 2020) concerning ambient EO concentrations in the vicinity of eight sterilization and other EO-emitting industrial facilities and at corresponding representative background locations.

Author Contributions: This study was conceptualized by the author team. Endogenous equivalent and total equivalent concentration evaluation were performed by C.R.K. Statistical analysis of EO monitoring data was performed H.N.W. EO sampling and analytical methodology was described by E.D.W. Writing was performed primarily by P.J.S., R.C.L., and C.R.K. Final review and editing was performed by J.S.B. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Publicly available datasets were analyzed in this study. These data can be found in the References section.

Conflicts of Interest: P.J.S., R.C.L., C.R.K., E.D.W., and J.S.B. provide consulting services to sterilization facilities or Industry Associations with interest in EO. None of these entities contributed to the planning, research, preparation or review of this manuscript. This manuscript is solely the work of the authors https://www.cdc.gov/exposurereport/index.html.

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Exhibit E

Exhibit F

EMERGING TECHNOLOGIES TEST REPORT

Proton Transfer Reaction/Time of Flight Mass Spectrometry (PTR-TOF-MS) Measurements of "Everyday Sources" for Ethylene Oxide

The Advanced Medical Technology Association
Washington, DC

Prepared For:

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Document Number: **928ET-641107-RT-23r1**
Test Dates: **August 21, 2019**
Submittal Date: **October 16, 2019**

Project Summary

Montrose Air Quality Services was contracted by The Advanced Medical Technology Association (AdvaMed) to conduct a study to measure the concentrations of ethylene oxide (EtO) in various "Everyday" sources. The study was conducted using Montrose's state-of-the-art mobile laboratory platform utilizing an Ionicon Proton Transfer Reaction Mass Spectrometer model PTR-TOF-MS-6000x3 (PTR-MS). The study took place on August 21, 2019 in Ashburn, Virginia.

The PTRMS was operated in oxygenal (O_2^+) chemical ionization mode to collect real time (1/5 sec) data for measurement of EtO. The TOF tube was operated at a voltage of 100V for measurement of EtO. These operational conditions were identified through method development experiments to provide optimal detection of EtO and resolution from its isomer, acetaldehyde.

Summary of Measurements

Eleven different "Everyday" sources were sampled, some at multiple conditions. Each source was sampled via a heated-head pump through a heated sample line with a heated stainless steel probe. Because of the complexity of the sample matrices, the samples were dynamically diluted using NIST traceable mass flow controllers (MFC) prior to measurement. Dilution decreases the sample complexity minimizing the main interferences such as isomers, fragmentation of other compounds, and/or reduction of the reagent ions available for the target compound to associate. The dilution process decreases the potential for measurement bias due to interferences.

Montrose has conducted research to identify possible interfering compounds for this method and verified by direct measurement that acetaldehyde, benzene, toluene, ethylbenzene, and xylenes, if present, would not bias the PTRMS response of target compound EtO. However, there is a small possibility that some other unknown compound(s) may be present in the sample matrix that could bias the analytical results as reported. However, the likelihood is small given that our experienced PTRMS operators failed to observe any evidence of this on-site.

The results listed in Table 1 below are the concentrations as measured directly on-site. However, a specialized sampling enclosure was not employed to guarantee a fully representative sample was collected for measurement.

Table 1: Analytical Results for Everyday Sources. (Worst Case)

Everyday Source	EtO Concentration	
	ppbv	ug/m3
Mercedes Sprinter Bluetec Diesel, idle	100	180
Mercedes Sprinter Bluetec Diesel, revved	140	252
Diesel generator from Sprinter	190	342
Toyota 4 runner, ~2003 model, idle	110	198
Toyota 4 runner, ~2003 model, high RPM	230	414
Gas generator cold start	18,000	32,400
Gas lawn mower cold start	3,000	5,400
Gas lawn mower	450	810
Gas grill	140	252
Charcoal fire	5,000	9,000
Wood fire pit	750	1,350
Kimchi (freshly opened)	1,800	3,240
Kombucha (freshly opened)	400	720
Sauerkraut (freshly opened)	100	180
Kimchi repeat (after sitting)	480	864

The results provided in this report relate only to the items tested. Data analysis and deconvolution was performed by Dr. Antonios Tasoglou of RJ Lee.

Prepared by:

David Berkowitz

Reviewed by:

Peter Zemek, Ph.D.

This is the last page of the report

Ethylene Oxide Ambient Concentrations at National Air Toxics Trends Stations
and Urban Air Toxics Monitoring Program stations
October 1, 2018 – March 31, 2019

Site Name	City	State	Network	AQS Site ID	Average by Site (in micrograms per cubic meter) [National average = 0.297]
PXSS	Phoenix	AZ	National Air Toxics Trends	04-013-9997	0.397
SPAZ	Phoenix	AZ	Urban Air Toxics	04-013-4003	0.345
GPCO	Grand Junction	CO	National Air Toxics Trends	08-077-0018	0.261
NBIL	Northbrook	IL	National Air Toxics Trends	17-031-4201	0.294
SPIL	Chicago	IL	Urban Air Toxics	17-031-3103	0.365
ASKY	Ashland	KY	Urban Air Toxics	21-019-0017	0.286
BLKY	Smithland	KY	Urban Air Toxics	21-139-0004	0.312
GLKY	Grayson lake	KY	National Air Toxics Trends	21-043-0500	0.185
TVKY	Calvert City	KY	Urban Air Toxics	21-157-0014	0.363
DEMI	Dearborn	MI	National Air Toxics Trends	26-163-0033	0.242
S4MO	St. Louis	MO	National Air Toxics Trends	29-510-0085	0.270
CHNJ	Chester	NJ	Urban Air Toxics	34-027-3001	0.361
CSNJ	Camden	NJ	Urban Air Toxics	34-007-0002	0.350
ELNJ	Elizabeth	NJ	Urban Air Toxics	34-039-0004	0.305
NRNJ	East Brunswick	NJ	Urban Air Toxics	34-023-0011	0.298
BTUT	Bountiful	UT	National Air Toxics Trends	49-011-0004	0.338
LAWA	Lacey	WA	Urban Air Toxics	53-067-0013	0.192
SEWA	Seattle	WA	National Air Toxics Trends	53-033-0080	0.185

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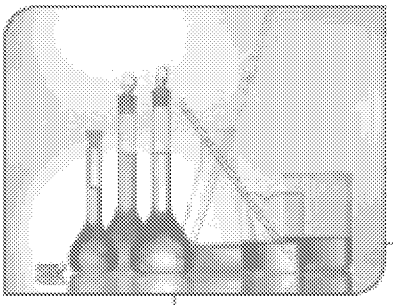
Exhibit G



OSHA FACT Sheet

Ethylene Oxide

What is ethylene oxide?

Ethylene oxide (EtO) is a flammable, colorless gas at temperatures above 51.3 °F (10.7 °C) that smells like ether at toxic levels. EtO is found in the production of solvents, antifreeze, textiles, detergents, adhesives, polyurethane foam, and pharmaceuticals. Smaller amounts are present in fumigants, sterilants for spices and cosmetics, as well as during hospital sterilization of surgical equipment.

How can ethylene oxide harm workers?

In addition to eye pain and sore throat, exposure to EtO can cause difficult breathing and blurred vision. Exposure can also cause dizziness, nausea, headache, convulsions, blisters and can result in vomiting and coughing. Both human and animal studies show that EtO is a carcinogen that may cause leukemia and other cancers. EtO is also linked to spontaneous abortion, genetic damage, nerve damage, peripheral paralysis, muscle weakness, as well as impaired thinking and memory. In liquid form, EtO can cause severe skin irritation upon prolonged or confined contact.

What should employers know about ethylene oxide?

Employee exposure is limited to one part EtO per million parts of air (1 ppm) measured as an 8-hour time-weighted average (TWA). Employee exposure may not exceed the short-term excursion limit of 5 ppm EtO averaged over any 15-minute sampling period. These limits are called permissible exposure limits (PELs).

Most occupational exposures to EtO are covered by the OSHA standard. The standard does not apply, however, when employers can demonstrate that the processing, use, or handling of products containing EtO will not release airborne concentrations of EtO at or above the standard's action level of 0.5 ppm. The action level is calculated as an 8-hour TWA and is the threshold for increased compliance activities (e.g., air monitoring, medical examinations, labeling, employee information, and training).

For details of the requirements in OSHA's EtO standard for occupational exposures, see *Title 29 of the Code of Federal Regulations* (*CFR*) Part 1910.1047. *Note*: Workplaces are exempt from this standard when objective data shows that the processing, use, or handling of products containing EtO cannot release airborne concentrations of EtO at or above the action level or in excess of the excursion limit during normal conditions.

What must employers do when exposures exceed the standard's permissible exposure limits?

If employee exposures exceed either the PEL or the excursion limit, employers must take the following actions:

- Use engineering controls and work practices to control employee exposure.
- Establish and implement a written compliance program to reduce exposures to or below the TWA and exposure limit.
- Establish personal air monitoring as well as information and training programs for employees exposed to EtO at or above the action level or above the excursion limit. Conduct training upon initial job assignment and annually.
- Establish a regulated area wherever airborne concentrations of EtO are expected to exceed the 8-hour TWA or the excursion limit.
- Establish a medical surveillance program for employees exposed to EtO at concentrations above the action level of 0.5 ppm, measured as an 8-hour TWA, for more than 30 days per year.
- Place warning labels on all containers that might cause employee exposures at or above the action level or excursion limit.
- Remember that employee rotation is prohibited as a means of compliance with the 8-hour TWA or exposure limit.
- Select, provide, and maintain appropriate personal protective equipment and ensure that employees use it to prevent skin and eye contact.

When must employers require workers to use respirators?

Employers must ensure that workers use respirators to control EtO exposure in the following circumstances:

- During installation or implementation of feasible engineering controls and work practices;
- During maintenance, repair, and certain operations when engineering and work practice controls are not feasible;
- When engineering and work practice controls are not currently available to reduce exposures to or below the PEL; and
- During emergencies.

What are employers required to do concerning exposure monitoring?

To help protect workers, employers must conduct the following exposure monitoring:

- Initial monitoring to determine the airborne concentrations of EtO that workers are exposed to (representative sampling of employees' exposures is permitted).
- Periodic exposure monitoring if the airborne concentration of EtO is at or above the action level or above the 15-minute excursion limit.
- Additional monitoring if there has been a change in workplace conditions, such as a change in the

process or materials used, and if the change could increase employee exposures.

Note: If the exposure level is maintained below the action level, you may discontinue TWA monitoring until there is a change in production, equipment, processes, personnel, or control measures that may result in new or additional exposure to EtO.

Employers must also do the following:

- Allow affected employees or their designated representatives to observe the monitoring.
- Notify affected employees of the results of the monitoring within 15 working days of receiving the results.

Do all businesses where EtO is present need medical surveillance programs?

Employers must implement a medical surveillance program, conducted or supervised by a licensed physician, for an employee under the following circumstances:

- If the employee is assigned to an area where exposure to EtO may be at or above the action level for 30 days or more during the year.
- If the employee has been exposed to EtO in an emergency situation.

What steps must employers take to communicate with workers about EtO exposure?

Employers must do the following to communicate information to affected workers:

- Establish regulated areas where occupational exposure to EtO exceeds the 8-hr TWA or excursion limit, and clearly mark them to limit the number of workers in the regulated area and to allow only authorized persons to enter.
- Provide the signs and labels specified by the standard clearly indicating EtO's carcinogenic and reproductive hazards in regulated areas.
- Train workers upon initial assignment and then annually if they are at risk of exposure at or above the action level or above the excursion limit.
- Maintain a material safety data sheet for EtO that conforms to the provisions of OSHA's hazard communication standard, 29 *CFR* 1910.1200(g).

Are there any recordkeeping requirements concerning employee exposures to EtO?

Employers are required to maintain the following records relating to employee exposure to EtO:

- Retain employee exposure records for 30 years.
- Keep employee medical records for the duration of employment plus 30 years.
- Keep records of objective data supporting any claimed exemption from the requirements of the OSHA standard.

What should employees do to protect themselves from EtO exposure?

To protect against EtO exposure, follow these safety precautions:

- Wear goggles and skin protection at all times in areas where there is a risk of splashes from liquid EtO.
- Wear proper protective clothing and other approved personal protective equipment when working with EtO.
- Discard clothing that has been degraded by EtO.
- See a doctor if you are exposed to EtO.
- Do not eat, drink, or smoke while working with EtO.

How can you get more information on safety and health?

OSHA has various publications, standards, technical assistance, and compliance tools to help you, and offers extensive assistance through workplace consultation, voluntary protection programs, grants, strategic partnerships, state plans, training, and education. OSHA's *Safety and Health Program Management Guidelines* (*Federal Register* 54:3904-3916, January 26, 1989) detail elements critical to the development of a successful safety and health management system. This and other information are available on OSHA's website.

- For one free copy of OSHA publications, send a self-addressed mailing label to OSHA Publications Office, 200 Constitution Avenue N.W., N-3101, Washington, DC 20210; or send a request to our fax at (202) 693-2498, or call us at (202) 693-1888.
- To order OSHA publications online at www.osha.gov, go to Publications and follow the instructions for ordering.
- To file a complaint by phone, report an emergency, or get OSHA advice, assistance, or products, contact your nearest OSHA office under the "U.S. Department of Labor" listing in your phone book, or call toll-free at 800) 321-OSHA (6742). The teletypewriter (TTY) number is (877) 889-5627.
- To file a complaint online or obtain more information on OSHA federal and state programs, visit OSHA's website.

This is one in a series of informational fact sheets highlighting OSHA programs, policies, or standards. It does not impose any new compliance requirements. For a comprehensive list of compliance requirements of OSHA standards or regulations, refer to *Title 29 of the Code of Federal Regulations*. This information will be made available to sensory-impaired individuals upon request. The voice phone is (202) 693-1999. See also OSHA's website at www.osha.gov.

OSHA
Occupational Safety and Health Administration
U.S. Department of Labor
2002

Exhibit H

Comments in Response to HCL RTR Request for Comments
On Use of 2016 IRIS Assessment for Regulatory Purposes (due April 26, 2019)

[EPA–HQ–OAR–2018–0417;
FRL–9988–70–OAR]
RIN 2060–AT74

National Emission Standards for
Hazardous Air Pollutants: Hydrochloric
Acid Production
Residual Risk and Technology Review
84 Fed.Reg. 1570 (Feb 4, 2019)

EPA has requested comment from interested parties on "the use of the [2016] update[d] [IRIS] risk value [for ethylene oxide ("EtO")] for regulatory purposes." 84 Fed. Reg. 1570, 1584 col. 2 (Feb. 4, 2019). For the legal, policy, and scientific reasons indicated below, the 2016 IRIS value should NOT be used for regulatory purposes. Rather the Air program should request the IRIS program and/or the National Academy of Sciences ("NAS") to review and clarify that the 2016 IRIS value reflects an extreme upper bound/worst case estimate of a dose-response relationship that is not appropriate for general regulatory use.

The 2016 IRIS Assessment of the toxicity of EtO

(1) is over *5 million times* more stringent than the scientific judgments underlying *all other regulatory limits* on EtO in the U.S. and worldwide, and this discrepancy has not been adequately explained or justified;

(2) is thousands of times more stringent than the level of EtO found in the ordinary breath that humans exhale, and hundreds of times more stringent than the naturally occurring background level of EtO in rural locations that are not affected by industrial releases;

(3) was computed in violation of EPA's own guidelines, prior National Academy of Sciences recommendations to the IRIS program, and EPA assurances to the Academy that the IRIS program was now following those recommendations, and is also contrary to the salutary principles regarding scientific objectivity in the 2006 proposed Office of Management and Budget ("OMB") Risk Bulletin:

> Risk assessments must be *scientifically objective*, neither minimizing nor exaggerating the nature and magnitude of the risks. . . . When determining whether a potential hazard exists, *weight should be given to both positive and negative studies*, in light of each study's technical quality. The original and supporting data

for the risk assessment must be generated, and the analytical results developed, *using sound statistical and research methods.*[1]

(4) was not peer reviewed by an objective body as required by Executive Order 12866. Draft versions were reviewed by EPA's own internal Science Advisory Board, which at the time had extensive conflicts of interest due the $140 million in EPA grants received by its members. The final assessment, which contained important substantive changes that altered the overall conclusions, was not peer-reviewed at all;

(5) was not subject to fair notice and an opportunity for comment by parties interested in its potential future use for regulatory purposes.

Because of these deviations from good scientific and regulatory practice, predictably the IRIS value is being widely misunderstood as indicating a public health crisis from exposure to part per *trillion* trace levels of EtO.[2] This is resulting in shutting down necessary facilities that are in compliance with their EPA permits and is likely to create a shortage of vital sterilizing facilities for medical instruments. At this time, the FDA believes that more than 100 medical device manufacturers and hundreds of devices may be affected.[3]

We explicate each of these points in more detail in what follows, but first a few facts about ethylene oxide (EtO) as background ....

- **Ethylene oxide plays a critical role in medical sterilization.**

Ethylene oxide is a gas that is used industrially in the production of other substances, such as ethylene glycol, and as a sterilizing agent for medical instruments and medical devices. It is the primary agent used worldwide for sterilizing surgical packs, such as those used in more than 130,000 medical procedures in the US every day—nearly 50 million each year—including open-heart procedures, C-sections, and hip replacements. In addition, more than 50% of all single-use medical devices manufactured worldwide are sterilized with ethylene oxide. Ethylene oxide is an alkaline agent that infiltrates packaged medical devices to kill microorganisms in order to achieve sterilization, and therefore it can be used to sterilize medical instruments and devices that will not stand up to other methods.

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[1] OFFICE OF MGMT. & BUDGET, EXEC. OFFICE OF THE PRESIDENT, PROPOSED RISK ASSESSMENT BULLETIN 14 (2006), https://obamawhitehouse.archives.gov/sites/default/files/omb/assets/omb/inforeg/proposed_risk_assessment_bulletin_010906.pdf (emphasis added).

[2] *See, e.g.*, Press Release, Sen. Tammy Duckworth, Trump EPA Proposes Limiting its Ability to Protect Public from Cancer-causing Ethylene Oxide Emissions (January 29, 2019), https://www.duckworth.senate.gov/news/press-releases/trump-epa-proposes-limiting-its-ability-to-protect-public-from-cancer-causing-ethylene-oxide-emissions.

[3] John Gever, *FDA: Device Sterilizing Facility Shutdown Could Have Impact*, MEDPAGE TODAY (Feb. 27, 2019), https://www.medpagetoday.com/hospitalbasedmedicine/infectioncontrol/78262.

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- **There is no effective substitute for ethylene oxide.**

Because ethylene oxide plays a unique role in ensuring the sterility of medical instruments and devices, imposing use restrictions in response to IRIS' revised cancer risk estimate could have devastating public health consequences. For example, in 1998 a hospital in St. Louis discontinued using ethylene oxide to sterilize instruments used in ophthalmic surgery and began using a vaporized mixture of peracetic acid, acetic acid, and hydrogen peroxide, which led to decomposition of patients' corneas and vision loss.[4] As potential alternatives to ethylene oxide, nitrogen dioxide, peracetic acid, and hydrogen peroxide all have niche medical device sterilization applications, but none are candidates to replace the broad sterilization application of ethylene oxide. According to the Department of Health and Human Services, health-care-associated infections "are a significant cause of illness and death — and they can have devastating emotional, financial, and medical consequences."[5]

- **Ethylene oxide is made naturally in the human body.**

In addition to its industrial uses, ethylene oxide is generated endogenously from ethylene, also a normal body constituent.[6] Sources of ethylene and ethylene oxide include metabolism by gut microflora, lipid peroxidation, and oxidation of hemoglobin and methionine.[7] Using hemoglobin adduct concentrations measured in non-workplace-exposed populations compared with exposed workers, a mean endogenous concentration of 1.9 ppb (range, 0.13–6.9 ppb) was calculated.[8] Thus IRIS' revised cancer unit risk estimate results in a one-in-a-million lifetime

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[4] *Corneal Decompensation After Intraocular Ophthamalic Surgery*, CDC (Oct. 5, 1998), https://www.cdc.gov/mmwr/preview/mmwrhtml/00052237.htm.

[5] *Health Care-Associated Infections*, OFFICE OF DISEASE PREVENTION & HEALTH PROMOTION, DEP'T OF HEALTH & HUMAN SERVS., https://health.gov/hcq/prevent-hai.asp (last visited Apr. 19, 2019).

[6] Filser et al., *Pharmacokinetics of ethylene in man; body burden with ethylene oxide and hydroxyethylation of hemoglobin due to endogenous and environmental ethylene* (1992) Arch Toxicol 66:157; Törnqvist et al., *Ethylene oxide doses in ethene-exposed fruit store workers* (1989) Scand J Work Environ Health 15:436.

[7] Clemens et al., *Volatile hydrocarbons from hydrogen peroxide-induced lipid peroxidation of erythrocytes and their cell components* (1983) Biochem Pharmacol 32:3877; Lieberman et al., *Genesis and Biogenesis of Ethylene* (1964) Nature 204:343; Törnqvist et al., *Ethylene oxide doses in ethene-exposed fruit store workers* (1989) Scand J Work Environ Health 15:436; Sagai et al., *Age-related changes in lipid peroxidation as measured by ethane, ethylene, butane and pentane in respired gases of rats* (1980) Life Sci 27:731.

[8] Kirman & Hays, *Derivation of endogenous equivalent values to support risk assessment and risk management decisions for an endogenous carcinogen: Ethylene oxide* (2017) Regul Toxicol Pharmacol 91:165.

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cancer risk estimate for exogenous exposure that is approximately 19,000 times lower than mean endogenous exposure and 10 million times lower (10^{-7}) than the consensus Threshold Limit Value, the Occupational Safety and Health Administration ("OSHA") workplace standard, and other workplace standards adopted worldwide, which are all 1 ppm or higher. In the context of much larger endogenous generation, restricting ethylene oxide based on the IRIS risk estimate is not scientifically defensible.

I. Why the 2016 IRIS Assessment of EtO Should NOT Be Used for Regulatory Purposes.

1. The 2016 IRIS Assessment is out of step with regulatory limits on EtO in the U.S. and worldwide, as shown in the table below.

Ethylene Oxide Regulatory Exposure Limits Worldwide

Regulator	**Limit**	**Comparison to IRIS 10^{-6} Lifetime Cancer Risk (0.1 part per *trillion*)**	**Source**
U.S. OSHA	1 part per *million* (8 hr) 5 parts per *million* (15 min)	10 million times higher	*Ethylene Oxide*, CDC NAT'L INST. FOR OCCUPATIONAL SAFETY & HEALTH (Nov. 29, 2018), https://www.cdc.gov/niosh/npg/npgd0275.html.
U.S. NAS Acute Exposure Guideline Level	7.9 parts per *million* (8 hr)	80 million times higher	*Ethylene Oxide Acute Exposure Guideline Levels*, NAT'L RESEARCH COUNCIL COMM. ON ACUTE EXPOSURE GUIDELINE LEVELS (2010), https://www.ncbi.nlm.nih.gov/books/NBK208167/.
U.S. FDA	50 parts per *million* (in spices)	500 million times higher	*Toxic Substances Portal - Ethylene Oxide*, AGENCY FOR TOXIC SUBSTANCES & DISEASE REGISTRY (Jan. 21, 2015), https://www.atsdr.cdc.gov/phs/phs.asp?id=732&tid=133.
U.S. American Conference of Governmental Industrial Hygienists Threshold Limit Value	1 part per *million*	10 million times higher	Int'l Agency for Research on Cancer, *Ethylene Oxide*, 97 IARC MONOGRAPHS 185, 204 (2018), https://monographs.iarc.fr/wp-content/uploads/2018/06/mono97-7.pdf [hereinafter "IARC Monograph"].
Belgium	1 part per *million*	10 million times higher	J.W. Cherrie et al., *Ethylene Oxide*, INST. OF OCCUPATIONAL MED. 2 (May 2011), http://ec.europa.eu/social/BlobServlet?docId=10165&langId=en [hereinafter "IOM Report"].
Brazil	39 parts per *million*	390 million times higher	IARC Monograph at 203.

Canada-Quebec	1 part per *million*	10 million times higher	IOM Report at 2.
China	2 mg/m^3 [1.2 parts per *million*] (time-weighted average) 5 mg/m^3 [3 parts per *million*] (short-term exposure limit)	12 million times higher	IARC Monograph at 203.
China, Hong Kong SAR	1 part per *million*	10 million times higher	IARC Monograph at 203.
China, Province of Taiwan	1 part per *million* (time-weighted average) 2 parts per *million* (short-term exposure limit)	10 million times higher	IARC Monograph at 204.
Czech Republic	1 mg/m^3 [0.6 parts per *million*] (skin)	6 million times higher	IARC Monograph at 204.
Denmark	1 part per *million*	10 million times higher	IOM Report at 2.
Finland	1 part per *million*	10 million times higher	IARC Monograph at 204.
France	1 part per *million*	10 million times higher	IOM Report at 2.
Germany	1 part per *million* (Technical Guidance Concentration) (skin)	10 million times higher	IARC Monograph at 204.
Ireland	5 parts per *million*	50 million times higher	IARC Monograph at 204.
Japan	1 part per *million*	10 million times higher	IOM Report at 2.
Malaysia	1 part per *million*	10 million times higher	IARC Monograph at 204.
Mexico	1 part per *million*	10 million times higher	IARC Monograph at 204.
Spain	1 part per *million*	10 million times higher	IOM Report at 2.
Sweden	1 part per *million* (time-weighted average) 5 parts per *million* (short-term exposure	10 million times higher	IARC Monograph at 204.

	limit) (skin)		
Netherlands	0.84 mg/m^3 [0.5 parts per *million*]	5 million times higher	IARC Monograph at 204.
New Zealand	1 part per *million*	10 million times higher	IARC Monograph at 204.
Norway	1 part per *million*	10 million times higher	IARC Monograph at 204.
Poland	1 mg/m^3 [0.6 parts per *million*] (time-weighted average) 3 mg/m^3 [1.8 parts per *million*] (short-term exposure limit)	6 million times higher	IARC Monograph at 204.
Romania	1 part per *million*	10 million times higher	IARC Monograph at 204.
South Africa	5 parts per *million* (Dep't of Labour ceiling limits)	50 million times higher	IARC Monograph at 204.
Switzerland	1 part per *million*	10 million times higher	IOM Report at 2.
UK	5 parts per *million*	50 million times higher	IOM Report at 2.

While the values in the table are mostly occupational exposure limits and thus are not directly comparable to cancer risk estimates for the general population, they do illustrate that daily exposure to ethylene oxide is regulated at concentrations millions of times higher than that which would be obtained by relying on the IRIS estimate for regulation. Converting the occupational exposure limits to continuous lifetime exposure, as would be done for the general population, produces concentrations that are consistent with the concentrations of endogenously formed, exhaled ethylene oxide.

In contrast, a regulatory limit calculated on the basis of the IRIS risk estimate for the general population would be thousands of times lower than what is naturally exhaled. Setting a regulatory limit that low would not only undermine the legitimacy of EPA's regulation, it would pose significant enforcement challenges for EPA, as people exhaling normally could cause violations. Moreover, the background level of EtO in rural coastal locations has been measured at 16 parts per trillion,[9] which is 160 times *above* the 10^{-6} lifetime cancer risk limit implied by

[9] *Research Note 93-6: Ethylene Oxide in the Atmosphere*, CAL. ENVTL. PROT. AGENCY AIR RES. BD. (Nov. 1993), https://www.arb.ca.gov/research/resnotes/notes/93-6.htm ("The lowest EtO concentration found was 16 ppt (parts per trillion) at remote coastal locations. This is believed to represent the hemispheric background for this persistent chemical.").

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the 2016 IRIS Assessment. Other commonplace sources of ethylene oxide might end up within the regulatory scope (e.g., automobile exhaust, produce sections of grocery stores, farms, compost sites), leading to the disruption of everyday, safe activities. In other words, it will be almost impossible for EPA to find any location that is *NOT* exceeding the IRIS lifetime cancer risk limit, which is hundreds of times *lower* than the natural background level.

As far as we have been able to determine, if the IRIS value were used for regulatory purposes, it would be the first time anywhere in the world that ethylene oxide exposure to the general population is regulated. Both California and the European Union, which are often more precautionary than EPA's national regulations, decline to regulate ethylene oxide to anything approaching the levels implied by the IRIS assessment. In 2013, the EU engaged in a comprehensive review of ethylene oxide under REACH and determined that a Derived Minimal Effect Level (DMEL) of 11.8 parts per billion (roughly one hundred thousand times greater than the IRIS number of 0.1 part per trillion) was sufficient to protect workers, but did not recommend setting a general population limit because there was no consensus on an appropriate risk level.[10]

2. The 2016 IRIS Assessment of EtO was developed in violation of prior National Academy of Sciences recommendations to the IRIS program and EPA's assurances to the Academy that the IRIS program was now following those recommendations. It is also contrary to the salutary principles regarding scientific objectivity in the 2006 proposed OMB Risk Bulletin.

The IRIS ethylene oxide assessment is inconsistent with a variety of recommendations made by the NAS, OMB, and EPA's own risk assessment guidance.

- **The statistical analysis used to develop a dose-response assessment for ethylene oxide violates standard statistical practices.**

Group-average exposures, as represented by a median or mean of the exposure groups, are commonly recognized as being less reliable than specific individual exposures. According to the NAS (2014) evaluation of the IRIS program, a fitted dose-response model based on group-average exposures can distort the true underlying dose-response relationship.[11] IRIS repeatedly asserts that its dose-response modeling for ethylene oxide is based on Steenland et al. (2004),[12] and not on the other epidemiologic studies available, because individual exposure data were estimated for each worker. IRIS then justifies its choice of a supralinear spline model for dose-

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[10] UMWELTBUNDESAMT GMBH, AUSTRIAN FED. MINISTRY OF AGRIC., FORESTRY, ENV'T & WATER MGMT., SUBSTANCE EVALUATION CONCLUSION DOCUMENT AS REQUIRED BY REACH ARTICLE 48 FOR ETHYLENE OXIDE 9 (2013), https://echa.europa.eu/documents/10162/52b90f61-7360-4d13-8524-c98c24a33537.

[11] *See, e.g.*, *Review of EPA's Integrated Risk Information System (IRIS) Process*, NAT'L RESEARCH COUNCIL, NAT'L ACAD. OF SCIS. (2014).

[12] Steenland et al., *Mortality analyses in a cohort of 18 235 ethylene oxide exposed workers: follow up extended from 1987 to 1998* (2004) Occup Environ Med 61:2.

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response assessment on the basis of categorical data, not on the individual data. If the individual data are considered, then other standard models such as the log-linear Cox model fit equally well or better. The choice of the supralinear model is not supported by the weight of evidence provided by the large body of epidemiologic data available.

- **The assumptions used to characterize occupational exposure to ethylene oxide are the opposite of what was actually observed.**

There were virtually no occupational exposure data available between 1938 and 1978. To estimate exposures for dose-response assessment, the authors of the NIOSH dose-estimation model used by Steenland et al. (2004) and relied on by IRIS made assumptions about pre-1978 exposures that resulted in their model predicting that exposures increased between 1938 and 1978 when in fact exposures decreased.[13] The authors acknowledge that exposures would have been higher prior to 1978, before improved engineering and processing practices and tighter exposure standards were in place, but they rely on assumptions that predict the opposite. In fact, when exposures between 1938 and 1977 were estimated using an independent engineering/industrial hygiene (E/IH) model, developed using empirical data from published literature, interviews with former sterilization operators, and input from sterilization experts on former and current technologies and practices, much higher estimates of exposure were obtained (12 times higher between 1938 and 1954, 4.4 times higher between 1955 and 1964).[14]

Thus the IRIS underestimation of exposure prior to 1978 substantially distorts the dose-response relationship, as does the choice of the supralinear dose-response model, together leading to a substantial over-estimation of ethylene oxide risk. EPA's Guidelines for Carcinogen Risk Assessment specifically warn against using a supralinear dose-response model because "a steep slope [i.e., supralinear] also indicates that errors in an exposure assessment can lead to large errors in estimating risk."[15]

- **The IRIS assessment of ethylene oxide does not rely on the weight of the scientific evidence.**

Failing to consider the larger body of epidemiologic data available for risk quantification of ethylene oxide is inconsistent with using the weight of scientific evidence, contradicting the direction to do so provided by EPA's own risk assessment guidance documents and, repeatedly, by various National Academy of Sciences committees. For example, EPA's Information Quality Guidelines state that when EPA develops "influential" scientific risk assessments, it intends to

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[13] Hornung et al., *Statistical model for prediction of retrospective exposure to ethylene oxide in an occupational mortality study* (1994) Am J Indus Med 25:825.

[14] Li et al., *Updated Modeling Indicates Historical Sterilization Worker Ethylene Oxide Exposures Were Higher Than Assumed in the US EPA IRIS Assessment* (2019) The Toxicologist 168:1855.

[15] RISK ASSESSMENT FORUM, U.S. EPA, GUIDELINES FOR CARCINOGEN RISK ASSESSMENT EPA/630/P-03/001F, at 3–19 (2005).

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use all relevant information and reach a position based on careful consideration of all such information, a process typically referred to as the "weight-of-evidence" approach.[16] EPA's Risk Assessment Principles & Practices documentation asserts that risk assessment involves consideration of the weight of evidence provided by all available scientific data.[17]

The National Research Council ("NRC")/NAS has encouraged EPA to move away from the old paradigm of selecting the "best" model and the "best" toxicity value, and instead to develop approaches for integrating multiple toxicity values rather than selecting one value or study that appears to be the "best."[18] The NAS also "strongly suggests that EPA consider approaches to integration of as much of the evidence as possible rather than selecting a limited segment of the evidence in deriving an organ-specific, system-specific, or an overall toxicity value."[19] In other words, the NRC/NAS has repeatedly admonished IRIS to avoid biases toward inclusion of certain outcomes, such as only positive outcomes, as was done here. The goal should be to interpret possible reasons for disagreement among studies, not to select the "best" ethylene oxide study and rely on it even if it is contradicted by other study results for ethylene oxide. Omitting studies that do not show a dose-response relationship in the direction IRIS favors, as was done for ethylene oxide, discounts valuable information, particularly information that could inform mode of action as well as dose-response.

3. The final 2016 IRIS Assessment of EtO was not peer reviewed by an objective body as required by Executive Order 12866. Instead, preliminary drafts were reviewed by EPA's own internal Science Advisory Board ("SAB"), which at the time had extensive conflicts of interest due to $140 million in EPA grants received by its members.

Executive Order 12866 requires "peer review" of influential scientific assessments. While the Executive Order does not specify the details of what constitutes "peer review," it is a fundamental concept that peer reviewers must be objective and not financially interested. For example, *Science* requires that peer reviews

> should be objective assessments of the research. If you cannot judge a paper impartially, you should not accept it for review, and you should notify the editor as soon as you appreciate the situation. If you have any professional or *financial affiliations that may be perceived as a conflict of interest in reviewing the manuscript*, or a

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[16] OFFICE OF ENVTL. INFO., U.S. EPA, GUIDELINES FOR ENSURING AND MAXIMIZING THE QUALITY, OBJECTIVITY, UTILITY, AND INTEGRITY OF INFORMATION DISSEMINATED BY THE ENVIRONMENTAL PROTECTION AGENCY EPA/260R-02-008, at 21 (2002).

[17] OFFICE OF THE SCIENCE ADVISOR, U.S. EPA, RISK ASSESSMENT PRINCIPLES AND PRACTICES EPA/100/B-04/001, at 71–72 (2004).

[18] NAT'L RESEARCH COUNCIL, NAT'L ACAD. OF SCIS., REVIEW OF THE ENVIRONMENTAL PROTECTION AGENCY'S DRAFT IRIS ASSESSMENT OF FORMALDEHYDE (2011).

[19] NAT'L RESEARCH COUNCIL, NAT'L ACAD. OF SCIS., REVIEW OF THE ENVIRONMENTAL PROTECTION AGENCY'S INTEGRATED RISK INFORMATION SYSTEM (IRIS) PROCESS 116 (2014).

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> history of personal differences with the author(s), you should describe them in your confidential comments.[20]

Citing information provided by the Congressional Research Service, members of Congress have alleged that the SAB had significant conflicts of interest when it reviewed the IRIS assessment of ethylene oxide:

> Over the years, the Science Advisory Board has silenced voices of dissent, limited public participation in its decisions, and *has shown potential conflict of interest. In fact, over half of the Board members have taken grant money from the EPA*, the very Agency they are supposed to provide impartial analysis to.
>
> This isn't chump change. Since 2000, board members have received roughly $140 million in taxpayer money from the EPA grants according to the Congressional Research Service, and the research they are reviewing is often directly related to the money they received.[21]

The extent to which members of the SAB that reviewed the 2016 IRIS assessment were receiving EPA grants should be made part of the public record of this proceeding.

Furthermore, *after* the preliminary draft was reviewed by the SAB but *before* it was finalized, substantive changes were made to the assessment, including an aggressive recalculation of the data on which it was based, performed by the author of the study that originally generated the data. Those changes are in part responsible for the very low risk number produced. Before the IRIS assessment is used for any regulatory purposes, it should be peer reviewed by an independent and objective body, such as the National Academy of Sciences.

4. Regulatory use of the 2016 IRIS Assessment of EtO was not adequately noticed or made available for comment by interested parties, or review by OMB/OIRA.

Persons affected by "promulgation or revision of . . . any standard under section 7412(d) [or] 7412(f)," i.e. an RTR such as this one, are entitled by statute to "notice of proposed rulemaking published in the Federal Register" which shall include "the factual data on which the proposed rule is based; [and] the methodology used in obtaining the data and in analyzing the data."[22] These provisions of the Clean Air Act implement the fundamental principle of administrative law that affected parties are entitled to *both* (1) adequate notice, and (2) an

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[20] *Peer Review at* Science *Publications*, SCIENCE, https://www.sciencemag.org/authors/peer-review-science-publications (last visited Apr. 19, 2019) (emphasis added).

[21] 161 Cong. Rec. H1685 (daily ed. March 17, 2015) (statement of Rep. McCarthy) (emphasis added).

[22] 42 U.S.C. §§7407(d)(1)(C), 7407(d)(3).

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opportunity to comment on the underlying data and scientific assumptions and methodology on which a rule is based.[23]

By dividing the assessment of ethylene oxide into two separate comment periods—one on the IRIS assessment, and another on regulatory use of the IRIS assessment in RTRs and other regulatory proceedings—EPA has effectively deprived interested parties of their statutory right to fair notice and an opportunity to comment in both proceedings.

The IRIS reassessment of EtO was made available for public comment in 2013, over five-and-a-half years before the assessment was proposed to be used for any regulatory purpose.[24] Stakeholders who may be later affected by its use in a regulatory proceeding affecting them would have had no "notice" or reason to comment on the IRIS reassessment of EtO in 2013.

On the other hand, when EPA seeks comment on the "regulatory use" of the IRIS assessment in a particular proceeding such as this one, it does not even mention "the methodology used in obtaining the data and in analyzing the data" as required by statute, and even if it did, the IRIS assessment is now a *fait accompli*.

This regulatory shell game effectively denies interested parties their statutory rights to adequate notice and an opportunity to comment in both proceedings: in the first, the implications of the IRIS assessment for regulation are not spelled out and cannot be anticipated, and in the second proceeding, the scientific methods and data underlying the IRIS assessment are no longer open to reconsideration.

This is analogous to segmentation of issues into separate proceedings under NEPA so that they cannot be effectively analyzed in either proceeding, a practice that the courts have uniformly condemned.[25]

5. If EPA does decide to use the 2016 IRIS EtO Assessment for regulatory purposes, the Agency must consider risk-risk tradeoffs with respect to public health.

For the reasons discussed above, the 2016 IRIS assessment should not be used for regulatory purposes. However, if EPA does decide to use the risk estimate derived by dubious dose-response modeling and exposure assumptions for regulatory purposes, the Agency must

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[23] *United States v. Nova Scotia Food Prods. Corp.,* 568 F.2d 240, 252 (2d Cir. 1977) ("To suppress meaningful comment by failure to disclose the basic data relied upon is akin to rejecting comment altogether."); *see also Chemical Mfrs. Ass'n v. U.S. E.P.A.*, 870 F.2d 177, 200 (5th Cir. 1989), *cert. denied*, 495 U.S. 910 (1990) ("[F]airness requires that the agency afford interested parties an opportunity to challenge the underlying factual data relied on by the agency.").

[24] Notice of a Public Comment Period on the Draft IRIS Carcinogenicity Assessment for Ethylene Oxide, 78 Fed.Reg. 44,117 (July 23, 2013).

[25] *See, e.g., Del. Riverkeeper Network v. F.E.R.C.,* 753 F.3d 1304, 1309 (D.C. Cir. 2014).

first consider the risk-risk tradeoffs between adopting a more stringent air toxics standard on the one hand and triggering detrimental public health consequences on the other. As explained in the introduction, ethylene oxide plays a critical role in the sterilization of medical equipment, including medical instruments and devices that cannot be sterilized using alternative methods. Because ethylene oxide is frequently the only method of ensuring the sterility of such equipment, imposing use restrictions in response to the 2016 IRIS EtO Assessment could have devastating effects on public health.

EPA has authority to interpret the statute to consider such risk-risk tradeoffs. The Clean Air Act explicitly provides that EPA may consider such risk-risk tradeoffs before promulgating emission standards. Section 112(f)(2) states that "[e]mission standards promulgated under this subsection shall provide an ample margin of safety to protect public health in accordance with this section (as in effect before November 15, 1990), unless the Administrator determines that a more stringent standard is necessary to prevent, taking into consideration costs, energy, *safety, and other relevant factors*, an adverse environmental effect."[26] This language is certainly broad enough to permit EPA to consider risk-risk tradeoffs.[27]

The public health consequences of eliminating a vital method of medical sterilization certainly qualify as "safety, and other relevant factors" that EPA may consider. EPA has made it clear that "other relevant factors" is a broad, circumstance-specific category.[28] Here curtailing one very small hypothetical or theoretical air toxics risk might subject the public to a much larger risk.[29]

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[26] 42 U.S.C. § 7412(f)(2) (emphasis added).

[27] *See Chevron U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 844 (1984) ("Sometimes the legislative delegation to an agency on a particular question is implicit rather than explicit. In such a case, a court may not substitute its own construction of a statutory provision for a reasonable interpretation made by the administrator of an agency.").

[28] *See* National Emission Standards for Hazardous Air Pollutants; Benzene Emissions From Maleic Anhydride Plants, Ethylbenzene/Styrene Plants, Benzene Storage Vessels, Benzene Equipment Leaks, and Coke By-Product Recovery Plants, 54 Fed.Reg. 38,044, 38,045 (Sept. 14, 1989) (the "Benzene rulemaking") ("A second step follows in which the actual standard is set at a level that provides 'an ample margin of safety' in consideration of all health information, including the number of persons at risk levels higher than approximately 1 in 1 million, as well as other relevant factors including costs and economic impacts, technological feasibility, and other factors relevant to each particular decision."); *accord Natural Res. Def. Council v. E.P.A.*, 529 F.3d 1077, 1083 (D.C. Cir. 2008) ("In [the Benzene] rulemaking, EPA set its standard for benzene 'at a level that provides an ample margin of safety in consideration of all health information . . . as well as other relevant factors including costs and economic impacts, technological feasibility, and other factors relevant to each particular decision.'").

[29] *See generally* RISK VS. RISK: TRADEOFFS IN PROTECTING HEALTH AND THE ENVIRONMENT (John D. Graham & Jonathan Baert Wiener eds., 1997).

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II. In Light of Widespread Public Misperceptions, the 2016 IRIS EtO Assessment Should Be Referred Back to the IRIS Office for Clarification.

The 2016 IRIS Assessment is a worst-case assessment based on highly dubious interpretations of data from a single study that contradicts a study of chemical workers with much longer follow-up and much heavier exposures, which found rates of cancer comparable to those in the general U.S. population.[30] Yet it is being widely misperceived and misinterpreted as indicating a public health crisis.[31]

The Air office should request that the IRIS program re-examine the matter and issue a clarification explaining accurately what the assessment does and does not really mean from a public health perspective.

III. EPA Should Request NAS Review of the 2016 IRIS EtO Assessment.

EPA should request National Academy of Sciences (NAS) review of the 2016 ethylene oxide assessment because

- The arguments supporting the alleged scientific basis of the outcome are inconsistent with the many recommendations that NAS has made to IRIS over the years.
- The outcome has needlessly provoked fear and anger among people who believe their health is in imminent danger from ethylene oxide.
- There is no effective substitute for use in sterilizing medical instruments and medical devices, so needlessly limiting its use would create a public health threat due to their subsequent unavailability.
- Serious yet needless economic damages will continue to result from plant closings, product shortages, and job loss.

A NAS committee would

- Review the approach IRIS used to characterize the alleged dangers of ethylene oxide and make recommendations for improvements.

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[30] See American Chemistry Council, Request for Correction under the Information Quality Act: 2014 National Air Toxics Assessment (NATA) (September 20, 2018), which is attached as an exhibit and incorporated by reference into these comments.

[31] *See, e.g.*, Press Release, Sen. Tammy Duckworth, Trump EPA Proposes Limiting its Ability to Protect Public from Cancer-causing Ethylene Oxide Emissions (January 29, 2019), https://www.duckworth.senate.gov/news/press-releases/trump-epa-proposes-limiting-its-ability-to-protect-public-from-cancer-causing-ethylene-oxide-emissions.

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- Use the best science and independent scientific experts to draw evidence-based conclusions about the nature and extent of ethylene oxide's potential risks to human health.

- Provide the objective scientific peer review necessary to establish consistency with Executive Order 12866 and other peer review standards.

The NAS is in a unique position to perform this review because it is the nation's pre-eminent source of high-quality, objective advice on science. Each year thousands of the world's foremost scientists volunteer their time to address some of society's toughest challenges by serving on the hundreds of study committees that are convened to answer specific sets of questions. The Academy's peer-reviewed reports present the evidence-based consensus of these committees of experts. In particular, the specific mission of the Board on Environmental Studies and Toxicology is "[t]o provide our nation with independent, objective advice and dialog on matters related to the impacts of human activities and environmental exposures on environmental quality and human health."[32] Thus the NAS is in the best position to review the ethylene oxide assessment.

While ethylene oxide's IRIS profile was reviewed by EPA's own Science Advisory Board ("SAB"), SAB review is not equivalent to review by the NAS. Unlike NAS review, the SAB review process is neither independent nor free from financial conflict. EPA staff oversees the formation and conduct of advisory panels by selecting reviewers, formulating charge questions, and providing staff support for the review process. In contrast, the NAS process for selecting scientific panel members and conducting reviews assures independence and objectivity. The substantial differences historically between many, but not all, IRIS assessments and NAS reviews of IRIS assessments clearly illustrate the continuing need for NAS review.

* * *

Gail Charnley, PhD
Principal, HealthRisk Strategies LLC

E. Donald Elliott
Covington & Burling LLP

Representing two companies that might be affected by the use of the IRIS assessment of ethylene oxide for regulatory purposes but do not wish to be identified because of the extensive public fear and anger generated by the IRIS assessment.

[32] *About BEST*, NAT'L ACAD. OF SCIS. BOARD ON ENVTL. STUDIES & TOXICOLOGY (2018), http://dels.nas.edu/global/best/About-Us.

ED_013218_00002875-00146

September 20, 2018

Information Quality Guidelines Staff
Mail Code 2811R
United States Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Re: Request for Correction under the Information Quality Act: 2014 National Air Toxics Assessment (NATA)

Dear Sir or Madam:

The Ethylene Oxide Panel of the American Chemistry Council (ACC), hereby submits this Request for Correction under the Information Quality Act (IQA) of 2000, Section 515 of the 2001 Treasury and General Government Appropriations Act, Pub. L. No. 106-554, the Office of Management and Budget (OMB) Guidelines for Ensuring and Maximizing the Quality, Utility, and Integrity of Information Disseminated by Federal Agencies,[1] and the Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency (EPA).[2] ACC represents producers and users of ethylene oxide (EO).

ACC seeks the correction of EO information disseminated in the 2014 update to the National Air Toxics Assessment (NATA), released on August 22, 2018.[3] The 2014 NATA relies upon the "Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (CASRN 75-21-8) In Support of Summary Information on the Integrated Risk Information System (IRIS)"[4] to determine the risk value for EO. As detailed below, the 2014 NATA does not meet the IQA's data quality requirements because the EO IRIS Assessment is not the best available science. Therefore, the 2014 NATA risk estimates for EO should be withdrawn and corrected to reflect scientifically-supportable risk values. Moreover, EPA should not use the EO IRIS Assessment's inhalation unit risk estimate (URE) of 5×10^{-3} per $\mu g/m^3$, which corresponds to a one-in-a-million increased cancer risk concentration of 0.1 parts per trillion (ppt), to calculate EO risk in

[1] 67 Fed. Reg. 8452 (Feb. 22, 2002) (OMB Guidelines).

[2] Available at https://www.epa.gov/sites/production/files/2017-03/documents/epa-info-quality-guidelines.pdf (EPA Guidelines).

[3] Available at https://www.epa.gov/national-air-toxics-assessment/2014-nata-assessment-results (2014 NATA).

[4] EPA/635/R-16/350Fa (December 2016) (EO IRIS Assessment).

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its ongoing Clean Air Act (CAA) Section 112 risk and technology review (RTR) rulemakings and other regulatory actions.[5]

As producers and users of EO, ACC members are directly impacted by the errors in the 2014 NATA. The risk estimates based on the EO IRIS value have significant regulatory implications for ACC member companies who produce commercial products of value to consumers using EO. Correcting these deficiencies will result in more accurate estimates of potential risk that will lead to improved regulatory outcomes, the dissemination of more accurate information to the public, and overall reduced misconception.

This Request for Correction is organized into four sections. The Executive Summary provides a high level overview of the key reasons why the 2014 NATA does not meet the objectivity, accuracy, integrity and utility requirements of the IQA and the OMB and EPA Guidelines due to its reliance on the EO IRIS Assessment. The second section provides background information on the 2014 NATA and the EO IRIS Assessment. The third section highlights the information in the EO IRIS Assessment that is not scientifically supportable. In the last section, each of the key deficiencies in the EO IRIS Assessment is discussed in detail with supporting scientific evidence.

I. Executive Summary

In the 2014 NATA, EPA relies on updated benchmarks for several substances, including EO. For EO, EPA updated its cancer risk calculations to reflect the URE in the EO IRIS Assessment. The use of the URE value, however, results in inaccurate and misleading conclusions about EO risk.

The EO IRIS Assessment is based on a supralinear spline slope for lymphoid and breast cancer exposure-response analyses from an epidemiology study conducted by the National Institute for Occupational Safety and Health (NIOSH). **This supralinear risk assessment model predicts high risk at low exposures, lower risk at higher exposures, and estimates an unrealistically low concentration of 0.1 ppt.** This 10^{-6} risk specific concentration (RSC) is the lower bound lifetime chronic exposure level of EO that corresponds to an increased cancer risk of one-in-a-million. **Both the supralinear slope and the RSC are implausible based on the epidemiological evidence and biological mode of action.**

[5] In a recently proposed RTR rule, EPA solicits comment on whether it should ban the use of EO for one of the source categories. *NESHAP; Surface Coating of Large Appliances; Printing, Coating, and Dying of Fabrics and Other Textiles; and Surface Coating of Metal Furniture Residual Risk and Technology Reviews,* 83 Fed. Reg. 46262, 46294 (Sept. 12, 2018).

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In addition, these implausible levels lack utility for regulatory purposes. **The RSC in the EO IRIS Assessment is 19,000 times lower than the air-concentration equivalent yielding normal, endogenous levels of EO in the human body. Likewise, the RSC is orders of magnitude lower than ambient levels of EO.** Thus, if the EO IRIS Assessment is to be believed, normal human metabolism and/or breathing ambient air is sufficient to cause cancer. The EO IRIS Assessment does not provide a meaningful basis for assessing and managing risk for EO.

As outlined below, the EO IRIS Assessment is substantially flawed and can be corrected by using the approach published by Valdez-Flores et al. (2010),[6] which models potential mortality excesses for lymphohematopoietic tissue (LH) cancers from the two strongest epidemiological studies (NIOSH and Union Carbide Corporation (UCC)) using a log-linear Cox proportional hazard model. **Valdez-Flores et al. (2010) estimated ranges for the maximum likelihood estimate (MLE) and the 95% lower confidence limit of the environmental concentration corresponding to an extra risk of one in a million [LEC (1/million)] of, respectively, 1.5-9.2 parts per billion (ppb) and 0.5-1.2 ppb.** The major reason for the large difference between these values and the EO IRIS Assessment estimates is that the IRIS Program uses a supralinear spline model and Valdez-Flores et al. (2010) uses the log-linear Cox model.

EPA's cancer risk assessment guidelines caution that "a steep slope [i.e., supralinear] also indicates that errors in an exposure assessment can lead to large errors in estimating risk."[7] This is relevant to the EO IRIS Assessment because the NIOSH exposure model has a much higher level of uncertainty between the late 1930s and 1978 when there was inadequate (1976-78) or no exposure data (<1976) to independently validate the model. Furthermore, the NIOSH exposure model was modified when estimating exposures prior to 1978 by fixing the effect of a key variable (calendar year) in the model.

Specifically, Hornung et al. (1994) determined that Calendar Year is a major predictor of exposure in the model after 1978, but they did not allow this variable to impact exposures in the model prior to 1978.[8] Hornung et al. (1994) surmised that Calendar Year acts as a surrogate for improvement in work practices. **Thus, the arbitrary decision to alter the model prior to 1978 essentially assumes there were no evolving work practices in contract sterilizer facilities**

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[6] Valdez-Flores C, Sielken RL Jr, Teta MJ. 2010. Quantitative cancer risk assessment based on NIOSH and UCC epidemiological data for workers exposed to ethylene oxide. Regul Toxicol Pharmacol, 56(3): 312-20.

[7] EPA, Guidelines for Carcinogen Risk Assessment (March 2005), at 3-19. Available at https://www.epa.gov/risk/guidelines-carcinogen-risk-assessment

[8] Hornung RW, Greife AL, Stayner LT, Steenland NK, Herrick RF, Elliott LJ, Ringenburg VL, Morawetz J. 1994. Statistical model for prediction of retrospective exposure to ethylene oxide in an occupational mortality study. Am J Ind Med, 25(6): 825-36.

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between 1938 and 1977 that influence exposure to workers. The EO IRIS Assessment did not critically evaluate the assumptions and uncertainties of the NIOSH exposure model.

Moreover, the EO IRIS Assessment makes an unsubstantiated and counter-intuitive claim that the EO sterilization process was historically constant and stable prior to 1978. Yet, even the authors of the NIOSH study predict higher exposures before installation of engineering controls ("e.g., increased ventilation and better door seals") in 1978, when OSHA standards were higher.[9] **Below, we provide information on evolving regulatory standards, residue levels of EO, equipment, engineering and processing practices that indicate that the NIOSH exposure model incorrectly predicted that exposures would decrease in earlier years compared to the 1970s for the most exposed jobs (e.g. sterilizer operator). In general, *underestimating exposures will overestimate risk*, and the EPA cancer risk assessment guidelines caution that use of a supralinear model will further exacerbate the impact of these exposure errors.**

The rationale for selecting the supralinear spline model is based on incorrect statistical procedures and visual misrepresentation of the data. The EO IRIS Assessment incorrectly calculates the statistical significance (e.g., p- and AIC values) of the supralinear spline dose-response model because it fails to account for the statistical impact of the trial-and-error exploration of different arbitrary values used in the EO IRIS Assessment's dose-response model, such as the exposure level where the slope changes in the model from a very steep slope to a shallow slope (i.e. the "knot").[10] In addition, the figures used to compare visual fits use categorical data rather than the individual cases that were modeled. Once the individual cases are used, the log-linear Cox model fits the data just as well as the more complex and ill-advised supralinear spline model. The log-linear Cox model best meets the objective of selecting the more parsimonious model with fewer assumptions and variables.

Biologically, selection of the log-linear Cox model is more consistent with the mode of action for EO. This is supported by the EO IRIS Assessment, which concludes it is "highly plausible that the dose-response relationship over the endogenous range is sublinear … that is, that the slope of the dose-response relationship for risk per adduct would increase as the level of endogenous adducts increases."[11]

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[9] Steenland K, Stayner L, Greife A, Halperin W, Hayes R, Hornung R, Nowlin S. 1991. Mortality among workers exposed to ethylene oxide. N Engl J Med, 324(20): 1402-07.

[10] *See, e.g.,* Li W, He C, Freudenberg J. 2011. A mathematical framework for examining whether a minimum number of chiasmata is required per metacentric chromosome or chromosome arm in human. Genomics, 97(3): 186-92.

[11] EO IRIS Assessment, at 4-95.

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Both the UCC and NIOSH studies should be included in the dose-response modeling so that the risk estimates are based on the best available human data. Although the NIOSH study cohort is much larger, both studies have comparable power for males when considering the number of events of interest, i.e., lymphohematopoietic tissue cancers. The EO IRIS Assessment excludes the UCC cohort based primarily on a comparison of the exposure assessments for both studies. The EO IRIS Assessment dismisses the UCC exposure estimates as "crude," "largely-uninformative," "much less extensive," and "greater likelihood for exposure misclassification," as compared with the NIOSH study, which is described as "well-validated" and "high-quality." These descriptions lack objectivity and obscure the fact that the majority of the UCC cohort exposure estimates are based on contemporary data from different plants with identical or comparable processes. **Although the NIOSH exposure model was validated with data after 1978, there were no contemporary data between the late 1930s and mid-1970s to validate the final model. Thus, the UCC exposure assessment uncertainties are no greater than the NIOSH study uncertainties and, therefore, are not a valid reason to exclude the UCC cohort.**

The EPA Science Advisory Board's (SAB) peer review of the draft EO IRIS Assessment did not remedy the shortcomings of the final EO IRIS Assessment. The presumption of objectivity that sometimes attaches to documents that have been peer reviewed does not apply in this case because authors of the NIOSH study influenced the analysis of the data as well as the responses to the SAB's comments. This influence compromised the objectivity and independent analysis of the NIOSH study, and especially the NIOSH exposure model, in the draft and final EO IRIS Assessments.

II. The 2014 NATA and the EO IRIS Assessment

The 2014 NATA uses emissions information to help state, local, and tribal air agencies identify which pollutants, emission sources, and places may warrant a better understanding for any possible risks to public health from air toxics. EPA further uses NATA results to improve data in emission inventories; identify where to expand air toxics monitoring; help target risk reduction activities; identify pollutants and source types of greatest concern; help decide what other data to collect; better understand risks from air toxics; and work with communities to design their own assessment.

The 2014 NATA results list EO emissions information across a range of categories, including location, cancer risks, hazard quotients, source type (e.g., stationary sources, mobile, airports, etc.). In building the NATA, EPA must select specific risk levels for certain air toxics that can lead to determinations of acceptable or unacceptable thresholds. Since air toxics have no universal, predefined risk levels that clearly represent acceptable or unacceptable thresholds,

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EPA makes case-specific determinations and general presumptions that apply to certain regulatory programs that further inform the interpretation of risk in the NATA. These benchmarks are drawn from a range of sources and updated. EPA notes that several substances' benchmarks were updated since the 2011 NATA, including EO. Specifically, EPA states that its risk value for EO was updated in 2016—the newly finalized IRIS value. As such, EPA updated its cancer risk calculations to reflect this new updated benchmark value. Due to the use of the EO IRIS value, more areas show elevated risks driven by EO in the 2014 NATA than in the 2011 NATA, even if emissions levels have stayed the same, or even decreased, in these areas.

The alleged elevated cancer risk driven by EO in the 2014 NATA has already caused alarm in some communities around facilities with EO emissions. This, in turn, has created media attention, and coverage of the issue has created further confusion and concern in the surrounding community. All of this could have been avoided had EPA relied on the best available science in calculating the unit risk estimate for cancer.

As discussed in detail below, the use of the updated EO IRIS value in the 2014 NATA and its Technical Support Document is extremely problematic given the EO IRIS Assessment's numerous shortcomings. A simple comparison of the results of the EO IRIS Assessment to the "real world," however, demonstrates its lack of credibility. Specifically, the RSC is 19,000 times *lower* than the normal, endogenous levels of EO in the human body. Likewise, the RSC is orders of magnitude *lower* than ambient levels of EO. Thus, if the EO IRIS Assessment is to be believed, normal human metabolism and/or breathing ambient air, without more, is sufficient to cause cancer. It strains scientific credibility to conclude that the EO IRIS Assessment presents a legitimate basis for determining risk for EO.

III. Request for Correction

The 2014 NATA relies upon the EO IRIS Assessment's inhalation URE of 5×10^{-3} per $\mu g/m^3$ to calculate EO risk. This URE implies a corresponding RSC of 0.1 ppt. The use of these values, however, results in inaccurate and misleading conclusions about EO risk because they are not supported by the scientific data. The RSC is also unrealistic, given that it is orders of magnitude lower than levels of EO in ambient air and levels that are consistent with normal, endogenous levels of EO present in human bodies.

A more reasonable and scientifically supportable approach to an exposure response analysis yields ranges for the MLE (1.5-9.2 ppb) and LEC (0.5-1.2 ppb) that are more than three orders of magnitude greater than the RSC.[12] Moreover, the ranges of MLE and LEC values are

[12] Valdez-Flores et al. (2010).

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conservative because (a) extra risk was calculated despite no statistically significant slope in the exposure-response analyses; (b) the NIOSH data was included without adjustment for likelihood of underestimation of exposures; and (c) the limited evidence of cancer risk based on the entire body of epidemiologic evidence (see Appendix 2). The 2014 NATA risk estimates for EO should be withdrawn and corrected to reflect these risk values. Moreover, EPA should not use the EO IRIS Assessment's RSC of 0.1 ppt or URE of 5×10^{-3} per $\mu g/m^3$ to calculate EO risk in its ongoing CAA Section 112 risk and technology review or other rulemakings.

A. The 2014 NATA Does Not Meet the Objectivity, Integrity, and Utility Requirements of the IQA and the OMB and EPA Guidelines.

Congress enacted the Information Quality Act (IQA) to "ensur[e,] and maximiz[e,] the quality, objectivity, utility and integrity of information (including statistical information) disseminated by Federal agencies" such as EPA.[13] The IQA required OMB to issue government-wide guidance, which each federal agency was to follow in its issuance of its own guidelines. The purpose of the EPA Guidelines is to apply the OMB Guidelines to the Agency's particular circumstances, and to "establish administrative mechanisms allowing affected persons to seek and obtain correction of information … disseminated by the agency that does not comply with the [OMB] guidelines…."[14] The 2014 NATA, therefore, must meet the OMB Guidelines as well as the EPA Guidelines.

OMB Guidelines include clear definitions to guide agency practices in adhering to the IQA. These include:

- "'Information' means any communication or representation of knowledge such as facts or data, in any medium or form, including textual, numerical, graphic, cartographic, narrative, or audiovisual forms."[15]
- "'Influential,' when used in the phrase 'influential scientific, financial, or statistical information,' means that the agency can reasonably determine that dissemination of the information will have a clear and substantial impact on important public policies or important private sector decisions."[16]

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[13] *See* Pub. L. No. 106-554. The IQA was developed as a supplement to the Paperwork Reduction Act, 44 U.S.C. §3501 et seq., which requires OMB, among other things, to "develop and oversee the implementation of policies, principles, standards, and guidelines to …apply to Federal agency dissemination of public information."

[14] Pub. L. No. 106-554.

[15] OMB Guidelines, at 8460.

[16] *Id.*

- "'Objectivity' involves two distinct elements, presentation and substance. 'Objectivity' includes whether disseminated information is being presented in an accurate, clear, complete, and unbiased manner.... In addition 'Objectivity' involves a focus on ensuring accurate, reliable, and unbiased information. In a scientific, financial, or statistical context, the original and supporting data shall be generated, and the analytic results shall be developed, using sound statistical and research methods."[17]

- "'Utility' refers to the usefulness of the information to its intended users, including the public. In assessing the usefulness of information that the agency disseminates to the public, the agency needs to consider the uses of the information not only from the perspective of the agency but also from the perspective of the public. As a result, when transparency of information is relevant for assessing the information's usefulness from the public's perspective, the agency must take care to ensure that transparency has been addressed in its review of the information."[18]

The 2014 NATA is influential scientific risk assessment information and must adhere to a rigorous standard of quality.[19] The 2014 NATA is "influential" scientific risk assessment information as set forth in the EPA Guidelines because it "will have or does have a clear and substantial impact (i.e., potential change or effect) on important public policies or private sector decisions" and involves "controversial scientific ... issues."[20] Results from the NATA are used by government agencies, non-governmental organizations, and air quality experts to gauge which hazardous air pollutants (HAP) and emission sources may raise health risks in certain places. These places are then given more attention and EPA uses the NATA to, among other things, target ways to achieve risk reduction.

The NATA can also lead to the development of local community-supported plans to reduce emissions as presented in each NATA version's results. Additionally, the National Research Council (NRC) has recognized the NATA as one of the largest EPA efforts to "develop baseline cancer risk estimates and hazard index calculations using dose-response information and exposure estimates."[21] In this context, NRC further acknowledges the importance of the NATA as a "tool for exploring control priorities" and its function "as a preliminary attempt to establish a

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[17] *Id.* at 8459.

[18] *Id.*

[19] Quality includes objectivity, utility, and integrity.

[20] *See* EPA Guidelines, at 19-20 (internal citations omitted); OMB Guidelines, at 8455.

[21] National Research Council, "Air Quality Management In the United States" (2004), at 247. Available at https://www.nap.edu/read/10728/chapter/1.

baseline for tracking progress in reducing HAP emissions."[22] Therefore, the 2014 NATA, and its underlying data, must adhere to a rigorous standard of quality, including meeting the higher standard of reproducibility.

With regard to the analysis of risks to human health, safety and the environment maintained or disseminated by the agencies, the OMB and EPA Guidelines also require either adoption or adaption to "the quality principles applied by Congress to risk information used and disseminated pursuant to the Safe Drinking Water Act Amendments of 1996 (42 U.S.C. 300g-1(b)(3)(A) & (B))."[23] In ensuring the objectivity of influential scientific risk information (i.e., the substance of the information is accurate, reliable and unbiased), the EPA Guidelines have adapted these principles by requiring the use of the "best available science and supporting studies" and the collection of data using by "accepted methods or the best available methods" using "a 'weight-of-evidence' approach that considers all relevant information and its quality."[24]

EPA has failed to apply a transparent and systematic weight-of-evidence approach in assessing the cancer risks of EO exposures in the 2014 NATA. Moreover, as detailed below, because the 2014 NATA relies upon the EO IRIS Assessment to determine the risk value for EO, the 2014 NATA is not based on the best available science.

B. The EO IRIS Assessment Does Not Meet Scientific Standards from Multiple Standpoints.

The EO IRIS Assessment is not the best available science because it: (1) exclusively relies on a NIOSH study despite its flawed exposure assessment; and (2) applies a supra-linear spline model, which is implausible based on the epidemiological and biological evidence and deficient due to statistical miscalculations and visual misrepresentations.

1. The EO IRIS Assessment incorrectly describes the NIOSH exposure model as a "state-of-the-art" validated regression model to estimate historical exposures prior to 1978. In fact, this "state-of-the-art" validated model was tested with post-1978 data only and arbitrarily altered for years prior to 1978. Specifically, a variable considered to be a major predictor of exposure after 1978 was not allowed in the model to impact exposures prior to 1978. The

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[22] *Id.*

[23] *See* EPA Guidelines, at 22-23; OMB Guidelines, at 8460.

[24] *See* EPA Guidelines, at 21-22. "In this approach, a well-developed, peer-reviewed study would generally be accorded greater weight than information from a less well-developed study that had not been peer-reviewed, but both studies would be considered." *Id.* at 26. The definition of best available science mirrors that articulated in Chlorine Chemistry Council v. EPA, 206 F.3d 1286 (D.C. Cir. 2000), referring to "the availability at the time an assessment is made." *See* EPA Guidelines, at 23.

reliability, validation and likelihood of exposure misclassification prior to 1978 were not objectively evaluated.

2. The results of NIOSH's statistical model for exposures prior to 1978 were not provided in the 2014 Draft EO IRIS Assessment or in the cited NIOSH publications. In the appendices of the final EO IRIS Assessment, two new figures (Figures D-22 and D-33) present new information on estimated exposures by worker, but no explanation or critical evaluation was added. There is a lack of transparency in the EO IRIS Assessment of these influential data used to derive the EO cancer slope factor.

3. The EO IRIS Assessment repeatedly asserts that the NIOSH exposure estimates were well-validated using a state-of-the-art model, when in fact there was no validation of exposure estimates prior to 1978. These assertions regarding verification procedures are incorrect for the late 1930s to 1978.

4. In response to public and SAB comments questioning the lower than expected exposures in earlier years predicted by the statistical regression model, the IRIS Program states that the decrease is related to the sterilizer volume. In other words, the model predicts that smaller sterilizer volume results in lower exposures. This response essentially uses the output of the model to answer a question about whether the model assumptions are correct, instead of independently verifying the validity of these assumptions. This circular reasoning does not address the underlying concern of whether the model assumption that Sterilizer Volume has an inverted parabolic (that is, an upside-down U-shaped) relationship with predicted EO exposure is correct. It also does not address whether other factors that might result in increased exposure during early years were properly accounted for in the model.

5. The EO IRIS Assessment makes the unsubstantiated claim that "the sterilization processes used by the NIOSH cohort workers were fairly constant historically, unlike chemical production processes, which likely involved much higher and more variable exposure levels in the past."[25] In fact, there was an evolution in technology and practices associated with the sterilization processes between the late 1930s and early 1970s. Data and information from industrial sterilization operators and the literature refute this claim.

6. Comparisons of relative reliability made between the NIOSH and UCC studies are inaccurate. These comparisons were a key basis upon which the IRIS Program rejected the UCC Study as a source of epidemiology study data for cancer risk assessment. The EO IRIS Assessment does not acknowledge and appropriately consider limitations of the NIOSH

[25] EO IRIS Assessment, at 4-4.

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exposure assessment posed by low extrapolations of NIOSH cohort exposures to EO prior to the late 1970s without any corroborating data or any supporting engineering/process considerations derived from or directly relevant to that period of time.

7. The EO IRIS Assessment relies solely on the NIOSH study of sterilant workers and fails to incorporate the important findings from the UCC study of workers in EO producing and using operations. The IRIS Program considered and characterized three factors in its selection of the NIOSH study: cohort size, exposure data, and confounding. Based on these factors, the IRIS Program dismissed the UCC study as a basis for EO cancer risk estimation. In considering cohort size, the IRIS Program ignored the most important comparison—the number of lymphohematopoietic tissue cancers, not the total cohort size.

8. The use of the supralinear spline model for the lymphoid and breast cancers in the final EO IRIS Assessment is based on an invalid statistical analysis. Because the analysis did not correctly calculate degrees of freedom associated with that fitted model, it contains erroneous measures of absolute and relative goodness of fit of that model. When both the p-values and Akaike Information Criterion (AIC) values characterizing fit quality are corrected, the supralinear spline model does not fit the NIOSH lymphoid tumor data statistically significantly better than the log-linear Cox model.

9. The selection of the supralinear spline model for the lymphoid tumors is also based on misleading illustrations of "visual fits" that do not convey either the actual data that were fit or the relative goodness of fit to these data of log-linear and supralinear spline models. Only in a footnote does the IRIS Program indicate that the visual comparison misrepresents the log-linear model being compared. Consequently, and erroneously, the fit to the data appears far worse than the supralinear spline model. The data plotted in that figure also were summary data that misrepresent the true magnitude of the scatter of the data that were used for model fitting.

10. The selection of a spline model as the preferred model for EO cancer risk estimation assumes a supralinear increase in tumor response in the low-dose exposure region with a subsequent plateauing of response at higher exposures. The body of cancer epidemiologic studies, including the NIOSH studies, does not support such a pattern of risk. While certain NIOSH sub-analyses suggest increases in male lymphoid tumors and female breast cancers, the findings are limited to the highest cumulative exposure groups, not the lowest.

11. The use of a supralinear spline model for cancer risk estimation is inconsistent with the assumed mode-of-action of EO toxicity and tumorigenicity. Such a model predicts higher risk at low exposures compared to risks predicted at higher exposures, which is contradicted by the well-understood mode of action of EO in experimental animals and humans

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as described in the EO IRIS Assessment. Thus, the EO IRIS Assessment relies on human cancer risk estimates based on spline-model dose-response extrapolations that are internally inconsistent with its own evaluation of the mode of action of EO. The mean air concentration equivalent to the endogenous concentration in non-smoking humans with no known EO exposures is 1.9 ppb (range 0.13-6.9 ppb; continuous), which is 19,000 times greater than the EO IRIS RSC of 0.1 ppt.[26] An alternative LEC (1/million) of 0.5-1.2 ppb is a more pragmatic, science-based approach for EO risk assessment.

12. The statistical, epidemiological and biological evidence does not support the selection of supralinear spline models to fit the NIOSH study data in the EO IRIS Assessment. A more scientifically sound conservative alternative is to use the Valdez-Flores et al. (2010) approach, which incorporates all the available data from the two strongest human studies (NIOSH and UCC). This approach has been adopted by the European Commission's Scientific Committee on Occupational Exposure Limits.[27]

IV. Because the 2014 NATA Relies Upon the EO IRIS Assessment to Determine the Risk Value for EO, the 2014 NATA Is Not Based on the Best Available Science.

1. The EO IRIS Assessment incorrectly describes the NIOSH exposure model as a "state-of-the-art" validated regression model to estimate historical exposures prior to 1978. In fact, this "state-of-the-art" validated model was tested with post-1978 data only and arbitrarily altered for years prior to 1978. Specifically, a variable considered to be a major predictor of exposure after 1978 was not allowed in the model to impact exposures prior to 1978. The reliability, validation and likelihood of exposure misclassification prior to 1978 were not objectively evaluated.

The EO IRIS Assessment's evaluation of the cancer potency of EO is dependent on an analysis of commercial sterilization worker exposure conducted by NIOSH. The NIOSH EO data for the sterilization work cohort were nearly all collected between 1978 and 1986 at 20 different facilities, but included just seven mean values based on 23 exposure measurements for the period 1976-77.[28] Ultimately, of the 20 facilities, 16 facilities were eliminated from the

[26] Kirman CR, Hays SM. 2017. Derivation of endogenous equivalent values to support risk assessment and risk management decisions for an endogenous carcinogen: Ethylene oxide. Regul Toxicol Pharmacol, 91: 165-72.

[27] *See* Recommendation from the Scientific Committee on Occupational Exposure Limits for ethylene oxide, SCOEL/SUM/160 (June 2012).

[28] Hornung et al. (1994).

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exposure assessment for lack of personal sampling, documentation of sampling, or links of sampling to job categories.

Based on the available worker data, the workers included in the NIOSH study cohort were employed in the sterilization industry as early as the 1930s. Noting that "there were no measurement data prior to 1976," Hornung et al. (1994) describe the statistical model[29] developed to estimate NIOSH EO-cohort worker exposures based on data collected after 1978. That model was applied to estimate worker exposures over a large timespan (1935-1975) during which not a single observed measurement was available to validate the application of that model extrapolation procedure.

Although the NIOSH statistical regression model estimated exposure measurements after 1977 with reasonable reliability, Hornung et al. (1994) highlighted that post-1978 regulatory standards and consequent progressively stringent operational EO-exposure controls accounted for the pronounced decreasing trend in measured NIOSH-cohort EO exposures that occurred after 1978. Prior to 1978, these EO standards and controls were largely or entirely absent. Thus, they were irrelevant to most of the 1935-1975 timespan, during which time the NIOSH statistical model was applied to estimate historical worker exposures without any empirical physical-modeling basis for direct validation.

The final statistical model selected to predict the natural logarithm (ln) of EO exposure included two nonlinearly modeled variables which were determined to be the two most EO-predictive variables identified: Calendar Year ("Year") and Sterilizer Volume ("Cubic Feet"). These two variables were each modeled to have an inverted parabolic relationship to predicted ln(EO) levels, resulting in predicted peak EO exposures to occur during 1978 as a function of Year. Hornung et al. (1994) note that their final statistical model arbitrarily set the value of Year to be 1978 for all years prior to 1978, explaining that:

> Since we felt that the decrease in ETO levels after 1978 (independent of engineering controls) was explained by improved work practices after ETO was identified as a potential carcinogen, we set each predicted ETO level prior to 1978 equal to the predicted level in 1978. Variation in exposure levels prior to 1978 were modeled as a function of the remaining terms in the model with the calendar year effect fixed at 1978. Therefore, there was no extrapolation by calendar year prior to 1978.

[29] Steenland NK, Stayner LC, Griefe AL. 1987. Assessing the feasibility of retrospective cohort studies. Am J Ind Med, 12: 419-30; Greife AL, Hornung RW, Stayner LG, Steenland KN. 1988. Development of a model for use in estimating exposure to ethylene oxide in a retrospective cohort mortality study. Scand J Work Environ Health, 14(Suppl 1): 29-30.

Thus, the "validated" model was arbitrarily and selectively altered for years prior to 1978 by fixing the calendar year value to 1978. Nonetheless, for the same period prior to 1978, the model still predicts that lower EO sterilizer volumes were associated with lower occupational EO exposures—a prediction made without any independent, pre-1978 measurement-based or physical-modeling-based evidence supporting such an association during that period. The IRIS Program should have questioned the reliability and validation of the model prior to 1978, and objectively considered the likelihood of exposure misclassification during this period.

2. **The results of NIOSH's statistical model for exposures prior to 1978 were not provided in the 2014 Draft EO IRIS Assessment or in the cited NIOSH publications. In the appendices of the final EO IRIS Assessment, two new figures (Figures D-22 and D-33) present new information on estimated exposures by worker, but no explanation or critical evaluation was added. There is a lack of transparency in the EO IRIS Assessment of these influential data used to derive the EO cancer slope factor.**

A basic standard quality expectation for a peer-reviewed publication of a statistical model for exposure is that the results section should include summary of the output of the model; in other words, the estimated exposures resulting from the model. Neither the NIOSH exposure modeling publications nor the NIOSH epidemiology studies that rely on this model provide any descriptive summary of exposures estimated by the model prior to the late 1970s. The IRIS Program should have independently evaluated the exposure data, especially after ACC provided the summary of NIOSH exposures by job (reprinted below as Figure 1).

Figures D22 and D23 in the EO IRIS Assessment are graphs of estimated annual exposures for the entire cohort by worker, but not by job. However, there is no discussion or analysis of these graphs in either Appendix D or the main report. These figures are less informative in understanding how the NIOSH exposure model estimated exposure by job because these figures are based on each worker who could have different job assignments. Nevertheless, the 95th percentile of annual exposures of the NIOSH cases in Figure D-23 has a very similar pattern of exposures as the job with the maximum exposure in Figure 1 below.

As described below, neither Hornung et al. (1994) nor the IRIS Program offer any realistic explanation for the counterintuitive trend backward in time from the late 1970s that is predicted by the NIOSH statistical regression model, other than such a trend just happens to be what that statistical model predicts. Thus, there is a lack of transparency and independent critical evaluation of the exposure estimates of the NIOSH exposure model in the EO IRIS Assessment.

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Moreover, the derivation of the NIOSH statistical regression model can no longer be reproduced, because the raw data on which it was based no longer exist.[30]

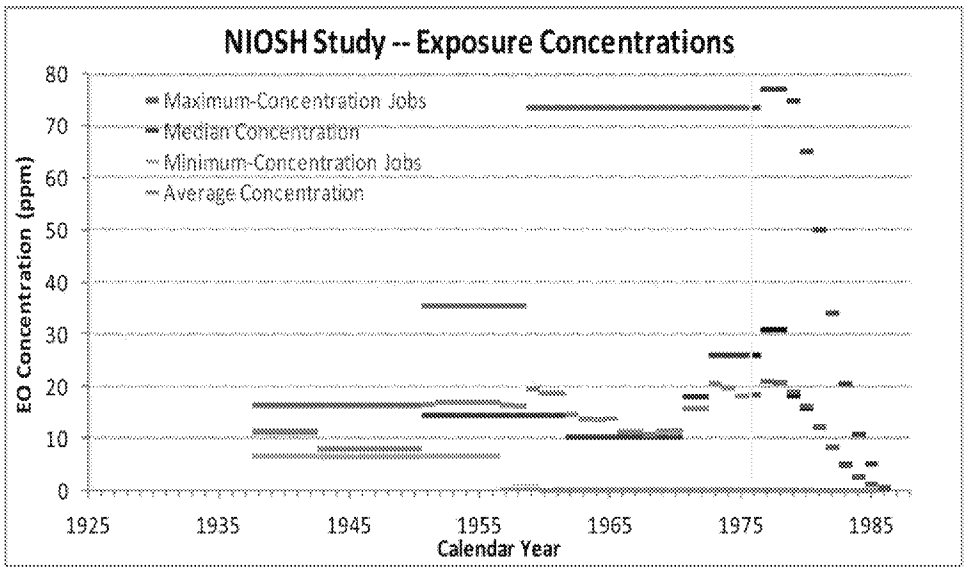

Figure 1. NIOSH statistical regression model predictions of 8-hour time-weighted average exposure to EO by job in each calendar year. This summary data for each job was provided by NIOSH and was used to estimate exposures for participants in the NIOSH cohort based on job code. This figure appeared on page 173 of Appendix M ("Comments on NIOSH Exposure Papers: Greife et al. (1988) and Hornung et al. (1994)") of Comments on the Revised External Review Draft Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide, Docket ID No. EPA-HQ-ORD-2006-0756 submitted to EPA by ACC on October 11, 2013, but did not appear either in Hornung et al. (1994) or any of the draft EO IRIS Assessments reviewed by SAB.

[30] Appendix H (Summary of 2007 External Peer Review and Public Comments And Disposition) of the EO IRIS Assessment states, "[i]n response to the panel's suggestion that the Hornung analysis represents an 'invaluable opportunity' for further analysis of the impact of possible errors in exposure estimation, the EPA investigated the possible use of the 'errors in variables' approach (page 27 of the panel report). Steenland visited the NIOSH offices in Cincinnati in order to review the data and assess whether it would support an errors-in-variables analysis. Unfortunately, the electronic data files used in the [NIOSH] exposure analysis were no longer available, so that analysis based on the errors-in-variables approach was not possible." *Id.* at H-28. Thus, the raw data on which NIOSH relied to derive its statistical regression model used to extrapolate historical NIOSH-cohort exposures to EO prior to the late-1970s, when measures of workplace EO first began to be made, no longer exist—implying that there is no longer any way to validate the claim by Hornung et al. (1994) that their model was able to predict the 85% of the variation in log values of EO concentrations measured starting in the late-1970s. Even if that claim were true, it has no logical bearing on the ability of that model to generate accurate extrapolations of occupational exposure to EO back in time prior to the late 1970s when, as emphasized by Hornung et al. (1994), occupational conditions were quite different because none or virtually none of many sterilization technology changes and sterilization workplace practices, which only began to be adopted starting in the late 1970s to greatly reduce EO exposures (as reflected by NIOSH-cohort exposure measures made starting in the late 1970s to which the NIOSH statistical regression model was fit), were in place prior to that time.

The pattern shown in Figure 1 indicates generally lower exposures for earlier time periods when the crudest technology was used under the least stringent worker protection standards. The SAB considered this pattern to be "surprising," as discussed in greater detail in Section 4, below. Indeed, the pattern of the NIOSH exposure data by job in Figure 1 is the reverse of patterns of historical exposure levels from published studies of exposures to volatile chemicals through time with improvements in technology and increased worker protection requirements[31] as illustrated in two relevant examples (Figures 2 and 3).

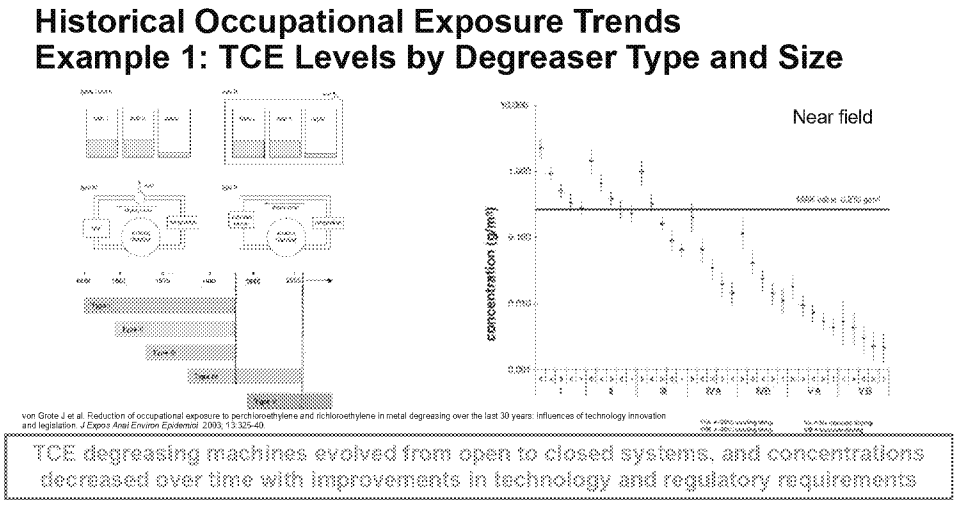

Figure 2. Historical occupational exposure trends, Example 1: TCE levels by degreaser type and size. Source: von Grote et al. (2003b).

[31] *E.g.*, von Grote JHM. 2003a. Occupational Exposure Assessment in Metal Degreasing and Dry Cleaning – Influences of Technology Innovation and Legislation. Doctoral Dissertation, Swiss Federal Institute of Technology, Zürich. Available at: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.628.1123&rep=rep1&type=pdf; von Grote J, Hürlimann C, Scheringer M, Hungerbühler K. 2003b. Reduction of occupational exposure to perchloroethylene and trichloroethylene in metal degreasing over the last 30 years: influences of technology innovation and legislation. J Expo Anal Environ Epidemiol, 13: 325-40; von Grote J, Hürlimann C, Scheringer M, Hunger K. 2006. Assessing occupational exposure to perchloroethylene in dry cleaning. J Occup Envir Hyg, 3: 606-19.

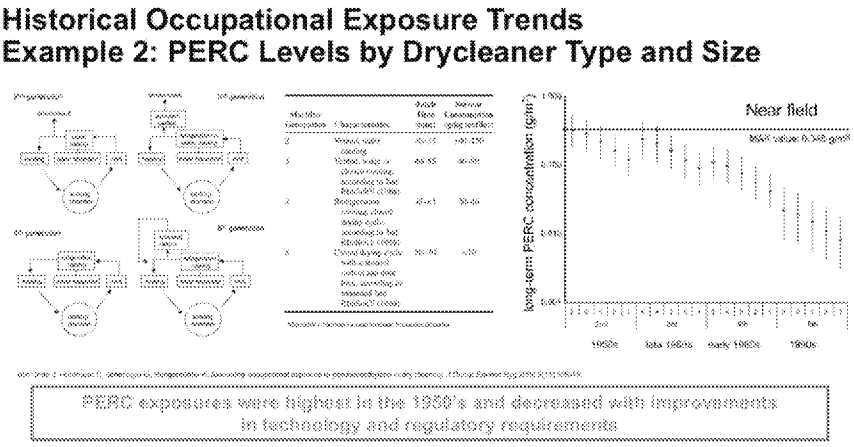

Figure 3. Historical occupational exposure trends, Example 2: PERC levels by dry cleaner type and size. Source: von Grote et al. (2006).

3. The EO IRIS Assessment repeatedly asserts that the NIOSH exposure estimates were well-validated using a state-of-the art model, when in fact there was no validation of exposure estimates prior to 1978. These assertions regarding verification procedures are incorrect for the late 1930s to 1978.

Assertions made in the EO IRIS Assessment about independent evaluation of model estimates are inaccurate. Table 1 lists the statements in the EO IRIS Assessment related to the UCC and NIOSH exposure assessments.

Table 1: List of EO IRIS Assessment statements regarding UCC or NIOSH exposure assessment

Page Number	Description of UCC exposure	Description of NIOSH exposure
1-1		Had a well-defined exposure assessment for individuals
1-2		"high-quality" study based on several attributes, including availability of individual worker exposure estimates from a high-quality exposure assessment
1-4		Retrospective exposure estimation is an inevitable source of uncertainty in this type of epidemiology study; however, the NIOSH investigators put extensive effort into addressing this issue by developing a state-of-the-art regression model to estimate unknown historical exposure levels using

Page Number	Description of UCC exposure	Description of NIOSH exposure
		variables, such as sterilizer size, for which historical data were available.
3-5	Crude exposure assessment, with a high potential for exposure misclassification	
3-6		… the exposure model and verification procedures are described in Greife et al. (1988) and Hornung et al. (1994). Briefly, a regression model was developed to allow estimation of exposure levels for time periods, facilities, and operations for which industrial hygiene data were unavailable. The data for the model consisted of 2,700 individual time-weighted exposure values for workers' personal breathing zones, acquired from 18 facilities between 1976 and 1985. The data were divided into two sets, one for developing the regression model and the second for testing it. Seven out of 23 independent variables tested for inclusion in the regression model were found to be significant predictors of EtO exposure and were included in the final model. This model predicted 85% of the variation in average EtO exposure levels.
3-7		Good-quality estimates of individual exposure
3-8	"cruder" especially for highest exposure	Based on a validated regression model
4-3 and 4-4	Exposure assessment is much less extensive than that used for the NIOSH cohort, with greater likelihood for exposure misclassification, especially in the earlier time periods when no measurements were available (1925-1973). Exposure estimation for the individual workers was based on a relatively crude exposure matrix that cross-classified three levels of exposure intensity with four time periods. The exposure estimates for 1974-1988 were based on measurements from air sampling at the West Virginia plants since 1976. The exposure	This is in contrast to the NIOSH exposure assessment in which exposure estimates were based on extensive sampling data and regression modeling. In addition, the sterilization processes used by the NIOSH cohort workers were fairly constant historically, unlike chemical production processes, which likely involved much higher and more variable exposure levels in the past.

Page Number	Description of UCC exposure	Description of NIOSH exposure
	estimates for 1957-1973 were based on measurements in a similar plant in Texas. The exposure estimates for 1940-1956 were based loosely on a "rough" estimate reported for chlorohydrin-based EtO production in a Swedish facility in the 1940s (Hogstedt et al., 1979). The exposure estimates for 1925-1939 were further conjectures based on the Swedish 1940s estimate. Thus, for the two earliest time periods (19251939 and 19401956) at least, the exposure estimates are highly uncertain. (See Section A.2.20 of Appendix A for a more detailed discussion of the exposure assessment for the UCC cohort.)	
4-5		It was judged to be substantially superior to the UCC study with respect to a number of key considerations in particular, in order of importance: (1) quality of the exposure estimates …
4-60	largely uninformative in terms of assessing the unit risk estimates derived from the NIOSH study because of the crude exposure assessment used in the UCC study	

The EO IRIS Assessment does not critically evaluate the uncertainties of the NIOSH linear regression model, and does not clarify that the NIOSH model was not validated with any data prior to 1978. In the appendices, similar deficiencies pertain to assertions concerning measures applied purportedly to validate the NIOSH statistical regression model,[32] purported empirical and unbiased bases for the NIOSH statistical regression model,[33] and purportedly unlikely inaccurate characterization of exposure by the NIOSH statistical regression model and its purported validation despite nonexistence of original data upon which it was derived.[34]

NIOSH historical extrapolations of occupational EO exposures prior to the late-1970s, were, as described by Hornung et al. (1994), "derived from a regression model based on

[32] *See* EO IRIS Assessment, Appendix A, at A-14.

[33] *See id.*, Appendix D, at D-75.

[34] *See id.*, Appendix H, at H-27 – H-28.

observed measurements." This regression model was applied to extrapolate worker exposures over a large timespan (1935-1975), during which not a single observed measurement was available to validate the application of that extrapolation procedure, and only a small subset of measures was available during 1976-77. Although the NIOSH statistical regression model reliably estimated exposure measurements made after 1977, Hornung et al. (1994) highlighted that post-1977 regulatory standards and consequent progressively stringent operational EO-exposure controls accounted for the pronounced decreasing trend in measured NIOSH-cohort EO exposures that occurred starting in 1978. Prior to 1978, EO standards and controls were largely or entirely absent. Thus, they were irrelevant to most of the 1935-1975 timespan.

4. **In response to public and SAB comments questioning the lower than expected exposures in earlier years predicted by the statistical regression model, the IRIS Program states that the decrease is related to the sterilizer volume. In other words, the model predicts that smaller sterilizer volume results in lower exposures. This response essentially uses the output of the model to answer a question about whether the model assumptions are correct, instead of independently verifying the validity of these assumptions. This circular reasoning does not address the underlying concern of whether the model assumption that Sterilizer Volume has an inverted parabolic (that is, an upside-down U-shaped) relationship with predicted EO exposure is correct. It also does not address whether other factors that might result in increased exposure during early years were properly accounted for in the model.**

During the review of the 2014 draft EO IRIS Assessment, the SAB questioned the general pattern of historical exposures that were lower in some or all years prior to 1975. The SAB had specifically requested EPA to address this issue in a substantive manner (i.e., using historical, physicochemical, and/or engineering facts or models independent of the NIOSH statistical regression model itself). The SAB noted:

> The SAB is also concerned that public commenters had exposure data from the NIOSH cohort that the EPA did not have. For instance, a few selected graphs were presented in **public comments to the Augmented CAAC that indicated exposure predictions for** four jobs in two of the fourteen plants **showed lower exposures in some or all years prior to 1975. The SAB was provided only a few carefully selected examples, and thus was unable to assess the extent of these surprising data.** This is an uncertainty that can easily be ruled out. **Upon reviewing the model equation in Hornung et al. (1994), <u>the SAB finds the surprising historical behavior to be unlikely</u>** and could be explained by changes

> in processes in specific plants, rather than some failure of the model to capture historically larger exposures. The EPA should ensure that they obtain all relevant data released from NIOSH to members of the public.[35]

Figure 1 above shows that the "surprising historical behavior" characterized by the SAB as "unlikely" does not pertain only to a few specific jobs in different plants, but is a general pattern going back in time prior to the late-1970s. EPA's response to the SAB's concern was:

> contrary to public comments made at the SAB meeting, the NIOSH EtO exposure patterns are not anomalous, but rather reflect the underlying changes in variables predicting exposure over time. One of the principal drivers of the NIOSH exposure levels was the cubic feet of the sterilizers used [see Table III, Hornung et al. (1994)]. It was not uncommon in these plants for sterilizer volume to have increased over time as the demand for EtO-sterilized products increased. **Increased sterilizer volume generally resulted in higher predicted average exposures until the late 1970s, when increased controls were used after it became known that EtO might be dangerous.**[36]

The IRIS Program provided quantitative examples illustrating the point emphasized in the quote above for two different plants, in effect illustrating that the response is consistent with the NIOSH statistical regression model defined in Tables III and VI of Hornung et al. (1994). However, the response is circular and, thus, nonresponsive to the SAB concern, because it relies on the same statistical regression model to attempt to validate its assertion that "increased sterilizer volume generally resulted in higher predicted average exposures until the late 1970s."

The NIOSH regression model predicts that EO exposure levels are proportional to an inverted parabolic (upside-down U-shaped) function of sterilizer volume. This function reaches a maximum predicted EO exposure level at a sterilizer volume value of approximately 4,000 ft^3. This regression function is estimated entirely from measurement data obtained nearly exclusively after 1977. However, NIOSH does not explain a plausible physical basis for this complex exposure/volume relationship observed nearly exclusively after 1977. Although this relationship explains a statistically significant amount of variation in the available EO measures, NIOSH offers no convincing evidence that such a relationship must also reliably apply to periods prior to 1978. Hornung et al. (1994) point out that regulatory constraints, sterilization operation, and

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[35] Science Advisory Board Review of the EPA's Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (Revised External Review Draft - August 2014) (Aug. 7, 2015), EPA-SAB-15-012 (2015 SAB Review), at 18 (emphasis added).

[36] EO IRIS Assessment, Appendix I, at I-26 – I-27 (emphasis added).

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sterilization technology all differed greatly from prior to 1978 vs. in/after 1978; they emphasize that in 1978, efforts to control EO exposure began to be implemented on an accelerated basis.

None of the three methods applied by Hornung et al. (1994) to validate their statistical regression model[37] is capable of providing any direct form of validation or verification of historical EO exposures actually incurred by the NIOSH cohort. The NIOSH regression model makes that prediction, based on its statistical regression fit to historical EO measurements that only began in the late 1970s, without any other empirical, physical-modeling, or engineering rationale upon which to establish even the plausibility of that model prediction (e.g., based on independent published literature, historical data, physical/compartmental modeling, or any type of reasoning whatsoever bearing on whether sterilizer chamber volume per se is or is not expected to have correlated with or determined historical EO exposure levels prior to the late-1970s).

Hornung et al. (1994) note that pounds of EO used each year served as a surrogate measure of potential EO exposure, but that since such EO utilization data "were not available for all plants in the study, the size of the sterilizer units (in cubic feet of capacity) was substituted after we determined that there was a high degree of correlation between these two variables." However, in order to achieve sterilization efficacy, EO concentrations used in sterilization chambers have remained approximately constant over time—*regardless* of the volume of sterilization chambers used—except insofar as EO concentrations used are well known (and were reported by experienced EO industry workers in interviews discussed below) to have *increased* going backwards in time from the late 1970s, because higher concentrations of EO were used in earlier decades during the evolution of sterilization operations and technology.

Likewise, because utilization of internal sterilization chamber volume has remained fairly constant over time, independent of reduced chamber volume going back in time from the late 1970s, opening of each chamber door and storage of off-gassing sterilized materials resulted in similar immediate concentrations of EO exposure to nearby workers. Reduced chamber volumes going back in time implied that greater numbers of such smaller chambers had to be used to process approximately the same load of sterilized material per plant. To the extent that smaller amounts of sterilized material were processed by plants earlier in time, then those

[37] Hornung et al. (1994) explain that, in the absence of historical exposure data to perform such verification, they applied a three-phase evaluation procedure consisting of 1) a statistical cross-validation procedure applied to a subset of post-1978 empirical measures of EO, 2) comparison of predictions made a by "a panel of 11 industrial hygienists familiar with ethylene oxide levels in the sterilization industry" to the latter subset of empirical data gathered subsequent to 1978, and 3) an evaluation of the ability of the statistical model to explain the empirical variance exhibited by the entire set of empirical measures of (as noted above, nearly all post-1977) EO exposures available for the NIOSH cohort.

processes are certain to have occurred in smaller facilities, implying that going back in time since the late-1970s there was either an increase (as noted above) or no substantial change in the mass-of-EO-used to workspace-volume ratio that determined the time-weighted average EO concentration to which sterilization workers were exposed throughout that period (particularly for the most heavily exposed workers).

Of greater significance, EPA's response does not take into account critical variables, such as level of EO residue in sterilized materials based on the number of air washes used, the length of time sterilized materials were stored prior to return to customers, and where they were stored relative to chamber operations—variables that changed substantially over the decades of EO sterilization prior to the late 1970s. Historical (pre-late-1970s) estimates of NIOSH cohort EO exposure rely on historical extrapolations made only by the NIOSH statistical regression model that were driven primarily by a correlation primarily between chamber volume and post-late-1970s measures of EO exposure. Operational changes that could have influenced EO exposure concentrations prior to 1976/78 were not investigated.

Even the NIOSH study expected higher historical exposures that would be influenced by the absence of engineering and regulatory controls: "Exposure levels are likely to have been higher [than "the late 1970s"], however, before the installation of engineering controls, when the OSHA standard was 50 ppm instead of the present 1 ppm."[38] Moreover, in the 1940s and 1950s, the MAC-TWA and TLV-TWA were 100 ppm.[39] In 1978, the U.S. Food and Drug Administration (FDA) published proposed "maximum residue limits" of 5-250 ppm for medical devices for human use that are sterilized with EO. Prior to 1978, there were no regulatory standards to reduce residues on medical devices, so the residues were around 10–30,000 ppm depending on the type of material.[40] But the IRIS Program failed to take this information into account when modeling the data.

5. **The EO IRIS Assessment makes the unsubstantiated claim that "the sterilization processes used by the NIOSH cohort workers were fairly constant historically, unlike chemical production processes, which likely involved much higher and more variable exposure levels in the past."[41] In**

[38] Steenland K, Stayner L, Greife A, Halperin W, Hayes R, Hornung R, Nowlin S. 1991. Mortality among workers exposed to ethylene oxide. N Engl J Med, 324(20): 1402-07, at 1406.

[39] ACGIH. 2001. Ethylene Oxide: TLV® Chemical Substances 7th Edition Documentation.

[40] Ernst RR and Whitbourne JE. 1971. Toxic residuals. In the Study of the requirements, preliminary concepts, and feasibility of a new system to process medical/surgical supplies in the field, pp. 46-57, Appendix pp. 1-2, Contract No. DADA17-70-C-0072. U.S. Army Medical R&D Command, Washington, D.C. (Defense Documentation Center Accession No. AD890320 and AD890321).

[41] EO IRIS Assessment, at 4-4.

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fact, there was an evolution in technology and practices associated with the sterilization processes between the late 1930s and early 1970s. Data and information from industrial sterilization operators and the literature refute this claim.

Interviews conducted by Exponent, Inc. with three former sterilization operators who began work in the mid-1960s and early to mid-1970s (one was a member of the NIOSH cohort) confirmed operational differences in the sterilization operations in the 1960s and 1970s, and in earlier decades, relative to operations post-1978. This new interview information is supported by information and data in the technical literature on sterilization operations in early decades, including high EO residue levels in and rates of EO off-gassing from EO-sterilized medical materials,[42] and by current quantitative measures of in-chamber EO concentration during sterilization operations after single and multiple air washes that were transmitted to Exponent, Inc. by an industrial sterilization company. These data indicate that the EO IRIS Assessment's assumption that the sterilization processes were fairly constant between the late 1930s and early 1970s is incorrect.

These data also indicate that the variables in the NIOSH model that predicted exposures after the mid-1970s do not capture important potential sources of exposures to sterilizer operators prior to the 1970s:

a. Technology improvements for worker protection such as back venting and use of aeration processing rooms to degas sterilized materials were implemented post 1978. Thus, the presence or absence of back venting or ventilated aeration rooms may help discriminate exposures after 1978, but not between the late 1930s and 1977.

b. Pre-1978 commercial sterilization operations typically included at most only a single post sterilization air wash (relative to numerous washes used typically in later decades); in a current sterilization unit using 100% EO, an EO concentration

[42] Perkins JJ. 1969. Principles and Methods of Sterilization in Health Sciences, 2nd ed. Charles C. Thomas, Springfield, IL; Bruch CW. 1972. Toxicity of ethylene oxide residues. In: Phillips GB, Miller WS, eds. Industrial sterilization, Duke University Press, Durham, NC, at 119-23; Bruch CW. 1981. Ethylene Oxide sterilization—technology and regulation. Industrial ethylene oxide sterilization of medical devices: process design, validation, routine sterilization, AAMI Technological Assessment. Report No. 1-81. Arlington, VA: Association for the Advancement of Medical Instrumentation, at 3-5; Roberts RB, Rendell-Baker L. 1972. Aeration after ethylene oxide sterilisation. Failure of repeated vacuum cycles to influence aeration time after ethylene oxide sterilisation. Anesthesiol, 27(3): 278-82; Stetson JB, Whitbourne JE, Eastman C. 1976. Ethylene oxide degassing of rubber and plastic materials. Anesthesiol, 44(2): 174-80; White JD. 1977. Standard aeration for gas-sterilized plastics. J Hyg Camb, 79: 225-32.

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of 17,200 ppm was measured in chamber air after a single wash cycle. Fewer wash cycles result in much higher peak exposures when opening the chamber doors, as well as higher residue levels remaining on the pallets of sterilized material. These higher residue levels contribute to higher exposure levels to those working in areas where pallets are stored.

c. Most 1960s and 1970s operations had evolved to storing the sterilized materials during degassing in a separate room from chamber operations, while operations in earlier decades had chamber operations and sterilized material stored in the same workspace. In the 1950s and 1960s, sterilizer operators would be expected to have higher exposures than in the 1970s because there was one (or no) air washes and the sterilized pallets with high residue levels were often stored in the same room as the chambers.

d. Systematic application of forced and efficient ventilation where sterilizers were operating and where treated pallets were stored was rare or absent prior to the mid-1970s.

e. The period of degassing of sterilized materials was generally about 7 days during the mid-1960s and 1970s, but was ≤1 day in earlier decades. This indicates that the levels of residues in the sterilized materials and, hence, exposures were consistently high in earlier decades.

f. Although with increasing time prior to the mid-1970s sterilization operations involved smaller sterilizers (i.e., having smaller sterilizer chamber volumes), sterilizer operations involved less mechanized or non-mechanized processes, less- or non-ventilated chamber and storage operations, more leaky EO containment during sterilization, and more direct operator exposure to EO vapor (e.g., during change of filters contacting liquid EO and manual connection/disconnection of EO tanks)—factors that likely acted jointly to generate EO exposures to sterilizer operators and other related workers that were greater prior to the late 1970s than during later periods.

g. According to interviewed operators with decades of experience in the EO sterilization industry, concentrations of EO applied in sterilizers currently and since the late 1970s (400–600 mg/L) have been lower by a factor of roughly 1.5 than those applied during earlier decades, and resulting chamber concentrations of EO upon opening of sterilizer chamber doors (which at that time were not actively

ventilated) thus are likely to have been equal to or (with increasing likelihood going back further in time) greater than those that occurred during 1978.

Each of these factors taken alone or in combination indicate that, compared to the sterilization worker environment starting in 1978, when technology improvements and regulatory controls were introduced with increasing frequency and stringency, it is highly probable that greater EO concentrations occurred in the sterilization worker environment from the mid-1960s to the late 1970s. Moreover, it is virtually certain that even greater EO concentrations occurred in the sterilization worker environment prior to the mid-1960s, contrary to trends in occupational exposures during those times that were extrapolated using the NIOSH statistical regression model.

The new information summarized above confirms that the SAB's concern was not effectively addressed by the IRIS Program, and therefore all assessments of EO cancer risk derived using NIOSH epidemiological study data are potentially confounded by greater magnitudes of uncertainty than are stated in the EO IRIS Assessment. These assessments are based on historical extrapolations of occupational exposures prior to the late-1970s produced by the NIOSH regression model and thus necessarily depend on the accuracy and reliability of those extrapolations. This major source of uncertainty in the EO IRIS Assessment is a key defect.

6. **Comparisons of relative reliability made between the NIOSH and UCC studies are inaccurate. These comparisons were a key basis upon which the IRIS Program rejected the UCC Study as a source of epidemiology study data for cancer risk assessment. The EO IRIS Assessment does not acknowledge and appropriately consider limitations of the NIOSH exposure assessment posed by low extrapolations of NIOSH cohort exposures to EO prior to the late 1970s without any corroborating data or any supporting engineering/process considerations derived from or directly relevant to that period of time.**

The EO IRIS Assessment argues inaccurately that the UCC exposure assessment was "too crude" to be used for exposure-response analysis (see Table 1). To the contrary, Greenberg et al. (1990) describe their categorization of departments into "high," "medium," and "low" categories based on a detailed reconstruction of processes using records and interviews of older employees.[43] The categorization was validated using frequencies of visits to the medical department for acute over exposures. The UCC exposure assessment was expanded to include

[43] Greenberg HL, Ott MG, Shore RE. 1990. Men assigned to ethylene oxide production or other ethylene oxide related chemical manufacturing: A mortality study. Br J Ind Med, 47: 221-30.

individual exposure estimates, as described in detail by Swaen et al. (2009).[44] All such efforts associated with epidemiology studies require assumptions and involve uncertainties.

The UCC study, however, includes actual UCC data based on monitoring data from the UCC Texas plant with very similar operations from as early as 1957. Estimates for the 1940-1956 period are based on the published literature for companies using a similar process for EO production. The greatest uncertainty is for 1925-39; however, only 4.8% of the cohort worked during that period. In contrast, **approximately 70% of the NIOSH cohort had workplace exposures prior to 1978, the period of unverified exposure estimates.**

The EO IRIS Assessment's criticism of the UCC approach, i.e., it includes data from a comparable plant that was not part of the cohort, is biased because NIOSH also used exposure data from plants that were not included in the cohort. The fact that UCC-cohort exposures estimated between 1957-1973 are based on contemporary actual exposure measurements obtained from a very similar plant is a major advantage (and certainly not a deficiency) of the UCC approach relative to the NIOSH study.

In contrast, critical limitations and uncertainties associated with NIOSH's statistical regression modeling for the period prior to the late 1970s (based entirely on a fit obtained to data gathered only starting in the late 1970s, since no actual measurements of EO exposure were available for the NIOSH cohort prior to that time) are not accurately characterized or even meaningfully acknowledged in the EO IRIS Assessment or in related NIOSH publications. For example, Hornung et al. (1994) did not reveal that their approach resulted in lower, rather than higher, exposures over the entire period addressed prior to the late 1970s, with no exposures prior to 1978 exceeding those that occurred in and also were reliably estimated for 1978. As noted above, the pattern predicted by the NIOSH statistical regression model conflicts with what is known about early processes in the sterilant industry, and was characterized as "surprising" and "unrealistic" by the SAB.

The EO IRIS Assessment is highly misleading because what it refers to as NIOSH statistical regression model "validation" was done only for its post-late-1970s predictions, since no earlier EO-measurement data were available. Model extrapolations of historical EO exposure prior to the late 1970s were conjectural, relying entirely on putative explanatory power of a regression model fit to EO-measurement data that, as acknowledged by Hornung et al. (1994), exhibited a steeply declining pattern of EO exposures over time post-1977 due to regulatory concerns and EO-control measures that simply did not exist previously. New information

[44] Swaen GM, Burns C, Teta JM, Bodner K, Keenan D, Bodnar CM. 2009. Mortality study update of ethylene oxide workers in chemical manufacturing: a 15 year update. J Occup Environ Med, 51(6): 714-23.

described above confirms that the NIOSH exposure estimates for periods prior to the late 1970s are substantially and unrealistically low, and therefore are likely to have biased all assessments of EO cancer risk that relied only on NIOSH cohort study data. Moreover, the IRIS Program has failed to investigate whether such bias may render assessments of EO cancer risk unreliable.

7. **The EO IRIS Assessment relies solely on the NIOSH study of sterilant workers and fails to incorporate the important findings from the UCC study of workers in EO producing and using operations. The IRIS Program considered and characterized three factors in its selection of the NIOSH study: cohort size, exposure data, and confounding. Based on these factors, the IRIS Program dismissed the UCC study as a basis for EO cancer risk estimation. In considering cohort size, the IRIS Program ignored the most important comparison—the number of lymphohematopoietic tissue cancers, not the total cohort size.**

As discussed in detail in the other sections, the NIOSH study does not have superior exposure data compared to the UCC study, so both studies have comparable applicability to risk assessment.

Cohort size is only one factor in assessing study informativeness. The most important factor is the number of events of interest, which for a mortality study is dependent on length of follow up and percent deceased. The most recent published study of the UCC cohort reports a sizeable number of deaths due to leukemia and lymphomas, comparable to the events among males in the NIOSH study that would make a meaningful contribution to the number of events for an exposure-response analysis.[45] Despite the smaller number of male workers in the UCC study, they have been followed for a longer period of time (37 yr on average compared to 25 yr for the NIOSH study) and include 51% deceased compared to 19% of the much younger NIOSH sterilant population. The EO IRIS Assessment criticizes the sample size in the UCC cohort, noting (erroneously) "only" 27 LHC cancers and 12 leukemias; the correct number of leukemias is 11 (EPA interchanged the numbers of leukemia and NHL deaths). However, the EO IRIS Assessment does not also note the male population of the NIOSH study had 37 LHC cancers and only 10 leukemias. Furthermore, no substantive criticisms of the NIOSH study appear in the EO IRIS Assessment, when in fact there are major uncertainties with respect to the NIOSH exposure estimates as described in detail above.

The EO IRIS Assessment raises concerns about confounding in the UCC study because of the presence of multiple chemicals in the workplace. This source of bias would only be

[45] Swaen et al. (2009).

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expected when analyses yield positive findings, i.e., increases that may not be attributed to EO but to other chemicals. This, in fact, was identified by Greenberg et al. (1990), which reported an increase in leukemia and pancreatic cancer that was found to be attributable to exposures to one or more chemicals in the ethylene chlorohydrin production unit that was characterized as a "low" EO department. The 278 workers involved in that department were removed from the cohort and separately analyzed in a companion publication,[46] which verified increased risk observed by Greenberg et al. (1990). The remaining EO workers did not exhibit cancer increases in subsequent updates.[47] The three central reasons cited in the EO IRIS Assessment for excluding the UCC study are not defensible as explained above, and therefore indicate a biased preference for using the NIOSH study as a sole basis for EO cancer risk estimation.

In addition, the EO IRIS Assessment diminishes the value of the most recent UCC cohort study claiming they were followed so long that background rates of lymphoid tumors would be so large as to miss increased risks due to EO. The important factor is to have sufficient time since first exposure (latency). The 37 yr. average follow-up of Swaen et al. (2003) is not excessive in light of the fact that the most recent hires (1988) have 15 yr. follow-up at most. It is desirable to have 20-25 yr. follow-up for a cancer outcome of interest and even longer when exposures are lower as they were post-1976. Furthermore, there were two earlier studies of this cohort (Greenberg et al., 1990 and Teta et al., 1993) when the cohort was younger, which failed to identify EO-related cancer increases. These studies examined the findings by hire date, duration of exposure, time since first exposure and performed comparisons to the non-exposed chemical workers adjusting for age. It is implausible and speculative that the aging of the cohort masked significant EO-related cancer increases.

The UCC study should have been incorporated in both the hazard characterization and the exposure-response analysis. Consequently, the IRIS Program's handling of these key issues—cohort size, exposure estimation, and confounding—is incomplete, inaccurate, and biased.

8. **The use of the supralinear spline model for the lymphoid and breast cancers in the final EO IRIS Assessment is based on an invalid statistical analysis. Because the analysis did not correctly calculate degrees of freedom associated with that fitted model, it contains erroneous measures of absolute and relative goodness of fit of that model. When both the p-values and Akaike**

[46] Benson LO, Teta MJ. 1993. Mortality due to pancreatic and lymphopoietic cancers in chlorohydrin production workers. Br J Ind Med, 50: 710-16.

[47] Teta MJ, Benson LO, Vitale JN. 1993. Mortality study of ethylene oxide workers in chemical manufacturing: A 10 year update. Br J Ind Med, 50: 704-09; Swaen et al. (2009).

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Information Criterion (AIC) values characterizing fit quality are corrected, the supralinear spline model does not fit the NIOSH lymphoid tumor data statistically significantly better than the log-linear Cox model.

The EO IRIS Assessment justifies why it does not account for the degrees of freedom by citing the 2015 SAB Review: "The knot is preselected and is not considered a parameter in these analyses, consistent with the SAB's concept of parsimony (SAB, 2015)."[48] However, the concept of parsimony is a preference for a simpler model with fewer estimated parameters when fitting and evaluating a single model. The SAB did not direct EPA to violate well founded and widely accepted statistical practice by ignoring the fact that a particular parameter (in this case, the knot of a bi-linear spline model) of a spline model was actually estimated when defining the total number of its estimated parameters, when comparing the goodness of fit of that spline model to another model (such as a log-linear model) that involves no estimated knot.[49]

The EO IRIS Assessment indicates to fit particular supralinear spline models, their "knots were obtained by doing a grid search by increments of 100 ppm x days and then interpolating where appropriate."[50] In other words, the knot of the final supralinear spline model selected was indeed an additional estimated (in this case, numerically optimized) parameter, standard statistical model-fitting procedures always require that p-values be evaluated for a goodness-of-fit statistic only after subtracting one degree of freedom ***for each one of the total number of parameters (a number typically denoted as k) that are estimated when fitting a model***, regardless of how such parameters are estimated.

Failure to follow this procedure always results in an erroneously inflated "p-value" for goodness of fit (only a model with a p-value for goodness-of-fit larger than 0.05 is typically considered acceptable), and thus also in an underestimated value of a corresponding AIC used to compare goodness of fit of different models (a model with a smaller AIC value is preferred, and AIC is defined as twice the sum of k [defined above] and a fit-specific positive quantity). If the proper procedure is not followed to define total degrees of freedom (k), the result is a p-value indicating a fit that is better than actually is the case (i.e., a p-value indicating that deviations between a fitted model and the observed/modeled data are more likely to have occurred by chance alone than actually is the case), and consequently also an AIC value that misrepresents a

[48] EO IRIS Assessment, Appendix D, at D-6.

[49] The EO IRIS Assessment quotes the SAB as follows: "in some settings the principle of parsimony may suggest that the most informative analysis will rely upon fixing some parameters rather than estimating them from the data. The impact of the fixed parameter choices can be evaluated in sensitivity analyses. In the draft assessment, fixing the knot when estimating linear spline model fits from relative risk regressions is one such example." Appendix D, at D-6, note 11.

[50] EO IRIS Assessment, Appendix D, Table D-27, note a.

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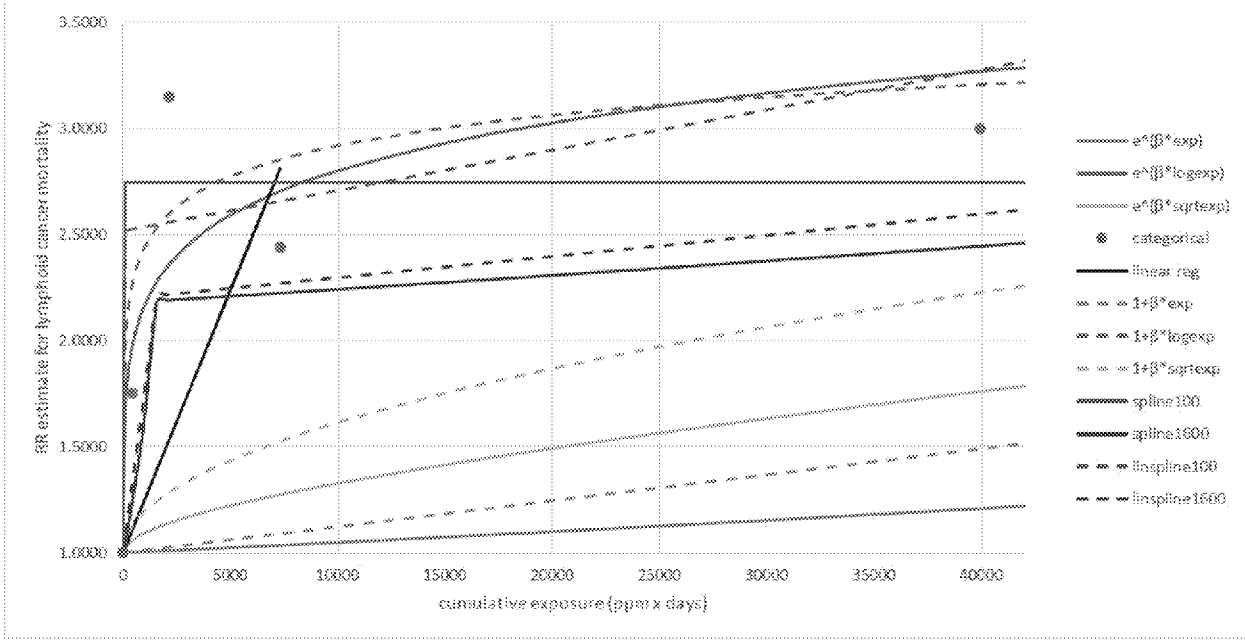
model's goodness of fit relative to that of another model for which degrees of freedom (k) are defined properly.

By ignoring this statistical procedure for its supralinear spline model fit, the EO IRIS Assessment artificially and erroneously inflates the p-value and reduces the AIC value that was used to compare that model to those of other models being compared for which degrees of freedom were defined correctly. **When both the p-values and AIC values are corrected, the selected supralinear spline model does not fit the NIOSH lymphoid tumor data statistically significantly better than the log- linear cumulative model (see Appendix 1).**

9. **The selection of the supralinear spline model for the lymphoid tumors is also based on misleading illustrations of "visual fits" that do not convey either the actual data that were fit or the relative goodness of fit to these data of log-linear and supralinear spline models. Only in a footnote does the IRIS Program acknowledge that the visual comparison misrepresents the log-linear model being compared. Consequently, and erroneously, the fit to the data appears far worse than the supralinear spline model. The data plotted in that figure also were summary data that misrepresent the true magnitude of the scatter of the data that were used for model fitting.**

The EO IRIS Assessment visually represents alternative models considered in relation to data used for model fitting in Figures 4-3 through 4-8, explaining that "to facilitate a visual comparison of the models, select models are replotted against the categorical data in deciles." Figure 4 below reprints Figure 4-3 from the EO IRIS Assessment and illustrates the incorrect basis for the conclusion that the NIOSH exposure-response is supralinear and that only models that are supralinear have good visual fit to the data.



e^(β*exp): RR = $e^{(\beta \times \text{exposure})}$; e^(β*logexp): RR = $e^{(\beta \times \ln(\text{exposure}))}$; e^(β*sqrtexp): RR = $e^{(\beta \times \text{sqrt}(\text{exposure}))}$; categorical: RR = $e^{(\beta \times \text{exposure})}$ with categorical exposures, plotted at the mean cumulative exposure; linear reg: weighted linear regression of categorical results, excluding highest exposure group (see text); 1 + β*exp: RR = 1 + β × exposure; 1 + β*logexp: RR = 1 + β × ln(exposure); 1 + β*sqrtexp: RR = 1 + β × sqrt(exposure); spline100(1,600): Two-piece log-linear spline model with knot at 100 (1,600) ppm × days (see text); linspline100(1,600): Two-piece linear spline model with knot at 100 (1,600) ppm × days (see text). (Note that, with the exception of the categorical results and the linear regression of the categorical results, the different models have different implicitly estimated baseline risks; thus, they are not strictly comparable to each other in terms of RR values, i.e., along the y-axis. They are, however, comparable in terms of general shape.)

Source: Steenland reanalyses for males and females combined; see Appendix D (except for linear regression of categorical results, which was done by EPA).

Figure 4-3. Exposure-response models for lymphoid cancer mortality vs. occupational cumulative exposure (with 15-year lag).

Figure 4. Figure 4-3 from the EO IRIS Assessment using categorical data (solid purple points) to compare the visual fits of the different models, including the selected two-piece log-linear-spline model (dashed red curve) and the standard Cox log-linear regression model (solid blue curve).

Figure 4-3 misrepresents the relative quality of true visual fits to the EO IRIS Assessment's preferred supralinear spline model compared to the more parsimonious log-linear Cox regression model in two important ways. First, Figure 4-3 plots data points that represent categorical data aggregated into quartiles (filled purple points in Figure 4, above) instead of the actual individual cases modeled. This comparison was used in earlier drafts of the IRIS Assessment when the 2014 draft EO IRIS Assessment modeled those categorical aggregated or summary data. However, when the final EO IRIS Assessment followed the SAB's recommendation to model individual cases, the data plots were not corrected accordingly to show the true magnitude of data scatter in relation to fitted models.

Second, the IRIS Program acknowledges in a footnote to Figure 4-3 that "the various models have different implicitly estimated baseline risks; thus, they are not strictly comparable to each other in terms of RR values (i.e. along the y-axis). They are, however, comparable in terms of general shape." It is not transparent, however, that these graphs cannot be used at all to compare some of the models shown in a valid way. In particular, the lower log-linear model fit shown (the solid blue "line" that appears to go through the origin of the plot shown in Figure 4-3) appears to provide a very poor fit to the cloud of individual data through which that model passes, because the place where that model is shown to intersect the y-axis was artificially forced (in that figure) to intersect the value of 1 along the y-axis, when in fact that model does actually pass centrally through the cloud of actual raw data to which it was fit. That is, although both the EO IRIS Assessment's preferred model and the log-linear model do more or less centrally pass through the cloud of data to which these models were fit, Figure 4-3 misleads the reader by showing a relatively poor fit of the simpler (i.e., more parsimonious) log-linear model compared to the more complex supralinear spline model that was selected in the EO IRIS Assessment.

Figure 5[51] more accurately compares the supralinear spline model (red dashed curve) and the standard Cox log-linear regression model (solid blue curve). The latter model is the approach used by Valdez-Flores et al. (2010) to fit the NIOSH, UCC, and combined NIOSH+UCC study data for lymphoid tumors. In Figure 5, the baseline (zero-exposure) value of hazard rate (HR) to which the log-linear model was fit is set equal to the same baseline HR as that estimated using the supralinear spline model. Therefore, Figure 5 shows more accurately than Figure 4 that the supralinear spline model fits the data no better than standard Cox log-linear regression model.

[51] Figure 5 improves comparison along the y-axis by dividing model-estimated values of hazard rate (HR) ratio by the baseline HR of the individual categorical cases (thus making an apples-to-apples comparison), and uses a logarithmic scale to improve comparison of the linear difference between the fitted models and observed values of relative risk measured as hazard rate ratio (RR). In Figure 4, RR values greater than one appear disproportionally more distant from 1 than RR values less than one, because of the linear RR scale used in that figure. RR values greater than one can be as large as infinity, but RR values less than one cannot be less than 0. In contrast, values of Ln(RR)—i.e., values of RR plotted on a logarithmic scale—as shown in Figure 5 can be as large as infinity and as small as minus infinity (see Appendix 1).

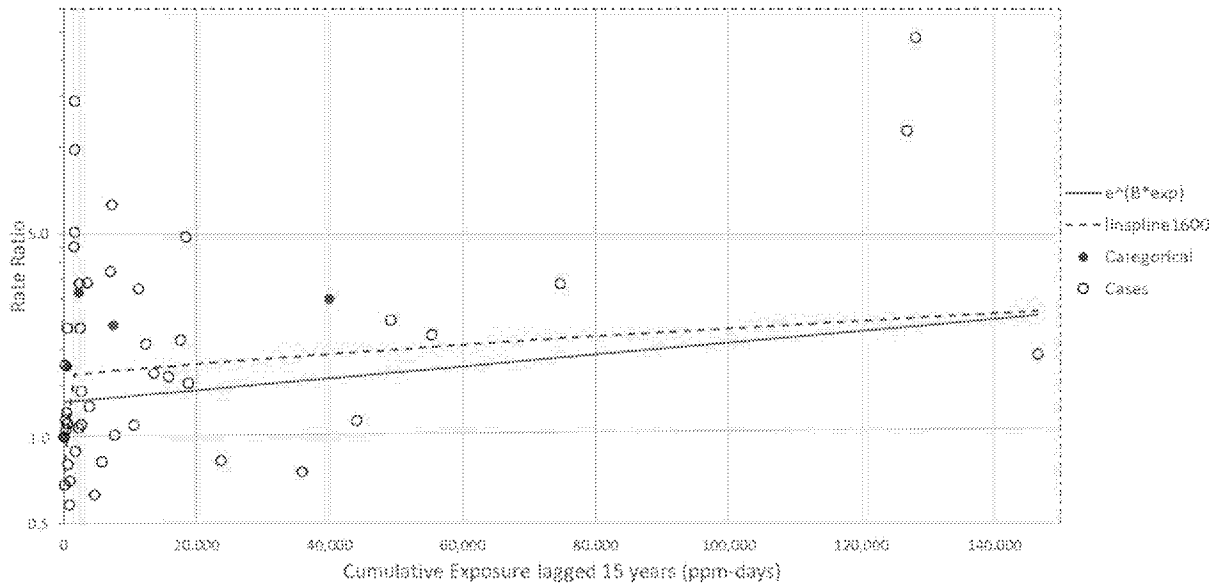


Figure 5. Apples-to-apples comparison of the EO IRIS Assessment's preferred supralinear spline model (red dashed curve) and the log-linear Cox proportional hazards model (solid blue curve), plotted in relation to categorical data (solid purple points) from Figure 4 together with corresponding actual (raw/individual-level) data to which these models were fit (open points).

The misleading plots of categorical data in the EO IRIS Assessment were a key justification for its rejection of the standard Cox log-linear proportional hazards model in favor of a supralinear exposure-response relationship, as indicated in Table 4-14 of the EO IRIS Assessment.

10. The selection of a spline model as the preferred model for EO cancer risk estimation assumes a supralinear increase in tumor response in the low-dose exposure region with a subsequent plateauing of response at higher exposures. The body of cancer epidemiologic studies, including the NIOSH studies, does not support such a pattern of risk. While certain NIOSH sub-analyses suggest increases in male lymphoid tumors and female breast cancers, the findings are limited to the highest cumulative exposure groups, not the lowest.

Steenland et al. (2003) state, "Exposure-response data do suggest an increased risk … for those with higher cumulative exposures to ETO."[52] The authors also say, "The dip in the spline

[52] Steenland K, Whelan E, Deddens J, Stayner L, Ward E. 2003. Ethylene oxide and breast cancer incidence in a cohort study of 7576 women (United States). Cancer Causes Control, 14: 531-39.

curve in the region of higher exposures suggested an inconsistent or non-monotonic risk with increasing exposure." The default expectation for a genotoxic carcinogen would be this pattern of monotonically increasing risk in relation to exposure, which is why the authors call it "inconsistent." The EO IRIS Assessment notes that it is not unexpected to have fluctuations in exposure-response curves due to random variation, yet in the exposure-response section the IRIS Program models such plausibly random fluctuation using a supralinear response model.

The EO IRIS Assessment cites Mikoczy et al. (2011)[53] to support the use of the supralinear spline model for breast cancer: "Although the reason for the observed supralinear exposure-response relationship is unknown, it is worth noting that the results of the Swedish sterilizer worker study reported by Mikoczy et al. 2011, …support the general supralinear exposure-response relationship observed in the NIOSH study."[54] However, Mikoczy et al. (2011) studied a low-exposure population that exhibited a significant increase in breast cancer incidence only when analyzed using an internal analysis comparing more-highly exposed to low-exposed workers, and exhibited no such significant increase in a corresponding external analysis involving comparison to matching members of a general population. The explanation for this anomaly lies in the dramatic and (as indicated by Mikoczy et al., 2011) statistically significant deficit of breast cancers in the low exposure group of the internal comparison; because in the internal comparison that low-exposed group was used as the referent group, the two higher exposure groups being compared showed significantly higher rates breast cancer relative to that lower-exposed group.

It might be argued that the non-representative and significantly low rate of breast cancer incidence exhibited by the low-exposure group used for internal comparison simply reflects a Healthy Worker Effect (HWE). However, the breast cancer rate for that group was remarkably low (only about half that of the reference population group of age-matched Swedish women used), and there is no HWE specific to breast (or to any other type of) cancer in Swedish female workers.[55] Thus, the EO IRIS Assessment does not accurately acknowledge and address the problematic nature of the internal-comparison reference group that served as the basis for results of internal comparisons of breast cancer incidence reported by Mikoczy et al. (2011).

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[53] Mikoczy Z, Tinnerberg H, Jonas Björk J, Albin M. 2011. Cancer incidence and mortality in Swedish sterilant workers exposed to ethylene oxide: updated cohort study findings 1972–2006. Int J Environ Res Public Health, 8: 2009-19.

[54] EO IRIS Assessment, at 4-71.

[55] Gridley G, Nyren O, Dosemeci M, Moradi T, Adami HO, Carroll L, Zahm SH. 1999. Is there a healthy worker effect for cancer incidence among women in Sweden? Am J Ind Med, 36(1): 193-99.

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The EO IRIS Assessment's extra risk estimate suggests a highly potent carcinogen. This is contrary to epidemiology findings which show overall weak positive findings (see Appendix 2). While interest has centered on leukemia, other blood related malignancies, and recently on breast cancer, there are numerous inconsistencies among the studies; elevated risks above background, in isolated studies, are of small magnitude; and there is an absence of a clear exposure-response for any specific cancer type. The most informative studies are the NIOSH (Steenland et al. 2003, 2004) and UCC studies (Swaen et al. 2009), which are studies of comparable utility for risk assessment purposes. These epidemiology studies do not support supralinearity (high risk at low exposures). Certain NIOSH subanalyses showed increase for males only (lymphoid tumors) in the highest (not the lowest) cumulative exposure groups. Extended follow up of chemical workers, UCC and others, and sterilant workers show little, if any, increases. The epidemiological evidence does not support the RSC of 0.1 ppt, which suggests a highly potent carcinogen.

11. The use of a supralinear spline model for cancer risk estimation is inconsistent with the assumed mode-of-action of EO toxicity and tumorigenicity. Such a model predicts higher risk at low exposures compared to risks predicted at higher exposures, which is contradicted by the well-understood mode of action of EO in experimental animals and humans as described in the EO IRIS Assessment. Thus, the EO IRIS Assessment relies on human cancer risk estimates based on spline-model dose-response extrapolations that are internally inconsistent with its own evaluation of the mode of action of EO. The mean air concentration equivalent to the endogenous concentration in non-smoking humans with no known EO exposures is 1.9 ppb (range 0.13-6.9 ppb; continuous), which is 19,000 times greater than the EO IRIS RSC of 0.1 ppt. An alternative LEC (1/million) of 0.5-1.2 ppb is a more pragmatic, science-based approach for EO risk assessment.

As a direct acting DNA- and protein-reactive toxicant, the high-level toxicological and cancer mode of action of EO importantly predicts a *sublinear* increase in dose-response at low exposures and an associated dose-disproportionate *increase* in toxicity at higher EO doses.[56] This expected dose-response pattern is due to attenuation of low-dose EO toxicity mediated by intervention of key detoxification pathways (EO conjugation with glutathione and enzymatic hydrolysis to oxidized metabolites; repair of EO-induced DNA adducts), and an associated dose-disproportionate (supralinear) increase in toxicity at higher doses due to saturation of those same pathway(s) as the EO dose increases, as summarized below in Figure 6.

[56] Kirman and Hays (2017).

The EO IRIS Assessment describes and supports this projected EO mode of action and its implications for the shape of the cancer dose response in the low- to high-dose regions as follows:

> [E]PA considers it *highly plausible that the dose-response relationship over the endogenous range is sublinear* (e.g., that the baseline levels of DNA repair enzymes and other protective systems evolved to deal with endogenous DNA damage would work more effectively for lower levels of endogenous adducts), that is, that the *slope of the dose-response relationship for risk per adduct would increase* as the level of endogenous adducts increases.[57]

The EO IRIS Assessment's analysis of the EO mode of action emphasizes that the dose-response is highly likely ("highly plausible") to be *sublinear* "over the endogenous range" of internal EO doses that result from well-characterized endogenous production of EO secondary to metabolism of ethylene originating from normal biological processes.

Exploiting the well-defined linear relationship between exogenous EO exposure and systemic hemoglobin adducts in humans, Kirman and Hays (2017) estimate that the contribution of endogenously generated EO exposures to the overall systemic dose of EO is substantially greater than the 0.1 ppt exogenous EO exposure projected by the EO IRIS Assessment as resulting in a 1×10^{-6} cancer risk in humans. A meta-analysis of 661 non-smoking individuals not exposed to external EO indicated that endogenous background EO exposures are equivalent to a mean external exogenous EO exposure of 1.9 ppb (range 0.13-6.9 ppb). This "endogenous equivalent" contribution to the overall systemic EO dose is 19,000 times greater than the 0.1 ppt exogenous EO one-in-a-million risk dose estimated by the EO IRIS Assessment.

It is clear that even a 1000-fold increase in exogenous EO exposures above 0.1 ppt would only approach the low end of the total systemic EO dose contributed by endogenous EO generation. Any contributions of exogenous EO to cancer risk below this low-end endogenous dose would not be detectable within the likely day-by-day intra- and inter-individual variability (0.13-6.9 ppb) associated with normal endogenous EO exposure loads.

[57] EO IRIS Assessment, at 4-95 (emphasis added).

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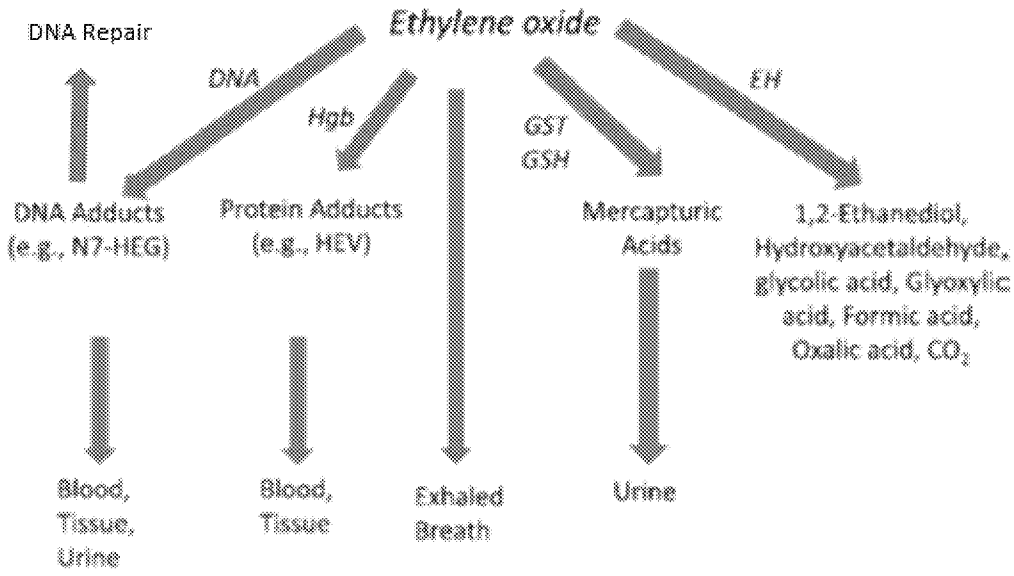

Modified from Kirman & Hays, Reg Toxicol Pharmacol 91: 165-172, 2017

Figure 6. EO metabolism (adapted from Kirman and Hays, 2017).

Kirman and Hays (2017) also recognize that increased EO hemoglobin adducts associated with smoking provided an opportunity to further check the EO IRIS Assessment's supralinear model predictions that moderately low external EO exposures realistically contribute to increased cancer risks. A meta-analysis of 379 smokers not otherwise exposed to EO found that smoking increased EO exposures approximately 10-fold above the endogenous equivalent dose for background (non-EO exposed) individuals (mean background endogenous equivalent exposure = 1.9 ppb; mean smoker exposure = 18.8 ppb). The spline-model relied on by the EO IRIS Assessment predicts that the moderate increase in EO exposure associated with smoking would result in a detectable increase in lymphohematopoietic and breast cancers. However, this expectation is not met despite the very large smoking cohort.

Kirman and Hays (2017) note that smoking has been causally associated only with one subtype of lymphohematopoietic cancer, acute myeloid leukemia (AML). Not only is this cancer not increased in the NIOSH occupational cohort specifically exposed to higher doses of EO than those resulting from smoking, but Valdez-Flores et al. (2010), using a non-spline-based risk model, also demonstrate a statistically significant negative slope between cumulative exposure to EO and AML in that same NIOSH cohort. Kirman and Hays (2017) also observe that evidence

of a causal relationship between smoking and breast cancer is considered only as suggestive and not sufficient. Thus, projections of low-dose elevations in specific EO-associated cancer risks based on spline model extrapolations from relatively high occupationally-exposed individuals are not consistent with cancer outcomes in the much larger smoking cohort experiencing moderately elevated EO exposures.

Kirman and Hays (2017) also address the concern that any additional exogenous EO exposures above background, regardless of how small, represent a plausible contribution to increased cancer risks. They conclude that the approximate four order of magnitude disparity between EO endogenous exposures (mean = 1.9 ppb) and EPA projected increased risk at exposures greater than 0.1 ppt "creates a signal-to-noise issue [in the biological plausibility of tumor outcomes] when exogenous exposures fall well below those consistent with endogenous exposures. In such cases, small exogenous exposures may not contribute to total exposure or to potential effects in a biologically meaningful way."

Recently, Calabrese (2018)[58] offers additional insight into the lack of plausibility of additivity to background of risks associated with low (and particularly less than background) exposures to EO. Calabrese reports that the mutational spectra of K-ras in EO-induced lung and Harderian gland tumors, and H-ras and p53 in mouse mammary tumors, were not at all similar to mutational spectra of these same tumors in control mice from the EO studies. These molecular-level data indicate that the mode of action of generation of control (background) tumors differs substantively from those originating from exogenous EO-exposed animals, even though control animals experience significant endogenous EO exposures. Thus, these data stand in contrast to the assumption of additivity to background that presumes that chemically-induced elevation of background tumors that are otherwise pathologically similar to chemically-induced tumors must share common mode(s) of action reviewed by Calabrese (2018).

The potential for additivity to background also is not supported by a comparison of total endogenous EO-specific DNA adducts in spleen, liver and stomach of rats relative to adducts in these same tissues resulting from a thousand-fold range of EO intraperitoneal doses (0.0001, 0.0005, 0.001, 0.005, 0.01, 0.05 and 0.1 mg/kg/day; 0.1 mg/kg/day approximately equivalent to a 1 ppm 6 hr/day EO inhalation exposure).[59] Importantly, Marsden et al. (2009) also emphasize that the increase in adducts associated with exogenous EO were not statistically significant at any

[58] Calabrese EJ. 2018. The additive to background assumption in cancer risk assessment: A reappraisal. Envir Res, 16: 175-204.

[59] Marsden DA, Jones DJ, Britton RG, Ognibene T, Ubick E, Johnson GE, Farmer PB, Brown K. 2009. Dose-response relationships for N7-(2-hydroxyethyl)guanine induced by low-dose [^{14}C]ethylene oxide: evidence for a novel mechanism of endogenous adduct formation. Cancer Res, 69(7): 3052-59.

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dose with the exception of adducts in liver in rats administered 0.05 mg/kg/day, suggesting that exogenous adducts may not present any additional risk over endogenous adducts over this range of EO doses (i.e., additivity to background). Interestingly, endogenous DNA adducts were statistically increased in spleen and liver at the 0.05 and 0.1 mg/kg/day EO, indicating that higher EO doses alter internal biological processes leading to increased potential for endogenous EO formation.

Further investigations demonstrated that the high-dose-specific in endogenous-only adducts may have been secondary to increased oxidative stress. Both the high level of background endogenous adducts and high-dose specific increases in endogenous-only EO adducts further supports the authors' conclusion that "if the compound [EO] is produced endogenously, low doses of exogenous exposure may be overwhelmed by the background levels, leading to no detectable statistically significant increase in risk due to the external exposure." This conclusion (see Figure 6) is entirely consistent with the analyses developed by Kirman and Hays (2017) in which endogenous EO equivalent exposures in humans (mean = 1.9 ppb) are estimated as being 19,000 times higher than the exogenous EO dose of 0.1 ppt presenting a one-in-a-million cancer risk from spline-model low-dose extrapolation.

An alternative LEC (1/million) of 0.5-1.2 ppb is within the range of endogenous EO levels. Taking into account the biological mode of action and the endogenous EO equivalent exposures in humans, this approach is more plausible and science-based than the EO IRIS assessment.

12. The statistical, epidemiological and biological evidence does not support the selection of supralinear spline models to fit the NIOSH study data in the EO IRIS Assessment. A more scientifically sound conservative alternative is to use the Valdez-Flores et al. (2010) approach, which incorporates all the available data from the two strongest human studies (NIOSH and UCC). This approach has been adopted by the Scientific Committee on Occupational Exposure Limits.

As described in previous sections, the selection of the supralinear spline model is based on incorrect statistical analysis and biased evaluation of the NIOSH exposure modeling relative to the UCC exposure estimates. Furthermore, the epidemiological evidence and biological mode of action do not support the supralinear spline model. A more scientifically supportable approach is that published by Valdez-Flores et al. (2010), who make full use of the available data from both the NIOSH and UCC cohorts. The effect was modeled as a standard Cox proportional log-linear hazards model (i.e., exponentiated linear) function of cumulative EO exposure (ppm-days) treated as a continuous variable.

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The EO IRIS Assessment focuses the cancer risk assessment on lymphoid tumors (defined by NIOSH as including non-Hodgkin's lymphoma, lymphocytic leukemia and multiple myeloma) and breast cancer incidence. The weight of evidence does not support breast cancer as an endpoint for risk assessment (see Appendix 2). Therefore, our analysis focuses on the mortality data for lymphohematopoietic (LH) tissue cancers including leukemia (and specific myeloid and lymphocytic leukemia), non Hodgkin's lymphoma (NHL), multiple myeloma (MM) and "lymphoid" cancers (a grouping developed in Steenland et al. (2004) that included NHL, MM, and lymphocytic leukemia).

Valdez-Flores et al. (2010) propose a range of 1-3 ppb based on the Maximum Likelihood Estimate (MLE) of the Effective Concentrations (ECs) associated with an extra risk of one-in-a-million [EC(1/million)] (see Table 2).[60] The authors select the MLE as the most reliable data for point of departure because the Lowest Effective Concentrations LECs), the 95% lower bound on the ECs, are insensitive to the magnitude of the best estimated slope, which can be negative, yet have a positive 95% upper confidence limit resulting in a finite LEC as occurred for multiple myeloma.

Table 2: Maximum Likelihood Estimate (MLE) of the EC (1/million) and Lowest Effective Concentration (LEC)

EO type of cancer (mortality)	MLE UCC & NIOSH (ppb)	LEC UCC & NIOSH (ppb)	LEC NIOSH only (ppb)
Lymphoid	1.5	0.5	0.2
Non-Hodgkin's lymphoma	2.3	0.9	0.8
Multiple Myeloma	Negative slope, value not calculated	1.2	0.8
Leukemia	9.2	0.9	0.9
Lymphocytic Leukemia	2.4	0.9	0.9
Breast cancer	0.7	0.1	0.1

[60] NIOSH only provided ACC with the breast cancer mortality and not the incidence data, despite multiple requests for the incidence data. The results from the breast cancer mortality are included in Table 2 for completeness.

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EO type of cancer (mortality)	MLE UCC & NIOSH (ppb)	LEC UCC & NIOSH (ppb)	LEC NIOSH only (ppb)
Range for LHC	1.5-9.2	0.5-1.2	0.4-0.9
Range for LHC and breast cancer	0.7-9.2	0.1-1.2	0.1-0.9

The MLE and LEC values reported in Table 2 are conservative values because (a) extra risk was calculated despite no statistically significant slope in the exposure-response analyses; (b) the NIOSH data was included without adjustment for likelihood of underestimation of exposures; and (c) the limited evidence of cancer risk based on the entire body of epidemiologic evidence (summarized in Appendix 2).

The EO IRIS Assessment and Valdez-Flores et al. (2010) identify several differences between the two approaches in deriving their recommended 1/million exposure levels to use as points of departure (see Table 3).[61]

Table 3: Approximate sources of differences between Valdez-Flores et al. (2010) and EO IRIS Assessment approaches

Valdez-Flores et al (2010) compared to EO IRIS Assessment	Reference	Factor
Extra risk at age 70 instead of 85 years	Valdez-Flores et al. (2010), p. 319	2.3
Different approaches to implementing age-adjusted adjustment factor (ADAF)	Valdez-Flores et al. (2010), p. 319 used an approach that adjusted the slope; EPA's cancer risk assessment guidelines (2005) use 1.66	1.66
Use of incidence background rates compared to mortality background rates in lymphoid tumor unit risk estimation (incidence/mortality ratio, $R_{i/m}$).	$R_{i/m}$ = 5.26/1.99 The EO IRIS Assessment unit risk using background lymphoid cancer incidence rates with model for lymphoid mortality data = 5.26/ppm, and unit risk using background	2.64

[61] *See* EO IRIS Assessment, Appendix A, at A-33 – A-35.

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	mortality rates with model for lymphoid mortality data is 1.99/ppm; see Table 4-7, page 4-23; whereas Valdez-Flores et al. (2010) unit risk using background lymphoid mortality rates with model for lymphoid mortality data	

Valdez-Flores et al (2010) used well-accepted statistical principles to guide decisions about whether to include a lag period, how to calculate the degrees of freedom, and whether the MLE for the EC (1/million) can be interpolated within the lower region of the experimental data set. For example, because there was no significance between the models with and without a lag period and no clear biological plausibility for selection of a specific lag period, the more parsimonious model (no lag) was selected. In contrast, the IRIS Program tested different lag periods and knots but did not fully account for the higher degrees of freedom typically considered when different ranges of values are tested.

Valdez-Flores et al. (2010) also modeled down to 10^{-6} risk, whereas the IRIS Program modeled to 10^{-2} risk and used the LEC01 as a point of departure (POD) for linear low-dose extrapolation. Valdez-Flores et al. (2010) suggest that PODs should be within the range of observed exposures, and chose a 10^{-6} risk level because the corresponding exposure level was in the range of the observed occupational exposures (converted to equivalent environmental exposures). Thus, Valdez-Flores et al. (2010) fully used the experimental data to derive a 10^{-6} risk level.

An additional difference that is not captured in Table 3 is the EO IRIS Assessment estimates risk for both lymphoid and breast cancer, whereas Valdez-Flores et al. (2010) estimates risk for lymphoid tumors alone. As discussed above and in greater detail in Appendix 2, breast cancer is not a target of EO. The EO IRIS Assessment recognizes that magnitudes of increased risks for breast cancer were not large and implies that the evidence is weaker than that for lymphoid tumors. Despite these issues, the EO IRIS Assessment introduces breast cancer as a target organ and inappropriately develops a risk value. Uncertainties described by Steenland et al. (2003) related to the breast cancer incidence study are dismissed as unimportant. It is notable that the ratio between risk for lymphoid plus breast cancer incidence (6.06 per ppm)[62] divided by the risk for lymphoid tumor incidence alone (5.26 per ppm)[63] is only 1.15.

[62] EO IRIS Assessment, at 4-58.

[63] *Id.* at 4-31.

As discussed above, the NIOSH exposure assessment was not validated prior to the late 1970s and likely underestimated exposures. In contrast, the UCC exposure estimation from the 1940s to 1970s was based on actual data from similar operations during the same time period.[64] The greatest uncertainty is between 1925-1939, but only 4.8% of the UCC cohort had work history before 1940.[65] These uncertainties are no greater than the NIOSH study uncertainties and do not justify study rejection for exposure-response analysis. Both studies are well-conducted epidemiology studies with comparable power in terms of number of events for males and of comparable utility in terms of individual exposure estimates. In fact, the UCC study was originally a NIOSH study, in that it was nested within a NIOSH/UCC collaborative study of 29,000 UCC workers in the Kanawha Valley of West Virginia.[66]

The EO IRIS Assessment also criticizes Valdez-Flores et al. (2010) for not using any log cumulative exposure models which were found to be statistically significant in analyses by Steenland et al. (2004), consistent with the apparent supralinearity of the NIOSH exposure-response data. Yet, the EO IRIS Assessment also considers the log cumulative exposure model to be "problematic because this model, which is intended to fit the full range of occupational exposures in the study, is inherently supralinear …, with the slope approaching infinity as exposures decrease towards zero, and results can be unstable for low exposures."[67]

Similarly, the IRIS Program rejected other statistically significant models due to unstable results for low exposures. As noted above, the assumption of supralinearity is based on a flawed statistical analysis of its preferred-model fit and on a misleading visual comparison of invalidly overlaid models plotted in relation to categorical data grouped in quartiles instead of considering the pattern of RR for individual cases, which more realistically reveals a very noisy data cloud through which the simpler and traditionally accepted Cox proportional model fits as well as the supralinear spline model.

Crump (2005) noted that:

> Because of these potential distortions of the exposure-response shape, one should be cautious in drawing conclusions about the shape of the exposure response from epidemiological data. Since even random, unbiased errors in exposure measurement will convert a linear exposure response, and can convert sub-linear

[64] Swaen et al. (2009).

[65] *Id.*

[66] Rinsky RA, Ott G, Ward E, Greenberg H, Halperin W, Leet T. 1988. Study of mortality among chemical workers in the Kanawha Valley of West Virginia. Am J Ind Med, 13: 429-38.

[67] EO IRIS Assessment, at 4-10.

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> response, into a seemingly supralinear shape, one should be particular[ly] cautious about concluding an exposure-response is truly supralinear. In particular, it could be inadvisable to extrapolate an observed supralinear exposure response to low exposures to predict human risk.[68]

Crump's caution is especially relevant to the NIOSH data in light of the high potential for exposure misclassification in the earlier years of the NIOSH study when there was no data to validate the NIOSH exposure model, as described above. EPA's cancer risk assessment guidelines echo this caution: "a steep slope [i.e., supralinear] also indicates that errors in an exposure assessment can lead to large errors in estimating risk."[69]

D. Conclusion

The 2014 NATA fails to meet the requirements of the IQA and the OMB and EPA Guidelines because its use of the EO IRIS Assessment is not the best available science. Therefore, the 2014 NATA risk estimates for EO should be withdrawn and corrected to reflect scientifically-supportable risk values and EPA should not use the EO IRIS Assessment's inhalation RSC of 0.1 ppt to calculate EO risk in its ongoing CAA Section 112 RTR rulemakings and other regulatory actions. As discussed above, a more reasonable and scientifically supportable approach to an exposure response analysis yields ranges for the MLE (1.5-9.2 ppb) and LEC (0.5-1.2 ppb) that are more than three orders of magnitude greater than the EO IRIS Assessment's environmental concentration associated with one-in-a-million risk.

Sincerely,

William Gulledge

William P. Gulledge
Senior Director
Chemical Products & Technology Division

Enclosures:

Appendix 1 – Statistical Issues with EPA's Calculation of p-values and AIC's for Spline Models and Linear Models in the EO IRIS 2016
Appendix 2 – Brief Summary of Epidemiological Data for EO

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[68] Crump KS. 2005. The effect of random error in exposure measurement upon the shape of the exposure response. Dose-Response, 3: 456-64.

[69] EPA, Guidelines for Carcinogen Risk Assessment, at 3-19.

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Appendix 1

Statistical Issues with EPA's Calculation of p-values and AIC's for Spline Models and Linear Models in the EO IRIS 2016

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Introduction

The document "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" (EO IRIS 2016) has several statistical inaccuracies that play an important role in model selection and, ultimately, in the risk assessment of EtO. The exposure-response modeling of lymphoid mortality for the NIOSH study is reviewed here, and statistical pitfalls are highlighted. EPA's statistical numbers are corrected herein and new results are derived. These corrected results question conclusions drawn by EPA about model selection. Although EPA's conclusions for the other endpoints are not analyzed herein, similar statistical pitfalls must have been incurred, as the statistical pitfalls are related to the methodology that was used for all endpoints analyzed by EPA.

Table 1 reproduces Table 4-6 of EO IRIS 2016. In this table EPA to summarizes how the linear spline model with knot at 1600 ppm × days was selected to describe the relationship between lymphoid mortality rate ratio and cumulative exposures to EO. The summary in the table indicates that the model was selected because: a) adequate statistical fit; b) adequate visual fit; c) including local fit (visual) to low-exposure range; linear fit; and d) AIC within two units of lowest AIC models considered.

It can also be shown (using the likelihood ratio test -- analyses not presented here) that EPA's selected linear spline model does not fit the NIOSH lymphoid mortality data statistically significantly better (at the 5% significance level) than the nested linear model. Similarly, log-linear spline model with knot at 1600 ppm-days does not fit the NIOSH lymphoid mortality data statistically significantly better (at the 5% significance level) than the nested log-linear model. Thus, according to the following SAB recommendation on page 12, the log-linear and the linear models should be preferred over the log-linear spline and linear spline models, respectively:

> Third, the principle of parsimony (the desire to explain phenomena using fewer parameters) should be considered. Attention to this principle becomes even more important as the information in the analysis dataset becomes even more limited.

Thus, models with very few estimated parameters should be favored in cases where there are only a few events in the dataset.

Table 1. The following table has been extracted from EO IRIS 2016 Table 4-6

Table 4–6. Models considered for modeling the exposure-response data for lymphoid cancer mortality in both sexes in the National Institute for Occupational Safety and Health cohort for the derivation of unit risk estimates

Model[a]	*p-value*[b]	AIC[c]	Comments
Two-piece spline models			
Linear spline model with knot at 1,600 ppm × days	0.07	462.1	**SELECTED.** Adequate statistical and visual fit, including local fit to low-exposure range; linear model; AIC within two units of lowest AIC of models considered.
Linear spline model with knot at 100 ppm × days	0.046	461.4	Good overall statistical fit and lowest AIC of two-piece spline models, but poor local fit to the low-exposure region, with no cases below the knot.
Log-linear spline model with knot at 1,600 ppm × days	0.07	462.6	Linear model preferred to log-linear (see text above).
Log-linear spline model with knot at 100 ppm × days	0.047	461.8	Good overall statistical fit and tied for lowest AIC[c] of two-piece spline models, but poor local fit to the low-exposure region, with no cases below the knot.
Linear (ERR) models (RR = 1 + β × exposure)			
Linear model	0.13	463.2	Not statistically significant overall fit and poor visual fit.
Linear model with log cumulative exposure	0.02	460.2	Good overall statistical fit, but poor local fit to the low-exposure region.
Linear model with square-root transformation of cumulative exposure	0.053	461.8	Borderline statistical fit, but poor local fit to the low-exposure region.
Log-linear (Cox regression) models (RR = $e^{\beta \times \text{exposure}}$)			
Log-linear model (standard Cox regression model)	0.22	464.4	Not statistically significant overall fit and poor visual fit.
Log-linear model with log cumulative exposure	0.02	460.4	Good overall statistical fit; lowest AIC[c] of models considered; low-exposure slope becomes increasingly steep as exposures decrease, and large unit risk estimates can result; preference given to the two-piece spline models because they have a better ability to provide a good local fit to the low-exposure range.
Log-linear model with square-root transformation of cumulative exposure	0.08	462.8	Not statistically significant overall fit and poor visual fit.

[a]All with cumulative exposure as the exposure variable, except where noted, and with a 15-yr lag.

[b]*p*-values from likelihood ratio test, except for linear regression of categorical results, where Wald *p*-values are reported. $p < 0.05$ considered "good" statistical fit; $0.05 < p < 0.10$ considered "adequate" statistical fit if significant exposure-response relationships have already been established with similar models.

[c]AICs for linear models are directly comparable and AICs for log-linear models are directly comparable. However, for the lymphoid cancer data, SAS proc NLP consistently yielded −2LLs and AICs about 0.4 units lower than proc PHREG for the same models, including the null model, presumably for computational processing reasons, and proc NLP was used for the linear RR models. Thus, AICs for linear models are equivalent to AICs about 0.4 units higher for log-linear models. No AIC was calculated for the linear regression of categorical results.

EPA's Misinterpretation of SAB Comments about the Knot of Spline Models

EPA justifies the p-values and AIC values for the linear spline and log-linear spline models in their Table 4-6 misquoting SAB's comments. In section D.3.2 of the appendices (reference), EPA states (emphasis added) "Table D-27 also presents the AIC values for the same models to facilitate comparison with the two-piece spline models, which include an extra parameter. [The knot is preselected and is not considered a parameter in these analyses, consistent with the SAB's concept of parsimony (SAB, 2015)].[14]" Their footnote 14 in the same sections states "[14] in some settings the principle of parsimony may suggest that the most informative analysis will rely upon fixing some parameters rather than estimating them from the data. The impact of the fixed parameter choices can be evaluated in sensitivity analyses. In the draft assessment, fixing the knot when estimating linear spline model fits from relative risk regressions is one such example" [page 12 of SAB (2015)]."

Although the SAB quote is accurate, the quote just a fragment of a response and is taken out of context. The full question and SAB response are as follows (emphasis added):

> *2b: For the (low-exposure) unit risk estimates, EPA presents an estimate from the preferred model as well as a range of estimates from models considered "reasonable" for that purpose (Sections 4.1.2.3 and 4.5 and Chapter 1). Please comment on whether the rationale provided for defining the "reasonable models" is clearly and transparently described and scientifically appropriate.*
>
> The SAB understands that the EPA considered four "reasonable" models for providing unit risk estimates; these all have unit risk estimates reported in Table 4-13. A few additional models are described in Tables 4-12 and 4-13, some of which could also be considered reasonable. The presentation of "reasonable" models considers model fit and some a priori (but not clearly articulated) notion about the acceptable shape of the dose-response function in the low-dose region. Because the data do not appear to conform to the a priori notion, the draft assessment also considers models based on an untransformed continuous exposure term or a linear regression of the categorical results as reasonable. However, these models do a poorer job reflecting the patterns in the data. Although much of the approach is scientifically appropriate, the SAB does not agree with all of the judgments. In order to strengthen the assessment and presentation, some modifications are suggested to the approach for comparing models and choosing which models are reasonable. The SAB recommends that

the discussion be revised to provide more clarity and transparency as well as making the disposition easier to follow. In general, discussion of statistical significance should occur in a more nuanced fashion so that important perspective about the results is not lost in the tendency to turn the statistical evidence into a binary categorization of significant vs. not significant. (This can mislead readers into interpreting a pair of results as inconsistent when their p-values, effect estimates, and 95% confidence intervals are very similar, but the two p-values happen to be on opposite sides of 0.05.) Consideration of reasonable models should address the quality of fit in the region of interest for risk assessment. Prioritizing sufficiently flexible exposure parameterizations (e.g., not linear) and exposure functions with more local behavior (e.g., splines, linear and cubic) reduces the impact of highly exposed individuals on the risk estimates for lower exposures. Discarding a model because the fitted curve is "too steep" needs scientific justification. Furthermore, follow-up by the EPA is needed to clearly articulate the criteria for determining that models are reasonable as well as providing transparent definitions for frequently used terms such as "too steep," "unstable," "problematic," and "credible" (p. 4-38). The SAB recommends assigning weight to certain types of models based on a modified combination of biologic plausibility and statistical considerations, and using somewhat different considerations for comparing AICs than those currently employed in the draft assessment.

Regarding statistical considerations about various models, the SAB recommends a different set of emphases in the priorities for the most reasonable models and gives guidance on the preference for their ordering. First, priority should be given to regression models that directly use individual-level exposure data. Because the NIOSH cohort has rich individual-level exposure data, linear regression of the categorical results should be de-emphasized in favor of models that directly fit individual-level exposure data. Second, among models fit to individual-level exposure data, models that are more tuned to local behavior in the data should be relied on more heavily. Thus, spline models should be given higher priority over transformations of the exposure. Third, the principle of parsimony (the desire to explain phenomena using fewer parameters) should be considered. Attention to this principle becomes even more important as the information in the analysis dataset becomes even more limited. Thus, models with very few estimated parameters should be favored in cases where there are only a few events in the dataset. To elaborate further, <u>in some settings the principle of parsimony may suggest that the most informative analysis will rely upon fixing some parameters rather than estimating them from the data. The impact of the fixed parameter choices can be evaluated in sensitivity analyses. In the draft assessment, fixing the knot when estimating linear spline model fits from relative risk regressions is one</u>

such example. Use of AIC can assist with adhering to this principle of parsimony, but its application cannot be used naïvely and without also including scientific considerations. (See further discussion below.) Beyond these recommendations for choosing among models, one advantage of fitting and examining a wide range of models is to get a better understanding of the behavior of the data in the exposure regions of interest. For instance, the models shown in Table 4-13 and Figures 4-5 and 4-6 can be compared, ideally with one or more of these presentations augmented with a few more model fits, including the square root transformation of cumulative exposure, linear regression of categorical results given more categories, and several additional 2-piece linear spline models with different knots. From the comparisons, it is clear that these data suggest a general pattern of the risk rising very rapidly for low-dose exposures and then continuing to rise much more slowly for higher exposures. It is reassuring to observe that many of the fitted models reflect this pattern even though they have different sensitivity to local data.

Results of statistical analyses do not always conform to an a priori understanding of biologic plausibility. When this is the case, investigators need to reassess whether the data are correct, a different approach to model fitting should be employed, or whether the prevailing notion of biologic plausibility should be re-examined. When sufficient exploration of the fitted models has been conducted and a range of models with different properties all suggest a dose-response relationship that would not have been predicted in advance (as is the case in these NIOSH data analyses), then the remaining two considerations should be reviewed. The response to Charge Question 4 further discusses uncertainty in the exposure data. The SAB also encourages finding opportunities to use other evidence from the literature to support the observed dose-response relationship. Specifically, the SAB encourages a discussion of the Swedish sterilization workers study results using the internal comparison group.

The application of AIC for selecting models is acceptable within some constraints as outlined in the following discussion. Burnham and Anderson (2004) is an additional reference that discusses the use of AIC for model selection. (The following discussion is intended to be fairly comprehensive and thus covers points that the SAB did not identify as problematic in the draft assessment.) AIC is an appropriate tool to use for model selection for both nested and non-nested models, provided these models use the same likelihood formulation and the same data. AIC is not the preferred way to characterize model fit. For model selection, (1) AIC is not an appropriate tool for comparing across different models that are fit using different measures, such as comparing a Poisson vs. least squares fit to count data; (2) one should not use AICs to compare models using different

transformations of the outcome variable; and (3) comparing AICs from models estimated using different software tools, including different implementations within the same statistical package can be challenging because many calculations of AIC remove constants in the likelihood from the estimated AIC. These AIC features require that users interested in comparing AICs across different software routines (even those within one statistical package) understand exactly what likelihood is being maximized and how the AIC is calculated. AIC can be used to compare the same regression model with the same outcome variable and different predictors whether or not these models are nested. This gives a consistent estimate of the mean-squared prediction error (MSPE), which is one criterion for choosing a model. Finally, the theory behind this MSPE criterion can break down with a large number of models. Thus, naïve applications of AIC for model selection can be problematic (but are not necessarily so in any particular application). In particular, differences in AICs could be an artifact of how the calculation was done. This is a possible difference between the linear and exponential relative risk models applied to the breast cancer incidence data. Although the EPA provided some clarification about its approach in its February 19, 2015 memo to the SAB, the SAB still does not have sufficient information to determine whether or not this is the case.

In conclusion, although the SAB concurs with the EPA's selected model, it believes that aspects of EPA's approach to model selection can be refined and that more transparency in the presentation is needed.

Summary of recommendations:

- Revise the discussion to provide more clarity and transparency as well as making the disposition easier to follow.
- Discarding a model because the fitted curve is "too steep" is only acceptable when there is scientific justification.
- Clearly articulate the criteria for determining that models are reasonable as well as providing transparent definitions for frequently used terms such as "too steep," "unstable," "problematic," and "credible".
- Assign weight to various models based on a modified combination of biological plausibility and statistical considerations; use somewhat different considerations for comparing AICs than those currently employed in the draft assessment.
- Use a different set of emphases in the priorities for the most reasonable models; detailed suggestions are provided by the SAB in this response.

2c: For analyses using a two-piece spline model, please comment on whether the method used to identify knots (Section 4.1.2.3 and Appendix D) is transparently described and scientifically appropriate.

The method used to identify the knots involves a sequential search over a range of plausible knots to identify the value at which the likelihood is maximized. This is scientifically appropriate and a practical solution that is transparently described.

The quote from EPA states "[The knot is preselected and is not considered a parameter in these analyses, consistent with the SAB's concept of parsimony (SAB, 2015)]." However, EPA also states on footnote a to Table D-27 "knots were obtained by doing a grid search by increments of 100 ppm x days and then interpolating where appropriate" and foot note b states "For models with very low knots, alternate knots were obtained from local maximum likelihoods because of the small number of cases informing the slope of the low-exposure spline for low knots (see Figure D-14)." EPA further states on page D-41 (emphasis added) "For the two-piece log-linear model, the single knot was chosen at 100 ppm-days based on a comparison of likelihoods assessed every 100 ppm-day from 100 to 15,000. The best likelihood was at 100 ppm-days. Figure D-15 below shows the likelihood versus the knots. Figure D-15 also suggests a local maximum likelihood near 1,600 ppm-days."

In summary, EPA's description of how the knots for the linear spline and log-linear spline models were found clearly indicate that the knots were not fixed parameters, but rather were optimized numerically and in this way were estimated from the data that were fit. That is, the knots used by EPA for the linear and log-linear spline models were determined using the NIOSH data, so that the knot maximized the likelihood of the spline model. The knots, therefore, were not fixed parameters independent of the NIOSH data, as would be the case in SAB discussion of an example. EPA contradicts itself when it states "[The knot is preselected and is not considered a parameter in these analyses, consistent with the SAB's concept of parsimony (SAB, 2015)].[14]" The latter EPA statement is simply false, because each knot value derived by EPA was in fact optimized (i.e., estimated) by EPA to best fit a corresponding model to a specific set of data. This fact has no relevance at all to the concept of parsimony in model selection, which refers to preference for selecting among different models the one(s) that has (have) the fewest total number (k) of estimated parameters. The parsimony concept is also expressed in the definition of the Akaike Information Criterion (AIC), which is proportional to the value of k, insofar as superior models are identified as those with smaller associated values of AIC. Likewise, a p-value for goodness of model fit is typically evaluated in relation to a corresponding value of the total number of degrees of freedom (DF) associated with that fit, and the latter number is always defined as the total number (n) of data points modeled minus the total number (k) of estimated model parameters, i.e., DF = n–k. An invalid reduction in k (e.g., by improperly considering a parameter "fixed" when in fact it was estimated to get a best fit for that model), therefore always improperly inflates the value of DF, which results in an erroneously high p-value for goodness-

of-fit that falsely magnifies the likelihood that deviations between data and a model fit to those data are due only to chance (i.e., due only to sampling error).

Misinterpretation of Degrees of Freedom Results in Miscalculated p-values, AIC and Incorrect Model Selection

The "log-linear spline model with knot at 1,600 ppm-days" has three parameters that each were estimated: slope below the knot, slope above the knot, and the knot itself. However, when EPA calculated a corresponding p-value associated with its reported chi-square test for improved fit relative to an associated null model, EPA used only two degrees of freedom for this calculation. This resulted in artificially and erroneously inflating the measure of improved fit used to compare the linear spline model to other models for which p-values were calculated using degrees of freedom that accurately reflected the total number of estimated parameters associated with other model fits being compared. Specifically, EPA did not include the degree of freedom associated with the separate procedure EPA applied to numerically and graphically maximize the log likelihood of each linear spline model for which an optimum knot value was also estimated. By failing to account for the degree of freedom associated with knot-estimation, the p-value EPA reported for each such linear spline model was miscalculated to yield a lower p-value (indicating an unrealistically improved fit) than would be produced had the correct number of degrees of freedom been used by EPA for each such calculation.

In using the approach EPA took in this regard, EPA may have misinterpreted comments of the EPA (2015) Science Advisory Board (SAB) review of the EPA (2014) draft IRIS document, which on pages 12–14 state that:

> the principle of parsimony (the desire to explain phenomena using fewer parameters) should be considered. Attention to this principle becomes even more important as the information in the analysis dataset becomes even more limited. Thus, models with very few estimated parameters should be favored in cases where there are only a few events in the dataset. To elaborate further, in some settings the principle of parsimony may suggest that the most informative analysis will rely upon fixing some parameters rather than estimating them from the data. The impact of the fixed parameter choices can be evaluated in sensitivity analyses. In the draft assessment, **fixing the knot when estimating linear spline model fits from relative risk regressions is one such example**. … differences in AICs could be an artifact of how the calculation was done.

Importantly (as shown above), although the SAB indicated that fixing a knot value can be done as part of a practical approach to knot-value estimation, it also stated that "differences in AICs could be an artifact of how the calculation was done." The SAB unfortunately failed to emphasize (but must be assumed to agree with the fact) that **differences in p-values from chi-square tests of improved fit relative to the null model can also reflect non-meaningful**

artifacts if associated p-value calculations are not done correctly. Specifically, it is not meaningful to compare (as EPA did) a p-value from a Cox linear-regression model of Log(RR) on ppm-days of exposure (defined to be associated with one degrees of freedom for each of the estimated slope of the line) to a p-value from EPA's linear spline model fit (assumed to be associated with only two degrees of freedom corresponding to its two estimated slopes) conditional on a knot value that EPA estimated by minimizing log likelihood in relation to the knot value. EPA incorrectly assumed its optimized knot-value estimate is not associated with one additional degree of freedom. Thus, EPA erroneously deflated the total degrees of freedom associated with their three-parameter linear model by evaluating it as if it had only two degrees of freedom (parameters) associated with it. Consequently, EPA miscalculated the p-value for its spline model resulting in an erroneously low p-values of ~0.07 (see Table 2), when (as explained in more detail in the next section) the correctly calculated p-value is ~2-fold greater (i.e., 0.14 to 0.15) and do not differ meaningfully from p-values associated with the more parsimonious linear Cox regression model (see corrected Table 4-6 discussed in the next section).

Table 2. SAS results given for this model in Table D-33 in Appendix D of EO IRIS 2016

Table D-33. Results of two-piece log-linear spline model for lymphoid cancer mortality, men and women combined, knot at 1,600 ppm-days

Model fit statistics						
Criterion	**Without covariates**	**With covariates**				
-2 LOG L	463.912	**458.640**				
AIC	463.912	**462.640**				
SBC	463.912	466.581				
Testing global null hypothesis: BETA = 0						
Criterion	**Without covariates**	**With covariates**				
Likelihood ratio	5.2722	**2**	**0.0716**			
Score	5.2666	2	0.0718			
Wald	5.1436	2	0.0764			
Analysis of maximum likelihood estimates						
Parameter	**DF**	**Parameter estimate**	**Standard error**	**χ2**	**Pr > ChiSq**	**Hazard ratio**
LIN_0	1	0.0004893	0.0002554	3.6713	0.0554	1.000
LIN_1	1	0.0004864	0.0002563	3.6014	0.0577	1.000

Miscalculated p-values: Example using the log-linear spline model with knot at 1,600 ppm-days"

The likelihood ratio test is used to test whether a fitted model significantly improves the fit of the data by estimating parameters instead of just assuming a baseline (null) model for the data. The likelihood ratio test is evaluated by comparing the likelihood of the model with the estimated parameters and the likelihood of the null model. If the likelihood of the model with the estimated parameters is equal to the likelihood of the null model, then the natural logarithm of the ratio of

these likelihoods multiplied by two follow a Chi-Square distribution with as many degrees of freedom as the number of parameters estimated for the fitted model. Thus, if the fit of the baseline (null) model and the model with estimated parameters are not different,

$$Chi - Square(k) = \chi_k^2 = -2\ln\left(\frac{likelihood\ for\ null\ model}{likelihood\ for\ fitted\ model}\right)$$

This can also be written as follows,

$$\chi_k^2 = -2LogL(null\ model) - 2LogL(fitted\ model)$$

Here k is the number of degrees of freedom (k is the number of parameters that were estimated in excess of the parameters estimated for the null model).

For the model in Table 2 (Table D-33 in EO IRIS 2016) the χ_k^2 value was equal to 5.2722 and k was set to 2. This resulted in a p-value of 0.0716. That is, the fitted model was assumed to have two parameters; namely, the slope below the knot and the slope above the knot. The results in Table 2 are from a SAS output for the model specified. The model specified included a knot. This knot was determined so that the likelihood of the spline model was maximized. That is, the knot is another parameter that was searched for outside SAS. Because the estimation of the "knot" was done outside SAS, the SAS program did not count the knot as a parameter and, consequently, the Chi-Square test SAS reported does not reflect the fact that the knot was also estimated. The correct Chi-Square that accounts for the fact that the knot was estimated outside SAS should then be 5.2722, but k (the degrees of freedom) should be 3. This corrected calculation would result in a p-value of 0.1529. That is, the corrected p-value indicates that the likelihood of the "log-linear spline model with knot at 1,600 ppm × days" is not different from the likelihood of the null model. In plain words, there is not enough evidence indicating that the fitted log-linear spline model explains the variability in the data any better than the null model.

Miscalculated AICs: Example using the log-linear spline model with knot at 1,600 ppm-days

The Akaike Information Criterion (AIC) is equal to $2k$ - $2LogL$ where k is the number of parameters estimated for the model and LogL is the logarithm of the likelihood. Here, Table 2 (Table D-33 in EO IRIS 2016) lists the -2LogL as 458.640 and the AIC as 462.640. That is;

$$462.640 = 2k + 458.640$$

The AIC and –2LogL implies that k equals 2. That is, the spline model was assumed to have estimated two parameters; namely, the slope below the knot and the slope above the knot. The results in the Table 2 consist of SAS output for the spline model specified. The model specified included a knot. This knot was pre-assigned (i.e., previously estimated using a separate optimization procedure outside the SAS run), so the likelihood of the model was maximized only

conditional on the estimated knot-value used for that calculation. Consequently, the knot must be treated as an additional parameter that was estimated outside SAS. Because the estimation of the "knot" was done outside SAS, the SAS run performed by EPA did not count the knot as a model parameter and, consequently, the resulting AIC value it obtained does not reflect that the knot was in fact estimated. EPA could have requested SAS to account properly for the extra degree of freedom properly associated with its estimated knot value, but EPA evidently elected not to make this request of SAS.

The correct AIC, which accounts for the fact that the knot was estimated outside SAS, should instead be

$$AIC = 464.640 = 2\times3 + 458.640$$

These differences are summarized in corrected Table 3 below.

Model selection with correct AIC and p-values

EPA selects the "linear spline model with knot at 1,600 ppm × days" for lymphoid for the following reasons:

a) Adequate statistical fit. EPA's uses the erroneous p-value of 0.07 (Table 1) to select the model arguing that it is close to 0.05. However, the corrected p-value is 0.14 (Table 3) once the fact that the knot was also estimated is accounted for by adding one more degree of freedom to the chi-square distribution. The corrected p-value is now in the range of the p-values for the log-linear and linear models; in fact, it is larger than the p-value (0.13) for the linear model.

b) Adequate visual fit. EPA's visual fit is dismissed in the footnote of Figure 4-3 of the EO IRIS 2016 report. The footnote reads "(Note that, with the exception of the categorical results and the linear regression of the categorical results, the different models have different implicitly estimated baseline risks; thus, they are not strictly comparable to each other in terms of RR values, i.e., along the y-axis. They are, however, comparable in terms of general shape.)" In addition to the visual-fit caveat listed by EPA in the IRIS report, they failed to indicate that the models are **not** fit to the five nonparametric rate ratios shown in the figure, but rather to the individual cases that includes nine cases of lag-15 EO unexposed workers and 44 cases with lag-15 EO cumulative exposure. That is, the graph shown in Figure 4-3 of the EO IRIS 2016 report does not show all the variability in the full data and visual comparisons can be misleading. Furthermore, the categorical rate ratios are not "the data", but rather, non-parametric estimate of the rate ratios.

c) Including local fit (visual) **to low-exposure range; linear model.** When the models are plotted against the non-parametric rate ratios of the 44 exposed cases, all models seem to fit the

non-parametric models about the same; which is consistent with the calculated p-values and AIC values.

d) AIC within two units of lowest AIC of models considered. EPA's uses the erroneous AIC value of 462.1 to select the model arguing that it is within two units from the lowest AIC (460.2 for the "linear model with log cumulative exposure"). However, the corrected AIC is 464.5 once the fact that the knot was also estimated is accounted for by adding one more parameter in the calculation of the AIC. The corrected AIC for the "linear spline model with knot at 1,600 ppm-days" is now larger than the AIC values for the linear model (463.6) and for the log-linear model (464.4).

Once the errors indicated above concerning calculating p-values, calculating AIC values, and associated adjustments for different calculations of likelihood values are all corrected, EPA's best model for lymphoid should be reconsidered. Using the criteria EPA EO IRIS uses to select a model, the best models for the lymphoid data are the "linear model" followed by the "log-linear model."

Table 3. The following table has been extracted from EO IRIS 2016 Table 4-6 and the p-values and AIC values have been corrected to reflect the degree of freedom for the knot in the spline models and to reflect the likelihood difference between SAS procedures used for linear and log-linear models

Table 4–6. Models considered for modeling the exposure-response data for lymphoid cancer mortality in both sexes in the National Institute for Occupational Safety and Health cohort for the derivation of unit risk estimates

Model[a]	*p-value*[b]	AIC[c]	Comments
Two-piece spline models			
Linear spline model with knot at 1,600 ppm × days	0.14	464.5	**SELECTED.** Adequate statistical and visual fit, including local fit to low-exposure range; linear model; AIC within two units of lowest AIC of models considered.
Linear spline model with knot at 100 ppm × days	0.11	463.8	Good overall statistical fit and lowest AIC of two-piece spline models, but poor local fit to the low-exposure region, with no cases below the knot.
Log-linear spline model with knot at 1,600 ppm × days	0.15	464.6	Linear model preferred to log-linear (see text above).
Log-linear spline model with knot at 100 ppm × days	0.11	463.8	Good overall statistical fit and tied for lowest AIC_c of two-piece spline models, but poor local fit to the low-exposure region, with no cases below the knot.
Linear (ERR) models (RR = 1 + β × exposure)			
Linear model	0.13	463.6	Not statistically significant overall fit and poor visual fit.
Linear model with log cumulative exposure	0.02	460.6	Good overall statistical fit, but poor local fit to the low-exposure region.

Appendix 1

Model[a]	*p-value*[b]	AIC[c]	Comments
Linear model with square-root transformation of cumulative exposure	0.053	462.2	Borderline statistical fit, but poor local fit to the low-exposure region.
Log-linear (Cox regression) models (RR = $e^{\beta \times \text{exposure}}$)			
Log-linear model (standard Cox regression model)	0.22	464.4	Not statistically significant overall fit and poor visual fit.
Log-linear model with log cumulative exposure	0.02	460.4	Good overall statistical fit; lowest AIC[c] of models considered; low-exposure slope becomes increasingly steep as exposures decrease, and large unit risk estimates can result; preference given to the two-piece spline models because they have a better ability to provide a good local fit to the low-exposure range.
Log-linear model with square-root transformation of cumulative exposure	0.08	462.8	Not statistically significant overall fit and poor visual fit.

[a]All with cumulative exposure as the exposure variable, except where noted, and with a 15-yr lag.

[b]*p*-values from likelihood ratio test, except for linear regression of categorical results, where Wald *p*-values are reported. $p < 0.05$ considered "good" statistical fit; $0.05 < p < 0.10$ considered "adequate" statistical fit if significant exposure-response relationships have already been established with similar models.

[c]AICs for linear models are directly comparable and AICs for log-linear models are directly comparable. However, for the lymphoid cancer data, SAS proc NLP (where NLP = nonlinear programming) consistently yielded −2LLs and AICs about 0.4 units lower than proc PHREG for the same models, including the null model, presumably for computational processing reasons, and proc NLP was used for the linear RR models. Thus, AICs for linear models are equivalent to AICs about 0.4 units higher for log-linear models. No AIC was calculated for the linear regression of categorical results.

Note: In order to make the AICs comparable for different models, the AIC's for the linear models have been increased by 0.4 to reflect the discrepancy in the -2LogL values reported by the SAS proc NLP and by SAS PHREG (as indicated in green in this table).

Figures 1 to 4 are versions of EPA's Figure 4-3. A model (TrueLogL – dotted light blue line in the graphs) was added to relieve the caveat posed by EPA in the footnote to Figure 4-3 about the visual comparability of fitted models. The TrueLogl model is an approximation to the correct visual representation of the log-linear (standard Proportional Hazards Model fit to the NIOSH full data set) after adjusting for the difference in baseline risks between the rate ratios and the loglinear model. In Figures 1 to 4, all the individual RR (categorical) in the light blue box of the figure are summarized by the red dot in the light blue box (EPA's 5 RRs for the last quartile). Similarly, all the individual RR (categorical) in the light yellow box of the figure are summarized by the red dot in the light yellow box (EPA's 5 RRs for the third quartile). In the same way, all the individual RR (categorical) in the light green box of the figure are summarized by the red dot in the light green box (EPA's 5 RRs for the second quartile). Finally, all the individual RR (categorical) in the clear box, next to the vertical axis of the figure, are summarized by the red dot in the clear box (EPA's 5 RRs for the first quartile).

Appendix 1

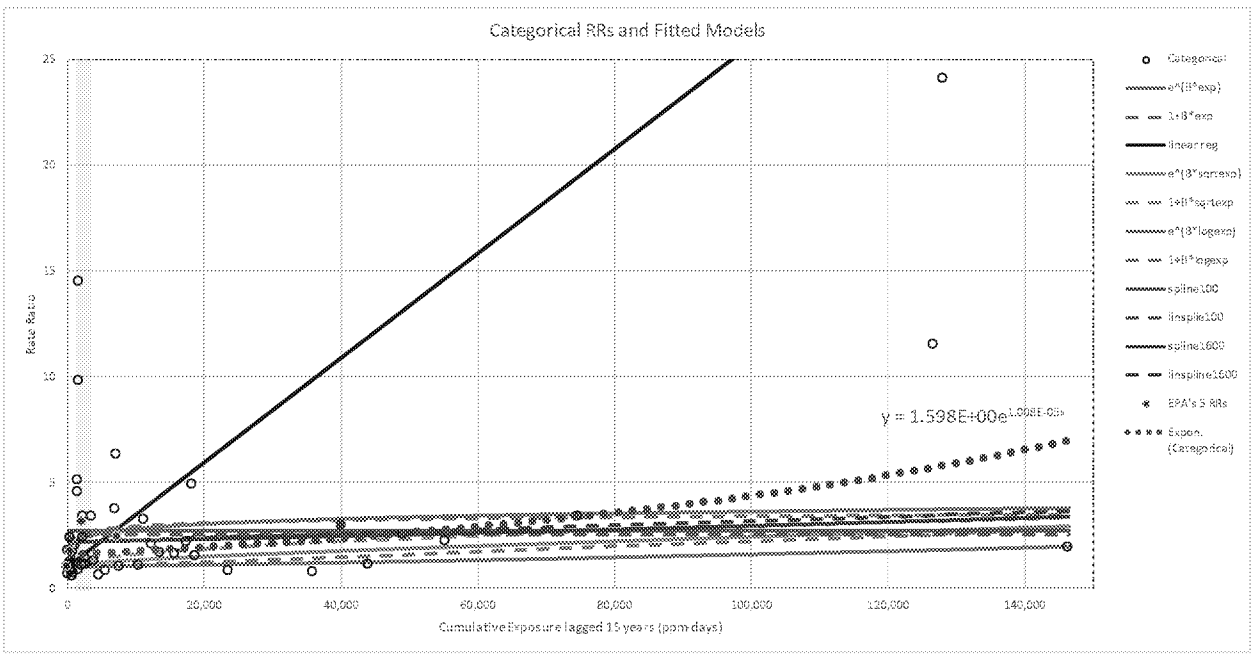
Figure 1 shows all EPA models plotted versus the individual nonparametric rate ratios (categorical) and grouped rate ratios (EPA's 5 RRs). The range of cumulative exposures when the rate ratios for all cases are plotted is much bigger than the range of cumulative exposures when the rate ratios are averaged over several cases (EPA's 5 RRs). The variability of the rate ratios for the individual cases (categorical) is much larger than the variability of the rate ratios averaged over several cases (EPA's 5 RRs). Except for the unacceptable linear model fit to four rate ratios (linear reg), all models fit approximately the same in Figure 1. The model Expon. (Categorical) is a plot of the approximate log-linear model (e^(B*exp)) adjusted by dividing the model for the hazard rate by the baseline hazard rate of the nonparametric estimates.

Figure 2 shows an expansion of the low-left corner of Figure 1. These are all EPA models plotted versus the nonparametric rate ratios with values between 0 and 3.5 and cumulative exposures between 0 and 40,000 ppm-days. This graph resembles Figure 4-3 of the EO IRIS 2016 report with the exception that rate ratios based on individual cases (categorical) that are in the range of the graph are plotted in addition to the aggregated four points used by EPA (EPA's 5 RRs).

Figure 3 is the same as Figure 1 except that the vertical scale is shown using a logarithmic scale of the rate ratios to visualize the linear difference between the fitted models and the rate ratios.

Figure 4 is the same as Figure 2 except that the vertical scale is shown using a logarithmic scale of the rate ratios to visualize the linear difference between the fitted models and the rate ratios.

Figure 1. EPA models plotted against all lymphoid rate ratios in the NIOSH data



Appendix 1

Figure 2. EPA models plotted against all lymphoid rate ratios in the NIOSH data in the low exposure concentration range and with the rate ratio truncated to the same range of EPA's Figure 4-3.

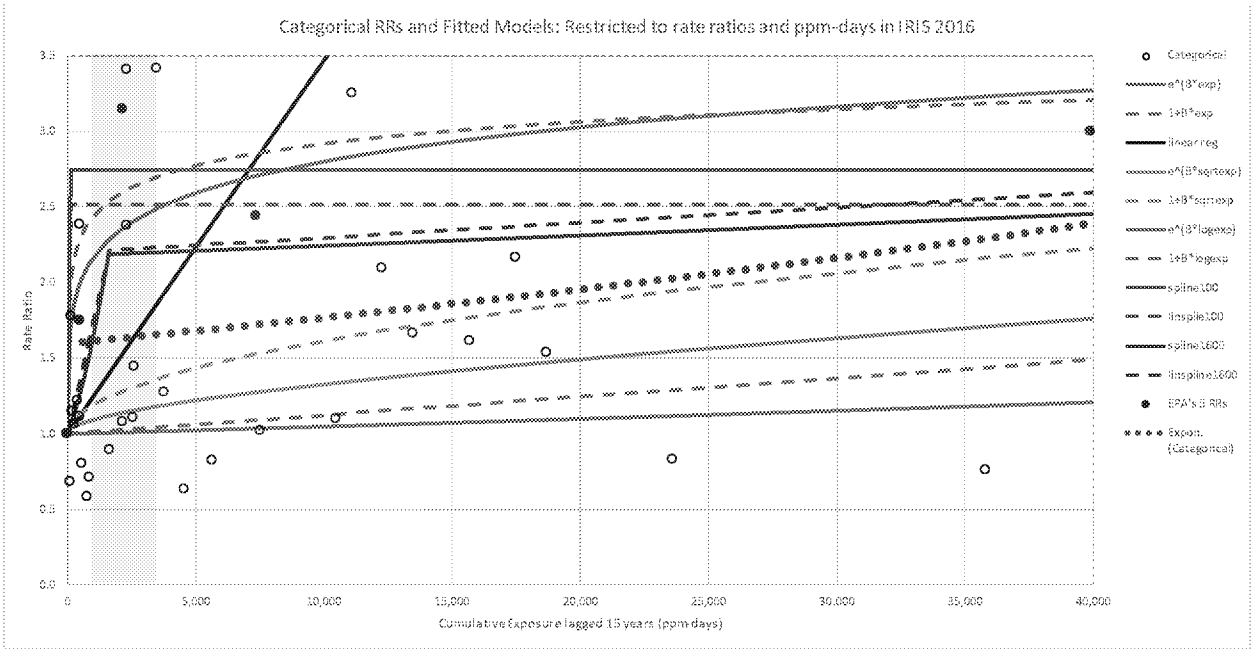
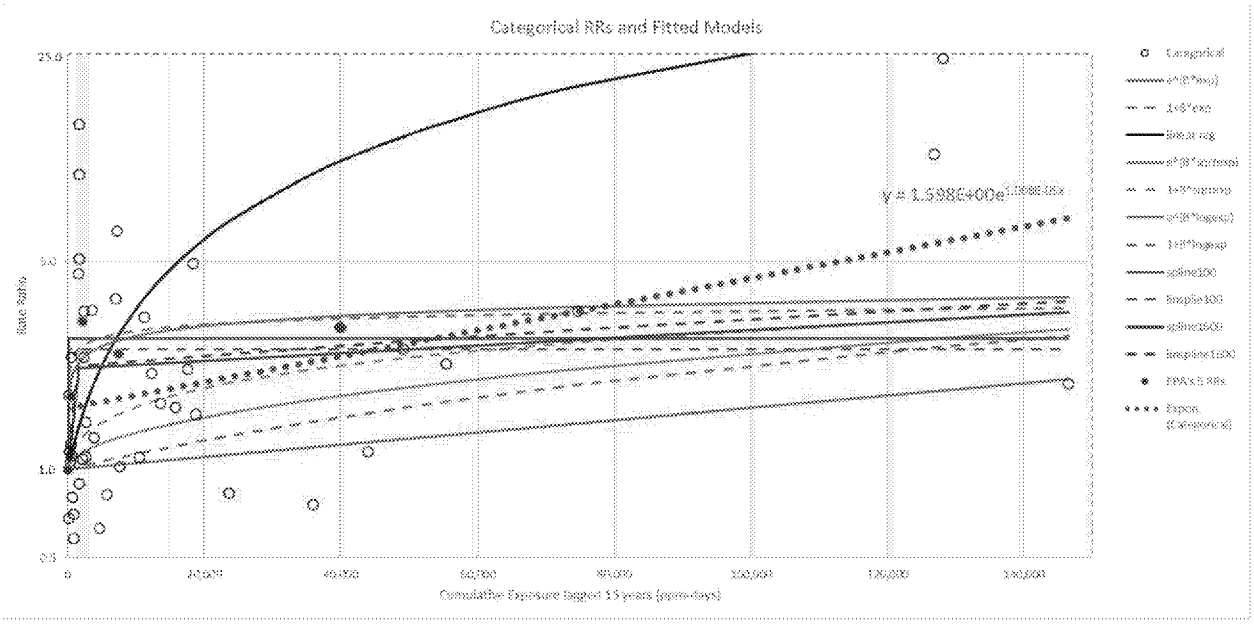
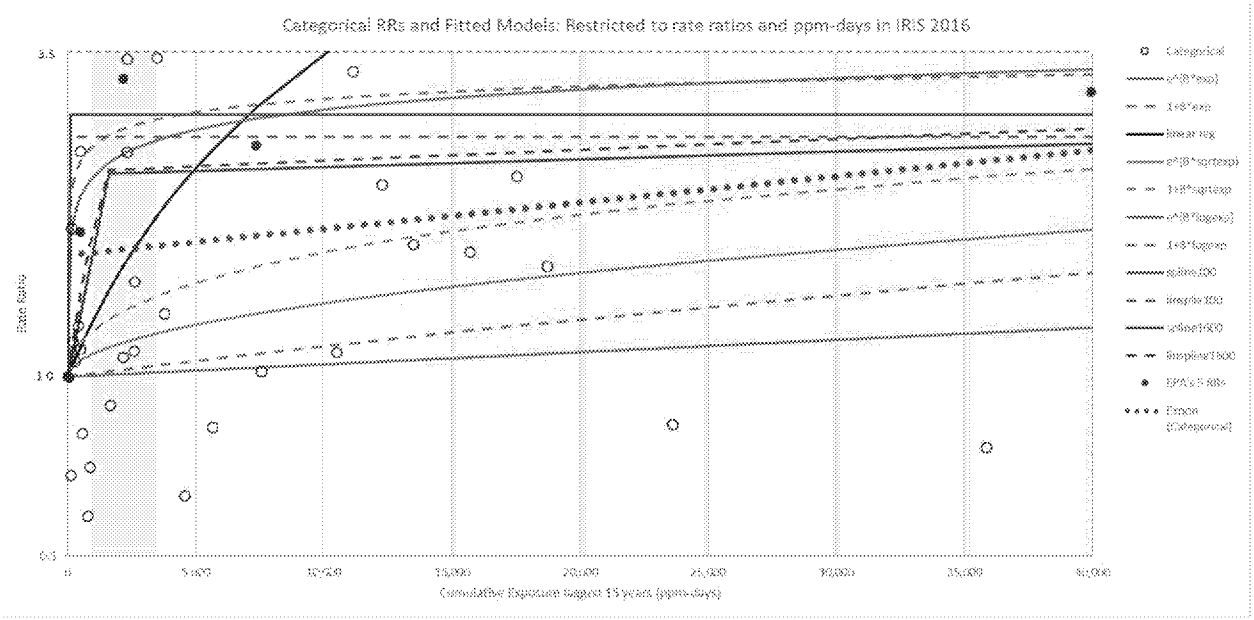


Figure 3. EPA models plotted against the logarithm of all lymphoid rate ratios in the NIOSH data



Appendix 1

Figure 4. EPA models plotted against the logarithm all lymphoid rate ratios in the NIOSH data in the low exposure concentration range and with the rate ratio truncated to the same range of EPA's Figure 4-3.



Appendix 2

Brief Summary of Epidemiological Data for EO

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The relevant epidemiology, despite the large number of studies published over a forty-year period, are not supportive of a determination that EO is a human carcinogen. While interest has centered on leukemia, other blood related malignancies, and recently breast cancer: (1) there are numerous inconsistencies across the studies, (2) elevated risks above background are found in isolated studies and the effect size is of small magnitude, and (3) there is an absence of a clear exposure-response relation for any specific cancer type.

Examination of the specific cancer subtypes (leukemia, non-Hodgkin's lymphoma [NHL], Hodgkin's disease [HD], multiple myeloma [MM] and lymphohematopoietic cancers [LH] overall) illustrates the absence of clear evidence of carcinogenicity and no clear choice for a target organ should a dose-response be attempted. Table 1 summarizes the individual and overall findings from the EO studies for leukemia. Taking the ratio of the total observed cases and the total expected number of cases yields a summary risk estimate. The total number of deaths due to leukemia is 64 with 56.86 expected for an SMR /SIR of 1.13 (95% CI: 0.87-1.44). It is noteworthy that Hogstedt's increase was mainly attributable to myeloid leukemias, while Steenland focused on lymphocytic leukemia in the lymphoid category. As shown by Shore and Teta in their meta-analyses, Hogstedt is an outlier that is statistically different in findings from the other studies, i.e., a cause of heterogeneity. Furthermore, it is incorrect to include a cluster which gave rise to the hypothesis in a summary risk estimate. Excluding Hogstedt, yields 57 observed leukemias and 56.06 expected for an SMR/SIR of 1.02 (95% CI: 0.77, 1.32). Clearly Hogstedt's hypothesis of EO as a cause of leukemia has not been confirmed.

Appendix 2

Table 1. Leukemia in Epidemiology Studies of Ethylene Oxide

Publication	Observed	Expected	Obs./Exp. (95% CI)
Hogstedt 1979, 1986, 1988	7	0.80	9.21* (3.70, 19.0)
Lymphocyctic	2	---	---
Myeloid	3	---	---
NOS	2	---	---
Hagmar 1991/Hagmar 1995/ Mikoczy 2011	5	3.58	1.40 (0.45, 3.26)
Thiess 1981/Kiesselbach 1990	2	2.35	0.85 (0.10, 3.07)
Morgan 1981/Divine 1990	0	0.60	0.00 (0.00, 6.57)
Greenberg 1990/Teta 1993/ Swaen 2009	11	11.8	0.93 (0.47, 1.67)
Steenland 1991/Stayner 1993/ Steenland 2004	29	29.3	0.99 (0.71, 1.36)
Bisanti 1993	2	0.30	6.50 (0.79, 23.5)
Gardner 1989/Coggon 2004	5	4.60	1.08 (0.35, 2.51)
Olsen 1997	2	3.00	0.67 (0.08, 2.40)
Norman 1995	1	0.54	1.85 (0.05, 10.3)
Summary	64	56.9	1.13 (0.87, 1.44)
Summary (-Hogstedt)	57	56.1	1.02 (0.77, 1.32)

For HD there were 17 observed compared to 10.84 expected (1.57; 95% CI: 0.91-2.51) (Table 2). The Swaen case-control study was included and an expected number was derived to combine these results with those of the cohort studies. (The proportion of controls exposed, 5%, was applied to the case group of 10 cases yielding an expected exposed of 0.5). Relying only on the two strongest studies (Swaen 2009 and Steenland 2004) yields for HD, 6 vs. 6.54 (0.92; 95% CI: 0.34, 2.0). The Swaen 2009 UCC cohort had no deaths due to HD.

Table 2. Hodgkin Disease in Epidemiology Studies of Ethylene Oxide

Publication	Observed	Expected	Obs./Exp. (95% CI)
Hogstedt 1979, 1986, 1988	0	---	---
Hagmar 1991/Hagmar 1995/ Mikoczy 2011	1	1.31	0.76 (0.02, 4.25)
Thiess 1981/Kiesselbach 1990	---	---	---
Morgan 1981/Divine 1990	3	0.40	8.34* (1.68, 24.4)
Greenberg 1990/Teta 1993/ Swaen 2009	0	1.70	0.00* (0.00, 0.22)
Steenland 1991/Stayner 1993/ Steenland 2004	6	4.84	1.24 (0.53, 2.43)
Bisanti 1993	---	---	---
Gardner 1989/Coggon 2004	2	1.05	1.91 (0.23, 6.89)
Olsen 1997	2	0.70	2.86 (0.35, 10.3)
Norman 1995	0	0.34	0.00 (0.00, 10.9)
Swaen 1996	3	0.50	8.50* (1.40, 39.9)
Summary	17	10.8	1.57 (0.91, 2.51)

Two studies provided no data for MM (Kiesselbach 1990 and Bisanti 1993) and four others failed to provide expected values (Hogstedt 1988, Divine 1990, Olsen 1997, and Swaen 2009) (Table 3). Upon contacting Dow, we were able to obtain the expected number of 5.1 for MM. Based on the studies with complete information, there are 22 observed and 24.0 expected for a summary estimate of 0.92 (Table 3). This result is heavily weighted by the largest study, Steenland et al. 2004, who reported 13 cases vs. 14.13 expected (SMR= 0.92). This summary risk estimate does not indicate an association with MM.

Table 3. Multiple Myeloma in Epidemiology Studies of Ethylene Oxide

Publication	Observed	Expected	Obs./Exp. (95% CI)
Hogstedt 1979, 1986, 1988	0	---	---
Hagmar 1991/Hagmar 1995/ Mikoczy 2011	2	2.08	0.96 (0.12, 3.47)
Thiess 1981/Kiesselbach 1990	---	---	---
Morgan 1981/Divine 1990	0	---	---
Greenberg 1990/Teta 1993/ Swaen 2009	3	5.10	0.59 (0.12, 1.72)
Steenland 1991/Stayner 1993/ Steenland 2004	13	14.1	0.92 (0.49, 1.57)
Bisanti 1993	---	---	---
Gardner 1989/Coggon 2004	3	2.50	1.20 (0.25, 3.49)
Olsen 1997	1	NR	NR
Norman 1995	1	0.23	4.34 (0.11, 24.2)
Summary	22	24.0	0.92 (0.57, 1.39)

Using the same method of pooling the observed and expected values of NHL across the different studies results in a meta-SMR/SIR estimate of 1.12 based on 62 observed and 55.4 expected, a small, non-statistically significant increase (Table 4).

Table 4. Non-Hodgkins Lymphoma in Epidemiology Studies of Ethylene Oxide

Publication	Observed	Expected	Obs./Exp. (95% CI)
Hogstedt 1979, 1986, 1988	2	---	---
Hagmar 1991/Hagmar 1995/ Mikoczy 2011	9	6.25	1.44 (0.66, 2.73)
Thiess 1981/Kiesselbach 1990	---	---	---
Morgan 1981/Divine 1990	0	0.90	0.00 (0.00, 4.04)
Greenberg 1990/Teta 1993/ Swaen 2009	12	11.5	1.05 (0.54, 1.83)
Steenland 1991/Stayner 1993/ Steenland 2004	31	31.0	1.00 (0.72, 1.35)
Bisanti 1993	3	0.20	16.9* (3.49, 49.5)
Gardner 1989/Coggon 2004	7	4.80	1.46 (0.59, 3.02)
Olsen 1997	5	NR	NR
Norman 1995	0	0.76	0.00 (0.00, 4.85)
Summary	62	55.4	1.12 (0.86, 1.43)

Examination across the ten studies of all LH cancers yields a non-statistically significant increase based on 175 observed vs. 156.97 expected (Meta-SMR/SIR = 1.11; 95% CI: 0.96, 1.29) (Table 5). Exclusion of Hogstedt would result in a weak excess (1.07) and narrow confidence interval (95% CI: 0.91, 1.25).

Table 5. All Lymphopoietic and Hematopoietic Cancers in Epidemiology Studies of Ethylene Oxide

Publication	Observed	Expected	Obs./Exp. (95% CI)
Hogstedt 1979, 1986, 1988	9	2.00	4.59* (2.10, 8.70)
Hagmar 1991/Hagmar 1995/ Mikoczy 2011	18	14.4	1.25 (0.74, 1.98)
Thiess 1981/Kiesselbach 1990	5	4.99	1.00 (0.32, 2.34)
Morgan 1981/Divine 1990	3	3.00	1.01 (0.20, 2.96)
Greenberg 1990/Teta 1993/ Swaen 2009	27	30.4	0.89 (0.59, 1.29)
Steenland 1991/Stayner 1993/ Steenland 2004	79	79.0	1.00 (0.79, 1.24)
Bisanti 1993	5	0.70	7.00* (2.27, 16.4)
Gardner 1989/Coggon 2004	17	12.9	1.30 (0.77, 2.10)
Olsen 1997	10	7.70	1.29 (0.62, 2.38)
Norman 1995	2	1.88	1.06 (0.13, 3.84)
Summary	175	157.0	1.11 (0.96, 1.29)
Summary (-Hogstedt)	166	155.0	1.07 (0.91, 1.25)

As discussed above, Steenland et al. (2004) grouped three LHC cancers into the "lymphoid" category and reported some positive findings for men only. This category included lymphocytic leukemias only. The original cluster reported by Hogstedt in 1979 consisted of myeloid leukemias (Table 2). The results from the only other study to examine the lymphoid category as defined by NIOSH (UCC cohort) are inconsistent with the NIOSH results (Swaen 2009). From an internal analysis using Cox proportional hazard model, no evidence of an exposure–related response was observed by Swaen et al. using the UCC EO cohort. In fact, the females in the NIOSH study are also inconsistent with the male findings for lymphohematopoietic and "lymphoid" tumors (Steenland 2004).

Steenland et al. also examined both incidence and mortality from breast cancer for the sterilizer cohort (Steenland 2003, 2004). Among the overall results for this disease endpoint among other studies, only Norman et al. (1995) reported an increase (Table 6). Hogstedt enumerated all the cancers from his numerous cohorts and updates. No breast cancer cases were identified. Similarly, there was no excess among the hospital workers studies by Coggon et al. (2004), even among those with "continual" exposure (5 observed, 7.2 expected). The data related to breast cancer derived predominately from the NIOSH studies of sterilant workers with 102 deaths and 103 expected for an SMR of 0.99 (95% CI: 0.81-1.20) (Steenland 2004) and 319 incident cases with 367 expected for a statistically significant deficit of 0.87 (95% CI: 0.77-0.97) (Steenland 2003) due to underascertainment of cases. When examined in various exposure subgroup analyses, however, NIOSH concluded there was some evidence of an increase for breast cancer.

Table 6. Ethylene Oxide Epidemiology Studies of Female Breast Cancer

Study	Observed	Expected	Obs./Exp. (95% CI)
Coggon et al. 2004	11	13.1	0.84 (0.42, 1.51)
Steenland et al. 2004	102	103.0	0.99 (0.81, 1.20)
Steenland et al. 2003	319	367.0	0.87* (0.77, 0.97)
Mikoczy et al. 2011	41	50.9	0.81 (0.58, 1.09)
Norman et al. 1995	12	7.0	1.72 (0.93, 2.93)
Hogstedt et al. 1986	0	---	---
Summary (incident cases only)	372	424.9	0.88* (0.79, 0.97)
Summary (mortality cases only)	113	116.1	0.97 (0.80, 1.17)

EPA recognizes that magnitudes of increased risks for breast cancer were not large and implies that the evidence is weaker than that for lymphoid tumors. Despite these issues, EPA proceeds to introduce breast cancer as a target organ in the IRIS Assessment and inappropriately develops a risk value. Uncertainties described by Steenland et al. (2003) related to the breast cancer incidence study are dismissed as unimportant by EPA. EPA agrees with Steenland that the breast cancer incidence findings are not conclusive, due to inconsistencies in the exposure-response and an incomplete cancer ascertainment. Using these data, the slopes of EPA's attempted exposure-response analyses were non-statistically significant or biologically uninterpretable, leading them to employ novel approaches for quantitative risk assessment. The modeling challenges could be anticipated given Steenland's statement of uncertainty with respect to breast cancer, "The dip in the spline curve in the region of higher exposures suggested an inconsistent or non-monotonic risk with increasing exposure."

The Agency downplays the potential for selection bias based on the consistency in the incidence study between results from full cohort and those from the subgroup interviewed (68% of study subjects). Selection bias (referred to by Steenland as "possible biases due to patterns of non-response") remains a concern, however, with duration reported as a stronger risk factor than cumulative exposure in both analyses. Those who work longer stay in the area longer and are more likely to get picked up in the state tumor registries and be found for interview, therefore with the potential to impact the results of both analyses. Shorter duration workers with lower exposures are more likely to leave the area and not be captured in the overall analyses and less likely to be interviewed. Their diagnoses get missed, creating a possible biased positive exposure-response. Steenland recognized this limitation and admitted he was unable to fully address it and listed it as one of his uncertainties:

> A second possible bias was the preferential ascertainment of breast cancer among women with stable residence in states with cancer registries; women with stable residency might be expected to have longer duration of employment in companies

under study, and hence greater cumulative exposure. Unfortunately, we did not have residential history, limiting our ability to explore this possibility.

The more recent study by Mikoczy et al. (2011) has been cited as supportive of an association with breast cancer, in spite of an overall deficit (SIR=0.81; 95% CI: 0.58-1.09) based on 41 cases observed. With 15-year latency it is 0.86, also suggesting no increase. Similar to NIOSH, however, the two higher cumulative exposure groups (of three total group) had statistically significant elevated rates of breast cancer (2.76; 95% CI: 1.20-6.33 and 3.55; 95% CI: 1.58-7.93) in an *internal* Poisson analysis, due, however, to a substantial and statistically significant deficit of breast cancer in the low dose reference group (SIR=0.52; 95% CI: 0.25-0.96). There are clearly advantages to comparing workers to workers in epidemiology studies to overcome possible biases in external comparisons to the general population. However, there may also be disadvantages to using an internal comparison group that are not recognized. One danger is selecting a referent group that has an unusual excess or deficit of the disease of interest as illustrated in this study. This illustrates the problem that can arise from internal comparisons and should not always to be preferred despite what EPA contends.

In addition to LH cancers, EPA uses breast cancer as a target endpoint. We conclude that the choice of breast cancer as a target organ for EO dose-response assessment is not justified for several reasons: (1) EPA agrees that the evidence for breast cancer is even weaker than the evidence for the lymphoid category, (2) the NIOSH findings suffer from potential selection biases, show a non-monotonic increase in risk with increasing exposure, and neither mortality nor incidence rates overall exceed background rates in the general population, and (3) the breast cancer findings from the other epidemiology studies are equivocal.

There is no obvious target organ for an EO exposure-response assessment for a quantitative risk assessment. Given the weak epidemiology evidence for carcinogenicity, the lack of consistency or a clear exposure-response, the selection of a specific target organ is problematic. Using cumulative exposure as the exposure metric and the standard proportional hazard modeling, none of the slopes for the endpoints of interest are statistically significant (Valdez-Flores, Sielken, and Teta 2010). Despite the absence of a clear exposure-response for any one of the combinations, the authors proceeded to use EPA's standard procedure for unit risk estimation and estimation of exposure associated with a one-in-a-million risk. This approach was adopted by Scientific Committee on Occupational Exposure Limits (SCOEL) for the European Union in 2012 for occupational standard setting.

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Exhibit I

Response to Public Comments Received on the 2019 Ethylene Oxide Draft Development Support Document

CAS Registry Number: 75-21-8

Response to Comments

January 31, 2020

TEXAS COMMISSION ON ENVIRONMENTAL QUALITY

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Response to Public Comments Received on the June 2019 Proposed Ethylene Oxide Development Support Document

The public comment period on the draft Development Support Document (DSD) for ethylene oxide ended September 26, 2019. The agency received numerous comments on the draft DSD from diverse groups (e.g., industry, academia, nongovernmental organizations, private citizens). The TCEQ appreciates the effort put forth to provide comments on the draft DSD for ethylene oxide. The goal of the TCEQ is to protect human health and welfare based on the most scientifically-defensible approaches possible (as documented in the DSD), and evaluation of these comments furthered that goal. Comments were divided into sections and are provided below, followed by TCEQ responses.

Comments from the American Chemistry Council (ACC)

Comment 1:

The Panel supports the inhalation-based unit risk factor (URF) derived by TCEQ for ethylene oxide (EtO). TCEQ's approach to ground-truth the selection of the extrapolation model based on biological and epidemiological evidence is a critical missing step in EPA's IRIS EtO assessment (IRIS, 2016). An overly conservative assessment can result in misplaced public concern, supply chain disruption of critical products, and the unnecessary use of resources.

Response:

The TCEQ appreciates the comment. Ground-truthing and reality checks based on both biological and epidemiological evidence are rarely possible, and in this case show USEPA's URF to be biologically implausible and over-predictive while TCEQ's is both plausible and relatively accurate. Scientists must objectively review the scientific weight of evidence and the consistency or inconsistency of scientific (e.g., dose-response) assessments with it, judging each based on a detailed and unbiasedly objective review of its own merits. This duty is critically important because this and similar assessments have important regulatory, public health, and risk assessment/communication implications (e.g., whether typical environmental exposures and those near sterilization facilities represent realistic health concerns/hazards or not, and the availability of ample sterile medical supplies).

Comment 2:

The TCEQ proposed EtO DSD calculated a URF of 2.5E-6 per ppb (1.4E-6 per $\mu g/m^3$) and a 1/100,000 extra risk chronic health-based effects screening level for non-threshold dose response cancer effect of 4 ppb (7 $\mu g/m^3$) based on the NIOSH epidemiology study and an assumption of a 15-year exposure lag period. Although ACC has previously recommended a different approach based on the two strongest epidemiology studies and zero lag period, ACC finds the TCEQ proposal acceptable because it is much more scientifically sound, biologically plausible, and statistically correct compared to the IRIS (2016) EtO Assessment. The IRIS' URF of 9.1E-3 per ppb (5.0 E-3 per $\mu g/m^3$) results in a 1/100,000 excess risk concentration of 1 ppt (0.0018 $\mu g/m^3$), which is inconsistent with the epidemiological and biological evidence and

unreasonably conservative. The major reason for the 4000-fold difference in the URFs derived by TCEQ and IRIS is the selection of different statistical models used for low dose extrapolation.

Response:

Based on biological considerations discussed in the DSD, the TCEQ used a 15-year exposure lag and disagrees with the 0-year exposure lag previously proposed by ACC. Additionally, based on weighting considerations, the TCEQ ultimately based the URF on the same NIOSH key study as USEPA (2016), so ultimately disagrees with ACC on inclusion of the UCC study in the final URF. The agency agrees that the major reason for the large difference in the URFs derived by TCEQ and IRIS is the selection of different statistical models used for low-dose extrapolation. USEPA (2016) did not calculate various p-values and AIC values correctly as demonstrated in the DSD, and cannot cite MOA data that support its overall supra-linear model or the application of its very steep low-dose slope. These and other considerations such as reality checks on the underlying key cancer data and normal endogenous levels do not support adoption of USEPA's unconventional, overall supra-linear model over a standard model such as the Cox proportional hazards model, which the TCEQ shows to be more predictive and biologically plausible.

Comment 3:

TCEQ used mode of action (MoA) information as the primary basis for informing the low dose extrapolation, and systematically considered endogenous levels, key epidemiological data and model prediction to check and ground-truth the selection of the final model. Although IRIS (2016) also considered the MoA, toxicology and epidemiology studies for cancer classification, IRIS (2016) did not fully utilize these studies in the final selection of the extrapolation model. Instead, IRIS relied primarily on incorrect statistical analysis and flawed visual representation of the exposure-response data. TCEQ's approach to ground-truth the selection of the extrapolation model based on biological, epidemiological and statistical model prediction evidence is the critical missing step in the IRIS assessment that TCEQ completes in the proposed DSD.

Response:

The TCEQ agrees that the agency used multiple lines of evidence that support its approach but not USEPA's approach. The agency further agrees and has demonstrated in the DSD that USEPA relied on incorrect statistical analysis (i.e., incorrectly calculated p-values and AIC values) and an unintentional visual misrepresentation of model fit for its flawed model selection (see the DSD for a more detailed discussion).

Comment 4:

ACC has five key recommendations for strengthening TCEQ's use of mode of action and epidemiological weight of evidence to ground-truth the final selection of the URFs. While TCEQ's reality check of the EPA-estimated 1 in a million to 1 in 10,000 extra risk levels is appropriate based on endogenously generated EtO relative to those contributed by exogenous EtO exposures, it can be strengthened by brief discussion of endogenously produced EtO DNA adducts (e.g., Marsden et al. 2009, Swenberg et al. 2011, Tomkins et al. 2009).

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Response:

TCEQ has chosen to now briefly highlight Recio et al. (2004) as part of the DSD MOA section as opposed to the studies referenced by the commenter. Since lymphoid cancer drove the USEPA carcinogenic assessment, perhaps the most relevant mutagenicity data discussed by USEPA (2016) was that in the bone marrow of mice exposed to EtO by inhalation *in vivo* (Recio et al. 2004), which USEPA indicates is *consistent with a linear dose-response* (see C-17 of USEPA 2016), at least at doses well above endogenous.

Comment 5:

TCEQ's arguments to support the selection of lymphoid cancer as the "critical cancer endpoint", while valid, would be enhanced by including a weight of evidence evaluation of the breast cancer findings from the six relevant epidemiology studies.

Response:

This type of information has now been included in Appendix 6 of the revised DSD.

Comment 6:

TCEQ should consider simplifying and clarifying a few sections and tables to better support TCEQ's principled approach of using MoA, biological plausibility and epidemiological weight of evidence to inform selection of the final model and the point-of-departure (PoD). The following are a couple of examples: ACC previously recommended use of zero-lag, but supports TCEQ's rationale for selecting the 15-year lag based on biological considerations and for consistency with the IRIS (2016) approach. Several tables can be simplified to only show the zero and 15-year lag data. TCEQ should clarify that the 1/100,000 extra risk level was estimated directly from the Cox proportional hazard model. This excess risk level is at the low end of the observable range of responses consistent with EPA (2005) guidance for selecting a PoD for cancer risk assessment.

Response:

Showing the results for all the various lags better documents TCEQ's extensive evaluation. Thus, the tables will not be simplified. The TCEQ has clarified in the DSD that the 1/100,000 extra risk level (the low end of the observable range) was estimated directly from the Cox proportional hazard model.

Comment 7:

ACC agrees with TCEQ's emphasis on the biological mode of action and the epidemiology weight of evidence as the primary basis for selecting the type of model for low-dose extrapolation. TCEQ also provides additional statistical evidence that the final adopted TCEQ model accurately predicts the observed number of lymphoid cancer deaths in the NIOSH cohort compared to USEPA's supra-linear spline model. Further clarifications and comparisons could be added to help the reader more fully appreciate these model-prediction results: TCEQ should clarify in Section 3.4.1.2.2.3 that regardless of whether the maximum likelihood estimate (MLE)

or the 95% upper confidence limit (UCL) model is used, the IRIS two-piece spline model over predicts the number of mortalities 95% of the time (Table 31, 95% CI). In contrast, both the MLE and the UCL for TCEQ's Cox proportional hazard log-linear model accurately predict the observed mortalities. Comparison of the prediction of the IRIS Cox proportional log-linear hazard model with the IRIS supra-linear two-piece spline model provides an additional "apples-to-apples" comparison based on similar IRIS assumptions for both model estimates.

Response:

The TCEQ appreciates the commenter's acknowledgment of the scientific weight of multiple lines of evidence approach utilized by TCEQ. To be abundantly clear, the lack of EtO-specific MOA data to justify an unconventional overall supra-linear model is the primary driver for rejection of USEPA's two-piece spline model in favor of a standard dose-response model (TCEQ 2015). However, other lines of evidence strongly support the biological plausibility and predictiveness of TCEQ's model over USEPA's model. For some additional information from Appendix 2 of the revised DSD, some sentences regarding USEPA versus TCEQ model predictions using the UCL and MLE were added to Section 3.4.1.2.2.3.

Comment 8:

TCEQ should clarify that contrary to USEPA SAB's recommendation, IRIS used only a subset of 100 randomly chosen controls from the NIOSH data (IRIS Appendix D-4, D-29), whereas, TCEQ's model estimates are based on the full NIOSH data set.

Response:

Text was added to the DSD to the effect that TCEQ lymphoid cancer risk estimates are based on the full NIOSH and UCC datasets (i.e., the individual data and not categorical results). Although USEPA IRIS used a random sample of 100 individuals in defining risks sets in the process of fitting the models, results are close to using all individuals. TCEQ used all individuals to define the risk sets, which makes a more robust set for estimating model parameters. This response to comments document serves as documentation of the comment that contrary to USEPA SAB's recommendation, IRIS used only a subset of 100 randomly chosen controls from the NIOSH data.

Comment 9:

TCEQ appropriately relies on the biological MoA as the primary basis for selecting the model for low-dose extrapolation to build a strong case for why TCEQ should not adopt the EtO IRIS assessment's inhalation of 1 in 100,000 excess risk-based air concentration of 1 ppt. TCEQ's conservative and scientifically supportable approach to an exposure-response analysis should be used. This alternative approach makes use of the full data set and yields a more realistic risk-based air concentration of 4 ppb at the no significant excess risk level of 1 in 100,000.

Response:

The TCEQ agrees that biological MOA should be the primary basis for selecting the dose-response model; the scientific weight of evidence strongly supports TCEQ's approach over

USEPA's modeling approach; and that TCEQ's approach incorporates appropriate conservatism yet remains realistic in terms of biological plausibility and risk predictiveness.

Comment 10:

p. 60- last paragraph regarding Table 10. TCEQ states that "NIOSH breast cancer incidence data were not publicly available for independent analysis. Therefore, Table 10 results will not be utilized." Perhaps these two sentences can be switched.

Response:

The TCEQ has clarified the referenced text in the DSD.

Comment 11:

p. 64- first sentence in italics explains the rationale for excluding breast cancer as a final endpoint. This section should incorporate consideration of the weight of evidence for breast cancer incidence. The epidemiology data does not support a potency for breast cancer that is stronger than for lymphoid cancer.

Response:

Relevant information has been included in Appendix 6 of the revised DSD.

Comment 12:

p. 84 and 90- the statement is made in reference to Swaen et al. (2009) and Mikoczy et al. (2011) that "Healthy Worker Effect (HWE)" likely influenced results". HWE is a well-known form of bias in occupational cohort studies in which increased risks may be missed when comparisons are made to an external, general population, considered to be less healthy than the worker population. However, the epidemiologic literature has shown that HWE is predominately related to shorter follow up and non-cancer causes (Monson 1986; Fox and Collier 1976). Swaen (2009) had a very long follow up (36.5 yr. average) and deficits in major non-cancer causes only among those hired after 1956. There is no indication that cancer increases have been missed due to HWE. Similarly, for Mikoczy et al. (2011), mortality was no longer decreased with a 15-yr "induction latency" period. A study to test HWE in Sweden as it relates to breast cancer has been published showing no HWE (Gridley et al. 1999). To avoid misleading the reader, we recommend deleting these statements in the report or specifying that they relate to non-cancer causes.

Response:

The TCEQ agrees that the healthy worker effect (as evidenced by decreased overall mortality, etc.) does not necessarily extend to specific cancers, particularly where the carcinogen operates via a mutagenic MOA. For example, the suggestion of the authors of Mikoczy et al. (2011) that a finding of significantly decreased overall mortality and cardiovascular disease mortality is indicative of a healthy worker effect for breast cancer incidence is inconsistent with the results of a relatively recent and large study (366,114 workers) conducted specifically to examine the potential for the healthy worker effect in cancer incidence studies (Kirkeleit et al. 2013).

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Similarly, the authors of Swaen et al. (2009) indicated that results for all-cause mortality, heart disease, non-malignant respiratory diseases, etc. indicated a healthy worker effect necessitating internal analyses for cancers of interest. In Kirkeleit et al. (2013), all-cause mortality and both ischemic heart disease and circulatory system disease mortality were statistically significantly decreased in male workers (n=283,002) and female workers (n=83,112) compared to the general population (Table 3 of the study), consistent with similar findings in Mikoczy et al. (2011) and Swaen et al. (2009). The SIRs for lymphoid and hematopoietic cancers in male workers and female workers were 0.97 (0.90, 1.03) and 1.09 (0.92, 1.27), respectively, consistent with the lack of a statistical difference; that is, the lack of a healthy worker effect for these cancers. Additionally, the Kirkeleit et al. (2013) study found that breast cancer incidence in over 83,000 female workers was as expected based on the general population (i.e., SIR of 1.02 (0.95, 1.09)). Thus, Kirkeleit et al. (2013) indicates the lack of a healthy worker effect for both lymphoid/hematopoietic and breast cancer incidence. In any event, both Mikoczy et al. (2011) and Swaen et al. (2009) conducted internal analyses to account for the presumed healthy worker effect, so these study results need not be caveated. Therefore, the referenced text was removed as the study authors accounted for the presumed healthy worker effect for cancers of interest.

Comment 13:

TCEQ should consider simplifying and clarifying a few sections and tables to better support TCEQ's principled approach of using MoA, biological plausibility and epidemiological weight of evidence to inform selection of the final model and the point-of departure (PoD).

Table 6 (p. 56) includes some cancer endpoints that are not relevant based on the epidemiological weight of evidence. This table should only include lymphohematopoietic and breast cancers, which are the only cancers that IRIS (2016, p. 3-13) associated with EtO exposures.

Response:

The TCEQ understands this perspective but does not perceive a need to change the table as it helps demonstrate the broader nature of analyses conducted for EtO.

Comment 14:

Table 7-10, 12-14 (pp. 57-62) can be simplified to just show the zero and 15-year lag. TCEQ should indicate in the text and footnote of these tables that a large number of lag periods were tested and none were statistically different from zero lag. ACC previously recommended use of zero-lag, but supports TCEQ's rationale for selecting the 15-year lag based on biological considerations and for consistency with IRIS (2016) approach. However, it should be noted that in some cases the 95% UCL URFs for zero lag were slightly higher (more conservative) than for the 15-year lag.

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Response:

The various exposure lags in Table 7-10 help demonstrate the broader nature of analyses conducted for EtO. The TCEQ did add language to the text and footnotes indicating that no lag duration fit statistically better than the model with zero lag. The other points made by the commenter are duly noted, including support for TCEQ's rationale for selecting the 15-year lag based on biological considerations and for consistency with IRIS (2016) approach.

Comment 15:

Tables 12-14 should add explanations that the 1/100,000 extra risk level was estimated directly from the Cox proportional hazard model, and that this is consistent with EPA (2005) cancer guidelines on selection of the PoD at the low end of the observable range of responses. For example, with rodent models, a 10% (1 in 10) PoD is typically used as a 10% extra risk and is near the limit of detection for a typical assay. For epidemiologic data, a lower PoD can be used. When the standard Cox proportional hazard (log-linear) model is used for the NIOSH males-only 15-year lag data, all of the lymphoid mortalities with non-zero exposure occurred below the 1 in 100 PoD (Table 2). Therefore, 1 in 100 is not an appropriate PoD for "extrapolation" in the conventional sense. A typical POD extrapolates from the edge of the observed range through the unobserved range of the data. Thus, for the NIOSH male only data, it is appropriate to use the model to extrapolate to 1 in 100,000, which is below the 50th percentile of exposure where there is only one lymphoid mortality for subjects with non-zero exposure. IRIS (2016) used a 1% (1 in 100) extra risk for the PoD but did not provide evidence that this level would establish a PoD near the edge of the observed data range. ACC does not have the NIOSH data to determine the validity of the 1% for the supra-linear spline model.

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Table 2. Number of male lymphoid cases out of approximately 18,000 workers with concentrations below the EC (1/100) and EC (1/100,000)

	Male Lymphoid EC 1/100		Male Lymphoid EC 1/100,000[2]	
	0-Lag	15-Lag	0-Lag	15-Lag
EC (1/100,000) Env. Conc (ppm)	3.52	5.80	5.83E-03	9.67E-03
Equivalent[1] Occupational Exposure 70 years (ppm-days)	326,105.9[2]	354,399.0[2]	453.4[2]	590.87[2]
Total Number of Deaths	27	27	27	27
Number with zero exposure	0	6	0	6
Number With Non-Zero Exposure below EC	27	21	1	1
Percentage of Deaths below EC	100%	100%	3.70%	25.93%

[1]Equivalent Occupational Exposure 70 years (ppm-days) = EC×(365/240)×(20/10)×365.25×(70-lag)

[2]The maximum occupational exposure concentration for lymphoid deaths was less than 326,106 ppm-days for the unlagged and 137,243 ppm-days for the 15-year lag exposure.

Response:

The relevant tables have been footnoted accordingly. TCEQ evaluated the LEC at an extra risk of 1 in a 100,000 consistent with USEPA cancer guidelines (2005) on the selection of a POD at the low-end of the observable range of exposures. Although for animal studies, a typical POD is an extra risk of 0.10 because it corresponds to doses near the low-end of the doses, in epidemiological studies a lower level of risk needs to be used.

TCEQ used the standard Cox proportional hazards model to calculate LEC for an extra risk of 1 in a 100,000 because the EC corresponding to the same risk level are in the range of the observed data in the NIOSH study. That is, the EC for an extra risk of 1 in 100,000 of lymphoid cancer mortality in males is 9.67E-03 ppm for 70 years with an exposure lag of 15 years, which correspond to a cumulative occupational exposure of

591 ppm-days. There are 7 male workers in the NIOSH cohort with cumulative exposures less than 591 ppm-days. That is, 25.9% of the male workers in the NIOSH cohort that died with lymphoid cancer were exposed to cumulative exposures of less than the EC for 1 in a 100,000. In contrast, the EC for 1 in 100 results in environmental concentrations corresponding to cumulative occupational exposures of 354,400 ppm-days, which exceeds the largest cumulative exposure of lymphoid male decedents in the NIOSH study.

The following table shows the EC corresponding to different risk levels and the corresponding cumulative exposures with the number of lymphoid mortality cases of the male workers in the NIOSH study.

Table 1. Environmental and equivalent occupational cumulative exposures for different potential points of departure using TCEQ's selected model for lymphoid mortality in the NIOSH study

Statistic	Extra Risk			
	1/100	1/1,000	1/10,000	1/100,000
Environmental EC (ppm) [1]	5.80×10^{-0}	8.99×10^{-1}	9.61×10^{-2}	9.67×10^{-3}
Equivalent Occupational EC (ppm-days) [2]	354,399	54,932	5,872	591
Lymphoid Deaths [3]	27	21	13	7
% Lymphoid Deaths [4]	100%	77.78%	48.15%	25.93%
% Male Workers [5]	99.84%	94.48%	66.45%	30.17%
LEC (ppm) [6]	2.44×10^{-0}	3.78×10^{-1}	4.04×10^{-2}	4.07×10^{-3}
URF (ppb^{-1}) [7]	4.09×10^{-6}	2.64×10^{-6}	2.47×10^{-6}	2.46×10^{-6}

[1] Environmental concentration in ppm for 70-year lifetime with lag of 15 years corresponding to a specified extra risk
[2] Equivalent Occupational Exposure 70 years (ppm-days) = EC (ppm) × (365/240 days) × (20/10 m^3) × (365.25 days/year) × (70 years – lag in years)
[3] Number of male workers in the NIOSH cohort that died of lymphoid cancer with cumulative exposure less than the EC (i.e., EC in ppm-days at 1/100, 1/1,000, 1,10,000, or 1/100,000)
[4] Percentage of lymphoid cancer decedent male workers in the NIOSH cohort with cumulative exposures less than the EC (ppm-days)
[5] Percentage of male workers in the NIOSH cohort with cumulative exposures less than the EC (ppm-days)
[6] 95% lower bound on the EC (ppm)
[7] Unit risk estimate based on the LEC (ppm)

The results in Table 1 show that the EC for an extra risk of 1 in a 100 is outside the range of cumulative exposures for the male lymphoid mortalities observed in the NIOSH study and in the upper 1% of cumulative exposures for all male workers. That is, all males that died with lymphoid cancers and more than 99% of all male workers had cumulative exposures less than EC(1/100). Thus, the NIOSH study does not support an extra risk of 1 in a 100 as a point of departure.

The EC for an extra risk of 1 in a 1,000 is a concentration that is in the high-end of cumulative exposures of male lymphoid mortalities observed in the NIOSH study. That

is, 77.78% of all males that died with lymphoid cancers and 94.48% of all male workers had cumulative exposures less than the EC(1/1,000). Thus, a point of departure of 1 in 1,000 is at the higher-end of the cumulative exposures of male workers of the NIOSH study.

The EC for an extra risk of 1 in 10,000 is a concentration that includes 48.15% of the decedent men with lymphoid cancer and 66.45% of all men in the NIOSH cohort with smaller cumulative exposures. *The EC for an extra risk of 1 in 100,000 includes 25.93% of male lymphoid decedents and 30.17% of all males in the NIOSH study with smaller cumulative exposures.* Thus, use of an extra risk of 1 in 100,000 is supported by the NIOSH observed data, being near the lower end of the observed range of cumulative exposures to EtO, and is consistent with USEPA and TCEQ guidelines (USEPA 2005a, TCEQ 2015) on the selection of a POD at the low-end of the observable range of exposures.

Based on Table 1 results, using either 1 in 10,000 or 1 in 100,000 extra risk PODs (as PODs in the range of the observed data and close to the low-end of the observable range) round to the same ADAF-unadjusted URF selected by the TCEQ (2.5E-06 per ppb). Looking at it from a different perspective, using the 1 in 10,000 excess risk LEC of 4.04E-02 ppm as the POD and linear extrapolation, the 1 in 100,000 air concentration (ADAF unadjusted) is still 4 ppb (i.e., 1E-05/2.47E-06 per ppb = 4.05 ppb). This information has been added to Appendix 7 of the revised DSD.

Comment 16:

ACC agrees with TCEQ's emphasis on the biological mode of action and the epidemiology weight of evidence as the primary basis for selecting the type of model for low-dose extrapolation. TCEQ also provides additional statistical evidence that the final adopted TCEQ model accurately predicts the observed number of lymphoid cancer deaths in the NIOSH cohort compared to EPA's supra-linear spline model.

Response:

The agency acknowledges the commenters concurrence with TCEQ's approach. As indicated, the model adopted by the TCEQ is demonstrated to relatively accurately predict the observed number of lymphoid cancer deaths in the NIOSH cohort compared to the over-prediction by USEPA's supra-linear spline model.

Comment 17:

Further clarifications and comparisons could be added to help the reader more fully appreciate model-prediction results.

P. 41-46, Section 3.4.1.2.2.3: TCEQ used the final selected 95% upper confidence limit (UCL) model to predict lymphoid mortalities. TCEQ may want to further clarify that regardless of whether the maximum likelihood estimate (MLE) or the 95% upper confidence limit (UCL)

model is used, the IRIS two-piece spline model over predicts the number of mortalities 95% of the time (Table 31, 95% CI).

Response:

This is now mentioned at the end of Section 3.4.1.2.2.3.

Comment 18:

In contrast, the MLE and UCL models for TCEQ's Cox proportional log-linear model accurately predicts the number of mortalities. The section on model prediction analysis could also clarify that this comparison is based on the model fit prior to any additional adjustments based on age or other factors.

Response:

The agency believes no such clarification is needed as it is well before the ADAF section of the DSD.

Comment 19:

Figures 8 to 12: TCEQ might consider including IRIS's Cox proportional log-linear model in Figures 8 to 12 for comparison with IRIS's supra-linear two-piece spline slope. Comparison of the prediction of the IRIS Cox proportional log-linear hazard model with the IRIS supra-linear two-piece spline model provides an additional comparison based on similar IRIS approach (i.e. using a random subset of the data).

Response:

While considered, the agency believes no such revision is needed since the TCEQ is using its own Cox proportional hazarding modeling results for comparison to USEPA's selected model.

Comment 20:

TCEQ should clarify that contrary to USEPA SAB's recommendation, IRIS used only a subset of 100 randomly chosen controls from the NIOSH data (IRIS Appendix D-4, D-29), whereas, TCEQ's model estimates are based on the full NIOSH data set.

USEPA SAB recommended that IRIS utilize the full NIOSH data set to estimate the cancer slope coefficients that would in turn be used to extrapolate risk instead of a small subset used by IRIS (IRIS Appendix H-10).

TCEQ's model estimates are based on the full NIOSH data set. However, the IRIS (2016) model use the subset of 100 controls. There is no strong biologic or statistical justification for selecting a subset of the data to estimate dose response curves. Thus, TCEQ's analysis is a more robust and complete analysis based on all the available data.

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Response:

See TCEQ response to Comment #8 (above). As noted in the next comment, TCEQ's model estimates are based on the full NIOSH dataset, consistent with the SAB recommendation. The agency acknowledges the commenter's concurrence with our approach.

Comment 21:

p. 14 and p.27 authorship should be corrected in the section in italics regarding update of the UCC cohort. Dr. Valdez-Flores is not a co-author of the Bender et al. 2019 paper (submitted), but is an author of a risk assessment paper based, in part, on the Bender et al. 2019 paper.

Response:

This clarification has been made.

Comment 22:

p.25, para.2: This text effectively describes how the implausibly high cancer risk associated with low dose EtO exposures as estimated by USEPA also infers an implausibly high cancer risk associated with exogenous long-term exposure to ambient levels of ethylene (due to its metabolism to EtO). However, the analysis should be expanded to clarify that, unlike EtO, the current risk assessments for ethylene are based on robust negative chronic rodent inhalation bioassays and genotoxicity assessments, and thus should not be targeted for cancer risk reevaluation based on extrapolation from the USEPA EtO cancer risk assessment.

Response:

Some clarifying language has been added to Section 3.4.1.2.1 of the DSD.

Comment 23:

Table 4 A footnote should be added next to Valdez-Flores et al. 2010 that only the first and fourth column are based on data from Valdez Flores et al. 2010.

Table 4 The breast cancer row incorrectly indicates the highest 5th quantile is elevated risk, but we believe this is incorrect because there was no statistical increase. Instead it should indicate Not Applicable.

Table 5 Similar to Table 4, a footnote should be added to clarify that only columns 1 and 4 are from Steenland et al. (2004, 2003).

Response:

The recommended footnote has been added to the referenced tables. Breast cancer was included in Table 4 of the proposed DSD by TCEQ for context, and column 1 denotes that it was not statistically increased. This caveat was added to the fourth column of this table.

Comment 24:

p. 57-60 This series of tables was difficult to follow. We recommend separating the p-value vs. null and p-value vs. zero lag into separate columns by themselves.

Response:

No changes were deemed necessary as the tables fulfill the purpose of adequately documenting the information contained therein.

Comments from Sierra Club, Texas Environmental Justice Advocacy Services, Air Alliance Houston, Coastal Alliance to Protect our Environment, Environment Texas, Public Citizen's Texas Office, Texas Campaign for the Environment, Earthjustice, and Environmental Integrity Project

In their letter to the agency, these commenters provided many general comments on ethylene oxide (EtO) as well as more specific comments relevant to the TCEQ carcinogenic dose-response assessment under consideration, which were assembled by the TCEQ and are considered below.

Comment 1:

EtO is a well-known human carcinogen. Children are particularly vulnerable to mutagenic carcinogens and exposure during early life further increases the likelihood of developing cancer.

Response:

Indeed, the TCEQ's assessment treats EtO as a mutagen that is *carcinogenic to humans* (i.e., a known human carcinogen). Consistent with USEPA guidance, the TCEQ uses age-dependent adjustment factors (ADAFs) to account for the potentially increased susceptibility of children. Additionally, the TCEQ uses the 95% UCL to err on the side of safety and help ensure that vulnerable people and communities are protected against the potential carcinogenic effects of EtO in ambient air (although normal endogenous doses produced within the human body are significantly higher than those resulting from typical ambient air concentrations).

Comment 2:

Due to the serious cancer risk from exposure to EtO, in 2016, USEPA completed a robust, scientific, and peer-reviewed process to protect public health and finalize a toxicity factor for EtO of 0.005 per $\mu g/m^3$, or 0.0091 per ppb. USEPA demonstrated that breathing just 0.0002 of a microgram of ethylene oxide per cubic meter of air, or 0.0001 parts ethylene oxide per billion parts air over a lifetime increases cancer risk by 1-in-1 million. EPA's cancer risk factor is "based on strong epidemiological evidence supplemented by other lines of evidence" on lymphoid and breast cancers, and accounts for the increased risk to children through applying age-adjustment factors. USEPA has "relatively high" confidence in its factor as an estimate of the upper bound on risk from lifetime exposure, with "particularly high" confidence for its breast cancer component.

Response:

The TCEQ has scientifically demonstrated in this DSD that USEPA's selected model assessment statistically significantly overestimates risk for workers in the underlying key study, whereas the TCEQ's model accurately predicts risk. Furthermore, USEPA has not demonstrated that breathing just 0.0002 $\mu g/m^3$ (or 0.0001 ppb) over a lifetime increases cancer risk by 1-in-1 million. This is a theoretical risk estimate based on an atypical dose-response model that was

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selected using incorrect p-values and AIC values (see Appendices 3 and 5 of the DSD). As discussed in other comment responses, the TCEQ also uses ADAFs to account for the potentially increased susceptibility of children. While USEPA had high confidence in its URF, the TCEQ has demonstrated it to overestimate risk for both workers in the underlying key study and the US general population. These demonstrations in conjunction with other information, particularly the USEPA-acknowledged lack of MOA information to justify their unconventional overall supra-linear dose response model, significantly diminished the TCEQ's confidence in USEPA's dose-response assessment choices and URF and prompted the TCEQ to conduct its own dose-response assessment. See Appendix 6 of the revised DSD, which is new, for a detailed discussion on the evidence for breast cancer as a candidate endpoint.

Comment 3:

Since USEPA finalized the IRIS factor for EtO in 2016, TCEQ has made every effort to ignore or discredit it. TCEQ appears to favor industry in pushing weaker and weaker factors that fail to protect Texas communities - especially those already overburdened by toxic air pollution, and particularly women and children.

Response:

In the 2019 EtO DSD, the TCEQ documents the completion of an objective and thorough scientific evaluation of USEPA's assessment, which concluded that the USEPA's URF is not scientifically sound. For example, reality checks conducted by the TCEQ on risk in the key worker population and the general population could have supported USEPA's URF (the outcome was unknown), but simply did not. The USEPA's assessment must stand or fall on the objective evaluation of its merit, and the TCEQ has thoroughly documented its objective evaluation of same. The TCEQ's goal is to have the most scientifically defensible URF possible, and the TCEQ will follow wherever the scientific weight-of-evidence leads. The TCEQ's only effort and motivation is to be on the side of the best available science in this case and in all the agency does to protect public health and the environment. The TCEQ's EtO URF is protective for all people, including sensitive populations, wherever they reside in Texas.

Comment 4:

In March 2017, TCEQ adopted a risk factor of 0.000076 per $\mu g/m^3$ - 65 times weaker than the 2016 IRIS factor. In a three-page document announcing the 2017 factor (that only became available after a Public Information Request to TCEQ by Sierra Club), TCEQ considered and rejected two studies - just as EPA had done: Valdez-Flores et al. (2010) and Kirman et al. (2004). TCEQ rejected Valdez-Flores et al. (2010) because it failed to capture cancer risk for all but the highest exposure groups, and rejected Kirman et al. (2004) for various reasons, including its failure to consider breast cancer. The value selected in 2017 by TCEQ was actually part of USEPA's IRIS assessment but based just on rodent data (as opposed to the final 2016 IRIS risk factor which was based on the entire systematic review, including human data). TCEQ selected the 2017 factor due to the "high quality" of the rodent study, without providing a reasoned basis then for rejecting the remaining conclusions of USEPA's determination or the final 2016 IRIS factor.

Subsequently, in August 2017, without reference to TCEQ's March 2017 factor or conclusions, without any explanation, and without any apparent reason, TCEQ began to create a new factor that was even weaker. TCEQ publicized a request for information on its website, and the American Chemistry Council (ACC) submitted comments urging TCEQ to develop a weaker factor, like that of Valdez-Flores et al. (2010). TCEQ was close to releasing its proposed assessment in June 2018 when it met with the ACC.

Response:

The TCEQ performs an expedited review of USEPA IRIS and other toxicity factors when they are promulgated and may adopt them or an alternative value on an interim basis. More specifically, the TCEQ adopted an animal-based URF for EtO on an interim basis (recorded with a 1.5-page document) until a thorough dose-response assessment could be conducted under the extensive TCEQ toxicity factor guidelines and a detailed discussion of scientific rationale could be documented in the DSD. A much longer period of time is required for a systematic review of the peer-reviewed literature and for producing detailed DSD documentation, including a thorough evaluation of the USEPA's selected model and URF in this case. A request for EtO information was put out by TCEQ later in the year following the interim value derivation, as it was obvious to TCEQ that a more detailed review was in order. In response to the TCEQ request for EtO information, *all* interested parties (e.g., industry, academia, NGOs, private citizens) were invited to submit whatever they believed to be relevant information (e.g., studies, presentations) for the agency's evaluation, to be considered along with the information that the TCEQ identified through an extensive systematic review process for EtO. In June 2018, the TCEQ was still in the early stages of conducting our systematic review and none of the extensive analyses had been conducted.

Comment 5:

Just as instructed by the ACC, and despite TCEQ's own March 2017 conclusions, TCEQ (1) selected Valdez-Flores et al. (2010) as its key study; (2) incorporated the unpublished, not peer-reviewed update, Bender et al., with the help of Dr. Valdez-Flores, an EtO and sterilant trade group consultant; (3) ignored breast cancer, even though TCEQ admits that breast cancer incidence data supports a much stronger toxicity factor, because the "results [were] not consistent with TCEQ conclusions;" and (4) ignored what it described as endogenous exposure. Neither TCEQ's proposed DSD, Dr. Valdez-Flores's analyses, nor the underlying study Bender et al. have undergone any independent peer review. And, the study measuring endogenous exposure suggests normal, endogenous levels of EtO more than 65 times higher than the equivalent exogenous exposure of living directly next to a sterilizer facility, like Willowbrook or Burr Ridge.

Response:

The TCEQ's derivation of toxicity factors is instructed by the best available science and risk assessment methodologies, as documented in the proposed EtO DSD. The revised DSD and accompanying analyses will be undergoing peer review in the first quarter of 2020. To the individual points in this comment:

1) The TCEQ conducted a systematic review of the literature (documented in Appendix 1 of the DSD), and based on this selected the methods used by Valdez-Flores et al. (2010) as the most scientifically valid. However, the agency did not use the results proposed by Valdez-Flores et al. (2010) to derive the final URF, but rather used their method with alternative model parameters that were dictated by the TCEQ.

2) Dr. Valdez-Flores is a Professor at Texas A&M University and has conducted excellent statistical work (as directed) for the TCEQ previously. The agency has found his expertise to be outstanding and his integrity to be beyond reproach. The TCEQ did consider the updated UCC cohort data (Bender et al.); however, data from this cohort ultimately received a zero weight for the final URF because this dataset was substantially smaller than the NIOSH cohort.

3) The TCEQ evaluated breast cancer as a candidate cancer endpoint. USEPA's assessment, however, is driven by lymphoid cancer as the primary contributor to the URF. Subsequent to USEPA's 2016 assessment and TCEQ's systematic review of the peer-reviewed literature for EtO, recent meta-analyses of available studies have been published (Marsh et al. 2019, Vincent et al. 2019). These new meta-analyses included Steenland et al. (2003, 2004) and the smaller Mikoczy et al. (2011) study cited by USEPA (2016), as well as other studies, and reported breast cancer meta-RRs of 0.97 (0.80, 1.18) (Marsh et al. 2019) and 0.92 (0.84, 1.02) (Vincent et al. 2019). The Marsh et al. study concluded [*emphasis added*], "Evaluations of workers exposed during sterilization processes *do not support the conclusion that EO exposure is associated with an increased risk of breast cancer*." Similarly, the Vincent et al. (2019) study concluded, "Higher quality epidemiological studies demonstrated no increased risk of breast cancers." In addition to evaluating epidemiological evidence, Vincent et al. (2019) evaluated animal study results and concluded that they provide no strong indication that EtO causes mammary tumors. These recent meta-analyses and other information (IARC 2019) further support TCEQ's decision not to base the URF on breast cancer. Human data are by far the most relevant for derivation of human toxicity factors, and the human data themselves are inconclusive (as acknowledged by USEPA 2016). The weight of evidence for EtO-induced breast cancer is now discussed in a new appendix (Appendix 6) to the revised DSD.

4) The TCEQ extensively evaluated endogenous EtO exposure and used it for context in the DSD. For example, the endogenous data show that normal endogenous doses are orders of magnitude higher than that associated with USEPA's maximum acceptable risk-based air concentration. The TCEQ's initially-proposed long-term ESL (4 ppb) and new revised, ADAF-adjusted ESL (2.4 ppb; adjusted per equation 5-17 of TCEQ 2015) correspond to internal doses within the range of EtO doses normal produced endogenously in the human body.

Comment 6:

The results of TCEQ's assessment appear predetermined. Industry wanted a weaker factor, and TCEQ is giving it to them. Far from rational and reasoned decision-making, TCEQ's attack on IRIS was and is merely a means to that end. For example, TCEQ had apparently chosen its factor before it decided how far off to allege the IRIS factor was, at one point claiming the IRIS factor overestimated 1,179 deaths, later revised to just 141. TCEQ still has refused to release the studies and calculations it relies on in its proposed DSD, such as Bender et al. Commenters and the public still have not been provided a reasonable opportunity to evaluate the basis for TCEQ's proposed DSD.

Response:

The TCEQ has conducted extensive analyses of multiple lines of evidence, each of which could have either supported a given approach for the EtO dose-response assessment, or not. The results of each set of analyses have guided TCEQ's decisions and approach, as is documented in the DSD. The proposed DSD does not indicate that the IRIS factor overestimates by 1,179 deaths because that figure was an interim placeholder figure in early draft documents while information about the relationship between the upper and lower splines of their two-piece spline model could be located in USEPA's documentation. The proposed TCEQ URF does not and would not rely on the unpublished Bender et al. study (which will likely be published in the peer-reviewed literature in 2020). TCEQ initially provided a 45-day review period, which was extended by an additional 45 days when Sierra Club requested more time. The TCEQ thinks that the 90-day public comment period on the DSD provided interested knowledgeable parties with sufficient time to formulate scientific comments, based on the extensive scientific comments received by the TCEQ.

As part of the proposed DSD, the TCEQ commissioned outside research on the subject. This research was conducted by a professor at Texas A&M University (Dr. Ciriaco Valdez-Flores), who had previously obtained access to and extensively analyzed NIOSH data that was not readily available to TCEQ researchers, but had also been analyzed by USEPA and others (e.g., Steenland et al. 2004). Much of this information consisted of Personal Identifiable Information (PII) of a large number of research subjects. PII is information that could potentially identify a specific person, including such sensitive information as birth dates, home addresses, phone numbers, and assorted other information (e.g., death dates, gender, race, job history, cause of death). This type of information is protected by law in Texas and cannot be released without specific reasons that do not exist here. TCEQ is serious about protecting PII. Consequently, TCEQ does not have the data to release to the public in this case, although USEPA and others have analyzed the same data (see results in USEPA 2016) using the model selected by TCEQ (Cox proportional hazards model) and Sierra Club can request access to the data from NIOSH. Indeed, USEPA recently proposed a rule that would require the release of PII used in scientific research such as at issue here. Sierra Club submitted comments on that rulemaking objecting that the release of such information was inadvisable, as it could potentially cause harm to those involved in such research. Thus, even if TCEQ had the data in its possession, the agency's

refusal to release such data to Sierra Club in this case would be both required by law and the appropriate way to protect those who participate as subjects in necessary scientific research.

Comment 7:

TCEQ's proposed value is not peer reviewed, ignores breast cancer risk and ignores increased risk to children. It also treats EtO that people breathe as equivalent to endogenous exposure that TCEQ argues can be ignored.

Response:

The TCEQ assessment has undergone internal peer review and public comment but will also undergo an external peer review in the first quarter of 2020. See the response to Comment #5 and Appendix 6 of the revised DSD concerning how the agency has evaluated breast cancer as a candidate cancer endpoint. The TCEQ has used ADAFs to account for the potentially increased susceptibility of children. Lastly, as discussed in response to Comment #5, the TCEQ carefully considers and quantifies the risk posed by endogenous EtO and uses it to provide context for the EtO URF. Furthermore, the dose-response for workers exposed to EtO in the cohort studies inherently captures endogenous EtO risk (a contributor to background) as the workers were also producing EtO endogenously in addition to being exposed to exogenous EtO via the inhalation pathway.

Comment 8:

TCEQ may not finalize the proposed DSD because it has not satisfied the rulemaking requirements of Texas law. TCEQ's proposed DSD is part of an unlawful rulemaking. TCEQ's proposed DSD is a major environmental rule, requiring an in-depth regulatory analysis and impacts.

Response:

TCEQ ESL values are not developed via rulemaking. ESLs are not rules, and the process of developing an ESL is not a rulemaking action subject to the Texas Administrative Procedures Act (APA); the ESL is also not a major environmental rule. TCEQ has been developing and using ESLs for decades, and that process has never been subject to the requirements of the Texas APA. The fact that TCEQ has solicited comments on the proposed ESLs and sought input from the public does not change the essential nature of the proposed ESLs. Seeking further information and public input when developing guidance ensures that TCEQ has the broadest possible set of information to use when evaluating possible changes to the proposed guidance.

ESLs are constituent-specific guideline concentrations used in TCEQ's effects evaluation of constituent concentrations in air. These guidelines are derived by the Toxicology, Risk Assessment, and Research Division and are based on a constituent's potential to cause adverse health effects, odor nuisances, and/or effects on vegetation. Health-based screening levels are set to protect the general public, including sensitive subgroups such as children, the elderly, or people with existing respiratory conditions. They are intended to be an aid in the process of reviewing permit applications for air quality permits. The use of an ESL simply assists the

permitting authority in determining if a more extensive review of potential health effects is necessary for particular proposed changes that may result in emissions of air contaminants. ESLs, expressed in terms of microgram per cubic meter ($\mu g/m^3$) or parts per billion by volume (ppb_v) in air, are used to evaluate the potential for effects to occur as a result of exposure to concentrations of constituents in the air. Again, ESLs are based on data concerning health effects, odor/nuisance potential, and/or effects on vegetation. They are not ambient air standards.

Lastly, the proposed guidelines will only potentially affect a small subset of plants in Texas. A search of TCEQ's emissions inventory shows between 27 and 50 plants that might potentially be subject to the guidance of the Ethylene Oxide ESL, of which only 11 had reportable quantities of emissions in 2017. The ESL guidance would only affect these plants should they make permitting changes to the facilities that produce or handle ethylene oxide after the proposed guidance is finalized.

Comment 9:

TCEQ guidelines and regulations require TCEQ to adopt the IRIS cancer risk factor for EtO. TCEQ guidelines and regulations direct use of the IRIS factor and TCEQ has given no valid basis for rejecting the 2016 IRIS factor. TCEQ cannot finalize the proposed cancer risk factor because TCEQ has not provided any valid reason to develop its own cancer risk factor.

Response:

TCEQ guidelines and regulations do not require TCEQ to adopt the IRIS cancer factor for EtO. The TCEQ has evaluated the USEPA assessment extensively and has determined, as documented in the DSD, that the USEPA URF is scientifically unsupportable; a valid basis for its rejection. For example, neither agency can cite MOA information for EtO supporting USEPA's overall supra-linear dose-response model, alone a valid reason under TCEQ guidelines for rejecting the model (other considerations are also detailed in the DSD).

Comment 10:

TCEQ claims that it has performed a "reality check" of the exposure-response model selected by USEPA and found that the observed cancer deaths would be higher if USEPA's value were accurate. Its argument has no rational basis in the record and does not provide a reasoned ground to refuse to apply the IRIS value.

Response:

A demonstration that a dose-response model is not predictive of the underlying data is a rational reason for rejection of that model. As documented in the DSD, the TCEQ also found that the USEPA URF is over-predictive for lymphoid cancer in the general population based on data about background levels of EtO. The primary deterministic factor for the rejection of USEPA's model under TCEQ guidelines is the USEPA-acknowledged lack of MOA data for EtO supporting an overall supra-linear dose-response curve. The scientific burden of proof for choosing a supra-linear dose-response is robust MOA data (including data over the endogenous

range where both agencies expect sublinearity). This burden of proof was not met. Relevant considerations (including MOA) support TCEQ's approach as opposed to USEPA's, as comprehensively documented in the DSD.

Comment 11:

TCEQ must use a supra-linear modeling approach; its discussion of "endogenous exposure" does not justify using, in effect, a threshold approach. USEPA properly applied a supra-linear model to assess cancer risk from EtO. TCEQ proposes, however, that the carcinogenicity of EtO "is no more than linear, and arguably sublinear."

Response:

The scientific burden of proof for choosing a supra-linear dose-response is robust MOA data. The USEPA's 2016 EtO assessment stated, and TCEQ agrees, that "EPA considers it highly plausible that the dose-response relationship over the endogenous range is sublinear (e.g., that the baseline levels of DNA repair enzymes and other protective systems evolved to deal with endogenous DNA damage would work more effectively for lower levels of endogenous adducts), that is, that the slope of the dose-response relationship for risk per adduct would increase as the level of endogenous adducts increases." This information does not support a supra-linear dose-response for air EtO concentrations that are in the range of endogenous concentrations (i.e. typical ambient air EtO concentrations). The TCEQ has demonstrated USEPA's supra-linear modeling approach to be: (1) over-predictive for the key cohort lymphoid cancer data as well as the general population; (2) unjustified due to the lack of MOA data to adequately support it under TCEQ guidelines (USEPA also acknowledges the lack of MOA data to justify their model); and (3) despite the above, applied by USEPA over the very range where both agencies would expect a sublinear dose-response. These considerations are important since the occupational cohort data (used to derive the dose-response model) are at daily exposures 15,000-32,000,000 times higher than typical environmental levels and cannot inform the shape of the dose-response at the environmental levels of interest (i.e., those being extrapolated to). While the TCEQ model itself can in theory be characterized as sublinear in nature, examination of the figures in the DSD (Appendix 5 of the revised DSD) show that the dose-response from the Cox proportional hazards model is actually indistinguishable from linear across doses of interest (i.e., the modeled dose-response is a straight line) and has no associated threshold. The Cox proportional hazards model is a standard dose-response model used throughout risk assessment (e.g., Steenland et al. papers, publications supporting USEPA NAAQS dose-response assessments, USEPA 2016).

Comment 12:

TCEQ's consideration of what it calls "endogenous exposure" levels of EtO creates in effect a threshold of exogenous exposure through inhalation of EtO. TCEQ disregards inhaled pollution and cancer risk resulting from that exposure at levels below that threshold. Specifically, TCEQ claims that EtO's effects "would be buffered by cellular repair mechanisms," "at doses near the endogenous range." TCEQ does not recognize that "any dose, no matter how small, increases the probability of causing an effect."

Response:

TCEQ's dose-response model is not a threshold model, but rather predicts excess risk all the way down to zero dose, recognizing that "any dose, no matter how small, increases the probability of causing an effect." The brief discussion of biological protective mechanisms in the DSD does not change that or affect TCEQ's rejection of an overall supra-linear model based on the absence of MOA data to adequately justify such a model. The discussion of endogenous EtO does demonstrate that relatively speaking, the internal exposures resulting from USEPA's risk-based values are orders of magnitude below normal endogenous doses and are therefore of implausible biological significance. To recognize this does not create a threshold in the TCEQ's dose-response assessment.

Comment 13:

TCEQ's model was considered by USEPA to have poor fit.

Response:

USEPA did not properly calculate model fit criteria (see Appendix 4 of the revised DSD). Briefly, USEPA (2016) did not account for statistically estimating the optimized knot value, making the degrees of freedom (*df*) inappropriately reduced for the spline models, which resulted in: (1) inappropriately decreased p-values for adequate statistical fit by spline models, incorrectly implying that the linear two-piece spline model for lymphoid cancer fit the data statistically better than other models; and (2) inappropriately decreased Akaike information criteria (AIC) for spline models, which did not allow for an appropriate comparison of model fit among models for lymphoid cancer (or breast cancer incidence). The knot values, being statistically estimated/optimized based on the NIOSH data, did not conform to the USEPA SAB's recommendation of potentially fixing some model parameters *not estimated from the data* in the interest of parsimony (see p. 12 of SAB 2015). The TCEQ presents corrected p-values for lymphoid cancer models (see Table 38 of the DSD), which indicate that the two-piece spline models do not explain the variability in the data statistically significantly better than the null model (zero slope) or the standard Cox regression model used by TCEQ. Additionally, the AIC values between most of the models are very similar (see Appendix 4 of the revised DSD).

Comment 14:

TCEQ has not cited and cannot point to any evidence demonstrating that the human body can negate cancer risk from inhaling any threshold level of EtO through a process of "cellular repair." In assuming endogenous levels are safe, TCEQ fails to consider that inhaling EtO results in exposure above and beyond any background endogenous exposure. The endogenous levels and background ambient concentrations of EtO likely contribute to the high background rates for both lymphatic and breast cancer incidence in the general population.

Response:

Please refer to TCEQ's response to Comment #12 above, which addresses the TCEQ's non-threshold dose-response model. In addition, the TCEQ does not consider endogenous levels as safe, just the opposite: the TCEQ quantifies risk to endogenous levels, and the dose-

response/URF based on the NIOSH cohort quantifies excess risk above and beyond background endogenous exposure. The TCEQ agrees that endogenous levels and background ambient air concentrations of EtO contribute to background EtO exposure for the general population, but TCEQ has also demonstrated that USEPA's dose-response model overestimates the general population background risk for lymphoid cancer and is therefore implausible, while results based on TCEQ's URF are plausible. The TCEQ assessment does not set a threshold or assume any amount of EtO, endogenous or exogenous, is without risk. In fact, it quantifies the risks from both.

Comment 15:

TCEQ relies on Kirman and Hays (2017) in regard to normal endogenous levels of EtO.

Response:

The TCEQ does use Kirman and Hayes (2017) to provide information about endogenous levels of EtO. These data are used to put the URF in context, and are not deterministic as to the rejection of USEPA's overall supra-linear dose-response model. The TCEQ will thoroughly consider any data or analyses that are provided that confirm, expand on, or rebut the peer-reviewed study of Kirman and Hays (2017). At the same time, the TCEQ notes that the reported mean human background endogenous HEV level of 21.1 pmol/g Hb appears reasonable given background HEV levels in control rats (≈42-50 pmol/g Hb) and mice (≈58-100 pmol/g Hb) (Walker et al. 1993, 2000).

Comment 16:

TCEQ acknowledges that children are more susceptible to the mutagenic effects of EtO, and claims to "include adjustments for [EPA (2005b) age-dependent adjustment factors (ADAFs)] using the approach described in Sielken and Valdez-Flores (2009)." However, USEPA found this study "misinterpreted the application of the [ADAFs] such that, even though they purported to apply the factors, this application had no impact on the risk estimate. TCEQ should apply a factor that is more protective than the 2016 IRIS value to account for the additional cancer risk a person faces over their lifetime due to cross-placental carcinogenic exposure during early fetal development. In 2009, California's Office of Environmental Health Hazard Assessment (OEHHA) published a review of the scientific literature surrounding prenatal susceptibility, and developed procedures for exposure assessment during fetal development. OEHHA specifically discusses the use of a 10X adjustment factor for cancer risk to account for prenatal (third trimester) to age 2 exposures. TCEQ should use the approach described by OEHHA to properly account for the effects of *in utero* exposure.

Response:

The TCEQ guidelines incorporate USEPA guidance on ADAFs, but not the referenced 10-fold OEHHA adjustment that USEPA ADAF guidance does not include. The TCEQ DSD now calculates the ADAF-adjusted ESL consistent with equation 5-17 of the TCEQ guidelines (TCEQ 2015), rounding it to two significant figures to produce an ESL of 2.4 ppb. This rounded value would be

insensitive to an additional 10-fold factor for the third trimester (i.e., with a 10-fold ADAF for *in utero* exposure, equation 5-17 would be 5.9E-06/URF = 5.9E-06/2.5E-06 per ppb = 2.36 ppb).

Comment 17:

TCEQ must consider breast cancer risk. TCEQ's proposed factor is invalid and unlawful because it fails to consider risks to women.

Response:

Please refer to the TCEQ's response to Comment #5 in regard to including breast cancer as an endpoint in this evaluation. The weight of evidence for EtO-induced breast cancer is now discussed in a new appendix to the revised DSD (Appendix 6).

In addition, the lymphoid cancer estimate is shown to be protective for women, because the lymphoid cancer effects in the NIOSH cohort (which included both male and female workers) were weaker in women than in men. The dose-response assessment evaluates lymphoid cancer risk to males and females combined as well as males alone. Analyses with both males and females combined compared to results based on males alone show that use of risk results based on males alone to predict lymphoid cancer in females generates a lower ESL and so is conservative. Thus, the long-term ESL and its associated URF used to evaluate lymphoid cancer risk in women will be protective for lymphoid cancer risk in women.

Comment 18:

TCEQ must consider cancer incidence, not only cancer mortality. TCEQ must consider a sufficient lifetime period of exposure of 85 years instead of 70 years. TCEQ must consider the disproportionate exposure of people of color and communities with multiple sources of EtO. TCEQ must follow all applicable civil rights law in this proceeding and all other actions. TCEQ has previously faced a complaint (No. 01R-00-R6) that it did not follow applicable requirements of Title VI of the Civil Rights Act, 42 U.S.C. § 2000d et seq., including public participation and calculations, in regard to an air permit modification. TCEQ entered into an agreement and under that agreement (see Section III), EPA is now requiring, and TCEQ has agreed, to hold at least two accessible community meetings to discuss opportunities for public involvement, with advance notice, accessibility, consideration of multilingual information and interpretation services for that process. TCEQ must ensure at least that it grants a public hearing and supports a similar level of public participation in this proceeding because TCEQ is proposing to use the ethylene oxide cancer risk factor for permitting proceedings. Failure to provide a meaningful opportunity for public participation here would contravene Title VI.

Response:

Partly in consideration of the issue of mortality versus incidence, the TCEQ utilized the 95% UCL on the slope, which is common in dose-response assessment. The TCEQ toxicity factor guidelines use the default exposure duration of 70 years, which is standard practice in risk assessment and consistent with TCEQ guidelines (TCEQ 2015). The long-term ESL applies equally for all people regardless of race, ethnicity, socioeconomic status, etc. and assumes 24

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hours/day, 365 days/year exposure to be protective of even those most exposed to ambient EtO air concentrations.

The agreement referenced by the comment concerned a complaint from 2001 that specifically concerned changes at the ExxonMobil refinery in Beaumont, Texas. Details of the complaint concerned TCEQ public participation process in regard to the air quality permitting process. Specifically, USEPA accepted two parts of the complaint relating to the approval of a permit amendment without allowing the public an opportunity to participate in a contested case hearing, and approval of an air quality permit amendment with an increase in emissions in an area that already had problems with hydrogen sulfide and disparate adverse impact of a predominantly African American community. A global settlement between USEPA and TCEQ in July 2003 addressed the public participation allegation, detailing the changes to TCEQ's public participation requirements for permitting procedures. In 2017, TCEQ and USEPA resumed discussions, which resulted in the final agreement cited here by the commenter. That agreement required TCEQ to hold at least two public meetings in Beaumont to discuss both the public participation process for permitting and air quality monitoring issues in the area. These meetings were held on February 18, 2018 and April 26, 2018, and USEPA acknowledged on May 23, 2018 that TCEQ had met the requirements of the 2017 Informal Resolution.

Neither parts of the complaint accepted by USEPA have direct relevance to the current proposal, which is not a permitting action. The TCEQ is committed to protecting the health of the citizens of Texas and its environment. Discrimination on the basis of race, color, national origin, sex, or disability in the administration of TCEQ programs or activities is not allowed as required by federal and state laws and regulations. Although there are no TCEQ rules addressing environmental equity issues such as the location of permitted facilities in areas with minority and low-income populations, disparate exposures of pollutants to minority and low-income populations, or the disparate economic, environmental, and health effect on minority and low-income populations, the TCEQ has made a strong policy commitment to address environmental equity. The Office of the Chief Clerk works to help citizens and neighborhood groups participate in the regulatory process to ensure that agency programs that may affect human health or the environment operate without discrimination and to make sure that citizens' concerns are considered thoroughly and are handled in a way that is fair to all. Those interested may contact the Office of the Chief Clerk at 512-239-3300 for further information. More information on Environmental Equity may be found on the TCEQ website: https://www.tceq.texas.gov/agency/hearings/envequ.html.

Comment 19:

TCEQ must rely on scientifically sound, independent, peer-reviewed and published studies which the public can reasonably evaluate. TCEQ relied heavily on a dataset—the UCC cohort—for the derivation of unit risk estimates. TCEQ has thus far declined to share this study with the public.

Response:

The published UCC study was evaluated as part of TCEQ's thorough systematic review and analytical process. However, both the published UCC study and the currently unpublished update received zero weight in selection of the final URF, which was based exclusively on the NIOSH cohort. Please see the response to Comment #6 above in regard to the release of study information that is PII.

Comment 20:

IRIS follows the USEPA's Office of the Science Advisor's Principles of Scientific Integrity. These principles "ensure scientific integrity throughout the USEPA and promote scientific and ethical standards" throughout agency actions. Regarding conflicts of interest, "the Principles of Scientific Integrity sets forth the Agency's commitment to conducting science objectively, presenting results fairly and accurately, and avoiding conflicts of interest." USEPA's IRIS value follows these principles but thus far TCEQ's proposal does not.

Response

TCEQ maintains the highest scientific and ethical standards.

Comment 21:

TCEQ's proposed DSD must be independently, externally peer reviewed. TCEQ continues to withhold from the public the very studies and calculations it relies on and directly cites. At every step, TCEQ has sided with industry.

Response

The TCEQ is conducting an external peer review for our draft EtO DSD in the first quarter of 2020. All studies relied on for the long-term ESL/URF are available to the public via the peer-reviewed literature, except for the update of the UCC cohort, which as noted above was not used to derive the URF. All methods and associated results are reported in the DSD. Lastly and importantly, the TCEQ sides with the best science available, regardless of who may stand with the agency in favor of the best science in any given circumstance. The agency follows wherever the weight of scientific evidence leads.

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Comments from Dr. Kyle Steenland

Dr. Steenland submitted several comments (see below). Dr. Steenland, along with Dr. Stayner and other NIOSH colleagues, conducted the original epidemiologic studies providing the key data investigating the association of EtO with lymphoid and breast cancer and has conducted several risk assessments for EtO and cancer, some under contract with USEPA in support of their 2016 risk assessment.

Comment 1:

A choice not to include risks to women from breast cancer in the quantitative assessment is an error. NIOSH conducted a breast cancer incidence study which clearly showed a significant positive exposure response for EtO, using an appropriate lag. Several smaller studies have supported this finding. Incidence is preferable to mortality for many outcomes, including breast cancer and hematopoetic cancer. TCEQ is choosing to simply ignore the breast cancer findings. I note that breast cancer incidence data also support a supra-linear exposure-response model, and that the incidence data are supported by breast cancer mortality findings.

Response:

The TCEQ evaluated breast cancer as a candidate cancer endpoint. USEPA's assessment, however, is driven by lymphoid cancer as the primary contributor to the URF. Subsequent to USEPA's 2016 assessment and TCEQ's systematic review of the peer-reviewed literature for EtO, recent meta-analyses of available studies have been published (Marsh et al. 2019, Vincent et al. 2019). These new meta-analyses included Steenland et al. (2003, 2004) and the smaller Mikoczy et al. (2011) study cited by USEPA (2016), as well as other studies, and reported breast cancer meta-RRs of 0.97 (0.80, 1.18) (Marsh et al. 2019) and 0.92 (0.84, 1.02) (Vincent et al. 2019). The Marsh et al. study concluded [*emphasis added*], "Evaluations of workers exposed during sterilization processes *do not support the conclusion that EO exposure is associated with an increased risk of breast cancer*." Similarly, the Vincent et al. (2019) study concluded, "Higher quality epidemiological studies demonstrated no increased risk of breast cancers." In addition to evaluating epidemiological evidence, Vincent et al. (2019) also evaluated animal study results and concluded that they provide no strong indication that EtO causes mammary tumors. These recent meta-analyses and other information (IARC 2019) further support TCEQ's decision not to base the URF on breast cancer. Human data are by far the most relevant for derivation of human toxicity factors, and the human data themselves are inconclusive (as acknowledged by USEPA 2016). The weight of evidence for EtO-induced breast cancer is now discussed in a new appendix (Appendix 6) to the revised DSD.

Simply for additional perspective, the cumulative exposure associated with a lifetime of environmental exposure to the revised long-term ESL of 2.4 ppb (≈60 ppm × days) is around 250 times less than the lowest cumulative exposure levels associated with a statistical increase in breast cancer incidence in the NIOSH cohort (>14,620 ppm-days, 15-year lagged exposure; see Table 6 of the revised DSD). This statistical increase in breast cancer incidence only occurred in the highest (5th) exposure group. If the underlying dose-response for EtO-induced breast cancer in humans were supra-linear, statistically significant increases in critical cancer

endpoints would be expected beginning in the lower occupational exposure groups. That is, if exogenous EtO had a steep dose-response slope (i.e., were a potent carcinogen) in the true low-dose region, such as near the range of endogenous levels, then statistically increased breast cancer rates would be expected at the "low" worker doses evaluated for the large NIOSH cohort, particularly considering that even "low" historical worker exposures have been significant.

Comment 2:

A choice to use the linear model among a variety of models for lymphoid cancer mortality that were previously examined by USEPA, even though this model did not fit as well as the other models which show that the exposure-response is supra-linear, is a major error (e.g., the two piece spline and the log cumulative dose model, both of which showed good fit to the data, $p<0.05$, unlike the linear model, see Appendix D in the USEPA's risk assessment). The linear model results in much lower estimates of risk in the low dose region, which is the region of interest.

Response:

The TCEQ disagrees that use of "the linear model" for lymphoid cancer mortality is an error. The commenter indicates that the reason for this is that the supra-linear two-piece spline model and log cumulative model show good fit to the data whereas the linear model does not, citing USEPA (2016). However, the USEPA did not properly calculate model fit criteria (see Appendix 4 of the revised DSD). Briefly, USEPA (2016) did not account for statistically estimating the optimized knot value, making the degrees of freedom (*df*) inappropriately reduced for the spline models, which resulted in: (1) inappropriately decreased p-values for adequate statistical fit by spline models, incorrectly implying that the linear two-piece spline model for lymphoid cancer fit the data statistically better than other models; and (2) inappropriately decreased Akaike information criteria (AIC) for spline models, which did not allow for an appropriate comparison of model fit among models for lymphoid cancer (or breast cancer incidence). The knot values, being statistically estimated/optimized based on the NIOSH data, clearly did not conform to the USEPA SAB's recommendation of potentially fixing some model parameters *not estimated from the data* in the interest of parsimony (see p. 12 of SAB 2015). The TCEQ presents corrected p-values for lymphoid cancer models (see Table 38 of the DSD), which indicate that the two-piece spline models do not explain the variability in the data statistically significantly better than the null model (zero slope) or the standard Cox regression model used by TCEQ. Additionally, the AIC values between most of the models are very similar (see Appendix 4 of the revised DSD). In addition, because the MOA data do not scientifically justify use of a supra-linear model (i.e., the steep lower-dose slope) for low-dose extrapolation (see Section 3.4.1.4.1 of the DSD), the two-piece spline models were not considered by the TCEQ for adoption; nor were other models that have an inherently supra-linear dose-response over the exposure range (i.e., log-linear or linear models with log cumulative exposure or with square-root transformation of cumulative exposure).

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Comment 3:

The TCEQ interpretation of data on protein adduct levels associated with EtO exposure is misleading. We don't know if endogenous (internal) levels of EtO contribute to background levels of cancer, but we do know that increasing them with exogenous (external) exposures leads to increased cancer. That is what is important. Furthermore, the animal (positive rat and mice studies) and mechanistic data (mutagenicity, effect on chromosomal aberrations) all support the positive human data. That combined evidence is what IARC has determined that EtO is a definite human carcinogen.

Response:

Consistent with the comment, the TCEQ's DSD adopts USEPA's/IARC's carcinogenic classification and treats EtO as a mutagen that is *carcinogenic to humans*. The TCEQ uses the data on protein adduct levels associated with EtO exposure to provide valuable context, although it is not deterministic in terms of the dose-response model selected. The endogenous EtO protein adduct data are a secondary consideration in the overall weight of evidence, with the primary consideration for TCEQ's selection of a standard dose-response model being driven by the mechanistic data that shows a standard mutagenic MOA that is not expected to cause a supra-linear dose-response. Even in the absence of data on EtO adduct background levels normally found in the population, TCEQ's model selection would not change. For example, since lymphoid cancer drove the TCEQ and the USEPA carcinogenic assessment, perhaps the most relevant mutagenicity data was that in the bone marrow of mice exposed to EtO by inhalation *in vivo* (Recio et al. 2004), which USEPA indicates is consistent with a linear dose-response (see C-17 of USEPA 2016).

The TCEQ's use of background/endogenous EtO adduct data is consistent with the USEPA using their URF to extrapolate to background endogenous doses and well below, and to USEPA's acknowledgement that endogenous EtO may contribute to background risk (pp. 4-95 to 4-96 of USEPA 2016), which makes sense for an endogenously-produced mutagen. Furthermore, in dose-response/risk assessment it is standard practice to consider equal internal doses as equipotent in producing both noncarcinogenic and carcinogenic effects (i.e., that equal internal doses of a chemical produce equivalent risk). This is scientifically reasonable, which is why it is standard practice, absent a scientifically robust demonstration that this standard assumption should not apply (e.g., mechanistic or toxicokinetic information). Thus, the standard risk assessment practice of considering equal internal doses as equipotent in producing carcinogenic effects underlies TCEQ's application of the USEPA and TCEQ URFs to internal endogenous doses of the same mutagenic chemical.

Regarding animal data, while laboratory animal data can help provide support, interspecies differences in carcinogenic responses such as tumor types and sensitivity are common, even between different rodent species (e.g., EtO-induced mammary tumors in mice but not rats). For example, IARC (2019) analyzed tumor site concordance using a dataset of the 111 distinct Group 1 (carcinogenic to humans) agents. Sixty agents had both a human tumor site and an animal tumor site identified and were used to evaluate concordance across 39 tumor sites in animals and humans (see Figures 21.1 and 21.2 of IARC 2019). Reported results show that

breast cancer, for example, is more frequently/commonly induced in laboratory animal species by these agents than in humans. More telling is that while there is 47% overlap between agents that cause lymphoid and hematopoietic cancers in humans and animals, there is only 20% overlap between agents that have been shown to cause breast cancer in humans and animals (Table 21.7 of IARC 2019). The IARC (2019) unanimous consensus statement was that *"At present, the state of the science does not support tumour site concordance as a general principle."*

Accordingly, animal data are not deterministic as to the sites of chemically-attributable carcinogenesis in humans; even more so when laboratory animal results are inconsistent (e.g., mammary tumors in mice but not rats) and the human database is relatively robust. For example, lung cancer was statistically increased in both male and female EtO-exposed mice at incidences of 53% and 45%, respectively (Table 3-3 in USEPA 2016), but is not a candidate endpoint in humans as data for this very strong carcinogenic response in mice is simply not predictive for humans (i.e., no interspecies site concordance; SMR of 1.05 (0.95, 1.17) in Table 1 of Steenland et al. 2004). Similarly, EtO statistically significantly increased brain tumors in rats of both sexes (Table 3-5 in USEPA 2016), but yet again, these results are not predictive for humans. In fact, brain cancer for the NIOSH cohort is statistically significantly decreased (i.e., SMR of 0.59 (0.36, 0.91) in Table 1 of Steenland et al. 2004), just the opposite of what the rat data would suggest. *Clearly, laboratory animal data for EtO-induced cancers cannot be relied upon to identity cancer sites in humans.*

Comment 4:

Extrapolating curve-fit model down to environmental dose. The Texas draft in contrast to the IRIS EtO assessment relies on direct extrapolation of the selected models from high to down to low (i.e., environmental) dose. This approach contrasts with the emphasis in USEPA's Cancer Guidelines on limiting use of curve fit dose response models to the observable range – to support estimation point of departure (BMDL) that can then be used for straight line extrapolation to low dose when appropriate (as for a direct acting mutagenic carcinogen like EtO). Choice of the better fitting model (the supra-linear model), then extrapolating down from a point of departure, is the best approach to EtO risk assessment.

Response:

TCEQ evaluated the lowest effective concentration (LEC) at an extra risk of 1 in a 100,000 consistent with USEPA cancer guidelines (2005) on the selection of a POD at the low-end of the observable range of exposures. Although for animal studies a typical POD is an extra risk of 0.10 because it corresponds to doses near the low-end of the doses, in epidemiological studies a lower level of risk needs to be used.

TCEQ used the standard Cox proportional hazards model to calculate the LEC for an extra risk of 1 in a 100,000 because the effective concentrations (ECs) corresponding to the same risk level are in the range of the observed data in the NIOSH study. That is, the EC for an extra risk of 1 in 100,000 of lymphoid cancer mortality in males is 9.67E-03 ppm for 70 years with an exposure lag of 15 years, which correspond to a cumulative

occupational exposure of 591 ppm-days. There are 7 male workers in the NIOSH cohort with cumulative exposures less than 591 ppm-days. That is, 25.9% of the male workers in the NIOSH cohort that died with lymphoid cancer were exposed to cumulative exposures of less than the EC for a 1 in a 100,000 excess risk. In contrast, the EC for 1 in 100 results in environmental concentrations corresponding to cumulative occupational exposures of 354,400 ppm-days, which exceeds the largest cumulative exposure of lymphoid male decedents in the NIOSH study.

Table 1 in TCEQ's response to ACC Comment #15 (above) shows the EC corresponding to different risk levels and the corresponding cumulative exposures with the number of lymphoid mortality cases of the male workers in the NIOSH study. The results in Table 1 show that the EC for an extra risk of 1 in a 100 is outside the range of cumulative exposures for the male lymphoid mortalities observed in the NIOSH study and in the upper 1% of cumulative exposures for all male workers. That is, all males that died with lymphoid cancers and more than 99% of all male workers had cumulative exposures less than EC (1/100). Thus, the NIOSH study does not support an extra risk of 1 in a 100 as a point of departure.

The EC for an extra risk of 1 in a 1,000 is a concentration that is in the high-end of cumulative exposures of male lymphoid mortalities observed in the NIOSH study. That is, 77.78% of all males that died with lymphoid cancers and 94.48% of all male workers had cumulative exposures less than the EC (1/1,000). Thus, a point of departure of 1 in 1,000 is at the higher-end of the cumulative exposures of male workers of the NIOSH study. The EC for an extra risk of 1 in 10,000 is a concentration that includes 48.15% of the decedent men with lymphoid cancer and 66.45% of all men in the NIOSH cohort with smaller cumulative exposures. The EC for an extra risk of 1 in 100,000 includes 25.93% of male lymphoid decedents and 30.17% of all males in the NIOSH study with smaller cumulative exposures. Thus, use of an extra risk of 1 in 100,000 is supported by the NIOSH observed data, being near the lower end of the observed range of cumulative exposures to EtO, and is consistent with USEPA and TCEQ guidelines (USEPA 2005a, TCEQ 2015) on the selection of a POD at the low-end of the observable range of exposures.

Based on Table 1 results, using either 1 in 10,000 or 1 in 100,000 extra risk PODs (as PODs in the range of the observed data and close to the low-end of the observable range) round to the same ADAF-unadjusted URF selected by the TCEQ (2.5E-06 per ppb). Looking at it from a different perspective, using the 1 in 10,000 excess risk LEC of 4.04E-02 ppm as the POD and linear extrapolation, the 1 in 100,000 air concentration (ADAF unadjusted) is still 4 ppb (i.e., 1E-05/2.47E-06 per ppb = 4.05 ppb).
This information has been added to Appendix 7 of the revised DSD.

Comment 5:

The draft's approach to comparing of observed and expected rates in the NIOSH cohort is incorrect. The use of national tumor rates to predict cancers in the NIOSH worker cohort is

inappropriate because it ignores the healthy worker effect, whereby working populations have lower mortality rates than the national population. The use of internal comparisons, as used by NIOSH investigators and USEPA risk assessors, avoids this issue, and is standard in occupational risk assessment. The models used by USEPA predict quite well the observed occurrence of cancer in the cohort.

Response:

The approach followed by TCEQ to compare the observed and expected number of deaths is correct, as it is the same approach used to calculate standard mortality ratios (SMRs). The approach for calculating SMRs is well established and has been used by regulatory agencies and researchers to compare mortality rates in target populations to mortality rates in reference populations. Thus, the approach used is well documented and has been extensively used.

Addressing the use of internal comparisons, the models used by TCEQ were also derived using internal comparisons and did not rely on the general U.S. population standard mortality rates. As indicated by Dr. Steenland, this is standard in exposure response models fit to epidemiological studies based on occupational cohorts.

To Dr. Steenland's assertion about the USEPA's model's predicting the observed occurrence of cancer in the cohort, the TCEQ cannot confirm this statement for two reasons. First, the USEPA's risk assessment document does not report any comparison between the number of cases in the NIOSH cohort and what is predicted by their models. Secondly, importantly the TCEQ did conduct the relevant analysis and found that if USEPA's chosen model were correct, then there should have been statistically significantly more lymphoid cancer mortalities in the NIOSH studies than the 53 that were actually observed, with statistically significant increases in every exposure quintile that in fact did not occur.

Lastly, we address the potential of the healthy worker effect to significantly affect TCEQ's calculations of model predictions (i.e., two-piece linear spline, Cox proportional hazards model) for the underlying lymphoid cancers in the NIOSH cohort (in Figures 8-12 and Appendix 2 of the revised DSD). Though opinions vary about using general population background rates for evaluating cause-specific mortality rates of occupational studies, it is standard practice/methodology in epidemiology studies to use general population background rates to evaluate the well-established and widely-accepted SMRs and SIRs because there is often no scientific evaluation of the magnitude of the healthy worker effect. In general, the healthy worker effect, if any, is cause-specific and cannot be ascertained very easily. However, Kirkeleit et al. (2013) researched the healthy worker effect in a large study of 366,114 randomly selected Norwegian workers and compared the incidence of numerous endpoints with the general population. Their findings indicate that there is potential for a healthy worker effect for some endpoints and increased incidence ("unhealthy" worker effect) for other endpoints. Kirkeleit et al. (2013) indicates that the healthy worker effect for mortality from cancer is minimal, if any, overall. Relevant to the EtO assessment, for lymphoid and hematopoietic cancer incidence Kirkeleit et al. (2013) did not find a healthy worker effect, with SIRs and 95% confidence intervals of 0.97 (0.90, 1.03) and 1.09 (0.92, 1.27) for male and female workers, respectively.

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The lack of a healthy worker effect was also true for breast cancer with an SIR and 95% confidence interval of 1.02 (0.95, 1.09).

The SMRs for the unexposed individuals in the NIOSH study indicate that the lymphoid mortality rate in unexposed male and female workers in the NIOSH study are not statistically significantly different from the lymphoid mortality rate of the general U.S. population. A footnote to Table 32 in the proposed TCEQ DSD states "Quintile 1 is the control (unexposed lagged-out) group with 9 lymphoid cancer mortalities observed and 11.5 mortalities predicted by all models with a 95% confidence interval of (6.0 and 25.2), which includes the 9 lymphoid cancer deaths." This confidence interval indicates that the observed 9 lymphoid cancer deaths in the unexposed male and female workers of the NIOSH cohort is consistent with the expected number of lymphoid cancer deaths in the general U.S. population during the same period of time after accounting for age, sex, and calendar year. Expressed in terms of SMRs, the SMR for lymphoid cancer deaths in the unexposed male and female NIOSH workers is equal to 0.78 (9/11.5) with a 95% confidence interval (CI) equal to (0.36, 1.50). The 95% CI on the SMR for unexposed workers includes the value of one, which indicates that the mortality rate in the unexposed workers in the NIOSH study and the U.S. population mortality rate are not statistically significantly different at the 5% significance level (p-value of 0.29). Similar results are obtained for the male NIOSH workers that drive lymphoid cancer risk: the SMR for lymphoid cancer deaths in the unexposed male NIOSH workers is equal to 1.03 (6/5.8) with a 95% CI of (0.38, 2.25). Thus, the lymphoid cancer mortality rate in unexposed male workers in the NIOSH cohort, the gender that drives the URF, is not statistically significantly different than that in the U.S. population (p-value of 0.64). In summary, these results demonstrate that there is no healthy worker effect for this critical endpoint in this key group (i.e., male workers, who drive lymphoid cancer risk in the cohort) or in males and female workers combined. These results based on the NIOSH cohort are consistent with the findings of Kirkeleit et al. (2013).

Despite the discussion above about the likely lack of a healthy worker effect for the endpoints of interest in the NIOSH study, to be thorough the TCEQ conducted a sensitivity analysis *assuming a healthy worker effect* for cancer mortality. Kirkeleit et al. (2013) estimates an overall cancer SMR of 0.85 and 0.84 for male and female workers, respectively. For purposes of a sensitivity analysis, the TCEQ assumed that these overall cancer SMRs apply to lymphoid cancers. That is, despite data to the contrary, the TCEQ sensitivity analysis assumes NIOSH workers were "healthier" than the general population as to cancer mortality by multiplying the U.S. male and female background hazard rates by 0.85 and 0.84, respectively, to account for the assumed healthy worker effect. *The results did not change significantly.* The maximum likelihood estimate (MLE) of USEPA's selected model still statistically significantly overestimates the number of observed (53) lymphoid deaths in the NIOSH study, predicting 77.5 lymphoid deaths with a 95% CI of (59.3, 103.6). By contrast, the number of lymphoid deaths in the NIOSH study (53) is encompassed by the estimate from the standard Cox proportional hazards model used by the TCEQ: 44.3 with a 95% CI of (33.9, 59.2). Thus, even conservatively assuming a healthy worker effect (in the face of more study-specific data to the contrary), USEPA's selected model significantly overestimates the observed data.

Comment 6:

The use of the UCC cohort as equivalent in importance to the NIOSH cohort is inappropriate. The UCC cohort was much smaller (2000 vs 18,000) and had far less developed exposure estimates, making conclusions about exposure-response in that cohort less valuable. This is why the EPA and its Scientific Advisory Board (SAB) recommended reliance on the NIOSH cohort.

Response:

The TCEQ agrees with Dr. Steenland and the SAB that the NIOSH cohort results should receive much more weight than the UCC cohort. In selecting the final URF the exposure-response analyses for the UCC cohort received zero weight in the TCEQ analysis (partially due to the cohort's smaller size). Thus, consistent with the SAB recommendation, the TCEQ URF exclusively relies on the NIOSH study.

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Comments from Miscellaneous Emails, Letters, and Postcards

The TCEQ received numerous emails and letters regarding the proposed DSD for EtO. While the correspondence did not contain specific scientific comments, common comments or themes are addressed by the TCEQ below.

Comment 1:

You suggest that the EPA over-estimated the cancer risk factor in its original assessment of EtO. Stop downplaying toxic cancer risks of EtO.

Response:

The TCEQ's DSD statistically demonstrates that our model relatively accurately predicts risk while USEPA's selected model assessment statistically significantly overestimates risk.

Comment 2:

Fully consider the health of Texas children and vulnerable communities and retract your dangerous proposal to Environmental Protection Agency to lower the national risk factor of EtO. It is better to err on the side of safety.

Response:

Consistent with USEPA guidance, the TCEQ uses ADAFs to account for the potentially increased susceptibility of children. Additionally, the TCEQ uses the 95% UCL to err on the side of safety and help ensure that vulnerable people and communities are protected against the potential carcinogenic effects of EtO in ambient air. Lastly, the TCEQ's DSD documents the derivation of a URF for use in air permits in Texas and is not a proposal directed to the USEPA.

Comment 3:

The report is flawed and incomplete in its risk assessment because it uses a male-only occupational study on lymphoid cancer to support its proposed risk value and does not account for the risk of breast cancer and other serious health risks EtO exposure poses (e.g., potential effects on human fetuses and child development).

Response:

The TCEQ DSD is restricted to a carcinogenic dose-response assessment, similar to how the USEPA (2016) assessment is limited to carcinogenic risk. Protecting against cancer endpoints is expected to also be protective of other health effects such as developmental effects.

The TCEQ URF is ultimately based on the same key epidemiological study as USEPA's URF, which included both male and female workers, not male workers only. The DSD evaluates lymphoid cancer risk to males and females combined as well as males alone, and the results demonstrate that to include female results in the final URF would actually make it less conservative for both males and females (i.e., the long-term ESL would be higher). Analyses with both males and females combined compared to results based on males alone show that

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use of risk results based on males alone is conservative for predicting risk in females. While technically less accurate, the TCEQ chose to be more conservative and use the male-only analysis because using male and female results combined would result in a less conservative (i.e., higher) long-term ESL value.

Lastly, the TCEQ evaluated breast cancer as a candidate cancer endpoint. USEPA's assessment, however, is driven by lymphoid cancer as the primary contributor to the URF. Subsequent to USEPA's 2016 assessment and TCEQ's systematic review of the peer-reviewed literature for EtO, recent meta-analyses of available studies have been published (Marsh et al. 2019, Vincent et al. 2019). These new meta-analyses included Steenland et al. (2003, 2004) and the smaller Mikoczy et al. (2011) study cited by USEPA (2016), as well as other studies, and reported breast cancer meta-RRs of 0.97 (0.80, 1.18) (Marsh et al. 2019) and 0.92 (0.84, 1.02) (Vincent et al. 2019). The Marsh et al. study concluded [*emphasis added*], "Evaluations of workers exposed during sterilization processes *do not support the conclusion that EO exposure is associated with an increased risk of breast cancer*." Similarly, the Vincent et al. (2019) study concluded, "Higher quality epidemiological studies demonstrated no increased risk of breast cancers." In addition to evaluating epidemiological evidence, Vincent et al. (2019) also evaluated animal study results and concluded that they provide no strong indication that EtO causes mammary tumors. These recent meta-analyses and other information (IARC 2019) further support TCEQ's decision not to base the URF on breast cancer. Human data are by far the most relevant for derivation of human toxicity factors, and the human data themselves are inconclusive (as acknowledged by USEPA 2016). The weight of evidence for EtO-induced breast cancer is now discussed in a new appendix to the revised DSD (Appendix 6).

Comment 4:

EtO is a toxic mutagen and known potent human carcinogen. I don't want this in my community or anyone else's in the USA. Environmental standards should be kept at levels that are far below a dangerous level.

Response:

The TCEQ's assessment treats EtO as a potent toxic mutagen that is *carcinogenic to humans* (i.e., a known human carcinogen). For example, TCEQ's revised long-term ESL for EtO (2.4 ppb, ADAF adjusted) puts it on the same order of magnitude level as benzene (1.4 ppb), another relatively potent known human carcinogen.

Typical EtO ambient air concentrations around the US represent an insignificant carcinogenic risk, especially considering the EtO doses normally produced endogenously in all humans. The TCEQ strongly agrees that environmental regulatory levels should be far below dangerous levels, and therefore TCEQ's revised 2.4 ppb value: (1) corresponds to an internal dose within the range of EtO doses normal produced endogenously in the human body; and (2) corresponds to a lifetime cumulative exposure (61 ppm × days) that is orders of magnitude below air concentrations found in the key epidemiological study (used by TCEQ/USEPA) to be associated with either increased lymphoid or breast cancer risk (see Table 5 and Figure 3 of the DSD).

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Comment 5:

TCEQ's flawed proposal ignores the best available science on toxicology. The TCEQ Toxicology Division needs to acknowledge the flaws in its internal EtO assessment and recognize the serious dangers that its weakened EtO risk factor would have on the state. The EPA has already completed a rigorous 10-year review of EtO potency through the Integrated Risk Information System (IRIS) program that has a more substantial scientific basis than the TCEQ's proposal for determining EtO's risk factor. I support the findings and conclusions of the IRIS chemical assessment.

Response:

The TCEQ's DSD fully considers the USEPA's derivation of their EtO URF and finds several serious flaws in USEPA's 2016 assessment. The DSD then carefully and completely lays out the scientific basis for our EtO URF derivation, based on the best available science and supported by multiple lines of evidence, some of which are newly available. The revised DSD and accompanying analyses will undergo peer review in the first quarter of 2020.

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Comments from the University of California, San Francisco

The authors of these comments collectively declared no direct or indirect financial or fiduciary interest in any chemical or product that is the subject of these comments. The TCEQ notes that the first author of these comments is also the first author on USEPA (2016).

Comment 1:

The DSD's final risk estimate does not include breast cancer risks.

EPA's conclusion of a potential breast cancer hazard from exposure to ethylene oxide (EtO) was supported by the SAB. TCEQ seems to acknowledge a potential breast cancer hazard and considers EPA's quantitative risk estimates for breast cancer, but then rejects EPA's estimates and includes no alternative estimates for breast cancer.

The SAB explicitly endorsed EPA's use of a two-piece spline model for modeling the breast cancer incidence data, and EPA's unit risk estimates for breast cancer incidence are based on this model. TCEQ's rationales for rejecting EPA's approach are flawed because TCEQ conflates endogenous (background) exposures with low exogenous exposures, assuming that small increases in exposure above background would not be biologically meaningful, despite the fact that breast cancer has relatively high background rates.

There is uncertainty about the risks at low levels of exposure, and this is why EPA applies a linear extrapolation from models derived in the observable range of the data. Use of linear low-exposure extrapolation was supported by the established mutagenic mode of action (MOA) and the SAB. These issues are discussed in more detail below (see Comment #3, 4, 6, 11e).

Having rejected EPA's human-based breast cancer risk estimates in the proposed DSD, TCEQ could have considered the rodent-based estimates presented by EPA, rather than completely discounting breast cancer risk. Indeed, in March 2017 TCEQ did exactly that, adopting a value of 7.6×10^{-5} per $\mu g/m^3$, the EPA IRIS value for total cancer risk based on rodent data (see Table and Appendix A). Yet, TCEQ's 2019 total risk estimates are for lymphoid cancers only, and the DSD does not provide a valid scientific rationale for not including breast cancer risks in the final unit risk estimate. Because the DSD fails to include breast cancer, TCEQ's final risk estimate is a major underestimation of the actual cancer risks posed by ethylene oxide.

Response:

The TCEQ evaluated breast cancer as a candidate cancer endpoint. USEPA's assessment, however, is driven by lymphoid cancer as the primary contributor to the URF. Subsequent to USEPA's 2016 assessment and TCEQ's systematic review of the peer-reviewed literature for EtO, recent meta-analyses of available studies have been published (Marsh et al. 2019, Vincent et al. 2019). These new meta-analyses included Steenland et al. (2003, 2004) and the smaller Mikoczy et al. (2011) study cited by USEPA (2016), as well as other studies, and reported breast cancer meta-RRs of 0.97 (0.80, 1.18) (Marsh et al. 2019) and 0.92 (0.84, 1.02) (Vincent et al. 2019). The Marsh et al. study concluded [*emphasis added*], "Evaluations of workers exposed during sterilization processes *do not support the conclusion that EO exposure is associated with*

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an increased risk of breast cancer." Similarly, the Vincent et al. (2019) study concluded, "Higher quality epidemiological studies demonstrated no increased risk of breast cancers." In addition to evaluating epidemiological evidence, Vincent et al. (2019) also evaluated animal study results and concluded that they provide no strong indication that EtO causes mammary tumors. These recent meta-analyses and other information (IARC 2019) further support TCEQ's decision not to base the URF on breast cancer. Human data are by far the most relevant for derivation of human toxicity factors, and the human data themselves are inconclusive (as acknowledged by USEPA 2016). The weight of evidence for EtO-induced breast cancer (i.e., "valid scientific rationale for not including breast cancer") is now discussed in a new appendix (Appendix 6) to the revised DSD.

USEPA (2016) acknowledges that human data are insufficient to establish that EtO is a human breast cancer carcinogen, which would be quite unexpected if EtO were in fact as highly potent of a carcinogen as USEPA (2016) purports given the large group of workers (including women) exposed to very high concentrations of EtO on a daily basis. As a result, USEPA must rely on support by laboratory animal studies in classifying EtO as carcinogenic to humans. However, upon closer inspection, the sites of EtO-induced cancers in animal models are of questionable direct human relevance for being predictive of, and therefore being used as confirming evidence for, the site(s) of human cancers. See the response to Comment #3 from Dr. Steenland above for EtO-specific examples of the lack of site concordance between tumors induced by EtO at high incidence in laboratory animals and epidemiological findings (i.e., lung cancer, brain cancer). Interspecies differences in carcinogenic responses such as tumor types and sensitivity are common, even between different rodent species (e.g., EtO-induced mammary tumors in mice but not rats). IARC (2019) analyzed tumor site concordance using a dataset of the 111 distinct Group 1 (carcinogenic to humans) agents. Sixty agents had both a human tumor site and an animal tumor site identified and were used to evaluate concordance across 39 tumor sites in animals and humans (see Figures 21.1 and 21.2 of IARC 2019). Reported results show that breast cancer, for example, is more frequently/commonly induced in laboratory animal species by these agents than in humans. More telling is that while there is 47% overlap between agents that cause lymphoid and hematopoietic cancers in humans and animals, there is only 20% overlap between agents that have been shown to cause breast cancer in humans and animals (Table 21.7 of IARC 2019). The IARC (2019) unanimous consensus statement was that "*At present, the state of the science does not support tumour site concordance as a general principle*." As a result, a URF based on mammary tumors in laboratory animals as a surrogate for human breast cancer, for which data are themselves inadequate to establish EtO as a human carcinogen (USEPA 2016), would be considered highly uncertain. [The 1.5-page March 2017 TCEQ EtO document referred to was merely an interim step prior to TCEQ being able to conduct a full review and produce a thorough DSD based on much more detailed analyses.]

Based on this information, it cannot be said that TCEQ's final risk estimate is an underestimation of the actual cancer risks posed by EtO, since it is not at all clear that EtO causes human breast cancer. In fact, the overall weight of evidence is against it (see Appendix 6 to the revised DSD). USEPA's *carcinogenic to humans* classification is best supported by the

lymphoid cancer data (e.g., NIOSH cohort), and TCEQ's final URF is best based on lymphoid cancer as the critical cancer endpoint.

Regarding endogenous EtO levels, assuming EtO does increase breast cancer risk despite the overall weight of evidence (see Appendix 6 to the revised DSD): given the background rate for breast cancer, exogenous EtO exposure resulting in higher than background internal doses would be more likely to be significant if endogenous EtO were known to be *the* cause of relatively high breast cancer background rates, but this is not the case. However, any risk associated with exogenous EtO exposures resulting in internal doses well within the range of normal endogenous background, particularly orders of magnitude below the 1st percentile of endogenous, will be indistinguishable from background biologically and inconsistent with the concept of excess risk. The TCEQ uses the data on protein adduct levels associated with EtO exposure to provide valuable context; it is not deterministic in terms of the dose-response model selected. The endogenous EtO protein adduct data are a secondary consideration in the overall weight of evidence, with the primary consideration for TCEQ's selection of a standard dose-response model being driven by the mechanistic data that shows a standard mutagenic MOA that is not expected to cause a supra-linear dose-response. Even in the absence of data on EtO adduct background levels normally found in the population, TCEQ's model selection would not change. For example, since lymphoid cancer drove the TCEQ and the USEPA carcinogenic assessment, perhaps the most relevant mutagenicity data was that in the bone marrow of mice exposed to EtO by inhalation *in vivo* (Recio et al. 2004), which USEPA indicates is consistent with a linear dose-response (see C-17 of USEPA 2016).

Lastly, consistent with the comment, the TCEQ uses linear low-dose extrapolation based on a mutagenic MOA (the Cox model is indistinguishable from linear over the doses of interest, as shown in the DSD, and a modeled POD is then used for URF derivation/linear extrapolation).

Comment 2:

The DSD discounts the role of expert peer review.

EPA's EtO carcinogenicity assessment was the subject of extensive review. In addition to review by other offices in EPA and other agencies in the federal government, the assessment twice underwent external peer review by EPA's independent SAB, which included discussions at open public meetings in 2006 and 2014; the SAB also considered public comments made at the meetings. In addition to addressing the SAB's comments, EPA considered public comments made at the 2006 and 2014 SAB meetings as well as at a public meeting in 2013. For the 2014 review by the SAB, the Board set up a panel of 14 experts from a range of relevant disciplines. After the review, the panel's report was reviewed and endorsed by the larger SAB.

As described in the comments below, the SAB explicitly endorsed EPA's approaches and rejected the model ultimately chosen by TCEQ, where the Commission's conclusions and approaches differed from those of EPA (e.g., discounting the breast cancer models, rejecting two-piece spline models, not using linear low-exposure extrapolation). The DSD does not present new data or evidence that was not considered by the SAB, nor does it provide an

appropriate scientific explanation for the significant departures from EPA's methodology. In contrast to the Agency, academic and public expert input and extensive peer review of the EPA assessment, the DSD has not been peer reviewed or subject to any external comments.

Response:

The TCEQ does not discount the value of external expert peer review. The TCEQ DSD has undergone internal peer review, and in addition to soliciting public comments and addressing those public comments, the TCEQ assessment will undergo an external peer review by a panel of experts in relevant fields of study in the first quarter of 2020.

USEPA's SAB had limited information and was not provided all the data needed to validate/invalidate USEPA's dose-response models. Appendix 4 of TCEQ's assessment develops a corrected analysis of model fit criteria (i.e., p-values and AIC values). This analysis showed that once USEPA's omission of a degree of freedom in the statistical evaluation of their two-piece spline models is corrected, the two-piece spline model does not fit the data statistically better than the standard Cox proportional hazards model (or even the null model with zero slope).

TCEQ also developed other new analyses not available to the SAB. Appendix 2 of the TCEQ revised DSD compares the number of lymphoid cancer deaths observed in the NIOSH epidemiological study with the number of lymphoid cancer deaths that would be expected in the NIOSH epidemiological study if the exposure-response models were correct. A good model should be able to estimate the data that were used to fit the model; that is, for example, the number of lymphoid deaths observed in the NIOSH epidemiological study. However, USEPA's selected model assessment statistically significantly over-predicts the number of lymphoid cancer deaths actually observed in the NIOSH study at the 5% significance level for the cohort overall and for every exposure quintile. In contrast, the predictions of the number of lymphoid cancer deaths by the TCEQ standard Cox proportional hazards model are reasonably accurate and consistent with the number of lymphoid cancer deaths observed in the NIOSH study for the overall cohort and for every exposure quintile.

In addition to this and a demonstration of how USEPA incorrectly calculated model fit criteria in a manner inconsistent with SAB comments, the DSD also presents other new data and evidence not considered by the SAB: important new data on the air concentrations corresponding to endogenous levels (Kirman and Hays 2017), new analyses demonstrating the over-prediction of background lymphoid cancers in the general US population, and robust data indicating the lack of a healthy worker effect for lymphoid cancer and breast cancer incidence (discussed in other comments below). Recent meta-analyses of the association between EtO and human cancer have also been added (Marsh et al. 2019, Vincent et al. 2019). The DSD quite plainly states that as USEPA acknowledges, MOA data do not support their model. Moreover, all other considerations discussed in the DSD also support TCEQ's approach over USEPA's approach (e.g., data on endogenous, reality checks on the key underlying data and background rates in the general population, etc.). Thus, as documented in the DSD, numerous scientific considerations constitute the scientific rationale for departure from USEPA's methodology.

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Comment 3:

The DSD incorrectly interprets EPA's statements regarding the plausible sublinearity of dose-response relationships for endogenous doses of EtO as also applying to exogenous exposures.

The DSD states EPA determined "that the low-dose region of the EtO dose-response curve is highly plausibly sublinear..." but this interpretation of the EPA assessment is incorrect. EPA made no such determination about low-dose exogenous exposures.

Rather, EPA made general statements in the context of conceptual models presented by Starr and Swenberg and Crump et al. In this context, EPA was referring to a range of hypothetical endogenous doses from no (zero) endogenous exposure to the point of no (zero) exogenous exposure. The rationale for postulating that the dose-response relationships for relevant cancers across that hypothetical range of doses are likely to be sublinear is based on the conceptual model presented in detail by Crump et al. (2014). In brief, the reasoning is that the body has defense mechanisms (e.g., DNA repair mechanisms) to deal with endogenous exposures. However, these defenses are imperfect and limited, which may account for some level of background cancer risk even without exogenous exposures; and as endogenous doses increase across this hypothetical range, the body's available defenses get diminished, such that the slope of the dose-response curve may be essentially linear at the point of zero exogenous exposure (see Figure 1 in Crump et al. (2014)). The postulated sublinearity is not meant to apply to the range of exogenous exposures.

EPA's unit risk estimates are explicitly for extra risk above background, i.e., above the risk from endogenous doses (unit risk estimates are derived from exposure-response modeling of exogenous exposures; endogenous doses are common to both exposed and unexposed subjects, independent of exogenous exposure, and thus are part of background risk). Variability in levels of background doses of endogenous EtO are accounted for in the modeling of the exogenous exposures, along with other sources of variability. While sublinearity across endogenous doses is plausible, one cannot infer anything from that about the exposure-response relationship at low exogenous exposures. Thus, the DSD's application of the hypothetical sublinear dose-response relationship for endogenous exposures to exogenous exposures, especially in light of background cancer rates (see Comment #4), is not scientifically supported.

Response:

The TCEQ's understanding is that the commenters are indicating that USEPA's unit risk estimates are derived from exposure-response modeling of exogenous occupational exposures and explicitly for extra risk above background, and that endogenous doses were common to both exposed and unexposed workers and thus were part of background risk, independent of the exogenous occupational exposure for which the URF had been derived. The comment further indicates that variability in levels of background doses of endogenous EtO are accounted for in the modeling of the exogenous occupational exposures, along with other sources of variability. However, what the comment fails to consider is that the background for both those exposed and unexposed to EtO at work includes not only endogenous exposure, but

also background exposure to ambient environmental levels outside the workplace in the areas where the workers live (likely reasonably proximate to the facility). Therefore, since endogenous + ambient environmental exposure actually represents background for both those exposed and unexposed at work, *this comment suggests that the URF does not apply to typical environmental levels but only to additional occupational exposure*.

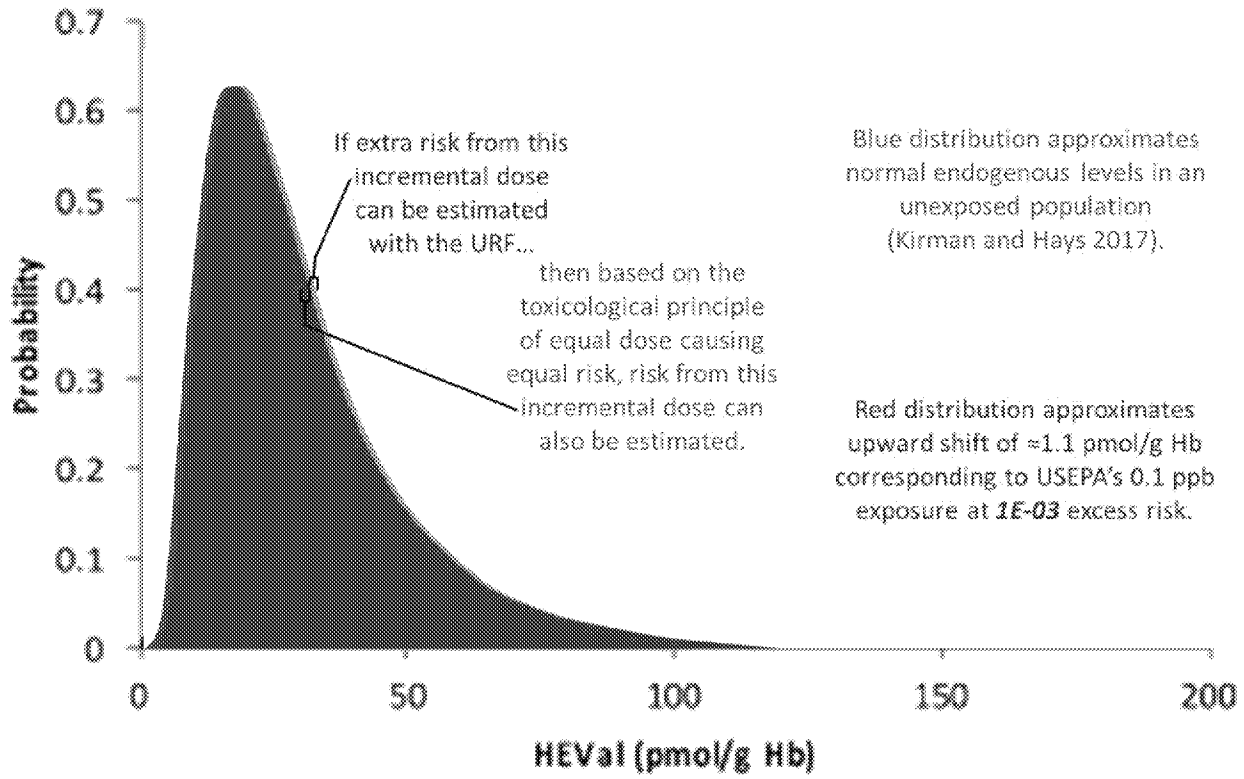

Figure 1. Probability distribution demonstrating the normal endogenous levels of the EtO-hemoglobin adduct in an unexposed population (blue) and in a population with an addition exposure to EtO at 0.1 ppb, associated with 1E-03 excess cancer risk as per USEPA's URF (red)

The basis for the TCEQ's application of the USEPA's URF to understanding risk from endogenous EtO is the toxicological principle that equal internal doses give rise to equal risk. That is, in dose-response/risk assessment it is standard practice to consider equal internal doses as equipotent in producing both noncarcinogenic and carcinogenic effects, absent a scientifically robust demonstration that this standard assumption should not apply (e.g., based on mechanistic or toxicokinetic information). Thus, the standard risk assessment practice of considering equal internal doses as equipotent in producing carcinogenic effects underlies TCEQ's application of the USEPA and TCEQ URFs to internal endogenous doses of the same mutagenic chemical. Internal doses that result from exogenous exposures that fall well within or below endogenous background are expected to be subject to the same defense mechanisms (e.g., DNA repair mechanisms) that deal with endogenous exposures. Thus, the postulated sublinearity still applies to exogenous exposures that result in internal doses within the range of endogenous background, particularly at doses orders of magnitude lower than the 1st percentile of

endogenous as with USEPA's assessment. Based on these toxicological principles, the statement made by the commenter that "the low-dose region of the EtO dose-response curve is highly plausibly sublinear" is a reasonable expectation for the area of the dose-response where total internal exposures (endogenous plus a relatively minor contribution from exogenous) fall within or extremely close to the range of normal endogenous background. This concept has been clarified in the revised DSD. Regardless, it is not deterministic in TCEQ's selection of model. TCEQ used linear low-dose extrapolation from a POD derived by the Cox proportional hazards model, which is indistinguishable from linear over the doses of interest as shown in various figures throughout the DSD (e.g., Figure 22).

Comment 4:

The DSD ignores background rates of cancer and incorrectly suggests that given endogenous EtO production, low exogenous exposures would not produce biologically meaningful internal doses.

The DSD states that "ambient EtO concentrations significantly less than 1 ppb...would not be expected to produce biologically meaningful internal doses considering the range of normal endogenously-produced background EtO levels." However, normal endogenous EtO exposures may contribute to background cancer risks for lymphoid cancers and for breast cancers in females, as these are relatively common cancer types in the general population. As cited on p. 4-95 of EPA's assessment, lymphoid cancers have a background lifetime incidence risk on the order of 3%, while the background lifetime incidence risk for breast cancer in females is on the order of 15%.

Low exogenous EtO exposures would be additive to the endogenous exposure and to background cancer processes, consistent with general principles of quantitative risk assessment. As to the variability in background doses of endogenous EtO, this is accounted for in the modeling of the exogenous exposures, as discussed in Comment #3 above. Thus, DSD ignoring low levels of exogenous exposure claiming they are not biologically meaningful is not scientifically justified and results in an underestimation of risk. For example, the DSD ignores levels of exogenous exposure that EPA determined to be associated with upper bound extra risks of 10^{-4} (0.01%).

Response:

The TEQ stands by the statement that "ambient EtO concentrations significantly less than 1 ppb...would not be expected to produce biologically meaningful internal doses considering the range of normal endogenously-produced background EtO levels." An internal EtO dose that is almost 40 times lower than even the 1st percentile of normal endogenous EtO levels (using USEPA's 0.01 ppb at 1E-04 risk) is very unlikely to be biologically meaningful as it is entirely within/below normal biological variation, indistinguishable from background endogenous exposure and risk. Further discussion of the TCEQ's evaluation of endogenous EtO levels is found in response to Comment #3.

The DSD directly addresses background rates of cancer by performing a reality check of USEPA's URF based on them. The TCEQ tested the biological plausibility of USEPA's model and URF and found it both: (1) over-predicted lymphoid cancers in the key NIOSH cohort (based only on exogenous EtO exposures); and (2) over-predicted U.S. population background lymphoid cancer rates based on population-weighted background EtO levels in nonsmokers and smokers.

Comment 5:

The DSD incorrectly attempts to estimate the cancer risks of endogenous EtO levels using EPA's unit risk estimate which is applicable to exogenous exposures only.

The DSD applies EPA's unit risk estimate to endogenous ethylene oxide exposures, but as noted above (Comment #3, 4), EPA's unit risk estimates are for exogenous exposures only (extra risk above background[21]) and cannot be used to infer anything about risks from endogenous exposure. The extent of cancer risks from endogenous levels of EtO is not something that can be estimated from current knowledge.

Response:

This comment is addressed in response to Comment #3. To summarize our response, the background EtO exposure in the workers included both endogenous production as well as ambient EtO exposure. Therefore, it seems that the commenter is suggesting that the URF does not apply to typical environmental levels but only to additional occupational exposure. However, based on the toxicological principle that equal internal doses produce equal risk, the TCEQ considers it reasonable to apply the risks estimated based on occupational exposure to equivalent doses from endogenous or ambient environmental exposure to EtO (i.e., equal internal doses, whether derived from endogenous production or exogenous exposure, should be assumed to be equipotent toxicologically).

Comment 6:

The DSD makes flawed claims about EPA's use of a two-piece spline model for lymphoid cancer and misstates the exposure range over which the model is applied for derivation of the unit risk estimate.

The DSD claims that the EPA model over-predicts the NIOSH cohort results. However, TCEQ's approach to predicting cases is flawed (see Comment #13 below for a discussion of problems in the TCEQ's approach). In fact, EPA's model provides a reasonably good representation of the NIOSH data, as demonstrated by the statistical and visual fits. As seen in Figure 4-3 of EPA's assessment, the model actually underestimates the categorical relative risks (RRs) determined nonparametrically (i.e., without any assumptions about the exposure-response relationship across the exposure categories) for the exposure quartiles.

The DSD claims that EPA was wrong to use a supralinear model. However, the underlying data exhibit a supralinear exposure-response relationship. This is demonstrated by the shape of the nonparametric categorical results, as well as by the fact that the best-fitting models are

supralinear (e.g., the Cox regression model with log cumulative exposure; see Table 4-6 of EPA assessment).

Furthermore, EPA's independent SAB endorsed the use of two-piece spline models for such data, recognizing the utility of such models for reflecting local behavior in the data more readily than the single-parameter models. In fact, EPA used a two-piece linear spline model to account for high-exposure plateauing while specifically avoiding the excessive supralinear curvature in the lower-exposure range objected to by TCEQ and sources it cites regarding supralinear models.

A mechanistic explanation for overall supralinear exposure-response relationships in the observable range of the EtO epidemiological data may not be known; however, such relationships are not uncommon with epidemiological data and there are other possible explanations. Moreover, after modeling all of the data using the two-piece spline model, EPA estimated a point of departure (POD) at the low end of the observable range and used linear low-exposure extrapolation from the POD to derive the unit risk estimate, consistent with EPA's guidelines. (See Comment #11e below for more discussion of EPA's approach to deriving unit risk estimates.) The conclusion of a mutagenic MOA, which was a finding of both EPA and the TCEQ, provides support for linear low-exposure extrapolation. Contrary to intimations by TCEQ, the mutagenic MOA does not preclude high-exposure plateauing, such as exemplified by tumors in rats exposed to vinyl chloride.

Similarly, the plausibility of sublinearity in the conceptual range of endogenous exposures from internal doses of zero up to the point of zero exogenous exposure does not rule out the models used by EPA for exogenous exposures, i.e., supralinearity in the observable range from higher exposures and linear extrapolation for lower exposures.

Thus, the DSD's rationales for rejecting the model used by EPA are not valid.

Response:

The TCEQ agrees that a mutagenic MOA provides support for linear low-exposure extrapolation. The TCEQ also agrees with the commenter that a mechanistic explanation for an overall supra-linear exposure-response relationship is not known, which is the primary (but not sole) basis for TCEQ rejecting USEPA's model (see the DSD). The scientific burden of proof for choosing a supra-linear dose-response is *robust MOA data*, including data over the endogenous range where both agencies expect sublinearity. This burden of proof was not met, and so the TCEQ adopted a standard default dose-response approach (Cox proportional hazards model). Using a standard dose-response model is further strongly supported by the corrected AIC and p-values, which show that the supra-linear model does not have a better fit than the standard model (see Appendix 4 of the revised DSD). The MOA, model predictions of the underlying worker cancer data (Appendix 2 of the revised DSD), and other considerations (e.g., endogenous data) also strongly support the TCEQ's model selection.

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The commenter cites a different chemical, vinyl chloride, as an example of a mutagenic carcinogen with high-exposure plateauing of cancer responses in animal models. For EtO, since lymphoid cancer drove the USEPA carcinogenic assessment, perhaps the most relevant mutagenicity data discussed by USEPA (2016) was that in the bone marrow of mice exposed to EtO by inhalation *in vivo* (Recio et al. 2004), which *USEPA indicates is consistent with a linear dose-response* (see C-17 of USEPA 2016). Even at 200 ppm the dose-response remains linear and has not plateaued, making this effect less likely to be occurring in humans.

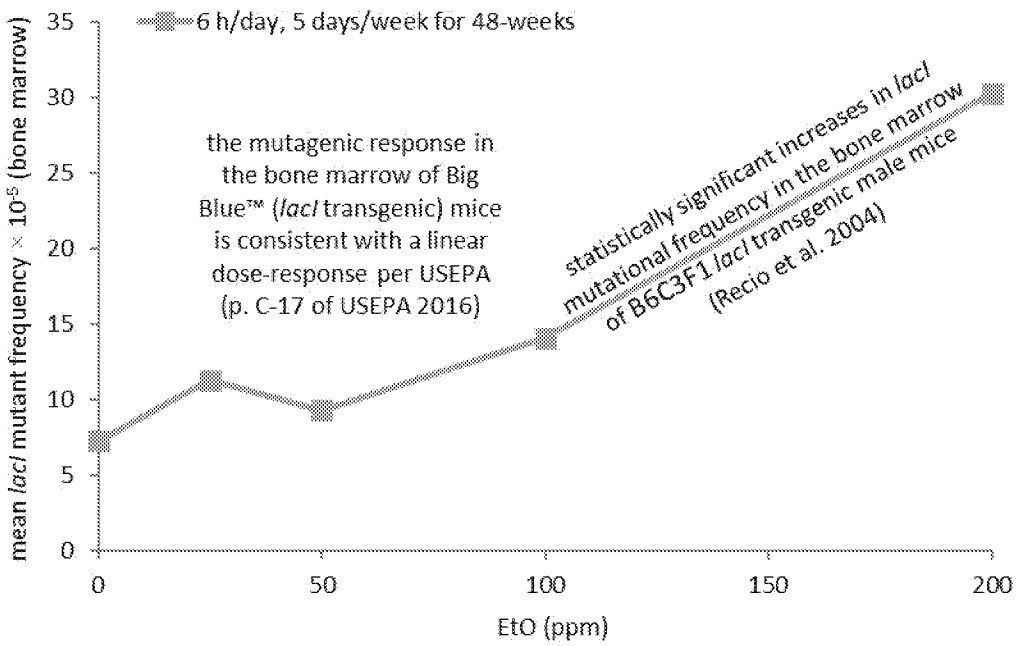

Figure 2. Overall linear dose-response for EtO-induced mutations in the bone marrow of Big Blue™ mice (Recio et al. 2004)

In reference to Figure 4-3 of USEPA's risk assessment, there is an important note at the end of the Figure that addresses model fit: "(Note that, with the exception of the categorical results and the linear regression of the categorical results, the different models have different implicitly estimated baseline risks; thus, they are not strictly comparable to each other in terms of RR values, i.e., along the y-axis. They are, however, comparable in terms of general shape.)" The misinterpretation of model fitting versus non-parametric rate ratios was discussed at length by Valdez-Flores et al. (2013), and USEPA (2016) responded by adding the note to the figures showing rate ratios. There are several reasons why this USEPA Figure 4-3 and other similar figures could be misleading to casual readers. As the models were fit to the individual data and not categorical data, a comparison of models to the categorical data do not actually show model fit at all since those are not the data to which the models were fit. A fair comparison to the individual RRs is shown in Figure 22 of the DSD, which TCEQ therein shows are consistent with the categorical RRs (see Appendix 5 of the revised DSD) but reveals no readily apparent superior fit by either model. This finding using a visual fit method is consistent

with the correctly calculated p-values and AIC values not demonstrating a clearly superior fit by either model. The individual RRs also do not show a high-exposure plateauing effect of EtO. Importantly, TCEQ's reality check on the models predicting the underlying lymphoid cancers for the cohort as a whole and the individual quintiles does show that TCEQ's model, the standard Cox proportional hazards model, more accurately predicts the actual number of lymphoid cancers in the cohort as a whole and in the exposure quintiles. The responses below provide more detailed information on related points.

Non-Parametric Rate Ratios are not Observed Data

Figure 3 reproduces Figure 4-3 in USEPA's 2016 risk assessment. This figure shows the rate ratios of twelve models. Eleven of those models have a parametric functional form and one model (labeled here "EPA's 5 RRs") estimates non-parametric rate ratios of lymphoid mortality grouped by quintiles. Each quintile summarizes information for 11 lymphoid deaths (9 in the non-exposed quintile). *The "EPA's 5 RRs" are not the data* – they are estimates of the rate ratios. Rate ratios are not observed, they are estimated. Furthermore, the non-parametric rate ratios derived by USEPA and shown in Figure 3 do not show the full range of possible rate ratios and cumulative exposures. Figure 4 is identical to Figure 3 with the full range of cumulative exposures of lymphoid decedents and the full range of rate ratios estimated for the individual decedents. Table D-28 of USEPA (2016) includes the uncertainty (i.e., 95% CIs) around USEPA's "categorical" RRs and is reproduced here as Table 2 for lymphoid cancer (males and females combined).

In addition to the categorical RRs not being the actual data or even the data that models were fit to, it must be noted that the apparent supra-linearity of USEPA's 5 RRs are an artifact of the grouping of individual decedents. The functional form implied by non-parametric estimates of the RRs changes depending on the number of lymphoid cancer decedents summarized in each RR. The individual RRs in the figures to follow show the whole spectrum of the RRs and do not suggest a specific shape of the relationship between RRs and cumulative exposures.

Figure 3. Reproduction of USEPA's 2016 Figure 4-3. Exposure-response models for lymphoid cancer mortality vs. occupational cumulative exposure (with 15-year lag). Spline1600 (solid red line) is the EPA's chosen model, and e^(β*exp) (solid light blue line) is the TCEQ's chosen model.) Spline1600 (solid red line) is the EPA's chosen model, and e^(β*exp) (solid light blue line) is the TCEQ's chosen model.

e^(β*exp): RR = e(β × exposure); e^(β*logexp): RR = e(β × ln(exposure)); e^(β*sqrtexp): RR = e(β × sqrt(exposure)); categorical: RR = e(β × exposure) with categorical exposures, plotted at the mean cumulative exposure; linear reg: weighted linear regression of categorical results, excluding highest exposure group (see text); 1 + β*exp: RR = 1 + β × exposure; 1 + β*logexp: RR = 1 + β × ln(exposure); 1 + β*sqrtexp: RR = 1 + β × sqrt(exposure); spline100(1,600): Two-piece log-linear spline model with knot at 100 (1,600) ppm × days (see text); linspline100(1,600): Two-piece linear spline model with knot at 100 (1,600) ppm × days (see text**). (Note that, with the exception of the categorical results and the linear regression of the categorical results, the different models have different implicitly estimated baseline risks; thus, they are not strictly comparable to each other in terms of RR values, i.e., along the y-axis. They are, however, comparable in terms of general shape.)** [Original footnote with emphasis added]

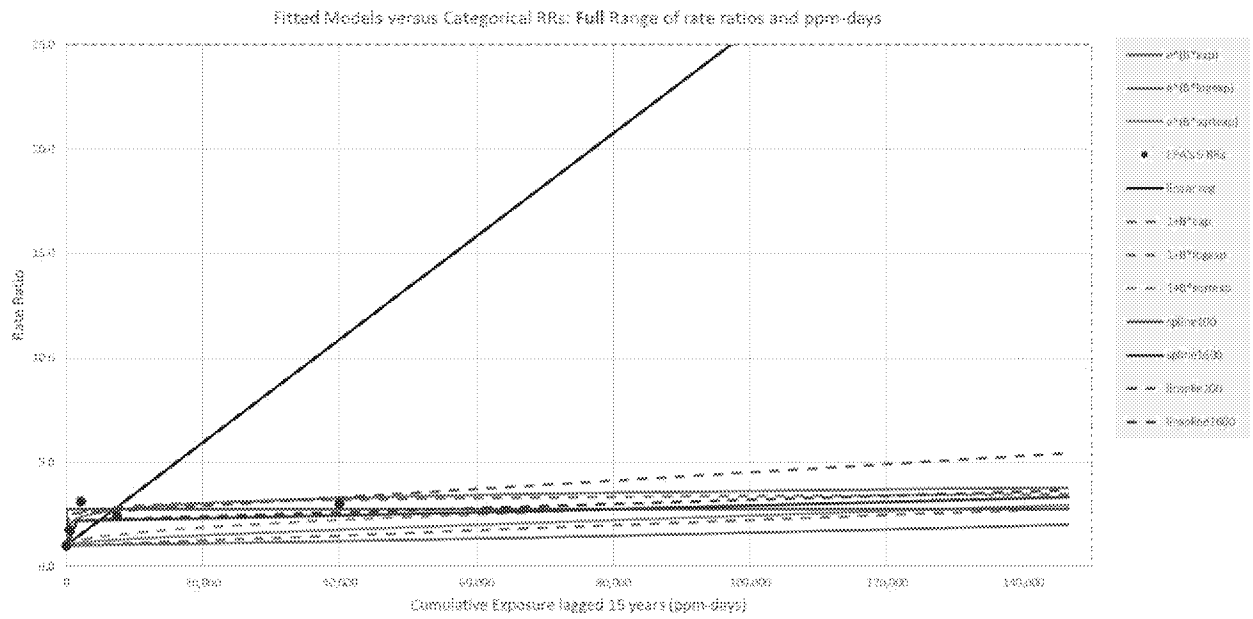

Figure 4. Same as Figure 3 plotted using the full range of cumulative exposures experienced by lymphoid decedents (horizontal axis) and the full range of possible rate ratios estimated for all lymphoid decedents [Note, the choice of y-axis values is based on comparison to Figure 5, discussed below].

Table 2. USEPA's 5 RRs and the 95% confidence interval for each of the quintiles

Cumulative exposure range, 15-year lag (ppm-days)	Mean* Cumulative Exposure (ppm-days)	Rate Ratio	Lower Confidence Limit on the Rate Ratio	Upper Confidence Limit on the Rate Ratio
0 (lagged out)	0	1.00	--	--
>0 – 1,200	446	1.75	0.59	5.25
1,201 – 3,680	2,143	3.15	1.04	9.49
3,681 – 13,500	7,335	2.44	0.80	7.50
>13,500	39,927	3.00	1.02	8.45

* Mean cumulative exposures as reported by USEPA in footnote 21 on page 4-14 of the 2016 assessment.

Estimated Non-Parametric Rate Ratios for Each Lymphoid Decedents

Judging a model fit by comparing to five summary RRs is tantamount to comparing a linear regression fit to 100 different points by comparing it to five averages of groups of 20 points each. Variability of data and goodness of fit of a model cannot be judged by comparing model predictions to five summary points. Similarly, model fit to individual data with 53 decedents cannot be judged by comparing it to five summary RRs. Just as USEPA estimated the non-

parametric RRs by grouping 11 decedents in each exposure quintile, the non-parametric RRs can be estimated for each individual decedent with non-zero exposure (i.e., by fitting a non-parametric hazards model using the Cox proportional hazards model with the RR for each individual adjusted for the covariates sex, race, etc.). The NIOSH study has 44 lymphoid decedents with exposures greater than zero (9 lymphoid decedents had zero lag-15 cumulative exposures). Figure 5 is similar to Figure 4 with the addition of the non-parametric RRs for the 44 lymphoid decedents with non-zero cumulative exposure in the NIOSH study.

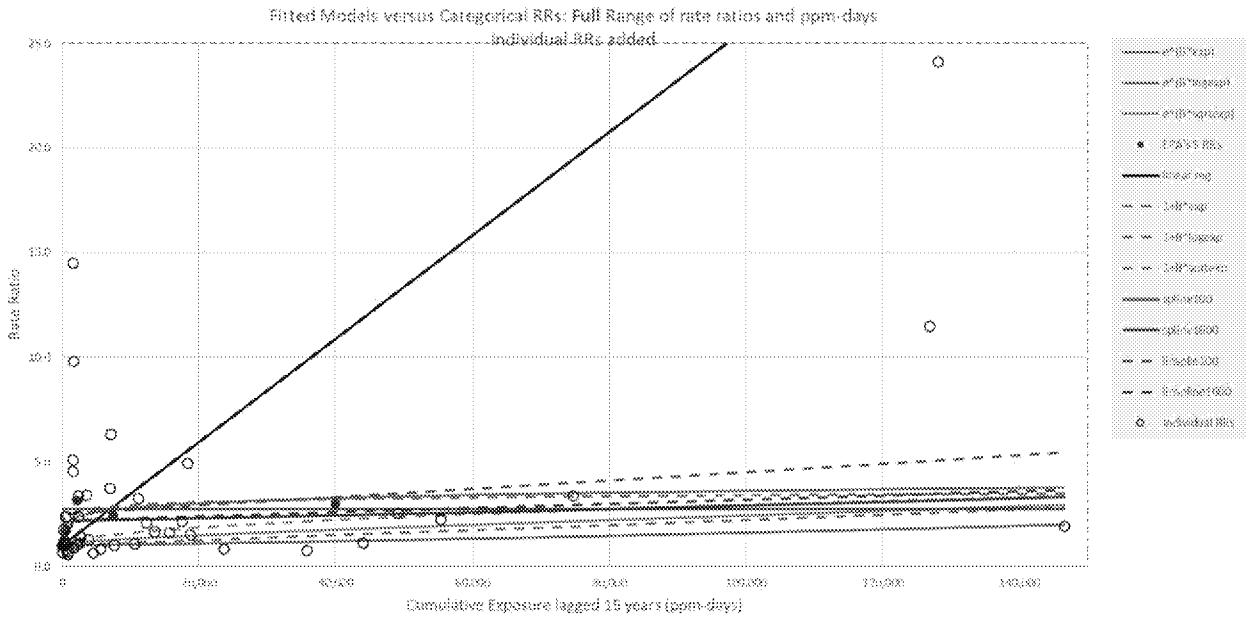

Figure 5. Same as Figure 4 after superimposing the rate ratios estimated for each one of the 44 decedents with non-zero cumulative exposures lagged 15 years.

Figure 5 shows that the non-parametric estimates of the RRs based on the individual decedents can be less than, equal to, or greater than one. This is in contrast to the summary RRs based on quintiles (red dots in Figures 3 to 5) that give the impression that the RRs are greater than one for any non-zero cumulative exposure. Figure 5 also shows that once all the individual variability is included, all models (excluding the "linear reg" model – black solid line) seem to fit the non-parametric estimates similarly. This is supported by correctly calculated p-values and AIC values (Appendix 4 of the revised DSD), although model performance in predicting the actual number of lymphoid cancers in the cohort as a whole and in each quintile demonstrates the superior fit of the Cox proportional hazards model (Appendix 2 of the revised DSD).

Model-Specific Implicitly Estimated Baseline Risks

USEPA's footnote to several figures (including Figure 4-3) indicates that the different models and the non-parametric RRs cannot be compared along the y-axis because "the different models have different implicitly estimated baseline risks." USEPA is correct. All models in Figure

4-3 of the USEPA 2016 EtO risk assessment (Figure 3 herein), with the exception of the "linear reg" model, are fit to hazard rates (not fit to rate ratios). The functional form of all models is

$$HR_i(d) = HR_i(0) \times f_i(d)$$

where $HR_i(d)$ is the hazard rate of model i at cumulative exposure *d*, $HR_i(0)$ is the "estimated baseline risk" for model i, and $f_i(d)$ is the function of the rate ratio at cumulative exposure *d* for model i.

Note that by dividing $HR_i(d)$ by the "estimated baseline risk" $HR_i(0)$, the function $f_i(d)$ is the rate ratio at cumulative exposure *d* for model i. Note also, that each model i could result in different estimates of the baseline risk, $HR_i(0)$. That means, all models would have rate ratio ($f_i(0)$) equal to 1 at cumulative exposure equal to 0. However, the "estimated baseline risk" $HR_i(0)$, could be very different for each model. The model for USEPA's 5 categorical RRs, USEPA's two-piece linear spline model, and TCEQ's standard Cox proportional hazards model have the following functional forms:

Model 1 ("EPA's 5 RRs" and "Individual RRs" in the figures): The non-parametric model fit to the data is given by the expression

$$HR_{NP,k}(d) = HR_{NP}(0) \times RR_{NP,k}(d)$$

where $HR_{NP,k}(d)$ is the hazard rate for the *k*-th group at mean cumulative exposure *d*, $HR_{NP}(0)$ is the "estimated baseline risk" for the nonparametric model, and $RR_{NP,k}(d)$ is the rate ratio for the *k*-th group. Although the function does not depend on the magnitude of the exposure *d*, the function is written with the *d* for the sake of consistency. (USEPA expresses the function $RR_{NP,k}(d) = e^{\beta_k \times d}$ where "*d*" is a "categorical exposure." Using USEPA's expression guarantees $RR_{NP,k}(d)$ is non-negative when doing a search for the optimal β_k values.)

Model 2 ("linspline1600" in the figures): The functional form of USEPA's selected two-piece linear model (linspline1600) is

$$HR_{spl}(d) = HR_{spl}(0) \times \begin{cases} 1 + \beta_1 \times d & d \leq knot \\ 1 + \beta_1 \times d + \beta_2 \times (d - knot) & d > knot \end{cases}$$

where $HR_{spl}(d)$ is the hazard rate at cumulative exposure *d*, $HR_{spl}(0)$ is the "estimated baseline risk" for the two-piece linear model, $1 + \beta_1 \times d$ is the rate ratio at cumulative exposures *d* below the *knot*, $1 + \beta_1 \times d + \beta_2 \times (d - knot)$ is the rate ratio at cumulative exposures *d* above the *knot*, and *knot* is the cumulative exposure where the slope of the rate ratio changes. USEPA estimated *knot* at 1,600 ppm-days from the data.

Model 3 ("e^(β*exp)" in the figures): The functional form of TCEQ's selected model ($e^{\beta * exp}$) standard Cox proportional hazards model is

$$HR_{Cox}(d) = HR_{Cox}(0) \times e^{\beta \times d}$$

where $HR_{Cox}(d)$ is the hazard rate at cumulative exposure *d*, $HR_{Cox}(0)$ is the "estimated baseline risk" for the standard Cox proportional hazards model at zero exposure, and $e^{\beta \times d}$ is the rate ratio at cumulative exposure *d*.

The rate ratios from each of the models described above are, by definition, equal to one at zero cumulative exposures. However, as indicated by USEPA's 2016 assessment and shown above for Models 1, 2, and 3, the "implicitly estimated baseline risks" ($HR_{NP}(0)$, $HR_{spl}(0)$, and $HR_{Cox}(0)$, for Models 1, 2, and 3, respectively) are different for different models. That is, the RRs for the models cannot be compared for non-zero cumulative exposures without accounting for the differences in the "implicitly estimated baseline risks" ($HR_{NP}(0)$, $HR_{spl}(0)$, and $HR_{Cox}(0)$). The partial likelihood methodology for the proportional hazards models described above do not explicitly estimate the baseline risks ($HR_{NP}(0)$, $HR_{spl}(0)$, and $HR_{Cox}(0)$) and they are unknown. However, an approximation of the ratio of the "implicitly estimated baseline risks" for Models 2 and 3 to the "implicitly estimated baseline risks" for Model 1 ($HR_{spl}(0)/HR_{NP}(0)$ and $HR_{Cox}(0)/HR_{NP}(0)$, respectively) can be estimated from the non-parametric RR's based on the individual lymphoid decedents (open circles in Figure 5).

<u>Adjusting Models for Differences in Implicitly Estimated Baseline Risks for More Appropriate Visual Comparison</u>

The ratio $HR_{spl}(0)/\ HR_{NP}(0)$ for Model 2 and $HR_{Cox}(0)/\ HR_{NP}(0)$ for Model 3 were calculated using weighted least squares and the corresponding RR functions for models 2 and 3, respectively. The best intercepts (ratios of baseline risk for each of the models to the baseline risk implied by the non-parametric RR estimates) multiply the rate ratio functions for Models 2 and 3. These adjusted Models 2 and 3 account for the differences in the baseline risks implied by the models and the implicitly estimated non-parametric baseline risks.

Figure 6 adjusts the two-piece linear spline model (linspline1600) and the standard Cox model (e^(β*exp)) by the estimated ratios $HR_{spl}(0)/\ HR_{NP}(0)$ and $HR_{Cox}(0)/\ HR_{NP}(0)$, respectively. These adjusted plots are more appropriate to compare.

The y-axis in Figure 6 has been re-labeled to indicate that the models are normalized to the baseline risk implied by the non-parametric model rather than the models' own implied baseline risks. Figure 6 is divided into four regions using different colors. Each color shows the range of individual RRs" and range of cumulative exposures that are summarized in each of "EPA's 5 RRs" based on quintiles.

[That is, the RR for the highest quintile of "EPA's 5 RR" (red dots) is equal to 3 and is placed at a cumulative exposure of 39,927 ppm-days. Table 2 and Figure 6 show that the RR for the fifth quintile summarizes the individual RRs for the 11 lymphoid cancer decedents (open circles) that had cumulative exposures greater than 13,500 ppm-days. Similarly, the RR for the fourth quintile summarizes the 11 individual RRs (open circles) based on lymphoid decedents with cumulative exposure between 3,681 and 13,500 ppm-days. The RR for the third quintile summarizes the 11 individual RRs (open circles) based on lymphoid decedents with cumulative

exposure between 1,201 and 3,680 ppm-days. Finally, the RR for the second quintile summarizes the 11 individual RRs (open circles) based on lymphoid decedents with cumulative exposure greater than zero and less than or equal to 1,200 ppm-days.]

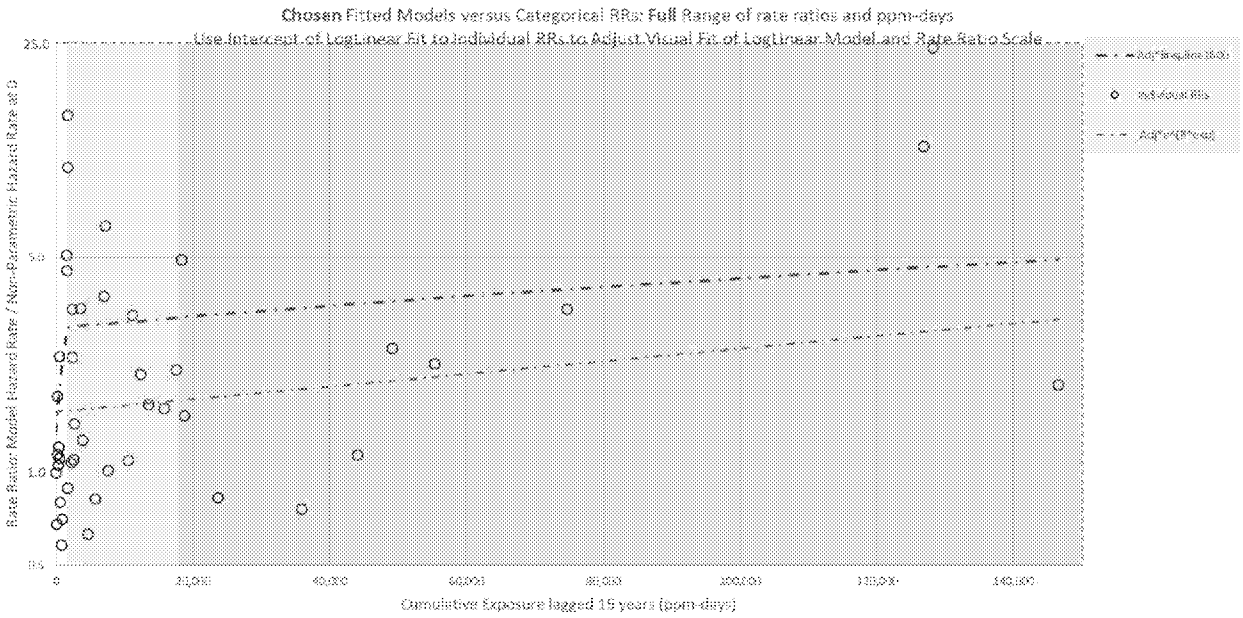

Figure 6. USEPA's and TCEQ's fitted models after adjusting the models for the difference between the implied background hazard rates of the models and the non-parametric background hazard rate compared to the RRs based on the individual decedents.

Figure 6 shows that the model selected by USEPA ("linspline1600") cannot be visually judged to be better than TCEQ's model ("e^(β*exp)").

In summary, although a secondary consideration to statistical analyses, visual comparisons of USEPA and TCEQ selected models fit the individual RRs approximately the same once differences in "baseline risks" of different RR models are reconciled. This conclusion is consistent with the conclusions drawn using correctly calculated standard model fit criteria (Appendix 4 of the revised DSD, also described in response to Comment #7 below). Moreover, the TCEQ's assessment of model performance at predicting the actual number of lymphoid cancers in the cohort as a whole and in each quintile demonstrates that the Cox proportional hazards model is reasonably accurate while USEPA's model is statistically significantly over-predictive (see Appendix 2 of the revised DSD).

Comment 7:

The DSD criticism of how EPA addressed the knot in the two-piece spline models are contrary to SAB recommendations to the EPA.

The DSD objected to the fact that EPA did not include the knot as a parameter in its estimations of the Akaike Information Criterion (AIC). Inclusion of the knot as a parameter would have been one way to do the calculation; however, the SAB supported EPA's approach. Consistent with SAB recommendations, the EPA did not make its model selections based solely on the AICs. As recommended by the SAB, EPA also gave consideration to the ability of models to reflect local behavior, e.g., prioritizing two-piece spline models, and to parsimony. The SAB singles out the knot as a parameter that could be fixed in the interest of parsimony, stating "To elaborate further, in some settings the principle of parsimony may suggest that the most informative analysis will rely upon fixing some parameters rather than estimating them from the data.... In the draft assessment, fixing the knot when estimating linear spline model fits from relative risk regressions is one such example." Moreover, the SAB fully understood how EPA determined the knot, having reviewed the Agency's approach as a charge question, finding it "scientifically appropriate and a practical solution that is transparently described." Thus, the DSD objections that the knot was estimated before it was fixed are not persuasive.

Response:

This comment addresses three different points related to the SAB review of EPA's EtO modeling: 1) whether the USEPA transparently described how the knot was set; 2) whether the knot should be considered to be a "fixed" parameter (and therefore not contribute to the number of degrees of freedom in the AIC and p-value calculations), or if the knot should be considered to have been estimated from the data, and therefore should contribute to the number of degrees of freedom; and 3) prioritizing models that reflect local behavior (such as spline models) and model parsimony.

Addressing the first point, the commenter refers to the following from the 2015 SAB document (p. 13), stating that "the SAB fully understood how EPA determined the knot" [*emphasis added*]:

> 2c: For analyses using a two-piece spline model, please comment on whether the method used to identify knots (Section 4.1.2.3 and Appendix D) is transparently described and scientifically appropriate.
>
> *The method used to identify the knots involves* a sequential search over a range of plausible knots to identify *the value at which the likelihood is maximized*. This is scientifically appropriate and a practical solution that is transparently described.

The TCEQ agrees that the method that was used to identify the knot was clear. However, how USEPA determined the knot ("the value at which the likelihood is maximized") is an entirely separate issue from whether USEPA appropriately accounted for the methods used in determining their degrees of freedom.

Relevant to the second point, the SAB stated that "To elaborate further, in some settings the principle of parsimony may suggest that the most informative analysis will rely upon fixing

some parameters rather than estimating them from the data" (p. 12 of SAB 2015). But as noted above, the knot values were statistically estimated/optimized based on the NIOSH data, so did not conform to the SAB's condition that some model parameters may be fixed in the interest of parsimony if they are not estimated from the data. Therefore, the TCEQ's conclusion that the knot derivation (which was estimated from the data) should be counted towards the degrees of freedom is not contrary to the SAB's recommendations that parameters that are not estimated from the data should be fixed in the interests of parsimony. More detailed discussion is provided below.

Model-fitting exercises were used in setting the knot values. Under the commenter's point of view, multiple parameter estimates from upstream model-fitting exercises could be used to "fix" a downstream model's parameter values (at a midpoint or mean of the estimates, for example), yet none of them would count as fitted parameters. Estimating parameters from the data, and then using the parameters as if they were not estimated is not statistically appropriate. Tables in the USEPA (2016) risk assessment and its appendices clearly indicate that the knot of the two-piece spline models were determined so that the likelihood was maximized. For example, on page 4-23 USEPA states, "For this assessment, the knot was generally selected by evaluating different knots in increments of 100 ppm × days over some range of cumulative exposures starting at 0 and then *choosing the one that resulted in the best (largest) model likelihood*. The model likelihood did not change much across the different trial knots for any of the data sets, but it did change slightly, *and the largest calculated likelihood was used as the basis for knot selection*." [*emphasis added*]. However, USEPA uses p-values and AIC values that do not account for the fact that the knot is being estimated. This is evident in Table D-30 of USEPA's appendices, which lists the p-value of 0.0482 and an AIC of 461.847. These numbers (with some rounding) are listed in USEPA's Table 4-6. What must be appreciated is that the number of degrees of freedom (DF in Table D-30, shown in Figure 7 below) is equal to 2 (one for LIN_0 and one for LIN_1). The table comes from an SAS run output that correctly accounts for the estimated parameters in the model being fit. However, SAS does not account for the fact that the output of Table D-30 is selected because it has the largest likelihood (smallest deviance) with covariates amongst all models with a knot. The number of DF reported in the SAS output (2), therefore, does not account for the fact that that the likelihood corresponds to the model whose knot maximizes the likelihood. To account for the fact that the model was selected so that the likelihood was maximized, USEPA would have to calculate the p-value and the AIC value externally. Instead USEPA quoted the p-value and AIC value as reported by the SAS output, which does not account for the fact that that the knot was estimated from the data to maximize the likelihood (inconsistent with the SAB's recommendation of a fixed parameter not estimated from the data). This error in the calculation of p-values and AIC values occurred for all two-piece models reported in the USEPA (2016) risk assessment.

The TCEQ DSD corrected these calculations in the USEPA (2016) risk assessment and reported the correct calculations in Appendix 4 of the revised DSD.

Table D-30. Results of two-piece log-linear spline model for lymphoid cancer mortality, men and women combined, knot at 100 ppm-days

Model fit statistics					
Criterion	Without covariates	With covariates			
-2 LOG L	463.912	457.847			
AIC	463.912	461.847			
SBC	463.912	465.787			
Testing global null hypothesis: BETA = 0					
Test	χ^2	DF	Pr > ChiSq		
Likelihood ratio	6.0658	2	0.0482		
Score	5.9648	2	0.0507		
Wald	5.8246	2	0.0544		
Analysis of maximum likelihood estimates					
Parameter	Parameter estimates	Standard error	χ^2	Pr > ChiSq	Hazard ratio
LIN_0	0.01010	0.00493	4.1997	0.0404	1.010
LIN_1	-0.01010	0.00493	4.1959	0.0405	0.990

Figure 7. Results of two-piece log-linear spline model for lymphoid cancer mortality, men and women combined, know at 100 ppm-days (USEPA 2016)

The third point in the comments indicate, "As recommended by the SAB, EPA also gave consideration to the ability of models to reflect local behavior, e.g., prioritizing two-piece spline models, and to parsimony." Although those words were taken from the SAB review, there is greater clarity in the full quote from the SAB:

> "First, priority should be given to regression models that directly use individual-level exposure data. Because the NIOSH cohort has rich individual-level exposure data, linear regression of the categorical results should be de-emphasized in favor of models that directly fit individual-level exposure data. Second, among models fit to individual-level exposure data, models that are more tuned to local behavior in the data should be relied on more heavily. Thus, spline models should be given higher priority over transformations of the exposure. Third, the principle of parsimony (the desire to explain phenomena using fewer parameters) should be considered."

The first SAB recommendation was taken into account by the USEPA (2016) risk assessment by using the individual data. USEPA also considered the second SAB recommendation. However, the SAB's second recommendation refers to prioritizing spline models over models with transformation of exposures (e.g., the model with log-transformed cumulative exposures). *The second recommendation is **not** prioritizing spline models over all other models*, only over models with transformation of exposure (e.g., square root of cumulative exposure, log of cumulative exposure, etc.). If the second recommendation were about prioritizing the spline model over all other models, then the SAB would be contradicting themselves in the third recommendation that appeals to prioritizing parsimony (i.e., preferring simpler models).

Comment 8:

The DSD inappropriately uses a Cox proportional hazards (PH) model for the NIOSH cohort, despite its lack of fit to the data.

a. As a central part of its analysis to calculate the cancer unit risk estimate, the DSD uses a model for the NIOSH cohort that they note does not provide a statistically significant fit to the data (though the DSD does not present a p-value). In addition, the approach that they used to demonstrate that their model provides good "predictions" of the number of cases in the NIOSH cohort is flawed (see Comment #13 below).

b. Furthermore, the model used by TCEQ is inherently sublinear and cannot reflect the overall supralinear shape of the exposure-response relationship (See model "e^(β*exp)" in Fig 4-3 of EPA's assessment and the p-values in Table 4-6). The Cox PH model for lymphoid cancers in males and females in the NIOSH cohort has a p-value 0.22, while the best-fitting supralinear model has a p-value of 0.02—a much lower and statistically significant value, indicating the supralinear model provides a better fit to the data. The Cox PH model was presented in EPA's assessment for comparison with other models, therefore the SAB was able to consider it as an option, and yet, the SAB did not promote it but instead endorsed two-piece spline models.

   EPA and the SAB recognized the importance of local fit to the data, as well as overall fit. The two-piece spline model used by EPA, and endorsed by the SAB, can represent the increasing response at lower exposures (without excessive curvature at the lowest exposures) and the relative plateauing at higher exposures, as discussed above (Comment #6). To estimate the risks of environmental exposure levels from higher exposure data, such as occupational data, capturing this local behavior at the lower exposure range of the data is especially important because it reflects the data range most relevant to the even lower exposures of interest.

c. In contrast, the Cox PH model used by TCEQ cannot accommodate supralinear exposure-response data and, in particular, cannot reflect the exposure-response relationship in the lower exposure range of the data. Instead, in order to attempt to fit the high-exposure plateauing, such a model must inflate the internal baseline hazard rate and depress the low-exposure slope. This is illustrated in Figure 21 of the DSD, where the dotted blue line depicts the model used by TCEQ with an approximated baseline hazard rate shown relative to the nonparametric baseline hazard rate. It is apparent from this depiction that the baseline rate in the Cox PH model has been markedly overestimated relative to the nonparametric (categorical) baseline (RR = 1). The nonparametric baseline, however, is the best available estimate of the baseline hazard rate in the cohort because it is based on the 0 (lagged) cumulative exposure group without any assumptions about the shape of the exposure-response model for the exposed workers and, thus, without any influence of the higher-exposure data on the model fit to the lower-exposure data.

d. Despite these clear problems, TCEQ goes on to calculate the point of departure (POD) using the sublinear Cox PH model, and Table 30 on p. 93 of the DSD presents a confidence score of "high" for the POD. This score is totally unwarranted because the Cox PH model does not provide a statistically significant fit to the data and is inconsistent with the overall shape of the exposure-response data. Moreover, the "predictive" value of the model is based on a flawed approach, as discussed in Comment #13 below. Finally, even if the model and predictions were valid, there are insufficient data in the range of the POD, which was calculated at a risk level of 1 in 100,000, to conclude that the model yields reliable estimates in that range, as discussed in Comment #11.

For all of these reasons, the DSD's model selection and POD derivation, and the subsequent cancer unit risk estimates based on them, are not scientifically supported.

Response:

a. Based on correctly calculated p-values and AIC values (discussed in response to Comment #7), the Cox proportional hazards model fits the data as well as USEPA's overall supra-linear model (see Appendix 4 of the revised DSD for correctly calculated p-values and AIC values). That being said, neither TCEQ's model nor USEPA's selected model (two-piece linear spline model with knot at 1600 ppm-days) is statistically significantly different than the model with zero slope once the correct degrees of freedom are correctly accounted for. However, the model TCEQ used is preferable to USEPA's selected model because it has a better AIC than the model USEPA selected (Table 38 in the proposed TCED DSD). The calculation of a unit risk factor is done for regulatory purposes and not because EtO exposures had shown increasing cancer risk in the NIOSH study. Valdez-Flores et al. (2010) fit the model to 72 combinations of 12 endpoints and 6 sub-cohorts, lagged and unlagged, and found none were statistically significantly related to cumulative exposures of EtO; these results are consistent with the recent meta-analyses by Marsh et al. (2019) and Vincent et al. (2019). Lymphoid cancer in NIOSH male workers had the lowest effective concentration found by Valdez-Flores et al. (2010), which the TCEQ conservatively choose to estimate unit risk factors (even though there is no significant increased cancer mortality with cumulative exposure to EtO for any of the endpoints examined). Also see the response to Comment #13.

b. Regarding the comment on the supra-linear shape of the exposure-response relationship, refer to the response to Comment #6 above as well as the following. While visual fit to the nonparametric RRs was used by USEPA (2016) as a criterion for model selection, no appropriate visual comparison of model fit to the lymphoid cancer mortality data can be made based on USEPA Figure 4-3 (p. 4-21 of USEPA 2016) since the data shown are not the data to which the models were fit. USEPA Figure 4-3 shows models compared to arbitrarily-chosen quintile categories of data used to estimate rate ratios. The actual data underlying the model fits are the individual data, not the less refined categorical data shown in USEPA Figure 4-3. Thus, because the model fits shown in USEPA (2016) Figure 4-3 are fit to the individual data (and not the categorical data depicted), the figure does not actually indicate model fit to the modelled data at all. Additionally, categorical non-parametric rate ratios

(RRs) should not be used for visually comparing models fit to individual data, particularly when appropriate statistical model fit criteria are available. The RRs of parametric models fit to the individual data are defined with respect to an underlying background hazard rate estimated by the model. However, the underlying background hazard rates estimated by the nonparametric RRs and the parametric model are generally different. Moreover, visual interpretation of the consistency of categorical RRs with the shape/slope of a modelled dose-response can change as the number of exposure categories changes. For example, Figures 1-3 of Valdez-Flores and Sielken (2013) demonstrate, among other things, how the dose-response (i.e., dose-RR) slope for breast cancer mortality in the NIOSH cohort appears very steep when compared to only four exposure categories but seems more shallow when additional categories are added. In the present case, the overall dose-response appears ill represented by only a few categorical RRs (see Valdez-Flores and Sielken 2013 and associated supplementary materials). The visual presentation of only a few exposure categories can blind the data user to the variability in the underlying dose-response data, and by corollary, preclude an appropriate visual assessment/comparison of model fit to the actual individual data. See Appendix 5 of the revised DSD for additional information. A better comparison of models fit to the observed data is to use the predictiveness of the model; that is, the capability of the model to estimate the observed number of deaths with a certain degree of confidence (see Appendix 2 of the revised DSD).

Regarding the SAB's opinions on model choice, none of the charge questions asked the SAB to make a recommendation as to which model was best. The SAB did however, include a discussion about using the AIC. They indicated that the AIC could be used to compare models as long as the models were not using a transformation of the cumulative exposures (e.g., log(cumulative exposure) or square root(cumulative exposure)). Thus, following the SAB recommendation and using the corrected AIC and p-values from Table 4-6 (as reported in Table 38 of the proposed TCEQ DSD and discussed in response to Comment #7), the TCEQ log-linear model has an AIC of 464.4 and the USEPA selected two-piece linear spline model has an AIC of 464.5 (lower AIC scores are generally preferable). Furthermore, the TCEQ log-linear model is more parsimonious (has fewer parameters) than USEPA two-piece spline models with a knot at 1600 ppm-days. While the SAB did recommend using a two-piece spline model *over the models that use the logarithm of the cumulative exposure or the square root model*, they did not dismiss the Cox proportional hazards model, which based on new analyses by the TCEQ clearly better predicts the observed number of deaths in the cohort overall and in every cumulative exposure quintile (see Appendix 2 of the revised DSD).

c. The commenters note that "the Cox PH model used by TCEQ cannot accommodate supralinear exposure-response data". It is true that the Cox proportional hazards model is not a supra-linear model; however, the conclusion that the data is supra-linear is based (as noted above) on the categorical quintile analysis that does not represent the underlying data. In fact, the best fitting model to the underlying data is a piecewise model that joins the individual RRs (44 individual RRs and the control group), producing a clearly meaningless relationship:

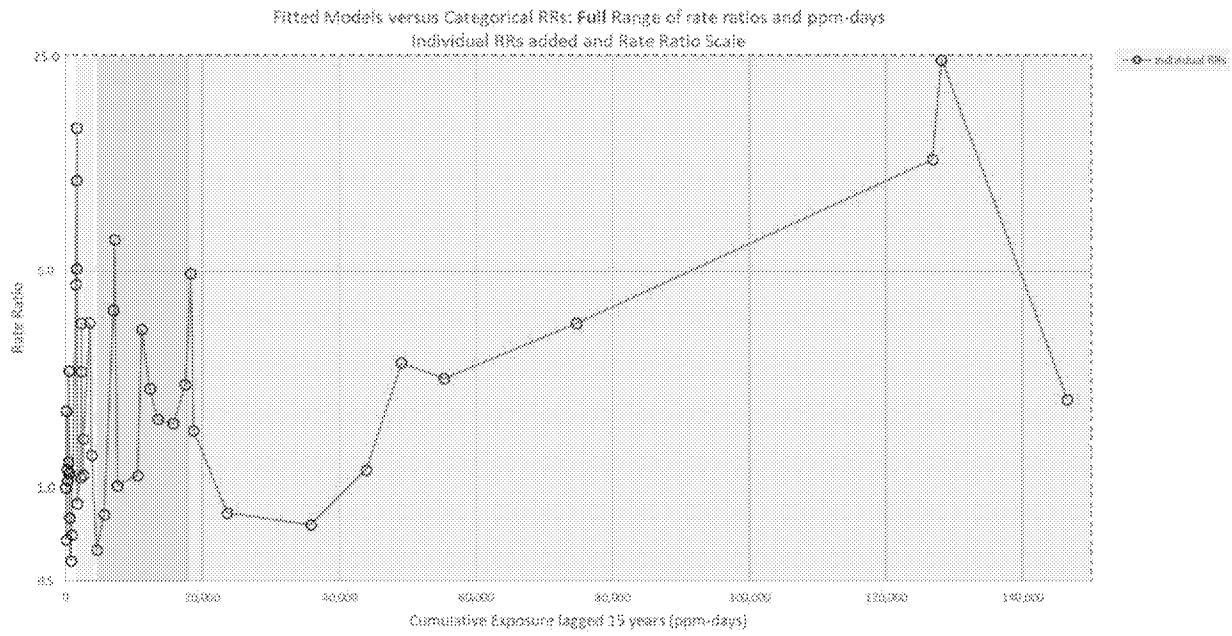

Figure 8. Piecewise model joining the 44 individual RRs and the control group.

The Cox proportional hazards model is a parsimonious model that compromises across the variability present in the data, weighting observations according to the risk set of each individual decedent (53 lymphoid decedents in the NIOSH study). The non-parametric rate ratios are estimated as the ratio of the mean hazard of a group of individuals (the group may include one or more decedent) and the mean hazard of all the individuals in the unexposed group (there are 9 decedents with 0 cumulative exposure when lagged 15-years in the NIOSH study). The mean hazard of the 9 individuals in the unexposed group is not a constant, fixed number. The implicitly estimated mean baseline hazards have variability that is not estimated in the Cox proportional hazards models (the non-parametric rate ratios are one such example). That is, the non-parametric rate ratios do not have the "true" implicitly estimated baseline hazards; they have the implicitly estimated baseline hazards that maximize their likelihood. That is true also for all Cox proportional hazards models (TCEQ and USEPA models) fit to the NIOSH individual data. In summary, an exposure-response model is not expected to go through any specific nonparametric rate ratio, nor is expected to implicitly result in the same baseline risk estimated non-parametrically. TCEQ response to Comment #6 elaborates on this issue and shows figures that may help the reader better understand how Cox proportional hazards models can be visually compared.

d. As indicated above, TCEQ developed a POD despite the fact that the recent EtO literature does not support any increased significant cancer risks in humans (Marsh et al. 2019, Vincent et al. 2019, Valdez-Flores et al. 2010). The calculation of a unit risk factor is done for regulatory purposes and not because EtO exposures had shown increasing cancer risk in the NIOSH study. Furthermore, the standard Cox model estimates the number of observed lymphoid deaths in the NIOSH study (the actual observed data, rate ratios are not observed

data) with 95% confidence. USEPA's selected model is shown by TCEQ to overestimate the observed number of lymphoid cancer deaths at the 5% significance level.

In contrast to the commenter's statement that there are insufficient data in the range of the POD (1 in a 100,000), the TCEQ calculated that 7 of the 27 male lymphoid decedents had cumulative exposures below the POD for 1 in 100,000 extra risk (Table 1). Similarly, more than 30% of the male workers in the NIOSH study were exposed to EtO concentrations below the 1 in 100,000 extra risk. In addition, the URF changes less than 8% if a higher POD (1/1,000 extra risk) is considered. A POD of 1 in 100 (as used by USEPA) results in concentrations that exceed the cumulative exposure for all male lymphoid decedents and the cumulative exposure of more than 99.8% of all male workers in the NIOSH study.

The rest of the comments in this paragraph are addressed in previous or subsequent comment responses.

Comment 9:

The DSD is incorrect in its claim that EPA should have considered environmental exposures to ethylene.

Environmental exposures to ethylene would be part of background risk and would not affect EPA's EtO unit risk estimate, which is for extra risk above background.

Response:

The TCEQ DSD does not state that USEPA (2016) should have considered environmental exposures to ethylene in their dose-response assessment. Rather, the TCEQ is noting that USEPA has not followed the implications of their EtO assessment for ambient ethylene; namely that based on the USEPAs URF for EtO, given the 3% conversion of ethylene to EtO in humans cited by USEPA, there would appear to be a nationwide ethylene carcinogenic risk issue (which the TCEQ does not find is the case).

Comment 10:

The DSD ignores issues with the Swaen et al. (2009) analysis that decreased the ability of that analysis to detect associations for lymphoid cancer.

The DSD cites the Swaen, et al. (2009) study of the Union Carbide Corporation (UCC) as reporting that "no indications were found for excess cancer risks from EtO exposures, including lymphohematopoietic malignancies," however the Swaen analysis has important limitations:

a) The trend analyses were done using the sublinear Cox model, which would be limited in detecting supralinear trends (see Comment #8).

b) The categorical analyses were based on standardized mortality ratios (SMRs), which are notoriously deficient for analyzing occupational epidemiology data because workers

often have background disease mortality rates below those of the general population. This concept is called the "healthy worker effect" (HWE), although it can reflect differences between an occupational cohort and the general population beyond health. In fact, EPA's SAB specifically recommended that epidemiological results based on external standards, e.g., SMRs, be down-weighted, stating "[t]he presence of the healthy worker effect cannot be denied in these occupational data and the use of an external standard for comparison does not avoid healthy worker types of biases."

c) The long follow-up in the UCC cohort, well past the occurrence of non-negligible exposures, was likely observing proportionately more background cases associated with increasing age of the cohort than cases associated with exposures in the distant past. In other words, most of the workers who would die of exposure-related lymphoid cancers would likely have already passed; thus, proportionately more of the new cases picked up in the extended follow-up would be background cases. This excessive follow-up, given the time that had lapsed since non-negligible exposures ceased, would make it more difficult to observe an exposure-related effect. (See also p. A-30 to A-31 of Appendix A of EPA (2016b) for more discussion.)

The DSD's interpretation of the Swaen study does not account for these critical limitations.

Response:

a) Regarding the statement that "The trend analyses were done using the sublinear Cox model, which would be limited in detecting supralinear trends (see Comment #8)", as shown in various figures in the DSD, the Cox model is indistinguishable from linear over the doses of interest for EtO. In addition, the analysis from Swaen et al. (2009) assessed whether the slope of the exposure-response relationship was statistically significantly different from zero; it was not, and does not reflect the shape of the exposure-response relationship.

b) In evaluating internal standard analyses, USEPA's SAB specifically stated, "[t]he presence of the healthy worker effect cannot be denied in these occupational data and the use of an external standard for comparison does not avoid healthy worker types of biases." However, the most pertinent question is whether a healthy worker effect can be assumed for the cancer endpoints being evaluated for EtO. That is, as SAB suggests, is the healthy worker effect for lymphoid cancer and breast cancer incidence in fact undeniable? Though opinions vary about using general population background rates for evaluating cause-specific mortality rates of occupational studies, it is standard practice/methodology in epidemiology studies to use general population background rates to evaluate the well-established and widely-accepted SMRs and SIRs because there is often no scientific evaluation of the magnitude of the healthy worker effect.

   The TCEQ investigated this question and finds that the healthy worker effect (as evidenced by decreased overall mortality, etc.) does not necessarily extend to specific cancers. More specifically, the results of a relatively recent and large study (366,114

workers) conducted specifically to examine the potential for the healthy worker effect in cancer incidence studies (Kirkeleit et al. 2013) found, for example, that while all-cause, ischemic heart disease, and circulatory system disease mortality were statistically significantly decreased in male workers (n=283,002) and female workers (n=83,112) compared to the general population (Table 3 of the study), the SIRs for lymphoid and hematopoietic cancers in male workers and female workers were 0.97 (0.90, 1.03) and 1.09 (0.92, 1.27), respectively, consistent with the lack of a statistical difference (i.e., lack of a healthy worker effect for these cancers). Additionally, the Kirkeleit et al. (2013) study found that breast cancer incidence in over 83,000 female workers was as expected based on the general population (i.e., SIR of 1.02 (0.95, 1.09)). Thus, Kirkeleit et al. (2013) found no healthy worker effect for both lymphoid/hematopoietic and breast cancer incidence, and SMRs for workers in the NIOSH and DOW/UCC are similar to those reported by Kirkeleit et al. (2013) for lymphoid cancer mortality. Footnote * to Table 32 in the TCEQ DSD states "Quintile 1 is the control (unexposed lagged-out) group with 9 lymphoid cancer mortalities observed and 11.5 mortalities predicted by all models with a 95% confidence interval of (6.0 and 25.2), which includes the 9 lymphoid cancer deaths." This confidence interval indicates that the observed 9 lymphoid cancer deaths in the unexposed male and female workers of the NIOSH cohort is consistent with the number of lymphoid cancer deaths in the general U.S. population during the same period of time after accounting for age, sex, and calendar year. Expressed in terms of SMRs, the SMR for lymphoid cancer deaths in the unexposed male and female NIOSH workers is equal to 0.78 (9/11.5) with a 95% confidence interval (CI) equal to (0.36, 1.50). The 95% CI on the SMR for unexposed workers includes the value of one, which indicates that the mortality rate in the unexposed workers in the NIOSH study and the U.S. population mortality rate are not statistically significantly different at the 5% significance level (p-value of 0.29). Similar results are obtained for the male NIOSH workers that drive lymphoid cancer risk. More specifically, the SMR for lymphoid cancer deaths in the unexposed male NIOSH workers is equal to 1.03 (6/5.8) with a 95% CI of (0.38, 2.25). Thus, the lymphoid cancer mortality rate in unexposed male workers in the NIOSH cohort, the gender that drives the URF, is not statistically significantly different than that in the U.S. population (p-value of 0.64).

In summary, these results demonstrate that there is no healthy worker effect for this critical endpoint in this key group (i.e., male workers, who drive lymphoid cancer risk in the cohort) or in males and female workers combined. These results based on the NIOSH cohort are consistent with the findings of Kirkeleit et al. (2013). Thus, the comments do not change TCEQ's overall conclusions on the findings reported by Swaen et al. (2009) using external background hazard rates (which were corroborated by Valdez-Flores et al. (2010) using internal background hazard rates).

c) To address the concerns from sections a, b, and c of these comments, the DSD now refers to section A.2.20 of USEPA (2016), which includes a discussion of Swaen et al. (2009), and language has been added regarding the long follow-up being viewed as a limitation by USEPA, as well as their characterization of the exposure assessment as

relatively crude. The TCEQ notes, however, that the UCC cohort data does not contribute to the final URF (i.e., TCEQ's URF is exclusively based on NIOSH cohort results). In addition, even given the lack of statistically significant association between lymphoid cancer and EtO concentrations in the UCC cohort, the TCEQ conservatively assumes that EtO causes lymphoid cancer in humans.

Comment 11:

The DSD's approach to deriving a quantitative cancer risk estimate for ethylene oxide exposure has a number of scientific problems that lead to underestimating risk.

a) TCEQ's quantitative risk estimates are for lymphoid cancer only and do not include the risks for breast cancer in females (see also Comment #1).

b) For lymphoid cancer, as discussed above (Comment #8), the DSD selected a sublinear Cox PH model that does not fit the data.

c) In addition, the use of a 70-year cut-off in the lifetable analysis is not consistent with a default (average) lifetime of 70 years. EPA also uses a default average lifetime of 70 years but recognizes that 70 years should not be used as a cut-off in lifetable analyses, because in such analyses, actual demographic data about mortality rates at different ages are incorporated rather than using an average default lifetime. Truncating the analysis at 70 years actually corresponds to an average lifetime of less than 70 years because the hypothetical population tracked in the lifetable analysis is allowed to die at younger ages than the would-be average of 70 years but not allowed to live beyond 70 years. In contrast, truncating the lifetable analysis at 85 years corresponds to an average lifetime of about 75 years, which is close to the default average of 70 years.

d) Another difference between the EPA and TCEQ approaches is that the EPA estimates are for cancer incidence, whereas the TCEQ estimates are for mortality. The SAB endorsed EPA's approach for calculating incidence estimates from mortality data.

e) Moreover, in the DSD, the modeling for lymphoid cancer was apparently done all the way down to a risk level of 1 in 100,000 using the (non-fitting) sublinear model. In so doing, the TCEQ over relies on a sublinear model that doesn't describe the overall data well and certainly can't reliably estimate risks at corresponding low levels of exposure where there are few data. In other words, this approach assumes that the sublinear model is valid not only in the observable range of the data, contrary to findings that the underlying exposure-response data are more supralinear in shape, as discussed above (Comment #8), but also in the lower exposure range, where the data are insufficient to estimate risks with any confidence. On p. 5 of the DSD, the TCEQ criticizes the EPA, stating "High-dose carcinogenicity data alone are incapable of informing truly low-dose risk"; however, it is the TCEQ, not the EPA, that models from the high-dose data down to a risk level of 1 in 100,000.

In contrast, EPA's approach does not presume to be able to estimate risks at such low levels. Instead, EPA's Guidelines on Carcinogen Risk Assessment advocate modeling the data and then selecting a POD near the low end of the observable range, i.e., the low end of the range in which increased risks might be reasonably detectable above background variability, and applying an extrapolation method from the POD. In the absence of sufficient evidence that a nonlinear approach is warranted, the default approach is to use linear extrapolation. In the case of EtO, the use of linear extrapolation from the POD is supported by the finding of a mutagenic MOA, in accordance with EPA's guidance. Linear extrapolation was also endorsed by the SAB. Given the background rates of lymphoid cancer, EPA chose a POD of 1% extra risk, or 1 in 100, which is far from the risk level of 1 in 100,000 used by TCEQ.

TCEQ's own protocol for developing toxicity factors provided in Section A1.1 of Appendix 1 of the DSD states that one "extrapolate[s] from the adjusted POD to lower exposures based on MOA analysis"; however, as discussed above, in this DSD, modeling was done all the way down to a risk level of 1 in 100,000 using a (non-fitting) sublinear model. The DSD's approach is inconsistent with the guidance of EPA and other agencies (including possibly TCEQ as well, according to their protocol), in which a POD is selected near the low end of the observable range and then the mutagenic MOA established for EtO would support linear low-dose extrapolation.

f) See also Section A.2.20 of Appendix A of EPA's assessment (2016b) for more discussion of the above issues related to the lymphoid cancer risk estimates. The section critiques the approach used by Valdez-Flores et al. (2010), which was largely adopted in this DSD.

All of these scientific flaws contribute to the DSD's final unit risk estimate being a gross underestimate of the cancer risks demonstrated by the evidence.

Response:

a) See TCEQ's response to Comment #1.

b) See TCEQ's response to Comment #8.

c) The use of a 70-year cut-off in the lifetable analysis (or any other cut-off) is unrelated to the lifespan of the population. The purpose of the lifetable analysis is to calculate the extra risk of dying of the specific cause by age 70 years (irrespective of what the average lifetime is). Thus, if the goal was to calculate extra cancer mortality risk within the first 50 years of life, then the lifetable would calculate that extra risk by running the table up to 50 years. However, that does not mean that a 50-year old has a life expectancy of less than 50 years, or that he/she may not die from the specific cause after 50 years. Truncating the lifetable analysis at a specific age (say 70 years) does not mean that the risk of dying from the specific cause beyond the specific age is zero but that the *extra* risk of dying from the specific cause beyond that age is zero. The calculated extra risk is

due to the assumed exposure to the agent purportedly increasing the specific cause of death hazard rate.

USEPA (2016) acknowledges that by truncating their lifetable at age 85 years "EPA did not assume an 85-year lifetime" (page H-35 of USEPA 2016 appendices). The reason USEPA stopped at 85 is not because stopping at 85 years implies an average lifespan of 75 years. USEPA stopped the lifetable analysis at 85 years "because cause-specific disease rates are less stable for those ages" (footnote 16 on page 4-9 of EPA 2016 risk assessment) above 85 years. However, USEPA (2016) did not consider the fact that less than 1% of the workers in the NIOSH study lived past 85 years, which implies that the rate ratio models derived from the NIOSH study are not reliably applicable (stable) for these ages. In contrast, more than 15% of workers in the NIOSH study lived more than 70 years. Using proportional hazards models based on the NIOSH study to calculate extra risks beyond 70 years (e.g., 85 years) is extrapolating beyond the observed data used to derive the models.

The TCEQ decided to use 70 years to calculate the extra risk, based both on the science described above as well as the TCEQ policy to calculate the risk up to age 70 per TCEQ guidelines (TCEQ 2015). TCEQ policy takes into consideration the uncertainties associated with models derived from studies with short lifespan. TCEQ guidelines indicate the following [*emphasis added*]:

> If the probability of the specified response in the exposure-response model includes time (age), then the excess risk and the definition of the [effect concentration] EC also includes a specified time (age). For example, most exposure-response models used for epidemiology data incorporate the time at which a response is observed. In these models, the excess risk and the definition of the EC also include a specified time (age). In the calculation of excess risk, it is assumed that the exposure scenario remains unchanged up to that time (age) (i.e., a constant exposure concentration up to that age is presupposed). Furthermore, it is assumed that the estimated exposure-response model is appropriate up to that time (age). *For example, if an exposure-response model is estimated using occupational epidemiology data that only includes workers up to age 65 years, then calculating an excess risk up to age 70 years or higher involves an extrapolation over age that may or may not be warranted*. Also, because the excess risks and ECs are often heavily dependent upon the specified time (age), it is important to consider what the specified time (age) is when interpreting the results. For example, time might be age and the specified time be set to 70 years. In which case, the excess risk refers to the excess risk by age 70 years. *As is common in regulatory risk assessment, the TCEQ uses a default exposure duration of 70 years* as discussed in Chapter 1. *Another reason* to use an exposure duration of 70 years for calculation of excess risk using epidemiology data is that the *background rates of the disease and survival rates for a*

population used in the life-table analysis (BIER IV approach) discussed in the following section are more uncertain after 70 years.

d) TCEQ risk estimates are based on lymphoid mortality because the NIOSH study made available only the mortality data. Scientifically, it is incorrect and inappropriate to use a model based on observed data (e.g., lymphoid mortality) to predict values for different data (e.g., lymphoid incidence). The exposure-response relationship for mortality could be significantly different than the exposure-response relationship for incidence (e.g., USEPA (2016) modeling results for breast cancer mortality versus incidence were very different). The discrepancies between the two for TCEQ's critical cancer endpoint, lymphoid cancer, would depend on several factors including the survival period after detection of the specific cause of death.

   TCEQ is committed to using scientifically defensible approaches in its regulatory practices and strives to maintain both scientific accuracy and an appropriate level of conservatism (e.g., use of the 95% UCL, ADAFs). The TCEQ URF adequately protects human health because of the following conservative considerations:

   1) The lack of human data sufficient to establish EtO as a human carcinogen despite occupational exposures up to millions of times ambient levels;
   2) The lack of statistically significantly increasing risk with exposure to EtO;
   3) Using the endpoint (lymphoid cancer), study cohort (NIOSH), and sub-cohort (males) that predicts the largest estimated risk of seventy-two non-increasing exposure-response models;
   4) Uncertainty in the model parameter estimate (i.e., use of the 95% UCL);
   5) *Continuous* exposure to EtO, 24 hours a day, 7 days a week, for every week of every year, from birth until 70 years of age; and
   6) Adjustment for early-age exposures using ADAFs.

   Adding another layer of protection to the already protective evaluation would have to be a policy decision (i.e., weighed against a procedure resulting in technical/scientific inaccuracy).

e) The TCEQ evaluated the LEC at an extra risk of 1 in a 100,000 consistent with USEPA cancer guidelines (2005) on the selection of a POD at the low-end of the observable range of exposures. Although for animal studies, a typical POD is an extra risk of 0.10 because it corresponds to doses near the low-end of the doses, in epidemiological studies a lower level of risk needs to be used.

   TCEQ used the standard Cox proportional hazards model to calculate LEC for an extra risk of 1 in a 100,000 because the EC corresponding to the same risk level are in the range of the observed data in the NIOSH study. That is, the EC for an extra risk of 1 in 100,000 of lymphoid cancer mortality in males is 9.67E-03 ppm for 70 years with an exposure lag of 15 years, which correspond to a cumulative

occupational exposure of 591 ppm-days. There are 7 male workers in the NIOSH cohort with cumulative exposures less than 591 ppm-days. That is, 25.9% of the male workers in the NIOSH cohort that died with lymphoid cancer were exposed to cumulative exposures of less than the EC for 1 in a 100,000. In contrast, the EC for 1 in 100 results in environmental concentrations corresponding to cumulative occupational exposures of 354,400 ppm-days, which exceeds the largest cumulative exposure of lymphoid male decedents in the NIOSH study.

Table 1 above (see response to ACC Comment #15) shows the EC corresponding to different risk levels and the corresponding cumulative exposures with the number of lymphoid mortality cases of the male workers in the NIOSH study. The results in Table 1 show that the EC for an extra risk of 1 in a 100 is outside the range of cumulative exposures for the male lymphoid mortalities observed in the NIOSH study and in the upper 1% of cumulative exposures for all male workers. That is, all males that died with lymphoid cancers and more than 99% of all male workers had cumulative exposures less than EC(1/100). Thus, the NIOSH study does not support an extra risk of 1 in a 100 as a point of departure.

The EC for an extra risk of 1 in a 1,000 is a concentration that is in the high-end of cumulative exposures of male lymphoid mortalities observed in the NIOSH study. That is, 77.78% of all males that died with lymphoid cancers and 94.48% of all male workers had cumulative exposures less than the EC(1/1,000). Thus, a point of departure of 1 in 1,000 is at the higher-end of the cumulative exposures of male workers of the NIOSH study.

The EC for an extra risk of 1 in 10,000 is a concentration that includes 48.15% of the decedent men with lymphoid cancer and 66.45% of all men in the NIOSH cohort with smaller cumulative exposures. *The EC for an extra risk of 1 in 100,000 includes 25.93% of male lymphoid decedents and 30.17% of all males in the NIOSH study with smaller cumulative exposures.* Thus, use of an extra risk of 1 in 100,000 is supported by the NIOSH observed data, being near the lower end of the observed range of cumulative exposures to EtO, and is consistent with USEPA and TCEQ guidelines (USEPA 2005a, TCEQ 2015) on the selection of a POD at the low-end of the observable range of exposures.

Based on Table 1 results, using either 1 in 10,000 or 1 in 100,000 extra risk PODs (as PODs in the range of the observed data and close to the low-end of the observable range) round to the same ADAF-unadjusted URF selected by the TCEQ (2.5E-06 per ppb). Looking at it from a different perspective, using the 1 in 10,000 excess risk LEC of 4.04E-02 ppm as the POD and linear extrapolation, the 1 in 100,000 air concentration (ADAF unadjusted) is still 4 ppb (i.e., 1E-05/2.47E-06 per ppb = 4.05 ppb). This information has been added to Appendix 7 of the revised DSD.

f) Given the overall lack of evidence of the relationship between cancer risk and exposure to EtO (e.g., with correctly calculated p-values, models do not fit the lymphoid data statistically significantly better than the null model with zero slope), any unit risk estimate may overestimate the true cancer risk due to exposure to EtO, and therefore, be health-protective. The lower URF derived by TCEQ, compared to the USEPA URF, is primarily due to differences in the selected model. The TCEQ selected a model based on scientific considerations and principles that are discussed at length in the response to other comments.

Section A.2.20 of Appendix A of USEPA's 2016 assessment critiques the approach used by Valdez-Flores et al. (2010). The TCEQ has carefully considered those critiques and has made modifications to our approach based on their scientific validity. For example, the TCEQ has revised its assessment to incorporate ADAFs consistent with equation 5-17 of the TCEQ guidelines as opposed to incorporating them into the lifetable analysis as implemented by Sielken and Valdez-Flores (2009b) (see p. A-35 of Section A.2.20). The TCEQ did not agree with all of the USEPA's critiques however. For example:

> Because the Valdez-Flores et al. (2010) categorical results are for unlagged analyses, however, their referent groups are different from those used by Steenland et al. (2004). Valdez-Flores et al. (2010) used the lowest exposure quintile (providing there were sufficient data) as the referent group, whereas Steenland et al. (2004) used the no-exposure (lagged-out) group as the referent. [pg A-32]

This statement does not accurately represent how the Cox proportional hazards model estimates non-parametric rate ratios. In the Cox proportional hazards model the "referent group" is not an "unexposed" group. The "referent group" is the group of individuals alive at the time of the case being evaluated. That is, regardless of what the exposure lag is, the "referent group" is the same for each individual at that particular timepoint. The rate ratios may change between unlagged and lagged cumulative exposures because the cumulative exposure (which is the main covariate) changes (this is true for Steenland et al. (2004) and Valdez-Flores et al. (2010) analyses). Statements like this in USEPA's risk assessment have resulted in many readers misunderstanding results of exposure-response modeling. In fact, it was in response to Valdez-Flores et al. (2010, 2013) publications through SAB recommendations that USEPA changed their dose-response modeling of a linear model using quintiles in 2006, 2011, and 2013 to modeling the individual data in 2016. The TCEQ also uses the individual data, and among other important considerations, demonstrates that: (1) USEPA's two-piece spline model does not fit the data better than the Cox model; and (2) USEPA's selected model assessment statistically overestimate the number of lymphoid cancers in the NIOSH cohort as a whole and for the individual exposure quintiles whereas TCEQ's model is relatively accurate. The TCEQ DSD extensively documents and justifies use of the Cox proportional hazards modelling results based on these and other scientific considerations.

Comment 12:

The DSD does not appropriately account for the science showing increased cancer risks from early life exposures to carcinogens with a mutagenic mode of action.

The DSD states that the approach of Sielken and Valdez-Flores (2009) was used to apply the age-dependent adjustment factors (ADAFs) to the cancer risk estimates; however, the ADAF calculations were not done correctly by Sielken and Valdez-Flores (2009). Early life exposures to chemicals with a mutagenic MOA such as EtO can increase lifetime cancer risk, and thus EPA guidance recommends the application of ADAFs in quantitative risk calculations to adjust for this potential increased susceptibility. This means that exposure to a mutagenic carcinogen at a young age can increase a person's risk of developing cancer later in life. Thus, the ADAFs are designed to adjust lifetime risk, to reflect increased lifetime cancer risk from increased susceptibility to early-life exposures. But Sielken and Valdez-Flores (2009) incorrectly multiply the ADAFs to the age-specific cancer mortality rates in the lifetable, which just applies the factors to risk for those younger age groups and ignores increased risks for older ages (discussed in more detail in EPA's assessment). In addition, assuming increased early-life susceptibility and applying the ADAFs along with the Cox PH model in the lifetable analysis, as done by Sielken and Valdez-Flores (2009), is inconsistent with a major assumption of the Cox model, that RR is independent of age.

In fact, because of the lagged exposures and low cancer mortality rates at young ages, applying the ADAFs just to young age groups had a negligible effect on the final risk estimates in Sielken and Valdez-Flores (2009). In contrast, the approach that correctly accounts for the science showing that early life exposures increase lifetime cancer risks (used by EPA) increased the lifetime risk estimates by about 22% (for both female breast cancer and lymphoid cancer combined).

The DSD's confidence score for sensitive populations was "medium." However this score is not warranted because TCEQ discounts the breast cancer risk in females and misapplies the ADAFs for susceptibility from early-life exposures, both of which result in underestimations of the risks posed by ethylene oxide.

Response:

The TCEQ DSD now calculates the ADAF-adjusted long-term ESL consistent with equation 5-17 of the TCEQ guidelines (TCEQ 2015), rounding it to two significant figures at 2.4 ppb. That being said, we do want to address some of the points made concerning the implementation of ADAFs by Sielken and Valdez-Flores (2009).

The Sielken and Valdez-Flores (2009) paper outlines issues regarding the use of ADAFs developed for animal studies that are exposed to a constant dose throughout their life. The article indicates that ADAFs as developed were meant for models that assume a constant dose metric (as is the case for most animal-based dose response models) and not for age-dependent dose metrics (as is the case for the models developed for EtO based on the NIOSH study). Sielken and Valdez-Flores (2009) work through a USEPA example to show that the ADAFs as

developed by USEPA do not apply to a model that uses cumulative exposure as a dose metric, as opposed to a model that uses average exposure as a dose metric.

TCEQ guidelines use ADAF for models based on a constant dose metric using USEPA (2005) guidelines. However, for models based on cumulative dose metrics (the dose metric used for EtO), the TCEQ guidelines allow for implementation of ADAFs in lifetable analyses (see Section 7.9.4 of TCEQ 2015). However, in the present case the TCEQ has elected to revise its assessment to incorporate ADAFs consistent with equation 5-17 of the TCEQ guidelines as opposed to incorporating them into the lifetable analysis since USEPA (2016) specifically objects to the ADAF implementation discussed in Sielken and Valdez-Flores (2009) (see p. A-35 of Section A.2.20 of USEPA 2016).

Comment 13:

The DSD uses a scientifically inappropriate comparison explicitly rejected by the SAB to "predict" the numbers of cases in the NIOSH cohort.

a) TCEQ's method for predicting the number of cases in the NIOSH cohort relies on a standardized mortality ratio (SMR) comparison. As discussed in Comment #10b, SMRs are notoriously deficient for analyzing occupational epidemiology data because workers often have background disease mortality rates below those of the general population. This concept is called the "healthy worker effect" (HWE), although it can reflect differences between an occupational cohort and the general population beyond health. In fact, EPA's SAB specifically recommended that epidemiological results based on external standards, e.g., SMRs, be down-weighted. The SAB states "The presence of the healthy worker effect cannot be denied in these occupational data and the use of an external standard for comparison does not avoid healthy worker types of biases."

   In the DSD, basing the "predictions" on an SMR comparison ignores the healthy worker effect apparent in the data and inflates the background risk expected in the cohort, equating it to the background risk in the general population. Therefore, all the relative risk (RR) models, which are based on an internal analysis estimating increases in risk relative to the actual (lower) background rates in the cohort, will overestimate cohort case numbers when the increases in risk are forced to be relative to the higher background rates of the general population. This will be true unless they're underestimating the risks to begin with, like the sublinear model selected by the TCEQ. The selected EPA models naturally "overpredict" case numbers under this flawed approach.

b) Instead, if one performs a more appropriate comparison based on the results of internal analyses (within the cohort), one can see that the sublinear model used by TCEQ is a poor predictor of the nonparametric categorical RR estimates for the exposure quartiles; see model "e^(β*exp)" in Fig 4-3 of EPA's assessment.

Comparing TCEQ's model, depicted by the solid blue curve near the bottom of the graph, to the nonparametric categorical RR estimates, depicted by the filled purple circles, shows that the model selected by the TCEQ substantially underestimates the nonparametric categorical RR estimates. In contrast, the EPA model depicted by the dashed red line (linspline1600) is a much better predictor of the nonparametric categorical RR estimates. As noted in Comment #8, the nonparametric baseline estimate is the best available estimate of the baseline hazard rate in the cohort because it is based on unexposed referent group without any assumptions about the shape of the exposure-response model for the exposed workers and, thus, without any influence of the higher-exposure data on the model fit to the lower-exposure data. Similarly, the categorical RR estimates for the exposed groups are estimated with no assumptions about the shape of the exposure-response relationship across the groups.

In addition, proper comparisons of models against data should be based on maximum likelihood estimates (MLEs), as done in Figure 4-3 of EPA's assessment, not upper bounds as primarily reported by TCEQ.

Thus the DSD's reliance on this flawed calculation to support its rejection of EPA's model and its own use of a poorly fitting model is not supported by the evidence.

Response:

This response provides both a more general response and a much more detailed response complete with additional statistical analyses.

a) The premise of the comment is that a healthy worker effect should be assumed for the cancer endpoints being evaluated for EtO. However, as discussed in response to Comment #10, the TCEQ finds that robust data from Kirkeleit et al. (2013) indicate the lack of a healthy worker effect for both lymphoid/hematopoietic and breast cancer incidence. In addition, the SMRs for workers in the NIOSH and DOW/UCC are similar to those reported by Kirkeleit et al. (2013) for lymphoid cancer mortality and show no evidence of a healthy worker effect (see Section A3.3.1 of the DSD).

b) As discussed in response to Comment #6, categorical RRs should not be used for visually comparing models fit to individual data, particularly when appropriate statistical model fit criteria are available. More specifically, estimated nonparametric RRs are calculated with respect to an underlying background hazard rate that is also estimated nonparametrically. The RRs of parametric models fit to the individual data are defined with respect to an underlying background hazard rate estimated by the model. However, the underlying background hazard rates estimated by the nonparametric RRs and the parametric model are generally different. A better comparison of models fit to the observed data is to use the predictiveness of the model; that is, the capability of the model to estimate the observed number of deaths with a certain degree of confidence (see Appendix 2 of the revised DSD). Moreover, visual interpretation of the consistency of categorical RRs with the shape/slope of a modelled dose-response can change as the

number of exposure categories changes (e.g., Figures 1-3 and supplementary materials of Valdez-Flores and Sielken 2013). The visual presentation of only a few exposure categories can blind the data user to the variability in the underlying dose-response data, and by corollary, preclude an appropriate visual assessment/comparison of model fit to the actual individual data. See Appendix 5 of the revised DSD for additional information.

In consideration of the comment that proper comparisons of models against data should be based on maximum likelihood estimates (MLEs), MLEs have been added to Figures 9-12 of the DSD.

The following provides more detailed responses to comments a) and b).

Detailed Response to Comment a)

The approach used by TCEQ to predict the number of cause-specific deaths in the NIOSH cohort use the SMR methodology to evaluate the models. The approach for calculating SMRs is well established and has been used by regulatory agencies and researchers to compare mortality rates in target populations to mortality rates in reference populations. Thus, the approach used is well documented and has been extensively used.

The models used by TCEQ were derived using internal comparisons and did not rely on the general U.S. population background mortality rates. U.S. population background rates are used to predict risks in the general population. The SAB comment about the healthy worker effect (HWE) was considered in the evaluation predictions reported by TCEQ. The HWE has been shown to be cause-specific in incidence studies. That is, there are endpoints for which workers experience a HWE and some endpoints for which the HWE is negative, and yet other endpoints for which the HWE is non-existent.

Kirkeleit et al. (2013) researched the HWE in 366,114 randomly selected Norwegian workers and compared the incidence of several endpoints with the general Norwegian population. Their findings indicate that there is potential for the HWE for some endpoints and increased incidence (i.e., an "unhealthy" worker effect) for other endpoints. *For lymphoid and hematopoietic cancer incidence Kirkeleit et al. (2013) did not find a HWE* with SIRs and 95% confidence intervals of 0.97 (0.90, 1.03) and 1.09 (0.92, 1.27) for male and female workers, respectively. That finding was also true for breast cancer with an SIR and 95% confidence interval of 1.02 (0.95, 1.09).

SMRs for workers in the NIOSH and DOW/UCC are similar to the SIRs reported by Kirkeleit et al. (2013) for lymphoid cancer mortality. That is, the mortality rate in unexposed male and female workers in the NIOSH study are not statistically significantly different from the mortality rate of the general U.S. population. Again, footnote * to Table 32 in TCEQ DSD states "Quintile 1 is the control (unexposed lagged-out) group with 9 lymphoid cancer mortalities observed and 11.5 mortalities predicted by all models with a 95% confidence interval of (6.0 and 25.2), which

includes the 9 lymphoid cancer deaths." This confidence interval indicates that the observed 9 lymphoid cancer deaths in the unexposed male and female workers of the NIOSH cohort is consistent with the number of lymphoid cancer deaths in the general U.S. population during the same period of time after accounting for age, sex, and calendar year. Expressed in terms of SMRs, the SMR for lymphoid cancer deaths in the unexposed male and female NIOSH workers is equal to 0.78 (=9/11.5) with a 95% confidence interval (CI) equal to (0.36, 1.50). The 95% CI on the SMR for unexposed workers includes the value of one, which indicates that *the mortality rate in the unexposed workers in the NIOSH study and the U.S. population mortality rate are not statistically significantly different* at the 5% significance level.

Kirkeleit et al. (2013) indicates that there is minimal, if any, HWE for mortality from cancer. Kirkeleit et al. (2013) estimates an overall cancer SMR of 0.85 and 0.84 for male and female workers, respectively. Despite: (1) that the mortality rate in the unexposed workers in the NIOSH study and the U.S. population mortality rate are not statistically significantly different (as discussed above); and (2) the lack of a HWE for more EtO-relevant lymphoid and hematopoietic cancer based on data from Kirkeleit et al. (as discussed above), the TCEQ conducted a sensitivity analysis assuming that these overall cancer SMRs apply to lymphoid cancers. That is, despite data to the contrary, the TCEQ sensitivity analysis assumes NIOSH workers had lesser cancer mortality than the general population by multiplying the U.S. male and female background hazard rates by 0.85 and 0.84, respectively, to account for the assumed HWE. The results did not change significantly. *USEPA's selected model still statistically significantly overestimates the number of observed (53) lymphoid deaths in the NIOSH study; 77.5 with a 95% CI of (59.3, 103.6)*. By contrast, the standard Cox proportional hazards model includes the observed number (53) of lymphoid deaths in the NIOSH study within the 95% confidence interval; 44.3 with a 95% CI of (33.9, 59.2). *Thus, even using this conservative HWE (in the face of more study-specific data to the contrary), USEPA's selected model significantly overestimates the observed data*.

<u>Detailed Response to Comment b)</u>

Part b) of Comment #13 is the same issue raised in Comment #6. Since these comments have been repeated, the response that follows is similar to the response for Comment #6.

There is over-reliance on Figure 4-3 of USEPA's risk assessment to judge model fit to lymphoid mortality in the NIOSH epidemiological study. This over-reliance and misinterpretation is despite the note USEPA wrote in the Figure 4-3 that reads: "(Note that, with the exception of the categorical results and the linear regression of the categorical results, the different models have different implicitly estimated baseline risks; thus, they are not strictly comparable to each other in terms of RR values, i.e., along the y-axis. They are, however, comparable in terms of general shape.)" The misinterpretation of model fitting versus non-parametric rate ratios was discussed at length by Valdez-Flores et al. (2013), and USEPA (2016) responded by adding the note quoted above to the figures showing rate ratios. However, USEPA (2016) still includes statements like "adequate visual fit" in several places of their risk assessment. There are several reasons why this Figure 4-3 and other similar figures showing rate ratios from different models

could be misleading to casual readers and these are described in detail in response to Comment #6.

Comments from the Union of Concerned Scientists

Comment 1:

The TCEQ's proposed cancer risk value is not an appropriate replacement for the EPA IRIS risk value. The EPA IRIS assessment on the carcinogenicity of ethylene oxide issued in 2016 incorporated the best available science, public comment opportunities, interagency review, and scientific peer review by EPA's Scientific Advisory Board.

Response:

The TCEQ is not proposing to replace the IRIS value. The TCEQ is deriving the agency's own value, and in doing so, evaluated the USEPA's 2016 EtO derivation. As documented in the DSD, the TCEQ determined that the USEPA's EtO URF lacked scientific justification and did not pass reality checks on lymphoid cancer predictions for the key worker cohort and the U.S. general population, as well as calculating incorrect model fit criteria. The TCEQ dose-response assessment has already undergone internal peer review and public comment and will also undergo independent external expert peer review in the first quarter of 2020.

Comment 2:

The proposed TCEQ risk value uses a sublinear dose response model to derive its toxicity factors that the EPA would deem inappropriate due to ethylene oxide's reactive, mutagenic, and multisite carcinogenicity.

Response:

The Cox proportional hazards model is a standard dose-response model and is commonly used by TCEQ, USEPA, and other regulatory agencies for dose-response assessment. Although described as sublinear, it is indistinguishable from linear across all doses of interest (as shown in many figures in the DSD such as Figure 22) and is used by TCEQ in calculating a point of departure for linear low-dose extrapolation. USEPA considered results from the Cox proportional hazards model as it is a model USEPA deems appropriate for chemicals such as EtO, although USEPA did not select it based on an assessment of model fit that TCEQ does not agree with (e.g., USEPA incorrectly calculated p-values and AIC values). While a model that is indistinguishable from linear across doses of interest is appropriate considering EtO's carcinogenic MOA (as is linear low-dose extrapolation), the TCEQ notes that USEPA acknowledges it cannot provide mechanistic support for its overall supra-linear model.

Comment 3:

Further, the TCEQ assessment relies on a key study that EPA chose not to include in its evaluation of the best available science because the data "were not of sufficient quality" and other recent studies considered in the TCEQ's assessment would benefit from further conflicts of interest scrutiny as several are funded by the American Chemistry Council, which has a vested interest in ethylene oxide production and regulation.

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Response:

The TCEQ does not rely on the referenced UCC cohort study to derive the EtO URF. While the UCC cohort data was evaluated, the TCEQ assigned 100% of the URF weight to the same NIOSH cohort as USEPA (2016) relied on.

Science is paid for and conducted by those who have interest in better understanding the underlying science and important scientific issues, which can include government, industry, academia, and others. The TCEQ used a systematic review process that included a risk of bias analysis for all articles (including the published peer-reviewed scientific articles being referenced), which is fully described in Appendix 1 of the DSD.

Comment 4:

Choosing to abandon EPA's IRIS risk value for ethylene oxide, especially without an external review process, would mean a departure from the use of best available science.

Response:

The TCEQ thoroughly evaluated the USEPA 2016 IRIS EtO URF and concluded that it did not represent the best-available science. The TCEQ's dose-response assessment has undergone internal peer review and public comment and will also undergo independent external expert peer review in the first quarter of 2020.

Comment 5:

Data on ethylene oxide released by EPA's National Air Toxics Assessment (NATA) in 2018 revealed that the chemical is significantly contributing to higher cancer rates in areas surrounding chemical manufacturers and sterilizers using the chemical across the country. About a quarter of the facilities contributing to these risks are located in Texas. According to the NATA data, the probability of developing cancer from air pollutants was beyond the EPA's acceptable level of risk in over 100 communities, and 91 percent of the risk can be attributed to ethylene oxide, formaldehyde, or chloroprene.

Response:

USEPA's NATA produces theoretical risk estimates based on emissions inventories and IRIS dose-response assessments. Because there are serious concerns about the USEPA's EtO IRIS assessment (discussed in detail in the DSD and in response to public comments in this document), then so too is the NATA evaluation questionable. The NATA has not revealed that EtO is significantly contributing to higher cancer rates in areas surrounding chemical manufacturers and sterilizers, nor has the NATA demonstrated that those areas actually have higher cancer rates.

Comment 6:

Further, EPA issued its findings from air monitoring outside of the Sterigenics facility in Willowbrook, IL that was shut down by the state, comparing emissions before and after the shutdown. The monitors revealed levels 90 percent lower at the sites closest to Sterigenics,

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illustrating the direct relationship between the facility's operations and ethylene oxide levels. A March report from the Illinois Department of Health found that cases of Hodgkin's lymphoma among women in the Willowbrook community were nearly 90 percent higher than in a nearby county. This data is in agreement with the systematic review conducted by IRIS that evaluated the toxicological and epidemiological evidence available on the chemical and determined that it was carcinogenic to humans, and exposure was linked to an increased risk of cancer of leukemia, lymphoma and breast cancer in women.

Response:

Hodgkin's lymphoma is not a cancer included in USEPA's dose-response assessment; non-Hodgkin's lymphoma is. Regardless, such ecological studies are not used and are insufficient for dose-response assessment, having much more uncertainty (particularly for the exposure assessment) and much lower numbers than the 17,000+ worker study that both USEPA and TCEQ relied on. The referenced assessment by the Illinois Department of Health indicated [*emphasis added*]:

> Living in a study area at the time of diagnosis was used to represent potential exposure to EtO, but it was a very crude proxy...data on actual exposure in individuals was non-existent...there is considerable uncertainty about the length and the level of exposure to EtO that each individual in Willowbrook, and surrounding areas, may have actually experienced in the past. *Any observed increase, in and of itself, is insufficient to draw conclusions regarding the potential impact of EtO exposure*.

In contrast to the Hodgkin's lymphoma findings referred to by the commenter, the following are findings from similar studies around EtO emitters [*emphasis added*]:

(1) The Colorado Department of Public Health and Environment found no evidence that there is more cancer in the communities around Terumo BCT than in surrounding areas (https://drive.google.com/file/d/1WEe0kCfkXW2RQC4jRFsIC803u_6P1Mub/view). Their 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). They state, "*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."

(2) The Michigan Department of Health and Human Services evaluated cancer incidence in the area surrounding Viant Medical Facility in Grand Rapids in response to the discovery of elevated levels of EtO in the area (https://www.michigan.gov/documents/mdhhs/Viant_Cancer_Incidence_Review_661354_7.pdf). Cancer registry incidence data was evaluated for female breast cancer, multiple myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, and leukemia. No statistical elevations in the frequency of any of the cancer types were observed over the 15-year time period of analysis, with the exception of multiple myeloma when compared to county rates but not state rates (see the table below; small number of cases resulting in an imprecise estimate with borderline statistical significance). The Michigan Department of Health and Human Services concludes

[*emphasis added*], "*Therefore, the results of the analyses presented in this report do not suggest that further investigation is needed at this time.*"

Table 2: Standardized Incidence Ratio (SIR)[1] for Invasive Cancers by Cancer Type, Comparing the Geographic Area of Analysis (10 Census Tracts) to Kent County and the State of Michigan, Adjusted for Age and Sex, 2001 – 2015[2]

		Kent County Comparison		State of Michigan Comparison	
Cancer Type	Observed Number of Cases in 10-Census Tract Area	Expected Number[1] of Cases	SIR (95% Confidence interval)	Expected Number[1] of Cases	SIR (95% Confidence interval)
Female Breast	177	219.48	0.81 (0.71, 0.91)	202.23	0.88 (0.77, 0.99)
Non-Hodgkin Lymphoma	71	66.76	1.06 (0.86, 1.30)	68.19	1.04 (0.85, 1.27)
Hodgkin Lymphoma	12	14.85	0.81 (0.47, 1.31)	15.07	0.80 (0.46, 1.29)
Multiple Myeloma	25	16.96	1.47 (1.02, 2.06)	19.28	1.30 (0.90, 1.81)
Leukemia	43	44.91	0.96 (0.73, 1.23)	48.06	0.89 (0.68, 1.15)

[1]SIR is the ratio of observed to expected cases, where expected cases are calculated by multiplying the age-sex specific cancer incidence rates for the comparison population (Kent County or State of Michigan) to population estimates for the 10-census tract region surrounding Viant (2010 US Census).
[2]Source of Michigan Cancer Cases: Michigan Resident Cancer Incidence File, 2001-2015, includes cases processed through November 30, 2018. Division for Vital Records & Health Statistics, Michigan Department of Health and Human Services. Cancer cases were defined by new malignant cancer diagnoses where the listed cancer site was the primary site.
Shading indicates that the SIR was statistically higher or lower than 1.00 (95% confidence interval does not include the value 1.0)

As can be seen in the table above, Hodgkin's lymphoma incidence is somewhat less than expected (in contrast to Willowbrook, IL), and breast cancer (one of the two endpoints used by USEPA 2016) is actually statistically significantly decreased around this EtO-emitting facility, using both county and state rates as comparators. Therefore, assessing evidence in a balanced manner demonstrates that there are mixed and largely insignificant associations between EtO and cancer in these communities, and that any single such ecological study cannot be cited as convincing evidence of a chemical's carcinogenicity (or lack thereof).

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Comments from the Environmental Defense Fund (EDF)

Comment 1:

TCEQ should not reduce a risk threshold to EtO, a known human carcinogen. The public health issues related to EtO pollution recently attracted national attention when Willowbrook, Illinois began to experience extremely high rates of lymphatic cancers which was directly linked to high concentrations of EtO emitted into the air from a medical equipment sterilization plant. Fully aware of these risks, TCEQ now proposes to move in the opposite direction by raising the threshold for EtO exposure to 4 ppb, a massive jump from the current air permit screening level of 1 ppb. This change is further significant because of the volume of EtO Texans are already exposed to under the current limit – Texas is responsible for around half of the EtO emissions in the United States. TCEQ should abandon its flawed approach in its proposed assessment and adhere to its clear mandate to protect public health and welfare.

Response:

As discussed in the response to the Union of Concerned Scientists comments, a full assessment of ecological epidemiology studies demonstrates that there are mixed and largely insignificant associations between EtO and cancer in these communities. Although there are significant uncertainties involved, the TCEQ provides the following for additional context.

Based on the 2014 National Emissions Inventory (NEI), Texas emits approximately 36% of the EtO in the US. As a result, tons of EtO emitted per square mile in Texas (1.8E-04 tons/square mile) is over 5 times higher in Texas compared to the rest of the US (3.5E-05 tons/square mile). Despite this and the very high carcinogenic potency purported by USEPA (2016) for EtO causing lymphoid and breast cancers, the incidences of leukemia and non-Hodgkin's lymphoma (both included in USEPA's dose-response assessment) as well as breast cancer are *lower* in Texas than in the general US population, with the same being true for all cancers combined (Table 3; National Cancer Institute). Again, leukemia, non-Hodgkin's lymphoma, and breast cancer are endpoints included in USEPA's carcinogenic dose-response assessment for EtO (USEPA 2016), along with multiple myeloma (for which state-specific versus US data were not available from the National Cancer Institute at https://www.cancer.gov/).

Table 3. Relevant Age-Adjusted Cancer Incidence Rates per 100,000 (2012-1016)

Area	NEI Emissions (tons)	Emissions per Area (tons/mile^2)	Non-Hodgkin's Lymphoma	Leukemia	Breast Cancer (female)	All Cancer Sites
US	133.72	3.52E-05	19.2 (19.1, 19.3)	14.1 (14.1, 14.2)	125.2 (124.9, 125.4)	448.0 (447.7, 448.4)
Texas	48.45	1.80E-04	17.4 (17.2, 17.6)	13.9 (13.7, 14.1)	111.9 (111.2, 112.7)	407.7 (406.6, 408.9)
Jefferson County	12.05	1.08E-02	17.5 (15.3, 19.9)	13.4 (11.5, 15.5)	102.4 (94.9, 110.3)	399.9 (389.3, 410.7)
Harris County	11.75	6.60E-03	16.9 (16.3, 17.5)	13.0 (12.5, 13.5)	111.9 (109.9, 114.0)	400.1 (397.2, 403.1)

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At the county level, although highly-industrialized Jefferson County (population ≈260,000) has more EtO emissions on a square mile basis than any other county in Texas (1.1E-02 tons/square mile) with over 300 times more than the US at large (3.5E-05 tons/square mile), the incidences of leukemia (13.4 (95% CI of 11.5, 15.5)), non-Hodgkin's lymphoma (17.5 (95% CI of 15.3, 19.9)), and breast cancer (102.4 (95% CI of 94.9, 110.3)) are lower in Jefferson County Texas than in the general US population (Table 3). In fact, breast cancer incidence is statistically significantly lower in Jefferson County compared to both Texas and the US, despite EtO emissions that are 60 times higher than Texas at large and 307 times higher than the US. Similarly, highly-industrialized Harris County is by far the most populated Texas county (≈4.6 million) with relatively high reported NEI EtO emissions per square mile (i.e., 6.6E-03 tons/square mile is ≈188 times higher than the US at 3.5E-05 tons/square mile), the incidences of leukemia (13.0 (95% CI of 12.5, 13.5)), non-Hodgkin's lymphoma (16.9 (95% CI of 16.3, 17.5)), breast cancer (111.9.4 (95% CI of 109.9, 114.0)), as well as all cancers combined (400.1 (95% CI of 397.2, 403.1)) are all statistically significantly lower than in the general US population (Table 3). Despite the associated uncertainties, these results are not consistent with EtO as a potent carcinogen causing observable increases in lymphoid or breast cancer at environmental concentrations.

Lastly, the sound scientific basis of the TCEQ assessment is set out in the DSD and is also addressed in other comment responses in this document. The DSD demonstrates that it is USEPA's 2016 assessment that is flawed, being over-predictive of lymphoid cancers in both the key cohort and the U.S. general population, using incorrectly calculated p-values and AIC values, and lacking MOA data to justify their non-standard overall supra-linear dose-response model, culminating in risk estimates shown to be biologically implausible.

Comment 2:

TCEQ's proposed assessment for EtO is flawed scientifically. The most egregious scientific error in TCEQ's proposed assessment is the dose-response analysis using the Cox proportional-hazards model fit to these data by Valdez-Flores et al. (2010) (Valdez-Flores et al. 2010). In the analysis, TCEQ estimates the slope of the dose response curve using the lowest exposure category rather than the 100 randomly matched unexposed individuals as done by Steenland et al. (2004) (Steenland et al. 2004). This is by far and away the most important difference between EPA's cancer risk analysis of ethylene oxide and the TCEQ analysis.

Response:

This comment may be due to a misunderstanding of how Cox proportional hazards models are fit to epidemiological data. The comment states that the Valdez-Flores et al. (2010) model fit uses the lowest exposure category rather than unexposed individuals. However, the Cox proportional hazards model does not use a control unexposed group to derive the slope of the model. Rather, Cox models define a risk set for every case (e.g., every cancer death from the specific cause) that includes all the individuals that are at risk at the time the case occurred (e.g., the time of the cancer mortality from the specific cause). The risk set includes exposed and unexposed workers (see e.g., Allison, 2010 and Steenland et al. 2004). Thus, every case in the NIOSH study has, possibly, more than 17,000 individuals in the risk set. The Valdez-Flores et

al. (2010) models and TCEQ models used the full risk set (which includes unexposed and exposed individuals) for every case.

USEPA's model fitting, developed by Professor Kyle Steenland, on the other hand, rather than using the full risk set with all individuals for every case, uses only 100 individuals randomly sampled from the full risk set. [EDF comments erroneously indicate that in Steenland et al. (2004), 100 individuals selected for the risk sets include only "unexposed individuals"; however, the "controls" in this analysis were actually exposed individuals from the dataset who had not yet died by the age of the cause-specific decedent.] Steenland used only 100 to speed up computer run time, possibly at the expense of precision. This is clearly stated in Steenland et al. (2004) where he writes, "risk sets were constructed in which 100 randomly selected controls were chosen for each case from the pool of all those who survived without haematopoietic or breast cancer to at least the age of the index case. Use of 100 controls has been shown to result in virtually the identical rate ratio with all possible controls (the full risk set), with approximately the same precision, while making possible more rapid computer runs." Although USEPA's and Steenland's approximation using only 100 randomly chosen individuals to form the risk set for every case may result in estimates that have "approximately the same precision", these estimates are not easily reproducible because of the randomness in the selection of the 100 individuals used instead of the full risk sets.

Based on the discussion above, it is clear that how the TCEQ and Dr. Steenland models were actually fit (i.e., full risk set versus 100 individuals randomly sampled from the full risk set) is not the most important difference between the USEPA and TCEQ analyses. Rather, the most important difference between USEPA's and TCEQ's assessments are the functional form of the exposure-response model. USEPA used a non-conventional exposure-response relationship that is supra-linear overall (two-piece linear model), whereas TCEQ used a standard exposure-response model that while sublinear in nature (standard Cox proportional hazards model) is indistinguishable from linear over the doses of interest in this case. Furthermore, TCEQ showed that USEPA's two-piece linear model did not fit the NIOSH data better than the standard Cox proportional hazards model (see Appendix 4 of the revised DSD).

Comment 3:

The obvious place to see the effect of this assumption is on page 133 of the TCEQ DSD document (Figure 22). It is clear that the dashed blue line used by TCEQ does not pass through 1 when the x-axis (15-year lagged ppm-days) equals zero, but instead almost passes through EPA's relative risk for the first quintile. This results in an over-estimation of the risk in the unexposed population quite dramatically, in fact treating this population as if the risk were the same as the risk in the first quintile. Because the relative risk climbs dramatically from the control response to the first quintile, using the first quintile as the denominator in the risk ratio for Cox modeling substantially reduces the slope, and thus the risk.

Surprisingly, TCEQ illustrates how bad their fit is relative to the control population in Figures 20 and 21 of the DSD. In these figures, rather than having the model run through the red dot for the first quintile, TCEQ's model (the blue solid line) is forced through the relative risk of 1 for

the unexposed group. We illustrate this point by placing the blue line (now a black thick line) running directly through the first quintile red dot on the same plot in Figure 21. One can see the resemblance to the lines shown in Figure 23 [sic].

By calculating the slope relative to the lowest exposure category (>0-1199 ppm days) instead of relative to unexposed, TCEQ has disregarded all of the increased risk at low external exposures in this data set and has calculated a slope factor that is meaningless. The arguments for the fit of the model are not convincing since TCEQ disregards the fact that their model is overestimating response in the unexposed group. Indeed, the fit of the TCEQ model as it is being used for risk calculations is the solid blue line passing through 1.0 in Figures 21 and 22. It is clear that the model used does not fit these data. Finally, TCEQ has ignored the fact that additivity to background is likely to lead to linear or supra-linear response.

Response:

As a note, the proposed DSD contained no Figure 23. That being said, the TCEQ figures are apparently being misinterpreted. *The rate ratios of TCEQ's model do go through 1* as estimated by the Cox proportional hazards model and shown in Figures 19, 20, and 21 (lowest blue solid line) of the proposed DSD. However, as USEPA recognized in similar graphs (one of them reproduced in Figure 19 of the proposed DSD) the models are not comparable on the y-axis. USEPA (2016) stated in their Figure 4-3 footnote [*emphasis added*], "Note that, with the exception of the categorical results and the linear regression of the categorical results, *the different models have different implicit estimated baseline risks; thus, they are not strictly comparable to each other in terms or RR values*, i.e., along the y-axis. They are, however, comparable in terms of general shape." The TCEQ sequence of graphs was meant to illustrate that the alleged bad fit of the standard Cox proportional hazards model to four rate ratios estimated for quintiles of grouped decedents is an artifact caused by the difference of the implicitly estimated baseline hazards. It is important to note first that rate ratios for the quintiles are nonparametric *estimates* of the rate ratios and are *not observed* rate ratios.

A much better representation of the spread, variability, and uncertainty surrounding the rate ratios is depicted in Figure 20 from the DSD (reproduced as Figure 9 below).

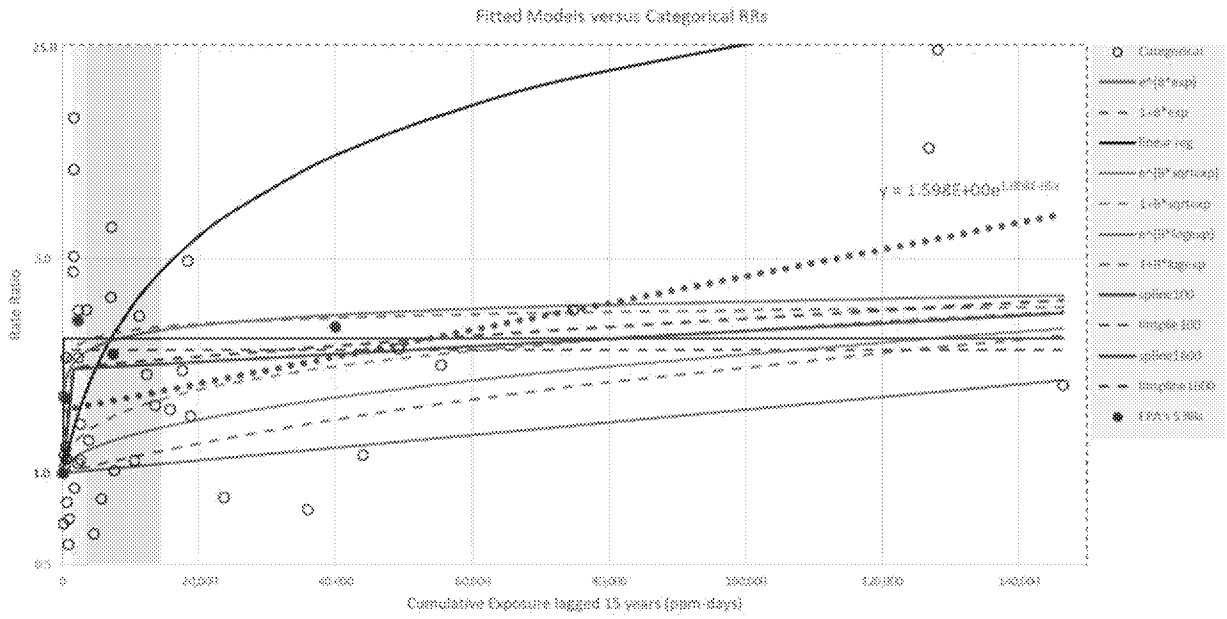

Figure 9. Lymphoid Cancer Death Categorical Rate Ratios (RRs) and Various Fitted Models for 15-Year Lagged Occupational Doses ≤150,000 ppm × days (NIOSH cohort)

Figure 9 above, which is Figure 20 of the DSD, shows both the estimated rate ratios for USEPA's quintiles and the estimated rate ratios for each individual case of lymphoid mortality. This figure shows the same models and data shown in Figure 19 of the DSD, but includes: (1) the estimates of the individual rate ratios (circles); (2) the y-scale in logarithmic increments for better resolution of the RRs; and (3) a line (purple-dotted line) fitted to the estimated risk ratios of the individual lymphoid decedents using least squares. The background colors in Figure 9 (Figure 20 of the DSD) show the range of lymphoid decedents included in each of USEPA's summary quintile RRs shown as red dots.

Figure 10 below, which is Figure 22 of the DSD, is similar to Figure 9 above (Figure 20 of the DSD) but is limited to showing only the two-piece linear spline model developed by USEPA and the log-linear model developed by TCEQ for visual comparison.

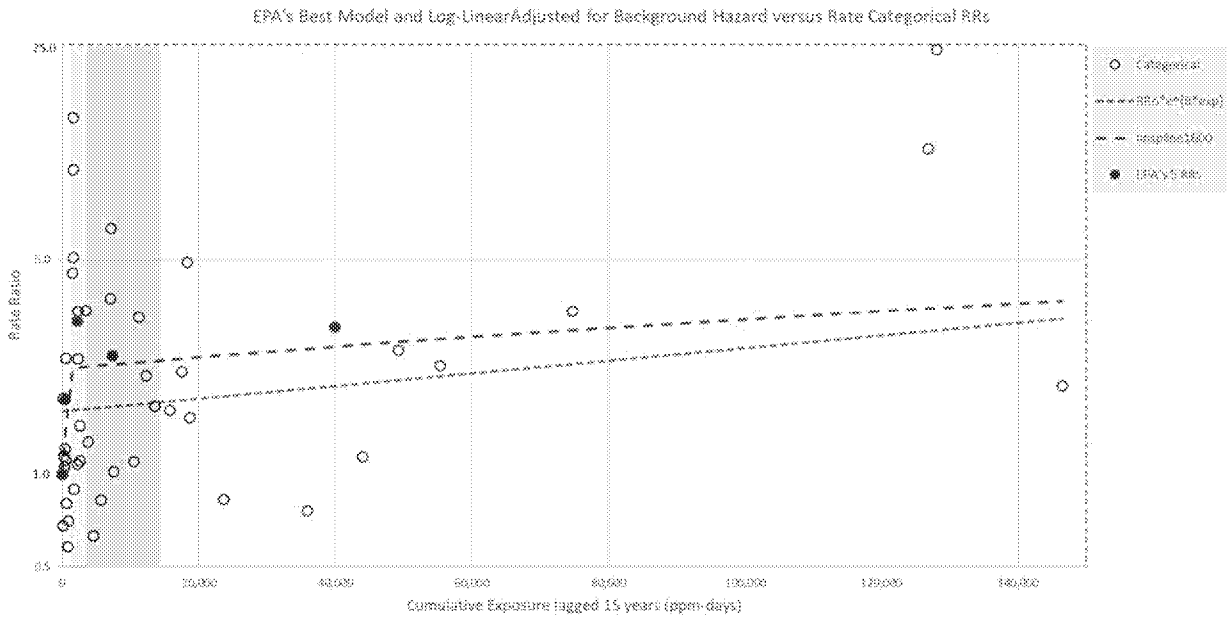

Figure 10. Lymphoid Cancer Death Categorical RRs and the Cox Proportional Hazards and Two-Piece Spline ("knot" at 1,600 ppm × days) Fitted Models for 15-Year Lagged Occupational Doses ≤150,000 ppm × days (NIOSH cohort)

TCEQ's log-linear model in Figure 10 (Figure 22 of the DSD) is plotted *after* adjusting its intercept in the y-axis to account for the different implicit estimated baseline risks (as noted by USEPA) of the non-parametric rate ratios and the log-linear model. The ratio of different implicit estimated baseline risks was estimated using the intercept of the purple-dotted fitted model to the individual estimates of the rate ratios shown in Figure 9 (Figure 20 of the DSD). The purpose of Figure 10 (Figure 22 of the DSD) is to show a fairer visual comparison of the fits of the TCEQ log-linear model, the USEPA two-piece linear spline model (USEPA's selected model for risk evaluation), and the individual estimated rate ratios. This visual comparison in this figure is an attempt to correct the misunderstanding that the RRs estimated by the log-linear model (TCEQ's selected model) are out of line with the RRs estimated non-parametrically (the open circles in the figures). Misinterpretation in the comparison of parametric and categorical (non-parametric) rate ratios used to judge model fit has been published in the peer-review literature (see Valdez-Flores and Sielken 2013).

See the response to Comment #2 regarding the slope not being calculated relative to the lowest exposure category, but rather to the full risk set.

Comment 4:

TCEQ's discussion of the fit of their model to quintiles 2-5 is very misleading because it does not mention the lack of fit of the model against the mortality expected in the unexposed population since the unexposed population has been ignored in the evaluation.

Response:

Because of the nature of the rate ratio going through 1 at zero cumulative exposures, all models result in the same background risk at zero cumulative exposures. That is, the USEPA model and the TCEQ model estimate the same background risk, by definition. This model characteristic is captured in a footnote to Table 32 in the TCEQ DSD [*emphasis added*], "*Quintile 1 is the control (unexposed lagged-out) group with 9 lymphoid cancer mortalities observed and 11.5 mortalities predicted *by all models* with a 95% confidence interval of (6.0, 25.2), which includes the observed 9 lymphoid cancer deaths." Consequently, "the mortality expected in the unexposed population" is the same for USEPA model and TCEQ model, and for that matter, for any relative risk model. The reason the first quintile (the unexposed, lagged-out person-years) was not explicitly included in the comparison in Table 13 is that all models (including USEPA's) result in the same 95% confidence interval that includes the number of observed lymphoid deaths in the NIOSH study.

Comment 5:

Steenland et al. fit the Cox model to their data using the unexposed group as the referent population and did the same thing using log (dose+1) and present their results in Table 7 of their paper. They concluded the log(dose+1) model fit best with the 15-year lag. That model is shown in Figure above (it is the brown solid line). What is noted is the rapid climb from non-exposed to exposed that has been eliminated in the modeling used by the TCEQ because of the intentional decision to rely only on the modeling within the exposed groups. The EPA model (solid red line) accounts for the early rise in risk ratios then flattens out in the higher doses.

TCEQ claims that there is no discernable pattern to the data based on risk ratios where the grouping only includes a single death in each group. What TCEQ has not shown is that there is no confidence in these numbers and that the confidence bounds around the individual risk ratios will be overwhelming. The grouping done by Steenland et al. (red dots, effectively) is the standard epidemiological approach to dealing with these types of data (have enough deaths in an exposure interval to insure reasonable estimates of risk ratios).

Response:

The misconception that TCEQ modeling relied only on "modeling within the exposed groups" has already been addressed above. See the response to Comment #2 regarding TCEQ's modeling including the full risk set, not just the exposed individuals. While EDF is correct that the model that resulted in a parameter estimate most significantly different from zero is the model with the logarithm of cumulative exposure, it must be noted that USEPA rejected this model because of its implausibility. This is indicated on pages H-26 and H-34 of USEPA's 2106 risk assessment [*emphasis added*]:

> "The Cox regression models with log cumulative exposure provided reasonable fits to the data, as described by Steenland et al. (2004) and in the 2006 draft assessment. However, the EPA concluded that these models represented exposure-response

relationships that were *excessively sensitive* to changes in exposure level in the low-dose region, and thus, were *not biologically realistic*."

The TCEQ has shown (Appendix 2 in the revised DSD) that even USEPA's unconventional two-piece linear spline model, which was used as a more realistic alternative to the log cumulative exposure model, is unrealistic in that it significantly over-predicts the number of observed cancer deaths in the NIOSH study.

Next, although the individual data were used for modeling (consistent with USEPA's SAB), as an issue related to USEPA's 2016 assessment, the variability in the estimated quintile rate ratios (RRs) cannot be denied. The purpose of graphing the individual RRs is to show the variability in the underlying individual data, and to help in visually judging model fit and any perceivable shape for an exposure-response. Summarizing the RRs by using fewer grouped individual cases without any confidence intervals masks the true variability in the underlying estimates of the RRs. [Note that the true variability is, however, accounted for by TCEQ correctly calculating p-values and AIC values that indicate USEPA's unconventional model does not fit the data statistically significantly better than the standard Cox proportional hazards model.] Furthermore, the table discussed in the next section shows that the estimated RRs for the individual lymphoid decedents and for the quintiles are consistent as the vast majority of the individual RRs are inside the 95% CIs for the quintile RRs. In the end, USEPA models and TCEQ models fit the same individual-level data, and the variability of the non-parametric estimates are meant to be a visual aid (that is turning out to be misunderstood by some readers).

USEPA used the RRs for quintiles of lymphoid decedents in the NIOSH study to judge model fit to the NIOSH data. Each exposure quintile includes 11 lymphoid decedents and the unexposed (lagged out quintile) includes 9 lymphoid decedents. Table 4-2 in USEPA (2016) lists the estimates of the RRs (ratios of the hazard rate for each exposure quintiles to the hazard rate for the unexposed workers). These RRs are shown in the proposed DSD as purple dots in Figure 19 and red dots in Figures 20 to 22. The RRs for the quintiles are summary estimates of the estimated individual RRs shown by circles in Figures 20 to 22 of the proposed DSD. The RRs for the quintiles are approximately located in the center of the 11 individual RRs included in the quintile and represented by the circles in Figures 20 to 22. The table below shows USEPA's quintile RRs (USEPA calls them ORs) with its corresponding 95% CIs along with the average RR of the 11 individual RRs and the range of the individual RRs (individual RRs are shown as circles in Figure 22). Each of the four exposure RRs in USEPA's 2016 risk assessment (red dots in Figure 22) is the summary of the closest 11 individual RRs (open circles in Figure 22).

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Table 4. USEPA Quintile-Specific RRs, 95% Confidence Intervals, and Individual RRs within Each Quintile

Quintile	USEPA's RRs[1] (95% Confidence Interval)	Average of 11[2] Individual RRs in the quintile	Individual RRs in the quintile[3]
2	1.75 (0.59, 5.25)	1.46	0.58, 0.68, 0.71, 0.80, 1.06, 1.11, 1.15, 1.22, 1.77, 2.38, 4.55
3	3.15 (1.04, 9.49)	4.04	0.89, 1.08, 1.11, 1.28, 1.44, 2.38, 3.41, 3.42, 5.11, 9.82, 14.49
4	2.44 (0.80, 7.50)	2.22	0.63, 0.82, 1.02, 1.10, 1.62, 1.67, 2.10, 2.16, 3.25, 3.75, 6.34
5	3.00 (1.02, 8.45)	4.99	0.76, 0.83, 1.14, 1.53, 1.94, 2.26, 2.54, 3.40, 4.93, 11.50, 24.11

[1] Source: Table 4-2 of USEPA's (2016) risk assessment report.
[2] The average of the 11 individual RRs are not statistically significantly different than the quintile RRs estimated by USEPA.
[3] Most individual rate ratios are inside the 95% confidence interval of the RR corresponding to the quintile.

Figure 22 of the DSD (Figure 10 above) and the table show that the alleged steep increase at low cumulative exposures and plateauing of the RRs at higher cumulative exposures is an artifact of summarizing the RRs into quintiles (red dots in Figure 22). The 95% CIs of the quintile RRs and the individual RRs based on each lymphoid decedent shown in the table represent the variability in the NIOSH data for lymphoid cancer. The alleged supra-linearity (steep increase for low cumulative exposures and plateauing at higher cumulative exposures concluded from the red dots in Figure 22) is not supported by the individual RRs (open circles) in Figure 22 (Figure 10 above), which form no discernable dose-response pattern. This figure shows that the two models fit the individual RRs about the same. This is corroborated by the p-values and AICs in Table 38 of the proposed DSD where the linear and the standard Cox proportional hazards model have preferable (i.e., lower) AIC values once the correct degrees of freedom are used for USEPA's selected model. These standard statistical measures of model fit (i.e., p-values, AICs) are calculated so that visual fit need not be relied upon, although visual examination of the actual individual data is consistent with the correctly calculated p-values and AIC values that indicate USEPA's overall supra-linear two-piece spline model does not fit the data better than the TCEQ's standard Cox proportional hazards model.

Figure 22 of the DSD (Figure 10 above) shows USEPA's selected model and TCEQ's selected model plotted against the individual RRs and the quintile RRs for lymphoid mortality. The TCEQ selected RR model goes through 1 for zero cumulative exposures (as do all RR models in Figures 20 and 21 of the DSD). Figure 22, however, shows an adjustment for TCEQ's selected model to account for the difference in the estimated baseline hazard rate estimated by the non-parametric estimates for the quintile RRs and the estimated baseline hazard rate for the

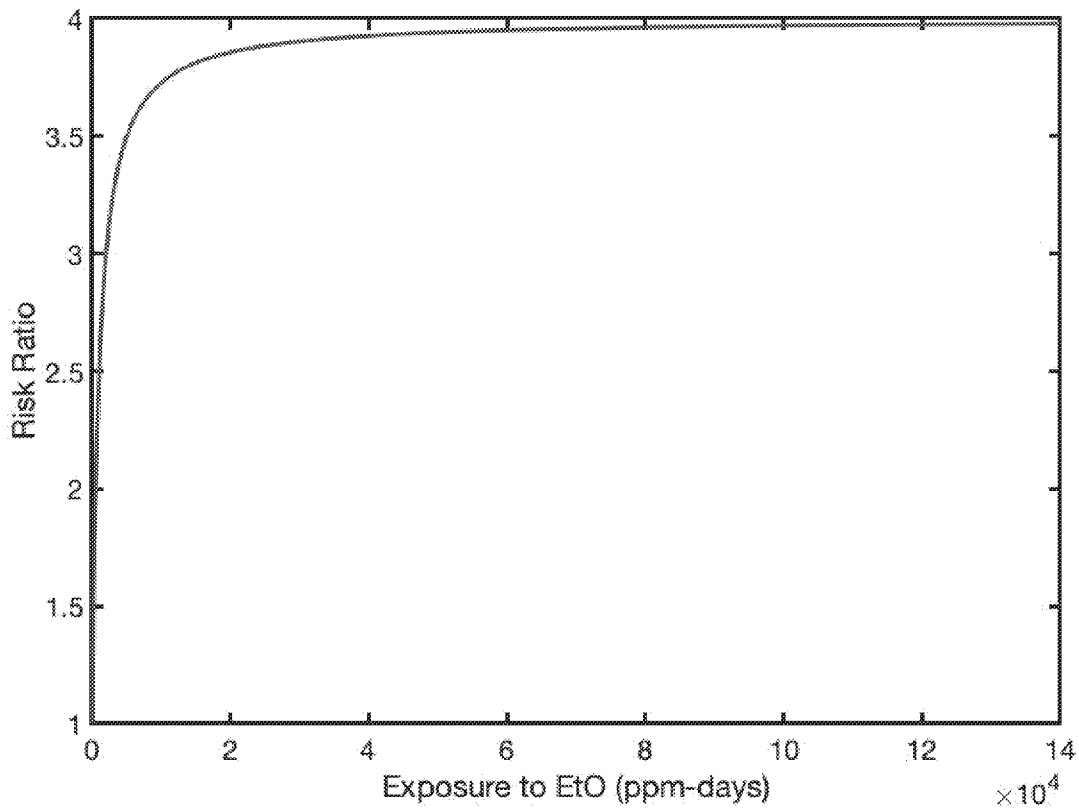
standard Cox model. This adjustment is for the sake of facilitating visual comparison of the two models and the nonparametric rate ratios as indicated by USEPA in the footnote to Figure 4-3 (Figure 19 of the DSD). In this footnote, USEPA states "(Note that, with the exception of the categorical results and the linear regression of the categorical results, the different models have different implicitly estimated baseline risks; thus, they are not strictly comparable to each other in terms of RR values, i.e., along the y-axis. They are, however, comparable in terms of general shape.)" While Figure 22 (Figure 10 above) is explicitly for this stated purpose, again, TCEQ's selected RR model as well as all RR models go through 1 at zero cumulative (see Figures 20 and 21 of the DSD).

In regard to EDF's comments on TCEQ dose-response modeling, most comments provided by the EDF seem to: (1) concern model fit to the observed data; and (2) be based on a belief or misunderstanding that the categorical RRs (non-parametric estimates) are the observed data. However, categorical RRs are not the observed data or the best basis to judge model fit. While USEPA (2016) has footnoted Figure 4-3, the figure remains visually misleading for comparing model fit (for reasons cited in the footnote) yet "visual fit" of parametric models to categorical RRs is still used as an argument in selecting/discarding parametric models (e.g., Table 4-6 of USEPA 2016, EDF comments above). *TCEQ uses a better approach to judge model fit to the observed data*. The number of cause-specific deaths for cumulative exposure ranges are observed as opposed to categorical RRs, which are not observed but rather are estimated. In Table 32 from Appendix 2 of the revised DSD, *the observed number of lymphoid deaths in each quintile were compared with the number of model-estimated lymphoid deaths in the NIOSH cohort. TCEQ's log-linear model estimated the number lymphoid deaths in each of the five quintiles within a 95% CI*. By contrast: (1) *USEPA's selected model (MLE of the two-spline linear model) statistically significantly over-estimated* the number lymphoid deaths in all but one of the four quintiles with non-zero exposure at the 5% significance level; and (2) *USEPA's selected model used for estimating risk (the upper 95% upper confidence limit on the two-spline linear model) statistically significantly over-estimated* the number of lymphoid deaths in all non-zero exposure quintiles. USEPA's model also statistically significantly over-estimated the number of lymphoid cancer deaths for the cohort as a whole. In contrast to USEPA's model, *TCEQ's model neither over- or under-estimated but rather was reasonably accurate*. Additionally, the TCEQ correctly calculates p-values and AIC values to aid in model comparison (Appendix 4 of the revised DSD), which in addition to the carcinogenic MOA do not support adoption of USEPA's overall supra-linear model over TCEQ's standard Cox proportional hazards model.

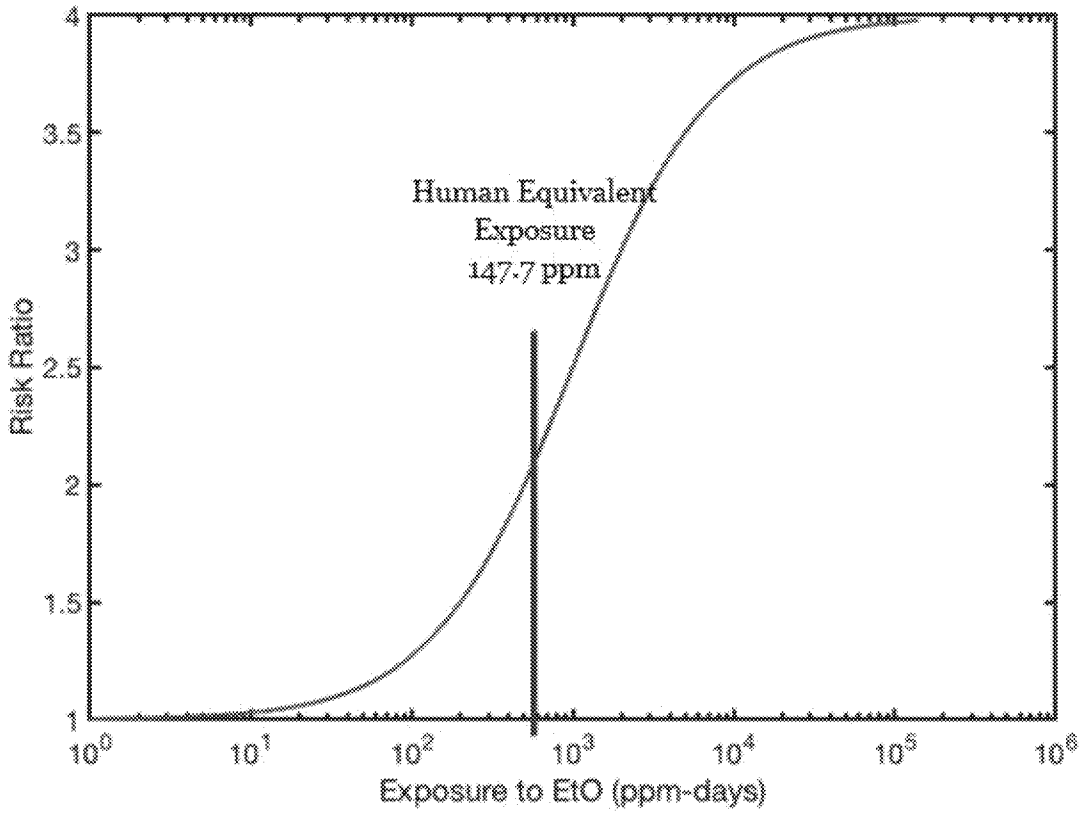
Although model selection for cancer risk assessment should be ideally driven by biology, physiology, and MOA, statistical arguments are oftentimes used for model selection. Statistical arguments need to be clearly understood to make a valid judgement in model selection. Visual representation of summary statistics can be misleading when the summary statistics are believed to be observations. Sound science-based decision making is based on scientific results and not on visual judgement. Though visual aids can be used for communicating results, the visual aids need to be clearly understood by the scientist and all stakeholders. The TCEQ has tried to highlight and clarify these issues.

Comment 6:

Theoretically, the pattern noted here is not unexpected if the chemical investigated is additive to a process that already exists in the body. As an illustration, consider the usual model for Michaelis-Menten kinetics used for most enzymatic reactions in the body (adding 1 to make it range between 1 and 4). To match this to these data, we will use Vmax=4 (the maximum risk ratio), a KD of 1000 (about 8 times higher than the 147 ppm-days mean TCEQ is using for human equivalent air exposure for endogenous EtO) and plot this as a function of EtO ppm-days. After doing this, you get the figure below.



The graph illustrates a rapidly climbing curve reaching its maximum fairly quickly. Putting this on a log(dose) scale allows greater detail of the low-exposure region and provides the following graph:



Here, it is clear that starting from the presumed human background exposure of 147 ppm-days used by TCEQ, there is no curvature at all, but instead the rapidly climbing relative risk that would be expected. The risk-ratio data from Steenland et al. (2004) demonstrates a similar, rapidly-rising risk for low exposures. TCEQ has ignored the fact that additivity to background is likely to lead to linear or supra-linear response.

Response:

The comments above were provided as a hypothetical example, as the included dose-response curves are not plotted using actual data. The second figure shows that in theory, 147.7 ppm-days could fall on the middle linear portion of the dose-response curve with the greatest slope. It is based on the previous figure that shows a supra-linear dose-response based on a model for enzymatic reactions. EDF indicated that the curve would plateau as metabolism becomes saturated (e.g., for a metabolically-activated carcinogen). However, EtO is a direct-acting mutagen and thus the applicability of Michaelis-Menten kinetics for enzymatic reactions as a surrogate for the expected EtO relationship with cancer mortality is very unclear. Even if this class of kinetics were the driver for the relationship of EtO with cancer mortality (not the case for direct-acting mutagens), there would be no data to show where on the curve the

background and occupational EtO concentrations would lie. The commenter suggests that a supra-linear dose-response may be expected if the chemical is additive to a process that already exists in the body. The carcinogenic MOA for EtO, mutagenicity, is one such example. Since lymphoid cancer drove the USEPA carcinogenic assessment, perhaps the most relevant mutagenicity data discussed by USEPA (2016) was that in the bone marrow of mice exposed to EtO by inhalation *in vivo* (Recio et al. 2004), which USEPA indicates is consistent with a *linear* dose-response (C-17 of USEPA 2016). This is inconsistent with the comment's suggestion that supra-linearity should be expected. Even at 200 ppm, much higher than the measured and estimated worker exposure means of 3.5-4.6 ppm (Tables IV and V of Hornung et al. 1994), the mutagenicity dose-response remains linear and has not plateaued (Figure 2 above). These bone marrow mutagenicity data are inconsistent with supra-linearity but consistent with a linear dose-response, despite additivity to a background process producing endogenous EtO already in effect at 0 ppm EtO in air.

Comment 7:

TCEQ argues that the amount that EPA is suggesting as protective of human health is far below the normal human range. This argument does not address the issue of additional human risk, but simply magnitude and associated error of their presumed human background exposure. The argument that the one-standard error estimate away from the estimated human background is much larger than EPA's proposal is confusing statistical noise with the effects in a population. That noise is a function of the response from the people included in the biomonitoring work (people who can clearly have some exposure to EtO, cigarette smoke, ethylene, and other agents in this metabolic pathway), instrument accuracy in calculating values in a urine sample, and the accuracy of the method used to back-calculate to the equivalent air exposure. It also does not mean that the concentrations seen in the population aren't already causing lymphatic cancers because it does not address that question. Additivity to background, as illustrated by the Michaelis-Menten kinetics example illustrated above, demonstrates how rapidly risk can change in the low-dose region for these reactions.

Response:

The normal human range of endogenous or background exposure is primarily provided for context in the DSD. Various examples provide this context, such as USEPA's maximum acceptable air concentration corresponding to an internal dose about 1/40th of the 1st percentile of normal endogenous levels. It is highly biologically implausible that such a small contribution to normal endogenous levels, all of which would be subject to operation of the same protective mechanisms (whether perfect or not), would produce a total internal dose that would be biologically distinguishable from background, giving rise to a biological perturbation resulting in unacceptable risk. This improbability is supported by the TCEQ's reality checks of the USEPA EtO URF on both lymphoid cancer in the key NIOSH cohort and in the U.S. population, as well as in the smoking population specifically.

Regardless of the endogenous or background EtO exposures, the primary deterministic factor for the rejection of USEPA's model under TCEQ guidelines is the USEPA-acknowledged lack of MOA data for EtO supporting an overall supra-linear dose-response curve. The TCEQ does not

state that concentrations seen in the population aren't already causing lymphatic cancers. In fact, the TCEQ assumes this and performs a U.S. population background reality check on USEPA's URF.

The response to Comment #6 addresses the question of Michaelis-Menten kinetics.

Comments from a citizen in the Austin area

Comment 1:

The most alarming thing about the proposed threshold change is that Texas already produces half of the country's ethylene oxide, and the rule change would no doubt lead to increased emissions in a time we are also experiencing hotter years. Ethylene oxide can be explosive when exposed to air and heated, so you can understand why a resident of an urban center would be concerned about an increase in toxic gas in the air.

Response:

Although EtO is a flammable gas, it takes very high concentrations in order for it to be explosive. The lower explosive limit, or LEL, for EtO is 3.6% volume in air, which is equivalent to 36,000 ppm. This concentration is significantly (i.e., orders of magnitude) higher than could be expected in ambient air (e.g., compared to the TCEQs revised EtO chronic ESL of 2.4 ppb).

Comment 2:

The assessment that is cited in the paper on the commission's website is based on comparisons to 'endogenous values', the calculation of and data sources for which are never discussed. The value of 'endogenous' EtO is not at all a consensus value. The article by Kirman and Hays cited as the basis of the assessment throughout the document was commissioned by the industry trade group, the American Chemical Council, as cited in the conflicts of interest section toward the end of the article "The analysis presented here was funded by the Ethylene Oxide Panel of the American Chemistry Council (contract 5478)."

The 'endogenous value' holding up the analysis has not been independently verified. The interests of the American Chemical Council, driven by nebulous 'market forces', and the interests of the general public, with which the TCEQ is entrusted, diverge in obvious ways. The American Chemical Council is entrusted with upholding the economic interests of its members, who are driven by the maximization of profit regardless of environmental impact. This is a story we have read many times.

Response:

Across a given field of study, scientists rarely come to a consensus on single values representing anything. In this case for example, a survey across regulatory and other agencies of health-protective environmental media concentrations (e.g., air, soil, water, fish tissue) for well-studied chemicals would yield many disparate values with no consensus value ever emerging. Kirman and Hays (2017) is a peer-reviewed article appearing in the scientific literature. Science is paid for and conducted by those who have interest in better understanding the underlying science and important scientific issues, including government, industry, academia, or others. Although TCEQ understands the commenter's concerns (i.e., ACC's interests), it should be noted that: (1) Scientific journals recruit independent and objective peer review experts to verify the scientific soundness of article approaches; (2) the TCEQ used a systematic review process that included risk of bias analysis for all articles, including the ones referenced that were published

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as peer-reviewed scientific articles (fully described in Appendix 1 of the DSD); and (3) while TCEQ used Kirman and Hays (2017) for context, it played no deterministic role in choice of the modeling approach or derivation of the URF.

Comment 3:

The endogenous equivalent value is a calculation of the ambient ethylene oxide air concentration to which non-smoking test subjects were exposed in the months leading up to sampling. The value is a calculation of the baseline exposure of these test subjects and not the endogenous production of ethylene oxide, the two being distinct scientific concepts. The 'endogenous values' based on reporting by Kirman and Hays reflect the baseline exposure of the study participants which has nothing to do with endogenous production at all. The value is an extrapolation of ambient EtO concentrations based on hemoglobin adduct quantitation, which does not discriminate between endogenous and exogenous exposure. To call this value 'endogenous' is to be factually incorrect and misleading to the public for the sake of profit at the expense of our health and environment.

Response:

The TCEQ appreciates the commenters note about the distinction between typical environmental exposure and endogenously-produced EtO contributions to EtO-hemoglobin adduct formation. For EtO, endogenous production overwhelmingly dominates the distribution. Based on the linear relationship between EtO exposure concentrations and the HEV biomarker of exposure, typical environmental levels of EtO would not significantly add to endogenous levels. For example, USEPA's maximum acceptable air concentration corresponds to an internal dose only about 1/40th of the 1st percentile of distribution in Kirman and Hays (2017). Subtracting the very small contribution from typical environmental levels would have no practical effect on the distribution, which is dominated by endogenous levels. The TCEQ also points out that the workers in the NIOSH cohort also had typical environmental exposure outside the workplace as a small part of their background exposure (i.e., endogenous plus a very minor contribution from environmental). As the dose-response assessment is for occupational exposures over and above such a baseline, the comparisons made by TCEQ are all the more appropriate. However, subtracting the insignificant contribution from environmental exposure would make no difference in terms of the outcome of comparisons to USEPA-risk based values or the doses associated with carcinogenicity in epidemiology studies. The reasonableness of endogenous levels cited in Kirman and Hays (2017) and the high likelihood that environmental EtO levels had no significant effect on the data is further strongly supported by endogenous data in laboratory control animals. More specifically, the TCEQ notes that the reported mean human background endogenous HEV level of 21.1 pmol/g Hb appears very reasonable given background HEV levels in control rats (≈42-50 pmol/g Hb) and mice (≈58-100 pmol/g Hb) (Walker et al. 1993, 2000). This information was added to the DSD for clarification.

Comment 4:

The ethylene oxide assessment is also difficult to read because data are frequently presented in relation to the non-consensus 'endogenous values' discussed above that are the linchpin of the

assessment. To compare real values and examine the relationships the authors put forth, a reader must pull all the relevant originals and comb through them for the data to recreate the basis for the likely inaccurate conclusions in the paper. An average Texan who wants to be engaged in the processes of her government and have a say should not have to work so hard to understand what is scientifically proven and what is vapor. The authors are obfuscating their wrong assertions by massaging numbers and conflating concepts.

Response:

Endogenous data are used for context and are not the linchpin of the assessment, which is essentially the lack of EtO MOA data supporting the adoption of a non-standard, overall supra-linear dose-response model. The TCEQ endeavors to present all calculations and methods in the DSD in a straightforward and repeatable manner, and has tried to clarify our discussion of endogenous levels of EtO in this DSD.

Comment 5:

The evaluation is also based on mortality from the cancers examined. Mortality rates vary as medical advances reduce mortality compared to incidence. Therefore, basing a calculation on mortality is muddying the waters. Incidence, however, directly correlates exposure with human impact. Cancer treatment itself is a significant medical expense and personal trauma that should not be discounted. Furthermore, the time frames of the studies make a mortality comparison questionable because the relationship between incidence and mortality was much closer in the older Union Carbide study than the more recent NIOSH study. NIOSH would be expected to have lower mortality rates due to medical progress over time in improving the survival rate of cancer incidence. In short, mortality is a measure of medicine and incidence is the true measure of toxicity.

Response:

The TCEQ recognizes the terrible personal and societal toll of cancer, which touches the lives of every family at one time or another. In the interest of public health, the agency is committed to the accurate prediction of the risks that environmental chemicals pose so that effort and resources can be appropriately prioritized and committed to mitigating those exposures commensurate with the risks they most realistically represent. Most often, epidemiology studies must rely on mortality data as opposed to incidence data, even though incidence information is a much better marker of potential toxicity, because there are no incidence data available. This is the case for lymphoid cancer data for the key NIOSH cohort, and is a primary reason why the TCEQ has chosen to use the 95% UCL on the slope as the more conservative estimate, in addition to incorporating ADAFs in consideration of childhood exposure. These conservative assumptions are health-protective and include protection for unknowns like the relationship between incidence and mortality. Furthermore, the health-protective assumptions made by TCEQ are above and beyond the presumption of carcinogenic effects of exposures to EtO. Workers in the NIOSH and UCC studies (and several other studies) do not show a statistically significantly increasing cancer response relationship with increasing exposure to EtO.

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Comment 6:

Finally, the assumptions and key evaluations chosen by the authors betray the purpose of re-evaluating the allowable limits in the draft assessment provided by the TCEQ, which appears to be to justify increased emissions by businesses located in Texas. In contrast, the US EPA IRIS report for ethylene oxide released in 2016 establishes throughout the document that its purpose is to develop a protective risk assessment that takes into account not only worker safety, but sufficient margins of protection for the general public and children.

Response:

The TCEQ was compelled by scientific duty to conduct our own EtO dose-response modeling when upon reviewing the USEPA assessment in detail, significant scientific flaws became apparent. These are outlined in the DSD and included such things as incorrectly calculated p-values and AIC values which were erroneously used by USEPA to justify an unconventional, overall supra-linear model that TCEQ has shown to be over-predictive both for the key NIOSH cohort and the U.S. population. The TCEQ DSD uses the 95% UCL on the slope in consideration of public health protection, as well as ADAFs in consideration of childhood exposure.

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Comments from the Ethylene Oxide Sterilization Association

Comment 1:

The URF for EO based on lymphoid cancer derived by TCEQ is 2.5E-6 per parts per billion (ppb) (1.4E-06 per μg/m^3) and results in a risk-based air concentration of 4 ppb at the no significant excess risk level of 1 in 100,000. This value is much more realistic and defensible than the EPA IRIS URF of 9.1E-3 per ppb (5.03E-3 per μg/m^3), which yields a 1 in 100,000 risk concentration of 1 part per trillion (ppt). EOSA agrees with TCEQ that the EPA IRIS assessment is not adequately supported by current scientific data. The EPA IRIS assessment should not be used as the basis for the exclusion of other estimates of cancer risk that are based on other robust studies and modeling methodologies with more representative exposure estimates. Reliance on the flawed, overly conservative, and outdated EPA IRIS assessment would result in disastrous consequences to the healthcare industry and public health in the United States. Decisions on how best to protect public health cannot be made on such demonstrably flawed science.

Response:

The TCEQ agrees and appreciates this comment.

Comment 2:

Though EOSA supports TCEQ's statements regarding the inaccuracies of EPA's modeling approach, the non-threshold effects screening level (ESL) of 4 ppb is overly conservative when you consider endogenous and background ambient EO levels. EPA's December 2016 IRIS assessment relies exclusively on a National Institute of Occupational Safety and Health (NIOSH) epidemiology study of sterilizer workers. The NIOSH study used a model to estimate exposures prior to 1978 because there were virtually no measured EO concentration data for sterilization workers prior to 1978. The NIOSH exposure model estimates job exposures that were lower than levels observed from 1978 and later. This would be an unusual pattern of historical exposure, based on industry experience with sterilization operations. This unusual pattern was also noted by the EPA Science Advisory Board (SAB) during its review of the IRIS assessment.

Response:

The TCEQ agrees that, as stated in the DSD, there appears to be appreciable uncertainty stemming from the lack of EtO exposure data for the NIOSH cohort prior to the time air monitoring data collection began. These exposures for much of the cohort would have been relatively high and significantly contributed to cumulative exposure estimates (ppm-days, both unlagged and lagged), which appear likely to be biased low (e.g., Bogen et al. 2019, Li et al. 2019). The USEPA SAB agreed that these exposure estimates are likely of lower reliability (because there were no exposure measurement data that could be included in the exposure model prior to 1979) and actual EtO exposures were likely to have been higher than reflected in the estimates (p. I-41 of USEPA 2016). Use of likely low-biased exposure estimates for earlier periods of time lend additional conservatism to the assessment. However, the TCEQ disagrees that in the absence of additional analyses, the TCEQ assessment can be characterized as "overly" conservative (i.e., that the proposed long-term ESL is significantly lower than it would

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have been had the earlier monitoring data been available). Similarly, data on endogenous levels and ambient levels do not lead or compel the TCEQ to conclude that the assessment is overly conservative. For example, the TCEQ URF for lymphoid cancer passes the NIOSH worker and U.S. population reality checks.

Comments from the Houston Health Department

Comment 1:

The Houston Health Department opposes the approval of the Texas Commission on Environmental Quality Developmental Support Document for Ethylene Oxide which conflicts with and presents a lower toxicity value for ethylene oxide than that used by the Environmental Protection Agency (EPA). According to the 2014 EPA National Air Toxics Assessment (NATA), ethylene oxide is of grave concern for Houstonians, not only is ethylene oxide the cancer risk driver for the highest risk census tracts in Houston/Harris County, census tract 343100 has the 7th highest cancer risk from ethylene oxide and the 11th highest total cancer risk in the nation (Table 1, Figure 1). In fact, ten census tracts in Harris County are in the top one hundred highest ethylene oxide cancer risks in the nation, out of a total of 76,727 census tracts (with another census tract just outside the top one hundred). Lowering the toxicity value will remove pressure from understanding and mitigating exposure to this pollutant.

Response:

Although the NATA data can be informative, it has a number of limitations that must be kept in mind when interpreting the results. Multiple assumptions go into the calculations that create the NATA data, which means that the output from the NATA cannot be specific for individuals or small areas. As stated on the USEPA website, "NATA results are best applied to larger areas – counties, states and the nation. Results for smaller areas, such as a census tract, are best used to guide follow-up local studies." Additionally, one of the factors used to calculate cancer risk within the NATA is the USEPA URF. The USEPA URF for EtO was updated in 2016, and this URF was used in the most recent 2014 NATA. This explains why the 2011 NATA data does not show the same EtO cancer risk. The TCEQ has determined that the dose-response model used by the USEPA to develop their URF is not supported by the scientific data for EtO, and therefore did not adopt it, and would therefore not agree with the putative excess risk presented in the NATA.

At the county level, while Harris County has relatively high reported National Emissions Inventory (NEI) EtO emissions per square mile (i.e., 6.6E-03 tons/square mile is ≈188 times higher than the US at 3.5E-05 tons/square mile), the incidences of leukemia (13.0 (95% CI of 12.5, 13.5)), non-Hodgkin's lymphoma (16.9 (95% CI of 16.3, 17.5)), breast cancer (111.9.4 (95% CI of 109.9, 114.0)), as well as all cancers combined (400.1 (95% CI of 397.2, 403.1)) are all statistically significantly lower than in the general US population.

Comment 2:

In general, the Houston Health Department advocates for consistency of toxicity values with the EPA. In this case, we are especially concerned with the departure from the use of the EPA toxicity values because the proposed value is less protective, and many residents are potentially affected. There is a high degree of uncertainty in understanding the toxicity of individual chemicals on humans, but even more so in Houston, where residents are exposed to mixtures

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of other toxic chemicals. The health of Houstonians is better protected with the current EPA toxicity value.

Response:

Across a given field of study, scientists rarely come to a consensus on any toxicity value. A survey across regulatory and other agencies of health-protective environmental media concentrations (e.g., air, soil, water, fish tissue) for well-studied chemicals would yield many disparate values with no "consensus value" ever emerging. The TCEQ has determined that the EPA statistically significantly over-estimated the risk associated with ethylene oxide exposure, and therefore we developed our own scientifically-sound assessment.

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Comments from Harris County, TX

Comment 1:

The EPA Unit Risk Factor (URF) model for ethylene oxide, referenced in the DRA [Dose Response Assessment], is clearly a more conservative approach to determine a health based screening value than the method proposed by TCEQ. The TCEQ Cox Proportional Hazard method uses a very different approach and results in a level that is higher and may not be protective of human health. The proposed TCEQ health based screening value is 4,000 times less protective than the EPA value. When human health is at risk, and sensitive populations are at risk of exposure, increasing a health-based value by over three orders of magnitude must be supported by ample scientific data. Harris County requests that TCEQ coordinate with the EPA and reach a concurrence prior to the determination of a final value.

Response:

Best science is not determined by the method that results in the lowest value. The issue in this case is which model assessment most accurately predicts cancer risk. The TCEQ has demonstrated that USEPA's selected model assessment over-predicts lymphoid cancer in the key NIOSH cohort and the U.S. population, its selection was based on incorrectly calculated p-values and AIC values, and it is biologically implausible. By contrast, TCEQ's assessment is supported by all these considerations. Across a given field of study, scientists rarely come to a universally accepted consensus. A survey across regulatory and other agencies of health-protective environmental media concentrations (e.g., air, soil, water, fish tissue) for well-studied chemicals would yield many disparate values. The TCEQ is always willing and ready to discuss our assessments with the USEPA or any other group, and is willing to reach consensus on scientific issues if such consensus can be reached.

Comment 2:

Section 3.4.2 of the DRA notes that there is a lack of chemical specific data on susceptibility from early-life exposures and as a result, the TCEQ utilized default ADAF numbers.

Response:

There is a general lack of chemical-specific data for most chemicals on susceptibility from early-life exposures, including for EtO. For this reason, both USEPA and TCEQ use ADAFs in consideration of childhood exposure when a chemical has been identified as acting through a mutagenic MOA, consistent with USEPA guidance. The TCEQ DSD now calculates the ADAF-adjusted ESL consistent with equation 5-17 of the TCEQ guidelines (TCEQ 2015), rounding it to two significant figures at 2.4 ppb.

Comment 3:

Harris County urges the TCEQ to conduct a study to determine the actual background ethylene oxide concentrations in Harris County and impacts of ethylene oxide on children and pregnant

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women. This data is necessary to understand our residents' chemical burden and health impacts.

Response:

Such ecological studies have significant uncertainties and are typically not useful in determining causation (i.e., attributing effects to a given chemical exposure) or for regulatory dose-response assessment. Previous studies at various locations have yielded mixed results and are of little regulatory use (see TCEQ response to Comment #7 from the Union of Concerned Scientists).

Comment 4:

Harris County requests that the TCEQ hold a public meeting to explain to the public the scientific process utilized in this determination as well as to present supporting data.

Response:

The process is outlined in the TCEQ toxicity factor guidelines (https://www.tceq.texas.gov/assets/public/comm_exec/pubs/rg/rg-442.pdf), and the DSD itself presents both key and supporting data. Both have undergone previous public comment.

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Comments from the Natural Resources Defense Council

Comment 1:

TCEQ process violates EPA peer review requirements.

EPA's process for developing its EtO IRIS assessment was consistent with its peer review requirements as described in the EPA Peer Review Handbook (4th Edition, 2015), and the Final Information Quality Bulletin for Peer Review (OMB, 2004). In stark contrast, TCEQ's EtO assessment and proposed risk estimate has not been vetted by an external scientific advisory committee or any other appropriate scientific peer review committee, and has not undergone any public peer review, scientific scrutiny, or public comment before this comment period.

The peer review process that TCEQ should undertake should be transparent, include EPA input, and be accountable to the recommendations that arise from that process. The Handbook and Bulletin require documents that are "highly influential," "novel, controversial, or precedent-setting," or have "significant interagency interest" to undergo peer review before being implemented. EPA has done this, while TCEQ has not.

Response:

Although the TCEQ is not required to do a peer review (TCEQ 2015) nor do we fall under the same requirements as the IRIS program, the TCEQ has decided to conduct an independent external scientific peer review in the first quarter of 2020 to strengthen our assessment. The TCEQ has also had the benefit of SAB and public comments provided on the USEPA (2016) assessment, as well as extensive public comments on the DSD from a diverse group of commenters (e.g., NGOs, academia, industry, private citizens).

Comment 2:

TCEQ fails to address all cancer and non-cancer risks.

TCEQ narrowed the focus of its assessment to lymphoid cancers only, disregarding the elevated breast cancer incidence in female workers. This results in an underestimate of the risks posed by EtO, and is one of the most significant differences between the TCEQ assessment and the EPA IRIS assessment, which included breast cancer data.

Response:

As with USEPA's 2016 assessment, the TCEQ DSD was limited to a carcinogenic dose-response assessment. The TCEQ decided to move forward with the cancer risk assessment first in order to expedite the process. Although long-term limits based on cancer risk are expected to determine allowable emissions in both the short- and long-term, the agency plans to return to the non-cancer assessment in the near future. TCEQ does have interim ESLs in place in recognition of these concerns.

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The TCEQ evaluated breast cancer as a candidate cancer endpoint. USEPA's assessment, however, is driven by lymphoid cancer as the primary contributor to the URF. Subsequent to USEPA's 2016 assessment and TCEQ's systematic review of the peer-reviewed literature for EtO, recent meta-analyses of available studies have been published (Marsh et al. 2019, Vincent et al. 2019). These new meta-analyses included Steenland et al. (2003, 2004) and the smaller Mikoczy et al. (2011) study cited by USEPA (2016), as well as other studies, and reported breast cancer meta-RRs of 0.97 (0.80, 1.18) (Marsh et al. 2019) and 0.92 (0.84, 1.02) (Vincent et al. 2019). The Marsh et al. study concluded [*emphasis added*], "Evaluations of workers exposed during sterilization processes *do not support the conclusion that EO exposure is associated with an increased risk of breast cancer*." Similarly, the Vincent et al. (2019) study concluded, "Higher quality epidemiological studies demonstrated no increased risk of breast cancers." In addition to evaluating epidemiological evidence, Vincent et al. (2019) evaluated animal study results and concluded that they provide no strong indication that EtO causes mammary tumors. These recent meta-analyses and other information (IARC 2019) further support TCEQ's decision not to base the URF on breast cancer. Human data are by far the most relevant for derivation of human toxicity factors, and the human data themselves are inconclusive (as acknowledged by USEPA 2016). The weight of evidence for EtO-induced breast cancer is now discussed in a new appendix (Appendix 6) in the revised DSD.

That being said, the assessment does not ignore risk to women as the lymphoid cancer estimate is shown to be conservative for women. The TCEQ URF is ultimately based on the same key epidemiological study as USEPA's URF. The study included both male and female workers. The dose-response assessment evaluates lymphoid cancer risk to males and females combined as well as males alone. Analyses with both males and females combined compared to results based on males alone show that use of risk results based on males alone is conservative for estimating lymphoid cancer risk in females, which is demonstrated in the DSD. Thus, a conservative long-term ESL and URF is used to evaluate lymphoid cancer risk to women, resulting in a lower long-term ESL for everyone (compared to using modeling results for males and females combined).

Table 5. Human Studies Relevant to the Breast Cancer Weight of Evidence

Study Type	Workers (n)	EtO Exposure Level (ppm)	Observed (O)	Expected (E) [a]	O/E (95% CI)
Individual Studies					
Steenland et al. (2003)	7,576 female workers	Median ≈14 ppm-years; Mean >1 ppm [b]	230 [c]	258.4	**0.89** [d] (0.78, 1.01)
Steenland et al. (2004)	18,235 workers (≈55% female)	Mean of 26.9 ppm-years	103	102	**0.99** (0.84, 1.17)
	only female workers				**0.99** [e] (0.81, 1.20)
Mikoczy et al. (2011)	2,046 workers (≈60% female)	Means ≤1.11 ppm; Peaks up to 40-75 ppm	33	38.54	**0.86** [f] (0.59, 1.20)

Study Type	Workers (n)	EtO Exposure Level (ppm)	Observed (O)	Expected (E) [a]	O/E (95% CI)
	615 female 287 female 295 female	Mean of 0.02 ppm in lowest cumulative exposure group Mean of 0.021 ppm in middle cumulative exposure group Mean of 1.11 ppm in highest cumulative exposure group			**0.52** [g] (0.25-0.96) 1.06 (**0.58**, 1.78) 1.12 (**0.65**, 1.79)
Norman et al. (1995)	928 female	TWA 50-200 ppm; 5-20 ppm post-corrective action 1980	12	7.64	1.57 [h,i] (**0.90**, 2.75)
Coggon et al. (2004)	1,012 female	TWA generally < 5 ppm; Peaks up to > 700 ppm	11	13.1	**0.84** [j] (0.42, 1.50)
Hogstedt et al. (1986)	153 female	TWA 20±10 ppm	0	---	**No breast cancer reported**
Meta-Analysis Studies					
Marsh et al. (2019) [k]					**0.97** (0.80, 1.18)
Vincent et al. (2019) [k]					**0.92** (0.84, 1.02)

[a] Based on external referent US population; see the text for information regarding why a healthy worker effect should not be expected for breast cancer incidence, an endpoint relied upon by USEPA (2016).

[b] Using the 233 cases with interviews as a surrogate, mean exposure level would be expected to be > 1 ppm since the mean is higher than the median in a lognormal distribution, median cumulative exposure for the 233 cases was 14.0 ppm-years, and mean years exposed was 13.0 (Table 2 of the study), so mean cumulative exposure >14 ppm-years/mean duration of 13 years = >1 ppm mean exposure.

[c] From Table 3 of the study based on workers whose exposure did not lag out using a 15-year lag period, consistent with USEPA (2016) and TCEQ; expected (E) value of 258.4 was calculated (i.e., E=O/0.89).

[d] For a 15-year lag, consistent with that used by USEPA (2016) and TCEQ.

[e] Breast cancer did not show any overall excess, although there was an excess in the highest cumulative exposure quartile (>12,322 ppm-days) using a 20-year lag and internal exposure-response analyses found positive trend for breast cancer using the log of cumulative exposure with a 20-year lag but not cumulative exposure (Tables 1, 5, and 8 of study).

[f] From Table 3 of Mikoczy et al. (2011) and includes induction latency period of ≥15 years, consistent with that used by USEPA (2016) and TCEQ.

[g] This statistically significantly decreased breast cancer risk occurred in female workers exposed to a mean of ≈20 ppb EtO; this inordinately decreased SIR for the lowest cumulative exposure group produced statistically increased SIRs for higher cumulative exposure groups which did not experience increased breast cancer risk compared to the general population despite EtO mean exposures up to ≈1,110 ppb and more robust female worker data suggest that it represents an anomalous study artifact.

[h] For the most appropriate method identified by the study authors (Method 2) for the longest follow-up period (through 1987) with the most appropriate/matching SEER rates (through 1987) used to calculate the expected number (E).

[i] Includes two breast cancers diagnosed within 1 month of employment; reasonably excluding these two breast cancers diagnosed within 1 month of beginning work would not be expected to significantly reduce person-years but would result in a lower and still statistically insignificant estimated O/E (e.g., 10/7.64 = 1.31).

[j] For female workers with known continuous workplace exposure, the breast cancer mortality SMR was 0.70 (5 observed vs. 7.2 expected).

[k] This meta-analysis included all the individual studies above except for Hogstedt et al. (1986), which found no breast cancers and therefore did not report any effect estimate for breast cancer.

Comment 3:

TCEQ fails to address environmental racism in cancer death rates.

TCEQ disregarded EtO-associated breast cancer risks in women workers by conducting assessments based only on morbidity, that is, deaths from breast cancer. Because many women that are diagnosed with breast cancer can survive it, this make is seem as if the risk is negligible. In addition to underestimating risks by counting only women that die of breast cancer, TCEQ's approach also underestimates risks to women of color more than white women. This is because cancer survival depends on access to quality health care, routine medical screening procedures, and medical insurance to allow timely and effective treatments – all of which have significant racial bias. That is, although over time there has been a decline in deaths from breast cancer, not all women have benefited equally. This is evidence by the striking divergence in mortality trends between black and white women beginning in the early 1980s. As treatment for breast cancers has improved, the racial disparity widened; in 2015, breast cancer death rates were 39% higher in black than white women. This is particularly relevant for EtO and other contaminating facilities that are disproportionately co-located in areas of Texas such as the Houston Ship Channel communities that are predominantly low-income and communities of color.

Response:

When deriving a chemical toxicity factor, the TCEQ (and the USEPA) incorporate multiple layers of conservatism into the value so that all members of the general public are protected, including sensitive subpopulations. The long-term ESL applies equally for all people regardless of race, ethnicity, socioeconomic status, etc., and assumes 24 hours/day, 365 days/year exposure to be protective of even those most exposed to ambient EtO air concentrations. The health-protective limit established by the TCEQ includes the following conservative considerations:

1) The lack of human data sufficient to establish EtO as a human carcinogen despite occupational exposures up to millions of times ambient levels;
2) The lack of statistically significantly increasing risk with exposure to EtO;
3) Using the endpoint (lymphoid cancer), study cohort (NIOSH), and sub-cohort (males) that predicts the largest estimated risk of seventy-two non-increasing exposure-response models;
4) Uncertainty in the model parameter estimate (i.e., use of the 95% UCL);

5) Assumed *continuous* exposure to EtO, 24 hours a day, 7 days a week, for every week of every year, from birth until 70 years of age; and
6) Adjustment for early-age exposures using ADAFs.

The TCEQ did consider breast cancer incidence in our EtO evaluation for this DSD, but ultimately concluded that evidence showing that EtO causes breast cancer is unconvincing. Please see the response to Comment #2 above and more specifically, Appendix 6 of the revised DSD for a more detailed discussion.

Comment 4:

TCEQ mis-represents endogenous exposures.

Understanding the endogenous exposures is a scientifically critically important component of the EPA's EtO assessment, whereas it is mis-represented by TCEQ in its assessment. Although the body produces EtO endogenously (through cellular metabolic processes), it has some defense mechanisms, albeit imperfect ones, to deal with some level of endogenous exposure. Given that both breast and lymphoid cancers are fairly common, it is possible that some may be due to endogenous EtO levels, suggesting that the body's defense mechanisms may be largely overwhelmed by additional exogenous EtO from preventable industrial sources, especially when considered across the whole population. While EPA has addressed this in its more sophisticated and scientifically accurate assessment, the TCEQ assessment simply 'zeroes out' the cancer risks at lower exposures as if they do not exist, and – even more flawed – that the body's cellular defense mechanisms will make additional cancer risks 'go away'. This makes as little scientific sense as it sounds, and even less when considered across a diverse population that includes sensitive individuals.

Response:

The normal human range of endogenous or background exposure is primarily provided for context. Various examples provide this context, such as USEPA's maximum acceptable air concentration corresponding to an internal dose about 1/40th of the 1st percentile of normal endogenous levels. It is highly biologically implausible that such a small contribution to normal endogenous levels, all of which would be subject to operation of the same protective mechanisms (whether perfect or not), would produce a total internal dose that would be biologically distinguishable from background, giving rise to a biological perturbation resulting in unacceptable risk. This improbability is supported by the TCEQ's reality checks of the USEPA EtO URF on both lymphoid cancer in the key NIOSH cohort and in the U.S. population, as well as in the smoking population specifically.

Regardless of the endogenous or background EtO exposures, the TCEQ uses the lack of MOA data justifying an overall supra-linear dose-response model as the primary determinant for rejecting the unconventional two-piece spline model and using a standard model (Cox proportional hazards model) to estimate additional risk. The TCEQ does not state that concentrations seen in the population aren't already causing lymphatic cancers. In fact, the TCEQ assumes this and performs a U.S. population background reality check on USEPA's URF.

Comment 5:

NRDC supports the calls of Texas residents and others in calling for TCEQ to simply adopt the U.S. EPA scientists' determination and cancer risk factor for ethylene oxide, finalized by the IRIS program in 2016. The EPA IRIS determination reflects the best available science.

Response:

The TCEQ's DSD fully considers the USEPA's derivation of their EtO URF and finds several serious scientific flaws in USEPA's 2016 assessment. The DSD then carefully and completely lays out the scientific basis for our EtO URF derivation, based on the best available science and supported by multiple lines of evidence, some of which are newly available. The revised DSD and accompanying analyses will be undergoing peer review in the first quarter of 2020.

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Comments from the Achieving Community Tasks

Comment 1:

We urge the Texas Commission on Environmental Quality (TCEQ) to follow the best available science and not to weaken protections for the thousands of Texans exposed to the carcinogen ethylene oxide. We respectfully request that TCEQ not finalize the proposed Development Support Document (DSD), and instead adopt the robust, final, peer-reviewed cancer risk factor that the Integrated Risk Information System (IRIS) of the U.S. Environmental Protection Agency (EPA) finalized in 2016.

Response:

The TCEQ strives to use the best available science for all our chemical risk assessments. It is our process to review the assessments conducted by other agencies to determine whether or not their methodologies and assumptions are consistent with our guidance (TCEQ 2015), and if not we conduct our own risk assessment. The TCEQ's DSD fully considers the USEPA's derivation of their EtO URF and finds several serious scientific flaws in USEPA's 2016 assessment. The DSD then carefully and completely lays out the scientific basis for our EtO URF derivation, based on the best available science and supported by multiple lines of evidence, some of which are newly available. The revised DSD and accompanying analyses will be undergoing peer review in the first quarter of 2020.

Comment 2:

We ask that TCEQ seek external scientific peer review and provide adequate time for public notice and comment, if it continues to consider the proposed DSD.

Response:

The TCEQ's EtO DSD has undergone a 90-day public comment period, and TCEQ will conduct an external independent expert peer review in the first quarter of 2020.

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Comments from the Advanced Medical Technology Association

Comment 1:

The Advanced Medical Technology Association (AdvaMed), the national association of medical technology providers, supports the Texas Environmental Quality Commission's (Commission) reasonable, risk-based approach to the exposure assessment for ethylene oxide and we also support the Commission's rejection of the faulty Integrated Risk Information System (IRIS) approach.

Response:

The TCEQ appreciates your support of this risk assessment.

References

Please see the TCEQ DSD for the referenced cited in this document.

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Exhibit J

2014 National Air Toxics Assessment: Fact Sheet

Overview

- On August 22, 2018, the U.S. Environmental Protection Agency (EPA) released the sixth National Air Toxics Assessment (NATA), the Agency's tool that provides information on potential health risks from breathing air toxics, also known as hazardous air pollutants.
- NATA is a *screening tool*, intended to help EPA and state, local and tribal air agencies determine if areas, pollutants or types of pollution sources need to be examined further to better understand risks to public health.
- NATA provides broad estimates of the risk of developing cancer and other serious health effects over census tracts across the country. It does not estimate any person's individual risk. (See "Using NATA," on page 2 of this fact sheet.)
- The version of NATA released today is based on emissions for the calendar year 2014. It includes estimates of exposure and risk for 180 air toxics that EPA regulates under the Clean Air Act. It also estimates exposure and risks for diesel particulate matter (noncancer effects only).

EPA Taking Steps to Address Emissions of Ethylene Oxide

The 2014 NATA shows that several areas could have elevated cancer risks from long-term exposure to the chemical *ethylene oxide*. These elevated risks are largely driven by an EPA risk value that was updated in late 2016.

Based on the NATA result, EPA is using its tools under the Clean Air Act to address emissions of ethylene oxide from certain types of industries.

Learn more

- Nationwide, total emissions of air toxics are declining, and air quality monitoring data show that concentrations of many toxics in the air, such as benzene, also are trending downward.
- The 2014 NATA estimates that the nationwide average cancer risk from air toxics exposure is 30 in 1 million. About half of that risk comes from the formation of formaldehyde – produced when other pollutants chemically react in the air. This is known as *secondary formation*, and comes from emissions from industries, mobile sources, and natural sources. The other half of the nationwide cancer risk comes from pollution that is *directly emitted* to the air.
- Despite improvements, some local areas still face challenges. The 2014 NATA results also indicate that some census tracts may have elevated risks of cancer from air toxics exposure

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(less than 1 percent of all tracts). Census tracts are small subdivisions of a county or county equivalent, such as a parish. Industrial emissions of three pollutants – ethylene oxide, chloroprene and coke oven emissions – contribute to most of the risk in these tracts. *See box above for more information on ethylene oxide.*

- When NATA shows a potential cancer risk of greater than 100 in 1 million at a census tract, it means there may be an elevated cancer risk in that tract. A risk level of 100 in 1 million refers to the likelihood that 100 in 1 million (1 in 10,000) people would develop cancer if they breathe air containing the same amount of the same air toxic for 70 years. This risk would be in addition to the cancer risk a person would have without being exposed to the air toxic.
- In developing air toxics regulations, EPA uses the 100-in-1 million risk level to help the Agency determine whether facilities need to reduce emissions.
- NATA estimates long-term risks – – those that may occur from breathing air containing elevated levels of air toxics continuously for many decades. It does not estimate short-term (acute) or intermediate risks. However, based on an examination of available data, EPA does not expect ethylene oxide levels in the air in these areas to be high enough to cause immediate harm to health.

Using NATA

- EPA and state, local and tribal air agencies use NATA to see if areas, specific air toxics, or types of pollution sources need to be examined further to better understand risks to public health. NATA does not estimate any person's individual risk. See the lists below for do's and don'ts of NATA use:
- **DO** use NATA results to:
  - identify pollutants and types of pollution sources of greatest concern,
  - improve understanding of air toxics-related health risks,
  - support communities in designing their own local assessments,
  - help inform community and local air toxics programs,
  - help set priorities for the collection of additional information, and
  - set priorities for improving emission inventories,

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- **DON'T** use NATA results:
  - as a definitive means to pinpoint specific risk values within a census tract,
  - to compare risks at local levels (such as between neighborhoods) or between states, or
  - as the sole basis for developing risk reduction plans or regulations, to control specific sources or pollutants or to quantify benefits of reduced air toxic emissions,
    - *Here's why:* NATA is a screening assessment. Its uncertainties vary by location and by pollutant and by type of pollution source. In many cases, more detailed assessments, including emissions testing and more refined modeling, may be needed to better understand local risks.
- **DON'T** use NATA results:
  - to examine trends from one NATA year to another.
    - *Here's why*: scientific information on air toxics and health can change between assessments. Computer modeling tools and inputs to modeling can change, too, making comparison across NATA versions inaccurate.
      - The 2014 NATA includes several improvements that were not available for the previous version (2011). Those include data that allow the Agency to better estimate where emissions are occurring within a county, improved modeling accuracy for some pollutants, and updated information about the health effects some pollutants cause.

DEVELOPING NATA

- EPA collaborates extensively with, state, local and tribal air agencies to develop and quality assure the data used in NATA.
- The 2014 NATA is based on emissions for the 2014 calendar year – the most complete and up-to-date U.S. emissions data available at the time of the assessment. It also uses the latest available scientific information on air toxics and health.
- NATA uses emissions information and estimated secondary and background air toxics concentrations to estimate potential health risks.
- For the 2014 NATA, EPA assessed 180 air toxics regulated under the Clean Air Act, from the following types of emissions sources:
  - **Point sources** – These are typically industrial facilities such as coke ovens for the steel industry, large waste incinerators and refineries, but also include some smaller sources such as dry cleaners.

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- **Nonpoint sources** – examples include small manufacturers and gas stations.
- **Mobile sources** – including cars, trucks and off-road vehicles like construction equipment and trains.
- **Fires** – including wildfires, prescribed wildland fires and agricultural burning,
- **Biogenics** – naturally occurring emissions from trees, plants and soil microbes.

- In addition, NATA includes estimated pollution from:
  - **Secondary formation** – This refers to pollutants that form in the air through chemical reactions; secondary air toxics often form via reactions between human-emitted and naturally occurring compounds.
  - **Background concentrations** – representing emissions from distant sources, emissions from prior years that persist in the environment, and natural source emissions other than those modeled as biogenics.
- EPA used all of these data to conduct computer modeling to create a snapshot of toxics in the air across the country in 2014.
- The Agency used that snapshot, combined with information about population and information about how different air toxics affect health, to estimate cancer risks and noncancer health effects for about 180 air toxics plus diesel particulate matter (noncancer only).

For more information

- For more information on NATA, visit https://www.epa.gov/national-air-toxics-assessment .
- For information on EPA's efforts to address emissions of ethylene oxide, visit https://www.epa.gov/ethylene-oxide .

Exhibit K

EPA Response to *Management Alert: Prompt Action Needed to Inform Residents Living Near Ethylene Oxide-Emitting Facilities About Health Concerns and Actions to Address Those Concerns Report No. 20-N-0128*

On March 31, 2020, the EPA's Office of Inspector General (OIG) issued a Management Alert related to the Agency's work to follow up on results of the most recent National Air Toxics Assessment (NATA), which identified a number of areas where cancer risks potentially could be elevated because of ethylene oxide emissions. The report recommended that the Agency:

> *Improve and continue to implement ongoing risk communication efforts by promptly providing residents in all communities near the 25 ethylene oxide-emitting facilities identified as high-priority by the EPA with a forum for an interactive exchange of information with the EPA or the states regarding health concerns related to exposure to ethylene oxide.*

Although we were surprised by, and disagree with, both the tone and substance of the report, we have made multiple attempts to offer the OIG a corrective action plan, with milestones, in the interest of resolving this matter. Our proposed plan was developed based on two guiding principles.

First, risk communication must rely on *accurate* information. Indeed, EPA's mission statement states, as the OIG noted in their report, that the Agency should work to ensure that "all parts of society ... have access to accurate information sufficient to effectively participate in managing human health and environmental risks." However, the report itself misses the part of the mission statement that includes providing access to *accurate* information.

As we noted in prior correspondence with the OIG, because NATA provides *screening level* results that have inherent uncertainties, additional work is necessary to more fully understand those potential risks and the emissions from facilities that contribute to them. We believe this follow-up work must be conducted prior to significant public outreach, so that we are providing residents information that is as detailed and up to date as possible. Public engagement based on outdated, preliminary, uncertain information is irresponsible and undermines the Agency's credibility.

Second, state leadership is essential to effectively address local air toxics issues like ethylene oxide. As part of the Agency's approach for addressing emissions of ethylene oxide in response to the most recent NATA, EPA is continuing to support state-led efforts not only to conduct additional, more refined investigations, but also to carry out appropriate outreach with affected communities. States, who have primary responsibility for air pollution prevention and air pollution control under the Clean Air Act, are best positioned to lead this work. As we noted in prior correspondence with the OIG, state-led efforts have already led to emission reductions and expected public health benefits in several areas.

In keeping with these guiding principles, we have offered the OIG a two-part corrective action plan with milestones: (1) conduct additional, more refined investigation of risk and (2) conduct outreach to affected communities.

Our initial corrective action plan (dated May 15, 2020) was developed in consultation with the OIG and **was submitted only after we were told by OIG staff that the plan "could be accepted" and that we should "go ahead and send it up formally." Based on a follow**-up conversation with the OIG on July 20, 2020, we submitted an amended plan on August 7, 2020. After another conversation with the OIG on October 2, 2020, we submitted a further-amended plan on October 9, 2020 (see Attachment 1).

The latest version of our plan reflects specific changes requested by the OIG – including providing for more timely and more interactive (two-way) risk communication with potentially affected communities. In the latest plan, we pointed out to the OIG that we are committing to conduct the necessary additional technical work and appropriate outreach on a timeframe that is five months shorter than that included in our original plan. In addition, we noted we intend to explore a wide variety of communication tools **to accomplish the goal of "interactive** exchange," recognizing that the appropriate first step is always to talk with local government officials and community leaders to determine what form of outreach will be most effective and most welcome in specific communities. We also noted that this outreach may need to occur virtually (through webinars, and virtual workshops, for example), because of current restrictions on in-person engagement due to COVID-19

The OIG informed OAR on October 28, 2020, that the proposed corrective actions do not fully address their recommendation and that, as such, their recommendation is unresolved. Nonetheless, OAR remains committed to its plan and intends to post the promised status reports to the Web shortly.

ATTACHMENT 1. EPA Corrective Action Plan (October 9, 2020)

Part 1. Conduct additional, more refined assessments of risk

a. Regions 2, 3, 4, 5, 7 and 8 (15 facilities/areas)[1,2]

Milestone: Technical work has already been conducted or is well underway for these facilities/areas, including updating information on emissions, air quality impacts, and risks. EPA will post quarterly status reports on these additional, more refined assessments to the **Agency's/Regions' Ethylene Oxide website**(s) beginning in November 2020. Each status report will provide a summary of the work completed and the work planned for each facility/area, along with relevant milestones and dates.

b. Region 6 (nine facilities/areas)

Milestone: EPA Region 6 has begun work with the states of Texas and Louisiana on facility/area-specific technical assessments. EPA will post quarterly status reports on the assessments to the **Agency's/Region's Ethylene Oxide website(s) beginning in November 2020.** Each status report will provide a summary of the work completed (including, as appropriate, updated information) and the work planned for each facility/area, along with relevant milestones and dates.

c. Regions 2 – 8 (24 facilities/areas)

Longer-Term Milestone: Additional, more refined assessments have already been conducted or are well underway for the one facility in Region 2, four facilities in Region 3, three facilities in Region 4, four facilities in Region 5, two facilities in Region 7 and one facility in Region 8. Please note that this work can consist of many different activities and can require coordination with state environmental agencies and other federal agencies. For example, in Region 4, one facility is the subject of a recent EPA risk and technology review and associated rulemaking. The other two Region 4 facilities have had additional emission controls added and are the subject of a Georgia EPD monitoring study with support from the Region. The Agency for Toxic Substances and Disease Registry (ATSDR) is also performing health consultations for the communities around these two facilities and providing health education. EPA will provide ATSDR technical assistance as needed. In Region 6, EPA will work with the states of Texas and Louisiana to conduct additional, more refined technical assessments for the nine facilities in Region 6 as expeditiously as possible, but no later than May 31, 2021.

For all 24 facilities/areas, the additional, more refined assessments will be conducted and completed on a timely, rolling basis with the expectation that assessments for many facilities/areas will be completed well before May 31, 2021.

Part 2. Conduct outreach to affected communities

a. Regions 2, 3, 4, 5, 7 and 8 (15 facilities/areas)

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[1] The facilities/areas referenced in this corrective action plan are those identified in Appendix A of the March 31, 2020, Management Alert.

[2] In some Regions, the work referenced here may be conducted by EPA or a non-EPA party, such as state environmental agencies or the Agency for Toxic Substances and Disease Registry (ATSDR).

Milestone: Public outreach (including interactive outreach) has already occurred or is planned for these facilities/areas. For example, state-led (and EPA-assisted) public meetings were held in 2018 or 2019 in Regions 4, 5, 7, and 8. Region 2 was forced to cancel a planned in-person public meeting in Puerto Rico because of COVID-19 and is reworking its outreach plans. In Region 3, West Virginia has requested that the Region take the lead in community outreach; the Region expects to begin outreach by sharing the findings of technical analyses once that work is complete (in up to three months). In Pennsylvania, the state remains the lead on addressing ethylene oxide from the Braun facility, which recently received a new state operating permit and for which the state provided a 30-day public comment period and the opportunity for a public hearing. Any additional outreach for these facilities/areas should proceed as planned and as appropriate – in accordance with local directives related to COVID-19. EPA will post quarterly **status reports of outreach activities to the Agency's/Regions' Ethylene Oxide website beginning** in November 2020. Each status report will provide a summary of the outreach completed and the outreach planned for each area, along with relevant milestones and dates.

b. Region 6 (nine facilities/areas)
Milestone: EPA Region 6 will work with the states of Texas and Louisiana, based on the wishes of those states and in accordance with local directives related to COVID-19, to explore appropriate communication tools and assist the states in developing facility/area-specific outreach information. EPA will post quarterly status reports of outreach activities, including descriptions **of this work, to the Agency's/Region's Ethylene Oxide website beginn**ing in November 2020. Each status report will provide a summary of the outreach completed and the outreach planned for each area, along with relevant milestones and dates.

c. Regions 2 – 8 (24 facilities/areas)
Longer-Term Milestone: Public outreach (including interactive outreach) has already been conducted or is planned for the one facility in Region 2, four facilities in Region 3, three facilities in Region 4, four facilities in Region 5, two facilities in Region 7 and one facility in Region 8, and will be summarized in the November 2020 status report. In Region 6, EPA will support the states of Texas and Louisiana in their efforts to conduct and complete initial public outreach, based on the wishes of the states, for the nine facilities/areas as expeditiously as possible, but no later than May 31, 2021.

For all 24 facilities/areas, we will support the states in their outreach, **based on the states'** outreach plans, that provides interactive (i.e., two-way) communication with affected communities. Additionally, we will consider a wide variety of communication tools (including Web content, virtual webinars, and virtual workshops), recognizing that the appropriate first step is always to talk with local government officials and community leaders to determine what form of outreach will be most effective and most welcome. Note, this public outreach will be conducted and completed on a timely, rolling basis, based on the wishes of the states, with the expectation that outreach for many facilities/areas will be completed well before May 31, 2021.

Exhibit L

Ethylene Oxide: Technical Reviews and Outreach to Potentially Affected Communities
Status Report for Sterigenics – Santa Teresa, NM

As EPA pursues its mission to protect public health and the environment, addressing ethylene oxide (EtO) remains a major priority for the Agency. EPA's National Air Toxics Assessment (NATA), released in August 2018, identified a number of areas (census tracts) with potentially elevated risk from continuous exposure, over 70 years, to EtO in the outdoor air. NATA estimated these risks based on EtO emissions from 2014, which were the most recently available at the time.

NATA is a screening-level analysis that is intended to identify pollutants or areas for closer examination. Because of this, additional work is needed to better understand emissions in areas that NATA identified as potentially having elevated risk. EPA has been supporting its state air agency partners as they conduct that work and identify opportunities for reducing EtO emissions from individual facilities, while the Agency reviews its national regulations for industrial facilities that emit EtO. Actual risks today may be higher or lower than NATA estimated due to several factors, including updated or more refined facility emissions information, or recent facility changes such as the installation of pollution controls.

The information below describes the status of EPA's work on the Sterigenics commercial sterilization facility in Santa Teresa, New Mexico. EPA is providing this information, in part, in response to the EPA Office of Inspector General's March 31, 2020, Management Alert which called on EPA to provide information to the 25 communities that NATA identified as potentially having the highest risk from EtO emissions.

Note: For commercial sterilizers, including Sterigenics, EPA is compiling more current and complete emissions data to generate new risk estimates for ethylene oxide sterilizers across the country as part of its work to develop a proposed revision for the National Emissions Standards for Hazardous Air Pollutants for EtO sterilization facilities. EPA will share this information, which will include refined risk estimates at the census block level, with the public as part of its upcoming proposed rule.

Technical information

In its response to the OIG's report, EPA noted that it believes the OIG erroneously included the Sterigenics Santa Teresa Facility in its list of facilities for follow-up. NATA-estimated risks for the census tract near the Sterigenics facility were 200 in 1 million based on *2014* emissions data. Prior to releasing NATA, EPA learned that the facility had installed a control device that reduced ethylene oxide emissions by 83 percent between 2014 and 2016, which would be expected to reduce risk. EPA included this information on the NATA products when the assessment was released in August 2018 and documented the emissions reduction in the emissions update file, available at https://www.epa.gov/sites/production/files/2018-08/documents/2014_nata_updates_to_emissions.pdf

Recent Lawsuit

The New Mexico Attorney General has filed a lawsuit against Sterigenics, alleging that the company emitted ethylene oxide "in excess of permissible limits" at the Santa Teresa facility and seeking changes to its sterilization process, along with damages and penalties. The lawsuit was filed December 22, 2020, in the Third Judicial District Court in Las Cruces, NM.

Exhibit M

2014 NATA Emissions Updates (as of July 28, 2020)

Emissions for the sources listed below have changed since EPA completed the modeling step of the NATA analysis. This list includes sources with:

- Known changes to emissions that occurred *after* 2014 (and therefore are not reflected in NATA);
- Changes that EPA incorporated into the NATA results via post-modeling corrections; and
- Recent corrections to 2014 emissions that are *not* reflected in the NATA results.

1. **Known changes to Emissions that occurred after year 2014**

The NATA reflects emissions in 2014. The following facilities have had reductions or elimination of emissions since 2014. This should be considered in your use of NATA to prioritize pollutants or sources for further study.

- Connecticut: Metal Finishing Techs Inc (EIS id 2790811). Respiratory should be eliminated after 2014 (Chlorine and chlorine related equipment were removed in October of 2014). This change impacts tracts in county 09003 (Hartford).
- Florida: SYNERGY HEALTH AST, LLC (EIS id 2747211). The facility shutdown in September of 2016. Key pollutants emitted were ethylene oxide and ethylene glycol. This change impacts tracts in county 12103 (Pinellas).
- Florida: CATERPILLAR INC. (EIS id 3868311). Shut down. This facility surrendered their air permit on 11/15/2016. Key pollutants emitted were hexamethylene diisocyanate and manganese. This change affects tracts in county 12031 (Duvall).
- Illinois: Custom Hard Chrome in Rosemont, IL (EIS id 2631311) closed in 2015/2016. The 2014 hexavalent chromium emissions of 143 lbs are no longer being emitted. This change impacts tract 17031819100.
- Illinois: Saint Anthony Hospital in Chicago, IL (EIS id 1849811) terminated its use of ethylene oxide in 2014. This change impacts tract 17031819100.
- Illinois: Swedish Covenant (EIS id 3340511) terminated its use of ethylene oxide sterilizers in February 2015. This change impacts tract 17031819100.
- Illinois: Radiac Abrasives Inc (EIS id 4150711) New controls (regenerative thermal oxiders) added in 2016; would reduce naphthalene and volatile organic compounds. This change impacts tracts in county 17121 (Marion county).
- Indiana: DUBOIS WOOD PRODUCTS INC PLT 1 & WHITE (EIS id 8207711). Wood boiler shutdown Aug 2015. This change impacts tracts in county 18037 (Dubois County).
- Louisiana: E I DuPont de Nemours & Co - Pontchartrain Site (now known as Denka Performance Elastomer facility) (EIS id: 8026611) in St John The Baptist parish installed a control device and has reduced chloroprene emissions by 85% between 2014 and 2019.
- Minnesota: 3M - New Ulm - Electrical Products Div (EIS id 7837011). Shut down unit emitting ethylene oxide, summer of 2017. This change impacts tracts in county 27015 (Brown County)
- New Jersey: The BASF facility (EIS id 7990911) in Washington, NJ, in Warren County no longer uses or stores ethylene oxide. Ethylene oxide use ended April 28, 2017, and having ethylene oxide onsite ended May 31, 2017. This change impacts tracts in county 34041 (Warren County).

- New Mexico: STERIGENICS-SANTA TERESA FACILITY (EIS id 7582111) in Santa Teresa, NM, Dona Ana County, installed a control device and has reduced ethylene oxide emissions by 83% between 2014 and 2016.
- Pennsylvania: Shenango Coke works (EIS id 7407611) in Pittsburgh, Neville Island, Allegheny County, began shutting down in the 2016/2017 timeframe. Coke oven emissions have decreased between 2014 and 2016 from 10.7 tons to less than 0.25 tons. This change impacts tracts in 42003 (Allegheny county).
- West Virginia: CAMC - GENERAL DIVISION (EIS id 4937911). In 2016 emissions will be eliminated due to a process change in sterilization, but 2014 emissions are correct. The two ethylene oxide sterilizers at this hospital were removed in May 2016. This change affects tracts in 54039 (Kanawha county).

2. **Changes from 2014 NEI – incorporated into the results via post-modeling corrections, after modeling was done**

   The state of Idaho and Davidson County, Tenn.: Emissions from nonpoint source category "NP-SolventsCoatings" for ethylene oxide should be 0; in the NEI nonzero emissions were estimated by these agencies based on methods/factors from a 1996 Emission Inventory Improvement Plan document that has since been updated with EPA's Solvents Tool. Changes made to NATA were made after modeling was complete. The approach was to zero out concentrations, exposures and risks from ethylene oxide for the "NP-SolventsCoatings" source group for all of Tennessee, Idaho and neighboring states.

3. **Corrections to 2014 emissions that are not reflected in the NATA results**

These corrections were identified in our final stages of QA/QC of the NATA information, and therefore EPA could not include them in the NATA results. Please consider this list in your use of NATA to prioritize pollutants or sources for further study.

- Colorado: Terumo BCT Sterilization Services Inc. in Lakewood, CO (EIS id 3832911) was found to have different geographic coordinates (300 meters different), release parameters and ethylene oxide emissions than the 2014 NEI (NATA modeled emissions). The 2014 NEI (1.11 tons) provided by Colorado were based on year 2011. In 2014 this facility reported 1.251 tons to the Toxics Release Inventory (TRI), but the allocation of emissions by unit and release point is not available for that year. Other years of data where the allocation is available are 2016 (1.126 tons total) and 2017 (1.376 tons total).
- Illinois: Ele Corporation (called Pelron Corp in the 2014 NEI and NATA) (EIS id 3213711). Emissions from a 2018 stack test for ethylene oxide which reflect operating conditions also in 2014 are 0.00078 lb/hour (63.28 lbs at 8760 hours per year) whereas the annual 2014 NEI emissions computed based on an emission factor approach were 436.8 lb/year. Also the stack parameters should be revised as follows, which would lower the modeled concentrations: increase stack height from 2.4 m to 8.08 m; increase stack velocity from 0.119 m/s to 8.42 m/s; increase stack diameter from 0.101 m to 0.2 m; increase temperature from 294K to 300K and

move geographic coordinates by 12 m to new location of 41.805139, -87.817376 decimal degrees.

- Illinois: Vantage Specialties Inc. (EIS id 5011811) in Gurnee, Illinois. The 2014 NEI (and NATA modeling) erroneously had 0 ethylene oxide emissions for Vantage Specialties Inc. (EIS ID 5011811) in Gurnee, Illinois. The facility provided a value of 2723 lbs in 2014 and 1547 lbs in 2017. The facility provided updated emissions for years 2010 through 2017 to EPA's TRI; these corrections will be reflected in the TRI in Spring 2019.
- Iowa: Van Diest Supply Company in Webster City, Iowa (EIS id 5383511) revised their emissions of ethylene oxide in May 2018, after the 2014 NEI and NATA modeling was completed. The modeled value (2014 NEI) is 1.27 tons. The revised value is 0.000336 tons. This affects tracts in 19079 (Hamilton County).
- Louisiana: Union Carbide Corp – St. Charles Operations (EIS id 7202911) revised their 2014 ethylene oxide emissions. The 2014 emissions in the 2014 NEI were 15.032 tons. The corrected value is 10.43 tons.
- North Carolina: WakeMed (EIS id 14642711) in Raleigh, North Carolina. Ethylene oxide emissions from this facility were missing in the 2014 NEI. The actual emissions from this facility are 0.013 tons.
- Texas: Houston Plant (also known as AzkoNobel) (EIS id 4853011) in Houston, Texas. NEI ethylene oxide emissions were re-estimated by facility staff to be 0.1018 tons. (They indicated that their original values were overly conservative). The 2014 NEI value is 0.2523 tons.
- Texas: Conroe facility in Conroe, Texas (EIS id 4945611). The facility indicated they reported 2.62 tons of ethylene oxide for 2014, not the 2.6693 tons that are in the 2014 NEI.
- Texas: Texas Operations (also known as Eastman Chemical Company) (EIS ID 4941511) in Longview, Texas. The facility indicated they revised their 2014 ethylene oxide emissions. The 2014 emissions in the 2014 NEI were 7.4 tons. The corrected value is 3.4 tons. The 2017 emissions (based on the 2017 NEI) are 5.4 tons.

Change log

August 22, 2018: Original file

October 31, 2018: Added Vantage Specialties Inc. (EIS ID 5011811) to section 2 (Corrections to 2014 emissions that are not captured in the NATA modeling)

June 27, 2019: Removed the information on "Louisiana: Union Carbide Corp – St. Charles Operations (EIS id 7202911)" from section 1 (because it is in section 3)

November 19, 2019: Added information on Texas Operations (EIS IS 4941511) in Section 3 (Corrections to 2014 emissions that are not reflected in the NATA results)

July 28, 2020: Added information on Denka (EIS 8026611) , Louisiana, to Section 1 (emission reductions that occurred after 2014)

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Exhibit N

Check for updates

Dose-Response:
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Ethylene Oxide: Cancer Evidence Integration and Dose–Response Implications

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Abstract

The International Agency for Research on Cancer (IARC) and the United States Environmental Protection Agency (USEPA) classified ethylene oxide (EtO) as a known human carcinogen. Critically, both noted that the epidemiological evidence based on lymphoid and breast cancers was "limited," but that the evidence in animal studies was "sufficient" and "extensive" (respectively) and that EtO is genotoxic. The USEPA derived one of the highest published inhalation unit risk (IUR) values (3×10^{-3} per [$\mu g/m^3$ EtO]), based on results from 2 epidemiological studies. We performed focused reviews of the epidemiological and toxicological evidence on the carcinogenicity of EtO and considered the USEPA's reliance on a genotoxic mode of action to establish EtO's carcinogenicity and to determine likely dose–response patterns. Higher quality epidemiological studies demonstrated no increased risk of breast cancers or lymphohematopoietic malignancies (LHM). Similarly, toxicological studies and studies of early effect biomarkers in animals and humans provided no strong indication that EtO causes LHM or mammary cancers. Ultimately, animal data are inadequate to define the actual dose–response shape or predict tumor response at very low doses with any confidence. We conclude that the IARC and USEPA classification of EtO as a known human carcinogen overstates the underlying evidence and that the IUR derived by USEPA grossly overestimates risk.

Keywords

chemical, dose response, modeling, cancer

Summary

Ethylene oxide (EtO) is a highly reactive chemical used as a sterilizing agent and a feedstock for producing other chemicals. The International Agency for Research on Cancer (IARC) and the United States Environmental Protection Agency (USEPA) classified EtO as a known human carcinogen.[1,2] Critically, both noted that the epidemiological evidence based on lymphoid and breast cancers was "limited" but that the evidence in animal studies was "sufficient" and "extensive" (respectively) and that EtO is genotoxic. The USEPA concluded, "Overall, confidence in the hazard characterization of EtO as 'carcinogenic to humans' is high" and derived one of the highest published inhalation unit risk (IUR) values (3×10^{-3} per [$\mu g/m^3$ EtO]), based on results from 2 epidemiological studies. This high IUR has fueled community-based risk assessments that predict alarmingly high cancer risks in communities surrounding facilities using EtO.

We performed focused reviews of the epidemiological and toxicological evidence on the carcinogenicity of EtO and considered the USEPA's reliance on a genotoxic mode of action (MOA) to establish EtO's carcinogenicity and to determine likely dose–response patterns. We then compared the EPA potency estimate with alternatives based on laboratory animal data.

Higher quality epidemiological studies demonstrated no increased risk of breast cancers (in fact, decreased risk was

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observed) or lymphohematopoietic malignancies (LHM), including the studies USEPA used to derive the IUR. Similarly, toxicological studies and studies of early effect biomarkers in animals and humans provided no strong indication that EtO causes LHM or breast/mammary cancers. Only one study demonstrated a clear monotonic dose–response with leukemia in female Fisher rats; however, this strain has a high background rate of leukemia and may not be an appropriate model for human leukemogenicity. Nevertheless, an IUR based on this toxicology study is 2 orders of magnitude lower than that derived by USEPA. Ultimately, animal data are inadequate to define the actual dose–response shape or predict tumor response at very low doses with any confidence. The USEPA's[1] conclusion that EtO is genotoxic and likely has a mutagenic MOA, according to USEPA policy, should have indicated a linear dose–response.

We conclude that the IARC and USEPA classification of EtO as a known human carcinogen overstates the underlying evidence and that the IUR derived by USEPA grossly overestimates risk.

Introduction

Ethylene oxide (CAS Number 75-21-8), also known as oxirane, is a highly reactive chemical used as a feedstock for the production of other chemicals, including glycol ethers and polyglycol ethers, as well as a variety of emulsifiers, detergents, and solvents. Ethylene oxide also is widely used to disinfect medical equipment, especially components that would be damaged if heat sterilized, and as a fumigant for disinfecting food products, including spices.[2]

The IARC classified EtO as a group 1 carcinogen (carcinogenic to humans), even though they determined that "There is *limited evidence* in humans for a causal association of ethylene oxide with lymphatic and haematopoietic cancers . . . and breast cancer." However, the IARC Working Group also concluded: "There is *sufficient evidence* in experimental animals for the carcinogenicity of ethylene oxide" and, "There is strong evidence that the carcinogenicity of ethylene oxide, a direct-acting alkylating agent, operates by a genotoxic mechanism." The IARC evaluation ended with the following: "In making the overall evaluation, the Working Group considered that there is sufficient evidence for the carcinogenicity of ethylene oxide in experimental animals, and relied heavily on the compelling data in support of the genotoxic mechanism described above."[2(p396)]

In December 2016, the USEPA issued in final form *Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide (CASRN 75-21-8)*, updating a 1985 risk assessment and a revised draft in 2006. The USEPA's final, 2016 version, following IARC's 2012 evaluation, classified EtO as a human carcinogen, upgrading its 1985 classification of EtO as "probably carcinogenic to humans" (Group B1), but "bordering on Group B2, however, because of limitation in the human evidence."[3] The USEPA justified the decision to classifying EtO as "carcinogenic to humans" as follows:

> . . . (1) strong, but less than conclusive on its own, epidemiological evidence of lymphohematopoietic cancers and breast cancer in EtO-exposed workers, (2) extensive evidence of carcinogenicity in laboratory animals, including lymphohematopoietic cancers in rats and mice and mammary carcinomas in mice following inhalation exposure, (3) clear evidence that EtO is genotoxic and sufficient weight of evidence to support a mutagenic mode of action for EtO carcinogenicity, and (4) strong evidence that the key precursor events are anticipated to occur in humans and progress to tumors, including evidence of chromosome damage in humans exposed to EtO. Overall, confidence in the hazard characterization of EtO as "carcinogenic to humans" is high.[1]

The USEPA also increased 30-fold the IUR estimate for adults from 1 in 10 000 to 30 in 10 000 excess cancers per microgram per cubic meter. Inhalation unit risks can be interpreted roughly as a standardized carcinogenicity potency index and can be compared with those of other carcinogens. For example, the updated IUR for EtO is 100 times higher than the IUR for 1,3-butadiene, and nearly 700 times higher than the IUR for vinyl chloride, both well-established human carcinogens. The USEPA IUR is 1000 times higher than the unit risk number of 4 ppb proposed by the Texas Commission on Environmental Quality for EtO, based on the same epidemiological evidence.[4] The USEPA IUR for EtO, if valid, suggests that EtO is one of the most potent known human carcinogens.

Because the IUR is high, the concentration of EtO considered "safe" (ie, associated with no more than a one in a million increased lifetime cancer risk) is very low: it was estimated to be 0.0002 $\mu g/m^3$ [0.0001 parts per billion (ppb), which is equivalent to 0.1 parts per trillion (ppt)]. This concentration is well below the current limit of detection[5] and thousands of times lower than estimated endogenous levels of EtO in humans.[6] Derivations of community-level cancer risks using this high-potency estimate for EtO have led to alarmingly high cancer risk estimates in some communities, as well as plant closings and proposed banning of the chemical.[7,8]

To better understand the basis for IARC and USEPA classifying EtO as a known and extremely potent human carcinogen, we performed a focused critical review and synthesis of the epidemiological and animal toxicological evidence on the carcinogenicity of EtO. Further, we considered USEPA's conclusion of a mutagenic mode of carcinogenic action and evaluated the possible dose–response and interspecies differences in potency. The USEPA's[9] guidelines for carcinogen risk assessment state that "The approach to dose–response assessment for a particular agent is based on the conclusion reached as to its potential mode(s) of action for each tumor type," meaning dose–response evaluations should be motivated by knowledge of biology and MOA, and not mathematical analysis alone. The goal of this review and integration of evidence was to validate, if possible, the dose–response analysis leading to USEPA's extremely high IUR estimate.

Methods

Epidemiology Literature Review

We conducted a critical review and synthesis of the epidemiologic studies on occupational exposure to EtO and cancer. Studies first were identified from the 2016 USEPA review. Additionally, we performed searches of PubMed using the terms "ethylene oxide" and "epidemiology"; however, no additional relevant case–control or cohort studies were identified.

We performed a quality-based evaluation of each study using the domains (except "Other") and associated criteria from the USEPA's Application of Systematic Review in TSCA Risk Evaluations[10] which was updated in 2019.[11] Specifically, an overall quality judgment was given for the most recent update of each of the relevant cohort or case–control studies based on the domains of (1) exposure characterization, (2) study participation, (3) potential confounding/variability control, (4) outcome assessment, and (5) analysis (see Supplemental Table S1). Each study was rated high, medium, or low quality on each domain separately for breast cancer or the combined category of all LHM, but numerical quality scoring was not used. In addition, an overall quality rating for each study was derived based on the average of the domain ratings.

Toxicology Data Selection and Review

We relied on the human and laboratory animal data described and summarized by the USEPA toxicological review (see Tables 3-3 to 3-8 of USEPA, 2016).[1] Additionally, we performed searches of the PubMed database to identify any additional relevant 2-year cancer bioassays; however, none were found. Studies that identified increases in effect (with reported mean and standard deviation) in 2 or more exposure concentrations above control were considered for dose–response modeling.

Ethylene oxide–induced DNA adducts and mutations were selected as early key events in the MOA for dose–response analysis and interspecies response comparison. Chromosome-level effects, including chromosomal aberrations and indicators of chromosome damage (ie, sister chromatid exchanges and micronuclei formation) were also assessed. Relevant studies with statistically significant findings, as reported by USEPA, were selected for evaluation.

Dose–Response Modeling

Dose–response modeling was conducted using the USEPA's benchmark dose software (BMDS 3.1.1.). All frequentist models were considered with default conditions, including extra risk assumptions for background and a benchmark response of 10%. We relied on the USEPA's model selection guidance[12] and made no professional judgments regarding model fit or selection. Any model with a goodness of fit P value >.1 was considered "adequate." When Bayesian model averaging was considered, the model had uninformative priors and assumed no difference in model weight on the average.

Epidemiology of Occupational EtO Exposure and Breast Cancer and LHM

All relevant publications reported results from occupational cohort studies except for one community-based case–control study. Kiran et al[13] conducted a community-based case–control study of 31 lymphoma cases from 22 centers in 6 European countries and evaluated 35 chemicals including EtO estimated by experts based on interview responses. No clear association was observed between "ever exposed" to EtO and risk of lymphoma (odds ratio [OR] = 1.3, 95% confidence interval [CI]: 0.7-2.1) or any other exposure surrogate except for workers with >5% of estimated working hours exposed to EtO (OR = 4.3, 95% CI: 1.4-13.0). We did not consider this study for further review because (1) it was the only population-based case–control study, which is considered a weaker study design, and (2) examined lymphomas only.

Hogstedt[14] is the most recent of 3 updates of a study of 709 workers from 3 Swedish plants producing EtO.[15-17] Exposure was based on duration of employment and job title; however, time-weighted average EtO exposures from 1963 to 1976 were estimated at 5 to 8 ppm.[17] Cancer incidence through 1983 and mortality through 1985 were ascertained from the cancer registry. Nine "blood and lymphatic" and no breast cancers were reported.

Kiesselbach et al[18] followed a cohort of 2658 men employed at 8 chemical plants in Germany and exposed to EtO for at least 1 year between 1928 and 1981. Exposure to EtO was based on job history with type of exposure, duration of exposure, date beginning and ending work, and a description of accidents or shutdowns. Cause of death was obtained through 1982 from lay statements, physician reports, and hospital reports. Only 5 LHM deaths were reported.

Bisanti et al[19] followed a cohort of 1971 chemical workers for mortality from 1940 to 1984. All were men employed at some point during 1938 to 1984 and licensed to handle EtO (637 were licensed only for EtO). Exposure to EtO was assumed as no exposure data were available. Five of 6 LHM deaths occurred among the EtO-only licensed cohort.

Norman et al[20] followed a cohort of 1132 sterilization workers employed between 1974 and 1980 for cancer incidence and mortality through 1987. Exposure to EtO was assumed but not quantified. Cancer outcomes were identified through interviews, review of medical records, mailed surveys, cancer registry data (1985-1989), and the National Death Index. Standardized incidence and mortality ratios (SIRs and SMRs, respectively) were estimated using reference rates from the NCI Surveillance, Epidemiology, and End Results Program (SEER; 1978-1981 and 1981-1985) and Western New York (1979-1984). Twelve of the 25 cancers in women were breast cancers, and only 3 cancers were identified in men. No LHM results were reported.

Olsen et al[21] followed through 1992 a cohort of 1361 men employed 30 days from 1940 to 1992 in 1 of 3 United States plants producing EtO. Work histories were evaluated by plant experts to determine exposure based on job titles and

departments. Mortality data through 1992 were obtained from plant health surveillance systems, Social Security records, and the National Death Index. Ten LHM deaths were identified.

Coggon et al,[22] updating Gardner et al,[23] evaluated cancer mortality risks through 2000 among a cohort of 2876 workers from 4 companies that had manufactured or used EtO and 8 hospital sterilization units. Exposure categories were based on job classification, and reported time–weighted average EtO concentrations prior to 1977 were less than 5 ppm in "almost all jobs." Cancer mortality was based on death certificates, with 11 breast cancer and 17 LHM deaths observed.

Steenland et al[24] evaluated breast cancer incidence in 7576 women employed in sterilization facilities for at least 3 months from the 1940s to the 1980s. Exposure to EtO was modeled for all years from limited measurement data and process change information. Breast cancer incidence data were obtained via interview, death certificates, cancer registries, and medical records; in situ cases were included. Standardized incidence ratio analyses were conducted using SEER referent rates by categories of cumulative EtO exposure. A nested case–control analysis also was used to evaluate the 311 observed breast cancer cases.

Steenland et al[25] updated the US National Institute for Occupational Safety and Health (NIOSH) cohort of 18 235 men and women employed in sterilization facilities.[26-28] Exposure to EtO was estimated based on modeled exposures for all years based on limited measurement data and process change information. A total of 2835 deaths were observed through 1998. Vital status and cause of death were ascertained via the National Death Index. Life table analyses were conducted using the US population as referent: 103 breast cancer and 79 LHM deaths were reported.

Swaen et al[29] updated through 2003 a cohort of 2,063 men employed at any time between 1925 and 1988 in 2 US facilities producing or using EtO; this cohort had been previously investigated in 4 studies.[30-33] Exposure was estimated based on interviews and industrial hygiene measurements. Cause of death was obtained from the National Death Index and analyzed using mortality rates for US men as the referent. A total of 27 LHM deaths were reported. Valdez-Flores et al[34] pooled the mortality updates of Swaen et al[29] and Steenland et al.[25]

Mikoczy et al[35] updated a cohort of 2,171 men and women employed for at least 1 year prior to 1986 in 2 sterilization facilities in Sweden.[36,37] Detailed exposure assessment was derived based on 2 plant-specific job exposure matrices. Incidence data were obtained from the Swedish Cancer Registry and cause of death from the Swedish population registry for 1972 through 2006. A total of 41 breast cancers and 18 LHM were analyzed using national referent rates. A nested case–control analysis also was performed.

Breast Cancer

Five updated occupational cohorts—primarily sterilization workers exposed to EtO—reported results for female breast cancer.[20,22,24,25,35] Steenland et al[24] reported results for breast cancer incidence and Steenland et al[25] for breast cancer mortality based on the same cohort. For exposure assessment, the Mikoczy et al[35] study was rated as high quality, Steenland et al[24] and Steenland et al[25] were rated medium quality, and finally, Coggon et al[22] and Norman et al[20] were deemed of low quality. All 5 studies were rated as high or medium for study participation and for potential confounding/variability control. Only Mikoczy et al[35] was rated as high for outcome assessment, while Norman et al[20] was rated as low. Steenland et al[25] and Coggan et al[22] were classified as high quality, both Mikoczy et al[35] and Steenland et al[24] were ranked as medium quality, and Norman et al[20] as low quality for analysis (note 1). Details of the ratings for each study are reported in Supplemental Table S2.

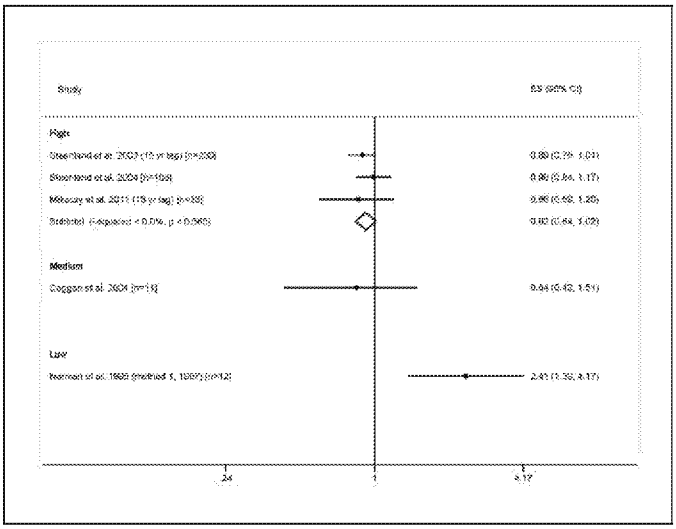

Figure 1. Forest plot of SIRs and SMRs for breast cancer by overall study quality rating with meta-analysis by study quality. ES indicates effect size; SMR, standardized mortality ratio; SIR, standardized incidence ratio.

Figure 1 presents forest plots of the results of the studies grouped by overall quality rating and random-effects meta-relative risk (RR) estimates for the high-quality studies (the only category with more than one study). The medium- or high-quality studies reported no increased risk and suggested slight deficits of breast cancers. The breast cancer meta-analysis resulted in a meta-RR of 0.92 (95% CI: 0.84-1.02) for the high-quality studies. The only study reporting an increase in breast cancers was classified as low quality.[20]

Despite reporting no overall increase in breast cancer risk and statistically significant deficits in the lowest exposure group (SIR = 0.52, 95% CI: 0.25-0.96 for 0-0.13 ppm-years[35] and SIR = 0.74, 95% CI: 0.57-0.97 for <647 ppm-years and no lag[24]), both Mikoczy et al[35] and Steenland et al[24] performed RR analyses for EtO exposure and breast cancer using the groups with risk deficits as the referent group. This presents interesting methodological questions of relevance and validity. Figure 2 presents the SIRs and corresponding confidence intervals from Steenland et al,[24] the breast cancer study with the most exposure categories, that ultimately served as the basis for

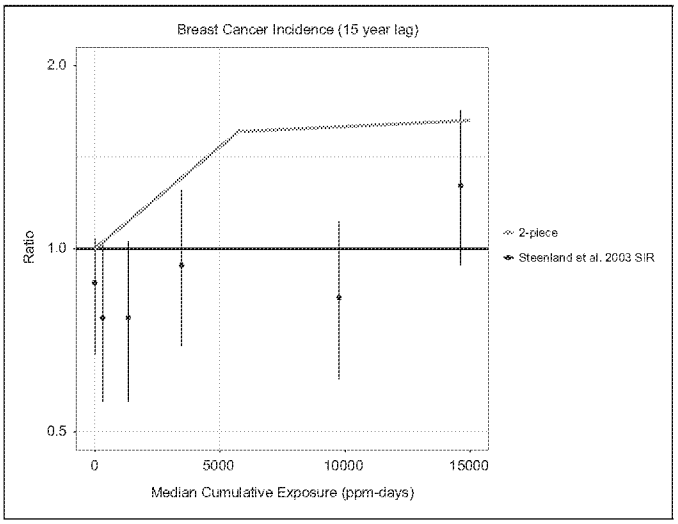

Figure 2. Standardized incidence ratios for breast cancer from Steenland et al[24] and the USEPA[1] 2-piece linear breast cancer model.

the 2-piece linear model for breast cancer used in part by USEPA[1] to derive the IUR for EtO. Although the original study data indicate risk deficits in all but the highest exposure levels (not statistically significantly), the USEPA selected the RR analyses from Steenland et al[24]—which USEPA claimed to be superior to estimates based on the general population—to construct a 2-piece dose–response model predicting positive risks at all nonzero exposure levels. The rationale for considering the recalibrated risk estimates to be preferable was not explained.

Figure 3 presents the breast cancer analyses and dose–response lines using USEPA's reanalysis of the data from Steenland et al.[24] This analysis also reclassified cumulative exposure into 10 arbitrary categories such that each contained about the same number of cases. The USEPA's dose–response analysis did not include a simple linear model; therefore, we fit a linear regression to the reported rate ratios from USEPA[1] and Steenland et al.[24] This figure demonstrates that these analyses, when recalibrated so that the referent group is reset from a statistically significant deficit to "background" (ie, RR = 1.0), exhibit a dose–response relationship that appears to be generally linear. Steenland et al[38] also examined numerous alternative models of the NIOSH cohort internal comparison data for breast cancer across multiple exposure categories noting that many of the different models reasonably fit the data. Steenland et al[38] highlighted that the 2-piece model exhibited a steep increase in risk across the lowest cumulative exposure categories followed by attenuation across higher levels. No discussion or rationale was provided for recalibrating the data using a referent group that demonstrated a statistically significant deficit. This gave rise to the "supra-linear" 2-piece dose–response model.

Lymphohematopoietic Malignancies

Several occupational cohort studies reported associations between EtO exposure and various lymphohematopoietic cancers.[13,14,18-22,25,29-32,35,37,39] Although the cancers within the broad category of lymphohematopoietic cancers have several different known or suspected causes, the combined LHM category may be the only way to provide a general summary across studies. Presumably, if a strong excess of any specific type or group of LHM, such as "lymphoid cancers," were caused by EtO, the all LHM category would reflect some modestly increased risk and that stratified analyses by specific LHM would identify the specific cancer(s) contributing to the increased risk of all LHM.

Eight publications reported results for combined LHM based on the most recently updated cohorts.[14,18,19,21,22,25,29,35] For exposure assessment, Mikoczy et al[35] and Swaen et al[29] were rated as high quality, Steenland et al[25] as medium quality, and the remaining studies as low quality. Four studies were rated high quality[21,25,29,35] and 4 studies were rated as medium[14,18,19,22] on study participation. For outcome assessment, Mikoczy et al[35] was rated as high quality and Kisselbach et al[18] as low quality with all others as medium quality. Only Steenland et al[26] was rated high quality for variable control and potential confounding. Kisselbach et al[18] and Hogstedt[14] were rated as low quality, while the remaining 5 publications were rated as medium quality. Bisanti et al,[19] Kisselbach et al,[18] and Hogstedt[14] were all rated as low quality for analysis. Steenland et al[25] and Mikoczyet al[35] were determined to be of medium quality with the remaining 3 studies achieving a high rating. Details of the ratings for each study are reported in Supplemental Table S3.

Figure 4 presents the results for LHM by category of overall study quality and a random-effects meta-analysis for each quality category. None of the 6 studies rated as medium or high quality reported statistically significant increases for LHM, and SMRs clustered around the null with relatively narrow confidence limits. In contrast, 3 of 4 studies we considered as low quality reported increased LHM, 2 of which were statistically significant.[14,19] These were notably the studies with the smallest numbers: the 2 largest studies, both rated as high quality, demonstrated no excess LHM as a group (SMR = 0.889 in Swaen et al[29]; SMR = 1.00 in Steenland et al[25]). The LHM meta-RRs were 0.98 (95% CI: 0.81-1.18) for the high quality studies, 1.31 (95% CI: 0.83-2.07) for the medium quality studies, and 3.55 (95% CI: 2.20-5.75) for the low quality studies.

Some studies reported results for specific LHM. For example, Hogstedt[14] and Bisanti et al[19] reported significantly elevated risks of leukemia (SMR = 6.11, 95% CI: 1.7-15.7) and lymphosarcoma/reticulosarcoma (SMR = 16.93, 95% CI: 3.49-49.53). Swaen et al[39] reported an increased risk of Hodgkin lymphoma (SIR = 4.97, 95% CI = 2.38-9.15). Steenland et al[25] presented results for non-Hodgkin lymphoma (NHL): SMR = 1.00 (95% CI: 0.72-1.35), based on 31 deaths overall, but was higher for men (SMR = 1.29: 95% CI: 0.78-2.01) and lower for women (SMR = 0.73: 95% CI: 0.38-1.29). A similar pattern was present for Hodgkin disease (overall SMR = 1.24, 95% CI: 0.53-2.43; SMR for men = 1.83, 95% CI: 0.59-4.27; SMR for women = 0.47, 95% CI: 0.05-11.87), but opposite for myeloma

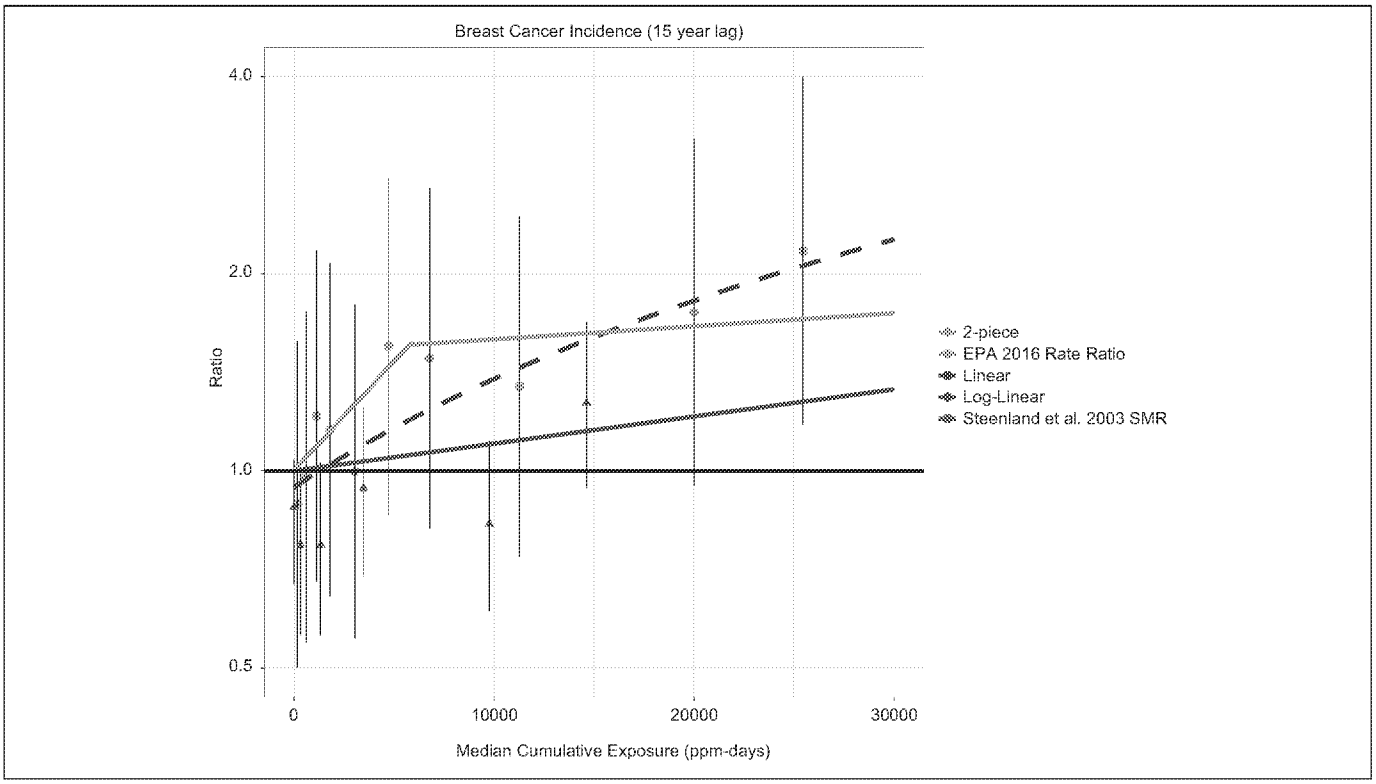

Figure 3. Standardized incidence ratios for breast cancer from Steenland et al,[24] RRs of the internal comparison data for breast cancer in USEPA,[1] the USEPA[1] 2-piece linear and log-linear breast cancer models, and a linear model of the RR data. SMRs are shown as triangles. RR indicates relative risk; SMR, standardized mortality ratio.

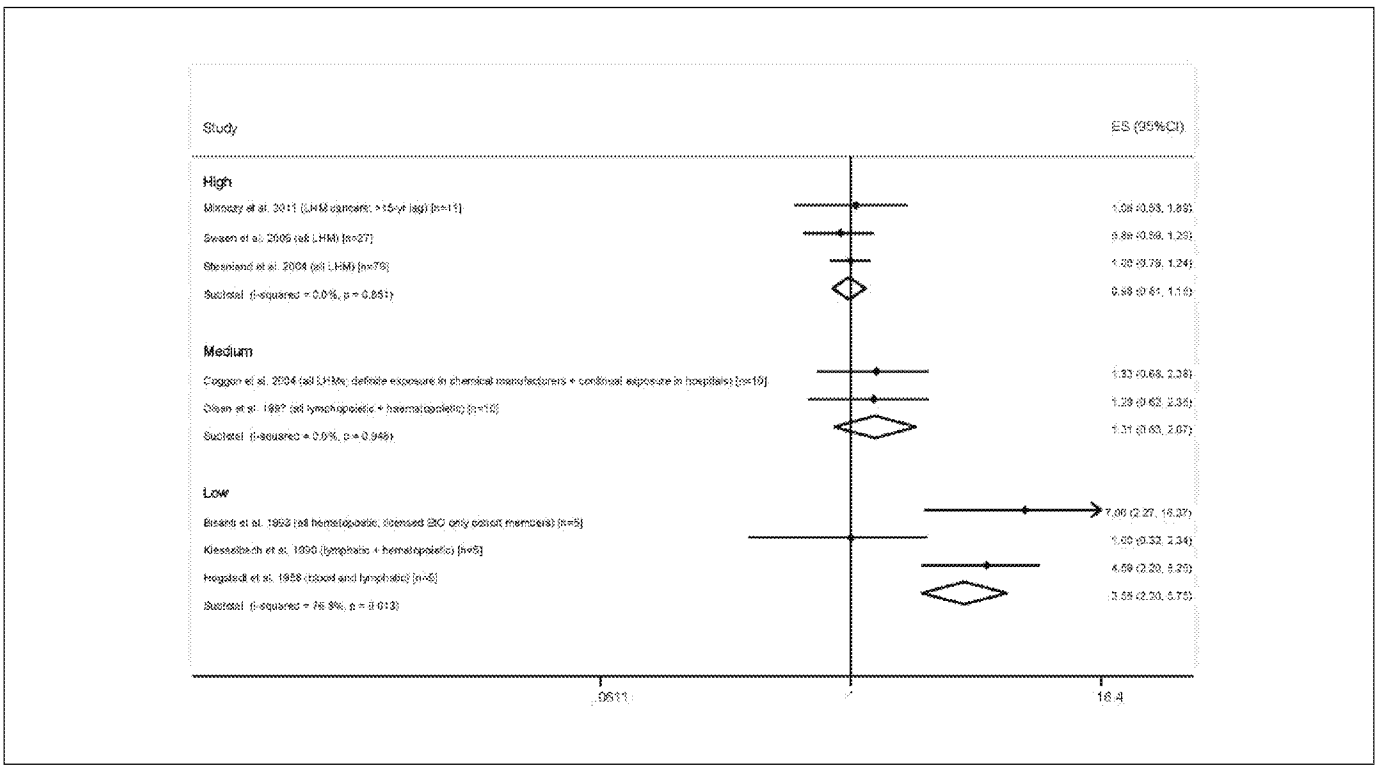

Figure 4. Forest plot of SIRs and SMRs for LHM by overall study quality rating with meta-analyses by study quality. ES indicates effect size; LHM, lymphohematopoietic malignancies; SMR, standardized mortality ratio; SIR, standardized incidence ratio.

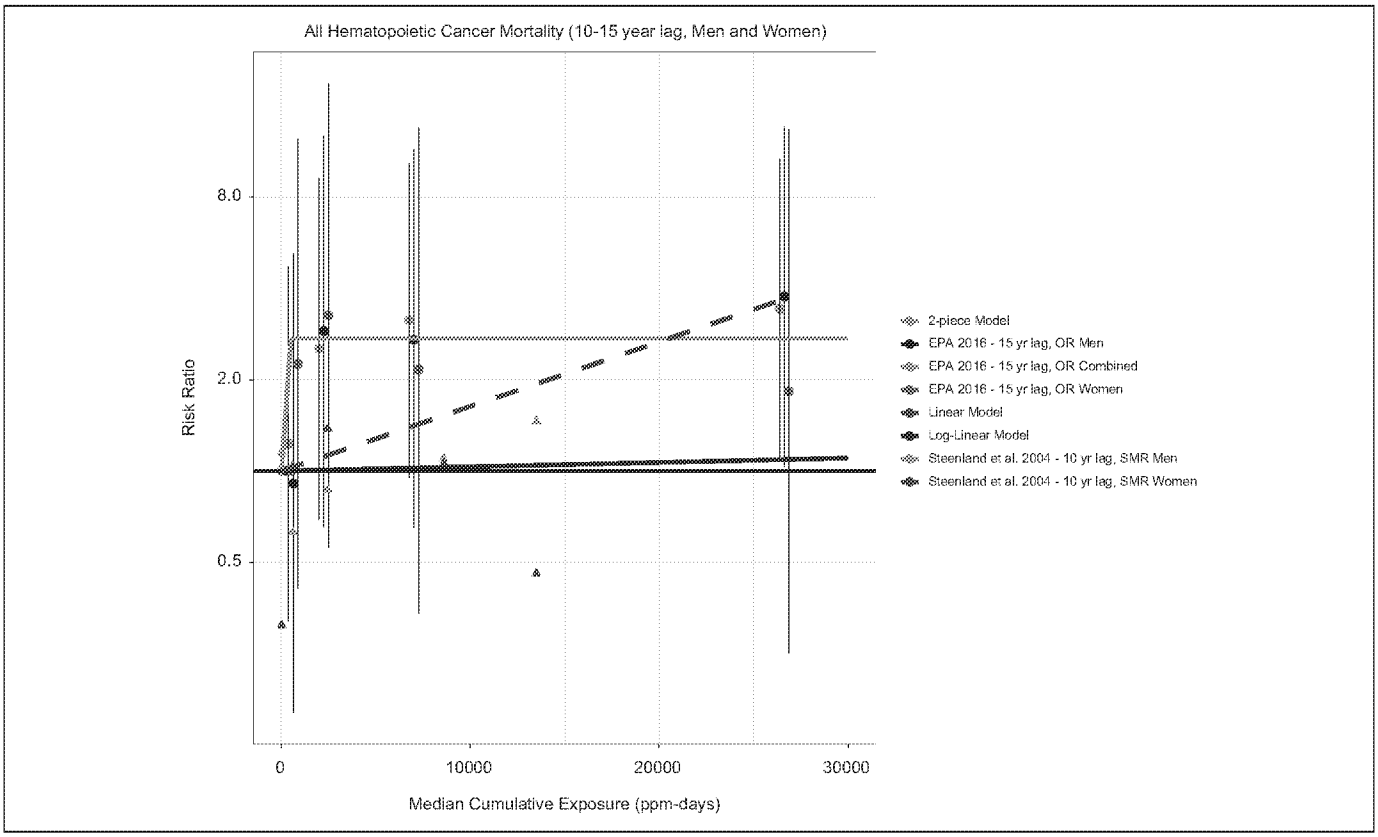

Figure 5. SMRs for hematopoietic cancer from Steenland et al[25] odds ratios (ORs) of the internal comparison data for breast cancer in USEPA,[1] the USEPA[1] 2-piece linear and log-linear hematopoietic cancer models, and a linear model of the RR data. SMRs are shown as triangles. RR indicates relative risk; SMR, standardized mortality ratio.

(SMR = 1.19, 95% CI: 0.54-2.26 for women and SMR = 0.61, 95% CI: 0.17-1.56 for men). Standardized mortality ratio results for lymphocytic leukemia were not presented in Steenland et al,[25] but leukemia SMRs were near unity overall, for both men and women. Because few studies reported results for the same specific LHM, the small numbers reported for each, and the apparent mixed results by gender, meaningful syntheses at the individual disease level is not possible.

Simple dose–response relationships between EtO exposure estimates such as duration of employment or cumulative exposure and LHM were examined in several studies.[13,19,21,25,29,35] No consistent evidence of any dose–response relationship was observed.

Given the large numbers of LHM deaths reported in Steenland et al[25] and the stronger exposure estimates, it in principle should present the best opportunity to evaluate potential dose–response relationships. Figure 5 presents Steenland et al's[25] hematopoietic cancer mortality analyses and dose–response lines using USEPA's reanalysis of the data from Steenland et al.[25] As with the breast cancer analysis, the USEPA's dose–response analysis did not include a simple linear model; therefore, we fit a linear regression to the reported odds ratios from USEPA,[1] with the intercept forced to the origin (as is done with the USEPA's other models). Based on a weak trend for lymphoid tumors for both genders combined, Steenland et al[25] presented a log cumulative exposure model with a 15-year lag for males as the "best fitting" model. However, the large discrepancy between this model and one based on the original study SMR results was not adjudicated.

Epidemiology Synthesis

For breast cancers, the studies indicated slightly lower risk overall, but among those in the lowest cumulative EtO exposure category, the risk was profoundly lower.[24,35] For LHM, the studies rated as medium or high quality demonstrated no increase or decreased risk, although some sporadic associations were reported for specific categories of LHM, with no consistency across studies or specific LHM. Limitations to this body of literature include small numbers of specific LHM, use of weak exposure surrogates in lieu of quantifiable individual exposure data, and possible mixed exposures. Nevertheless, the evidence from several studies of workers exposed to relatively high concentrations of EtO over relatively long duration in a range of workplace settings fails to demonstrate clear or consistent associations between occupational exposure to EtO and breast cancer or LHM as a group. The literature currently precludes evaluation of specific LHM.

Table 1. LHM and Mammary Tumor Incidence From 2-Year Bioassays.[a]

Study	Species	Concentration (ppm)	Malignant Lymphoma Incidence	Mammary Carcinoma Incidence	Leukemia Incidence
National Toxicology Program[40]	Female B6C3F1 mice	0	18%[b]	2%	NR
		50	13%[b]	17%[b,c]	NR
		100	45%[b,c]	12%	NR
Lynch et al[41,43]	Male Fischer 344 rats	0	NR	NA	31%
		50	NR	NA	48%[c]
		100	NR	NA	39%
Snellings et al,[42]/Garman et al[44]	Male Fischer 344 rats	0	NR	NA	13%
		10	NR	NA	18%
		33	NR	NA	31%
		100	NR	NA	30%
	Female Fischer 344 rats	0	NR	2%-4%[d]	9%
		10	NR	4%[d]	20%
		33	NR	4%[d]	29%
		100	NR	8%[d]	58%*

Abbreviations: LHM, lymphohematopoietic malignancies, NA, not applicable; NR, none reported; NTP, National Toxicology Program.
[a]The original study did not report or identify a tumor-response for this end point.
[b]Incidences reported in this table reflect those reported by the NTP.[40] The EPA's reported incidence is slightly different.
[c]Statistically significant.
[d]The EPA did not report incidence of mammary carcinoma, likely due to the lack of a significant increase in tumor incidence. However, data from the original study[42] are reported here.

Toxicological Evidence of Carcinogenicity

The lack of association between occupational EtO exposure and breast cancer or LHM may reflect the lack of an underlying causal association, at least at the levels to which workers historically had been exposed to EtO. In order to perform quantitative risk assessment, the evaluation of the tumorigenic dose–response for EtO in animals is needed to eliminate these uncertainties and to allow confirmation of the biological relevance (or lack thereof) for these tumors. Tumor incidence data from relevant end points (ie, LHM or breast cancer–related tumors) are summarized in Table 1.

The available *in vivo* 2-year cancer bioassays provide limited evidence that EtO causes mammary tumors or LHM,[40-42] contradicting the USEPA's justification for classifying EtO as a known human carcinogen.[1] The USEPA stated that there was "extensive" evidence of cancers in laboratory animals (specifically LHM and mammary cancers), but when considering these data for dose–response analysis, only the leukemia incidence data in female Fischer 344 (F344) rats, reported by Snellings et al,[42] meet the USEPA's[12] requirements for estimating a benchmark dose (BMD). Specifically, a study requires the following minimal criteria: (1) a minimum of 2 doses with tumor incidence above control and (2) a significant dose-related trend.

Other tumors are noted by the USEPA,[1] specifically lung, brain, and uterine cancers. However, BMD models on these end points are not as sensitive as the models of leukemia incidence (data not shown) and would not be recommended for use in derivation of an IUR. Testicular mesothelioma may be equally sensitive to leukemia incidence, but this cancer type is uncommon in humans and the incidence across studies[42,43] is highly variable (ie, 13%-27% response at 100 ppm). There is no epidemiological evidence of an EtO-related increase in these tumors.[2]

Although the F344 rat data[42] show an apparent dose–response trend in leukemia incidence, the National Toxicology Program (NTP) ceased use of F344 rats in their 2-year bioassays due to high background control incidence of mononuclear cell leukemia (MNCL).[45,46] Historically, approximately 20% to 50% of F344 controls develop MNCL over the course of their lifetime.[45] Therefore, the observed leukemia dose–responses in F344 rats may not be relevant to humans.

Although most of the animal studies on EtO-associated LHM and mammary tumors are negative and/or do not meet the USEPA's[12] recommended requirements for data selection in dose–response modeling, quantitative dose–response models can be fit to some of the cancer incidence data presented in Table 1. Examples of possible dose–response shapes for lymphoma, mammary carcinoma, and leukemia are shown in Figures 6, 7, and 8, respectively. All models were fit using the USEPA's BMD Software (BMDS Version 3.1.1). The USEPA's[12] BMD guidance states that only models with a goodness of fit P value >.1 are adequate for use in BMD estimation, although multistage models with a goodness of fit P value >.05 may be considered. For lymphoma, only 2 models, the γ and log-logistic models are appropriate for estimation of a BMD and benchmark dose lower limit (BMDL) for malignant lymphoma, with a P value >.1. The multistage model (2 degrees) has a goodness of fit P value of .07. All of these models predict a concave dose–response (Figure 6). None of the models fit to the mammary carcinoma incidence had adequate fit, but the multistage model (with 1 and 2 degrees) had a goodness of fit P value of .057 and is shown in Figure 7. For leukemia, all models adequately fit the data (Figure 8). Multiple dose–response shapes can be fit to

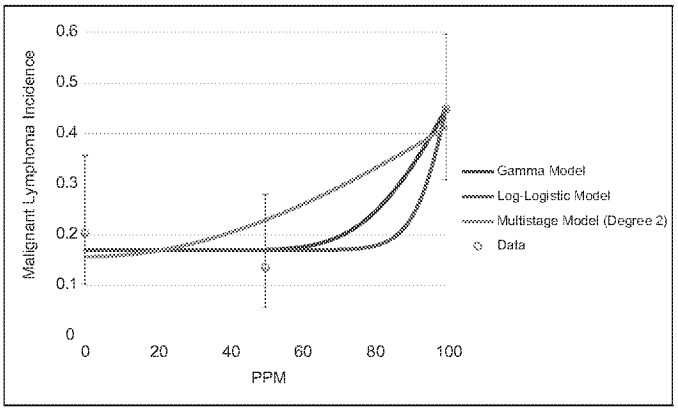

Figure 6. Array of potential dose–response models fit to NTP's[40] malignant lymphoma incidence data (female mice). NTP indicates National Toxicology Program.

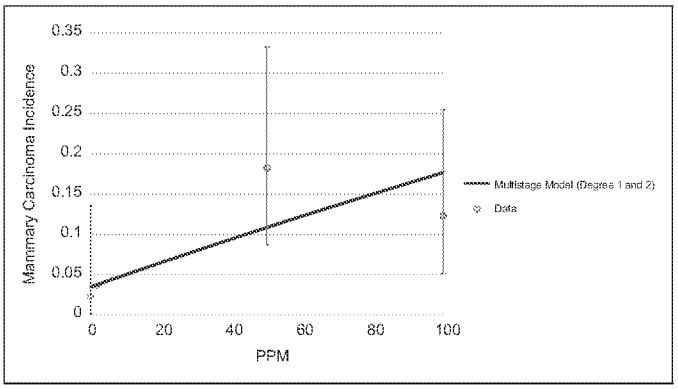

Figure 7. Multistage (degree 1 and 2) dose–response models fit to NTP's[40] mammary carcinoma incidence data (female mice). NTP indicates National Toxicology Program.

these data with satisfactory model performance, including models with thresholds or concave and convex curves. Additional information on model fit for each end point is provided in the Supplemental Material.

Regardless of the model selected, there is no compelling evidence to indicate—at least at the relatively high doses administered—that the toxicological dose–response data follow a supralinear dose–response, such as the 2-step model used by USEPA in deriving the IUR for EtO. Although threshold or biphasic models may be feasible, there are too few data points associated with exposures clearly below the lowest observable adverse effect level (LOAEL) to validly select one of these.

As with the epidemiological evidence, there is no strong indication of a dose–response relationship between EtO exposure and lymphoma or breast and mammary cancers in rodents. However, a clear dose–response relationship is observed for leukemia (Figure 8) in one study, although the responses were within the range of historical controls. Nevertheless, as shown in Figures 6 to 8, dose–response models can be fit to the animal data and used for estimation of an IUR. The USEPA's[1] assessment did calculate unit risk estimates of approximately 3 to 4.55 10^{-5} μg/m^3 (1-2.5 ppb) from the animal bioassays (see table 4-20 of the USEPA 2016 risk assessment) using a software program called Tox_Risk, rather than the USEPA's own BMDS. Furthermore, only one model type (multistage) was used, and the USEPA inappropriately dropped data due to non-monotonic risk patterns. Current USEPA practice is to consider the full suite of models since no model is biologically informed, although USEPA's BMD guidance does denote an agency preference for the multistage model.[9,12] Additionally, although removal of high-dose groups to address non-monotonic dose–responses can be appropriate, it should not be done when there are only 2 exposed groups. The USEPA's model choices resulted in (ultimately) a straight line between the control and lowest evaluated dose. We therefore reevaluate these unit risk estimates using the USEPA's recommend BMDs and BMDLs, as calculated by the USEPA's BMDS software, which has multiple, flexible, dose–response shapes.

The recommended BMDL for lymphoma is approximately 51 ppm, which is adjusted to a lifetime equivalent of 9.1 ppm, based on the dosing regimen (ie, 6 h/d 5 d/wk).[40] This translates to an IUR of 0.011 or a 10^{-5} risk at 0.9 ppb EtO. Mammary carcinoma incidence is not recommended for dose–response evaluation, but a BMDL of 37 ppm, or 6.6 ppm after duration adjustment (6 h/d 5 d/wk),[40] was predicted by the multistage model (degrees 1 and 2). All of the models adequately fit the leukemia response in female rats,[42] but the USEPA's BMDS software recommends the log-logistic model (BMDL of 6.9 ppm EtO). Because no model was markedly better than another, the modeled average BMDL, as calculated with BMDS Bayesian averaging, of 8.9, or 1.9 ppm after duration adjustment (ie, 7 h/d 5 d/wk) is also considered. This translates to an IUR of 0.053 or a 10^{-5} risk at 0.2 ppb.

Synthesis of Animal Carcinogenicity Studies

The animal bioassay data confirm that there is no observed clear treatment-related risk of breast or mammary cancers. Lymphohematopoietic malignancies incidence in animals is unclear and may be a result of high historical background in the tested species. The ability to calculate an IUR for LHM, including lymphoma and leukemia, indicates a possible exposure–response relationship, although the animal data predict exposure-responses that are significantly less potent than those of the EPA's 2016 analysis. However, the IUR calculated from the leukemia incidence in female rats[42] is 20-fold more potent than the risk calculated by Texas Commission on Environmental Quality (TCEQ).[4] The IUR calculated from lymphoma incidence in female mice[40] is approximately 4-fold more potent than the TCEQ unit risk, under the same assumptions. However, the USEPA's[1] risk estimation is approximately1000-fold more potent than the IURs derived from animal data and the TCEQ unit risk estimate based on the same epidemiological evidence.

Because both the epidemiological and toxicological evidence do not clearly demonstrate an association between EtO exposure and LHM or breast/mammary cancer (contradicting

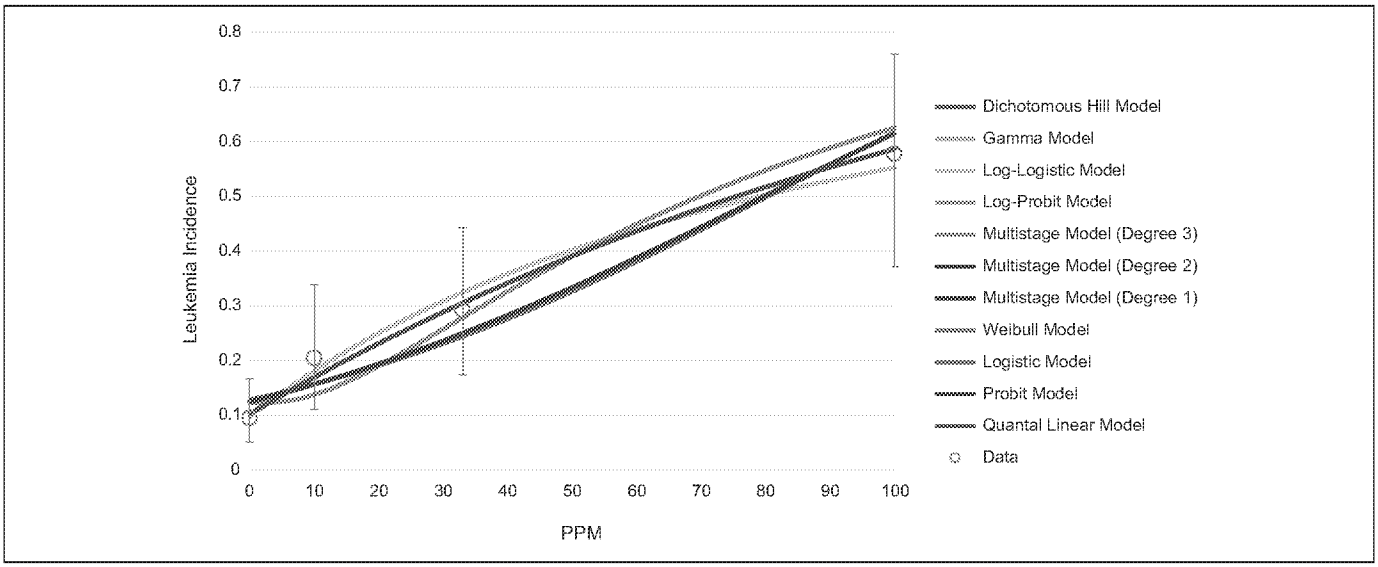

Figure 8. Array of potential dose–response models fit to Snellings et al's[42] leukemia incidence data (female Fischer rats).

the USEPA[1] and IARC[2] cancer classifications), we consider MOA information to establish the plausibility of the association between EtO exposure and cancer risk, as well as predict the potential dose–response relationship(s).

Mode of Action

Description of the USEPA's Proposed MOA

The USEPA's[9] *Guidelines for Carcinogen Risk Assessment* emphasize use of MOA information in the assessment of the human carcinogenic potential of an agent. Mode of action refers to "a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation."[9] The term key event refers to "an empirically observable precursor step that is itself a necessary element of the MOA or is a biologically based marker for such an element."[9] Chemicals may exhibit carcinogenic action via numerous different modes of action, including mutagenicity, mitogenesis, inhibition of cell death, cytotoxicity with reparative cell proliferation, and immune suppression.[9]

The USEPA conducted a MOA analysis for EtO carcinogenicity based on the Agency's MOA framework and concluded that "the weight of evidence supports a mutagenic MOA for EtO carcinogenicity" based on mutagenic, genotoxic, and carcinogenic outcomes in laboratory animal and human evidence.[1,9,47] Specifically, the USEPA proposed a mutagenic MOA for all tumor types with the following key events: "(1) DNA adduct formation by EtO, which is a direct-acting alkylating agent; (2) the resulting heritable genetic damage, including DNA mutations, particularly in oncogenes and tumor suppressor genes, and chromosomal alterations; and (3) clonal expansion of mutated cells during later stages of cancer development; eventually resulting in (4) tumor formation."[1] According to the USEPA, while other processes (eg, oxidative stress) may contribute to EtO-induced tumor formation, the available evidence suggests that mutagenesis is the primary MOA and limited to no evidence exists for alternative modes of action.[1] This mutagenic MOA is considered to be relevant to both breast cancer and lymphohematopoietic cancers, although additional tumor-specific mechanisms may apply.[1] Notably, according to the USEPA's 2005 Guidelines, a linear low-dose extrapolation approach should be used for a mutagenic MOA.[9] Based on this mutagenic MOA, the low-dose response for tumor formation is expected to be linear, but more recent arguments for nonlinear dose–responses and even thresholds also apply.[48]

Given the USEPA's conclusion that EtO exhibits a mutagenic mode of carcinogenic action and using their supporting evidence, the intent of the present analysis was to identify key events in the MOA and evaluate the dose response and interspecies differences in potency for these end points. To identify end points for analysis, we organized the key events proposed by USEPA into response stages and described the proposed MOA in more detail in Figure 9. Further, we have also drawn out details of the mutagenic and genotoxic mechanisms, which expands on the MOA and describes the biochemical and molecular interactions and responses for the key events, for the molecular initiating event and biochemical responses in Figure 10.[49] As summarized by the USEPA, EtO is a direct alkylating agent, which upon exposure to cells, reacts with DNA to form DNA adducts.[1] EtO-induced DNA adduct formation is the molecular initiating event, or the initial chemical–organismal interaction at the molecular level that perturbs the cell and triggers the mutagenic MOA.[1,50] At the biochemical level, insufficient repair or misrepair of DNA adducts can lead to genetic mutations (potentially in proto-onco and tumor suppressor genes), as well as cytogenetic effects.[1] At the cellular and organ levels, proliferation of preneoplastic foci results in clonal expansion of mutated cells, which leads to progression and ultimately formation of

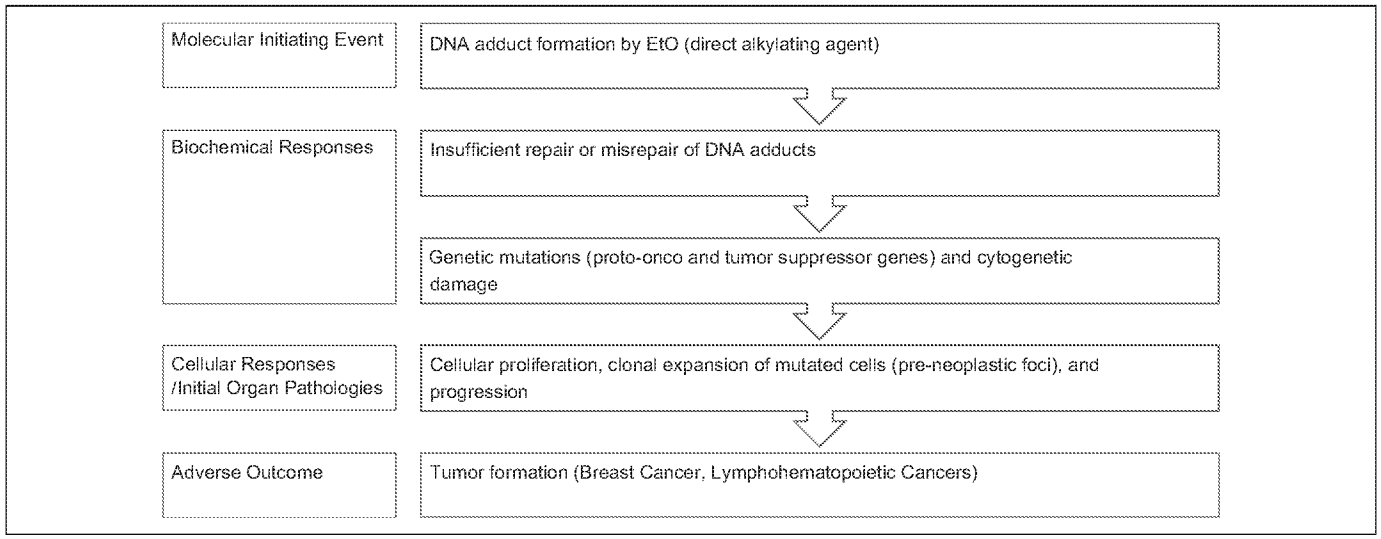

Figure 9. Proposed mutagenic mode of action for ethylene oxide carcinogenicity.

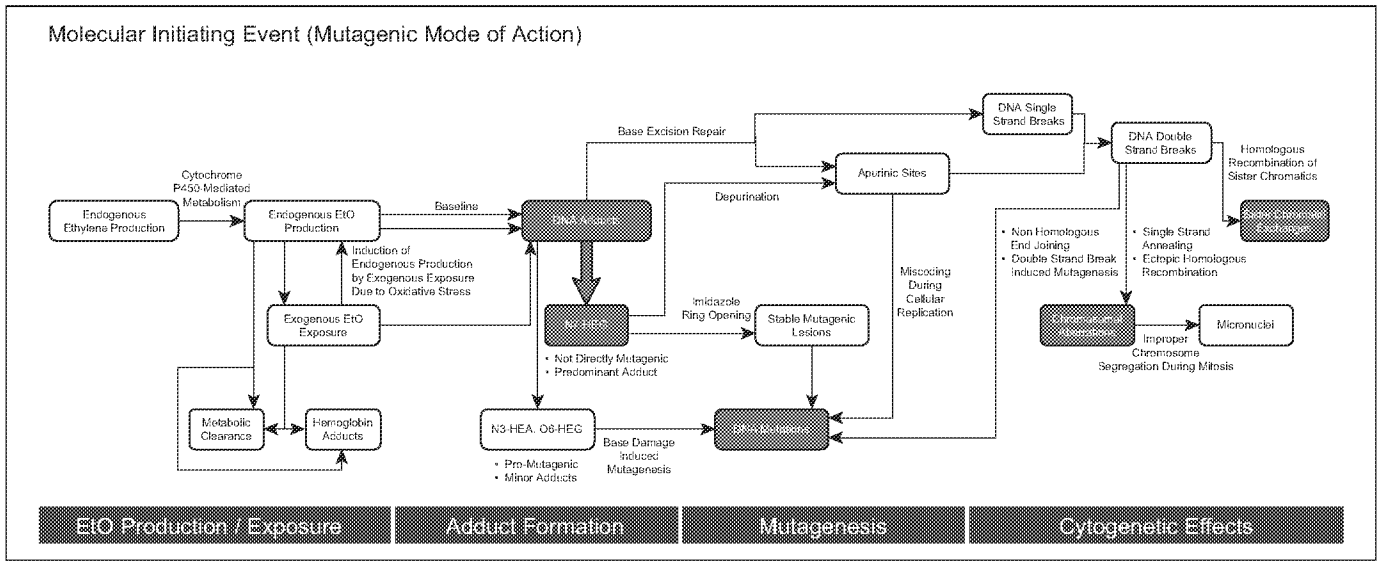

Figure 10. Molecular initiating event (mutagenic mode of action).

mammary tumors or breast cancers and LHM (the adverse outcome).[1,49] More detailed descriptions of the 4 key stages are supplied in Supplemental Material, and as expanded in Figure 10.

Evaluation of Dose–Response for Key Events

Overall, the proposed genotoxic MOA predicts that, in the low-dose region, the dose–response for cancer is expected to be linear. This predicted dose–response pattern is consistent with the animal tumorigenicity data (see Figures 6–8) in the range of the data. Dose–response analysis of the early effect data in humans and animals provides no evidence that a dose–response other than linear is justified, given the genotoxic MOA assumption and EPA policy. This determination is not due to an abundance of data suggesting clear, linear dose–response shapes but, instead, a general impression of linearity across the doses administered, as well as uncertainty and variability in the underlying human data that do not suggest departures from the linear low-dose extrapolation default from the current analysis. For example, only one study identified a significant dose–response relationship between EtO exposure and adduct arising from exogenous exposures. Yong et al[51] measured exogenous adduct formation in hospital workers and determined that the "high" exposure group had elevated exogenous adduct levels. The study had a sample of only 58 employees, divided between "low" and "high" exposure groups, and compared with 6 controls. The exposure estimates were imprecise and the authors reported "considerable interindividual variation" in adduct levels.[51] Because of these study limitations and

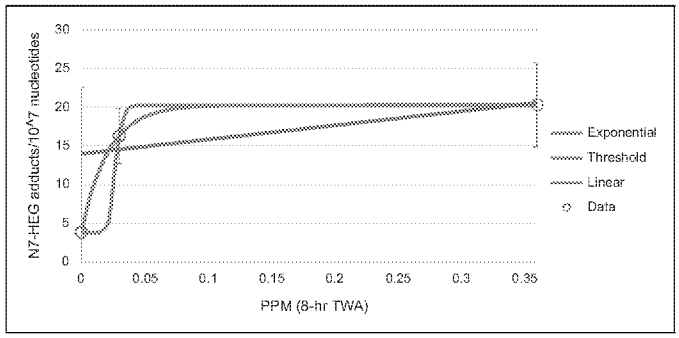

Figure 11. Uncertainty in the human data on ethylene oxide exogenous adduct formation allows for fitting of multiple dose–response shapes.

uncertainties, the observed numbers of adducts are highly variable, allowing for adequate fitting of an array of dose–response models with drastically different shapes (Figure 11). The uncertainties in dose–response shape for the key events, especially when human early effect data are used, demonstrate the importance of MOA when considering and selecting dose–response model shapes.

Evaluation of Species-Specific Differences

As noted in previous sections, there are dramatic differences in the expected cancer potency of EtO predicted by studies in animals and humans. Herein, we compare the potency of key events in the USEPA's proposed genotoxic MOA to determine whether underlying species-specific sensitivity may account for the 100-fold difference in cancer potency calculated by the USEPA.

Figure 12 shows the no observed adverse effect level (NOAELs; or NOAEL equivalents) from humans and laboratory animals for selected key end points from the mutagenic MOA. For the interspecies response comparison, we used the USEPA tables 3-6, 3-7, and 3-8 to identify NOAELs or calculate NOAEL equivalents for each end point and study. When a NOAEL was not available, the LOAEL was divided by 10 to obtain a NOAEL equivalent, per the US USEPA's default LOAEL-to-NOAEL uncertainty factor.[52] For animal studies evaluating more than one exposure duration, the longest exposure duration was selected for analysis. For human studies reporting only a range of exposure concentrations, instead of a mean, the mean was calculated and used as the LOAEL or NOAEL. Measurements from human studies that evaluated only acute exposures (not in addition to chronic exposures; ie, accidental exposure group[53]) or reported exposure concentration as peak or cumulative exposure rather than a time-weighted average or range[54,55] were excluded from the figure.

The ranges of NOAELs shown in Figure 12 substantially overlap for the selected key end points. The same pattern was observed for micronuclei formation, another indicator of chromosome-level effects (not shown) with a NOAEL range from 20 to 50 ppm for animals and 0.0125 to 22.5 ppm for humans. Although the data suggest some possibility that humans are more sensitive than rodents, this is likely due to artifacts of study design and dosing selection (eg, animal studies use high doses that might not characterize responses at lower doses). Overall, these data demonstrate minimal difference in the human and animal responses to EtO exposure for selected key end points from the mutagenic MOA. Any differences would be in sensitivity, not dose–response shape based on dose–response modeling. This finding is in contrast to the roughly 2 orders of magnitude difference in the USEPA's total extra cancer IUR calculated based on human and animal data.[1]

The differences in human and animal responses may be due to human data uncertainty (eg, small sample size, imprecise or uncertain exposures, higher interindividual variability for early biomarkers), or high environmental background exposures. Other possible explanations include differences in baseline physiology as well as toxicokinetics and toxicodynamics between humans and animals. However, comparisons of various measurements of endogenous conditions, exogenous exposures, ADME (absorption, distribution, metabolism, and excretion) characteristics, and effects do not suggest a 100-fold difference in sensitivity between humans and laboratory animals, which again does not justify the 2 orders of magnitude higher cancer potency in humans compared to animals predicted by the USEPA.[1]

Endogenous production of ethylene is similar between humans and laboratory animals (41 and 2.8 nmol/h in humans and rats, respectively).[56] Background N7-HEG adducts in DNA of unexposed laboratory animals and humans and the levels of adducts detected in rodents and humans vary widely and depend on the analytical method used.[1] However, Föst et al[57] evaluated N7-HEG adducts in lymphocytes from both humans and rats using gas chromatography-mass spectrometry and reported adduct levels on the same order of magnitude (8.5 and 5.6 picomoles/milligram [pmol/mg] DNA, respectively).

Additionally, blood concentrations of EtO in humans, mice, and rats exposed to a particular air concentration of EtO are approximately equal and are linearly related to inhalation concentration.[58] Ethylene oxide air/blood partition coefficients for humans and laboratory animals are on the same order of magnitude (61 in humans, 64 in rats, 74 in mice), which the USEPA[1] uses to justify using ppm equivalence for cross-species scaling for extrarespiratory effects.[58-60] Ethylene oxide blood elimination half-lives are also not 100-fold different between humans and laboratory animals (42 minutes in humans, 11-14 minutes in rats, 2-3 minutes in mice).[61-63] These findings further do not support the 2 order of magnitude difference in cancer potency between humans and animals predicted by the USEPA.[1]

Notably, the available data regarding EtO metabolism suggest that glutathione conjugation dominates in smaller animals such as mice and to a lesser extent rats (~20% in humans, ~60% in rats, ~80% in mice) and hydrolysis dominates in larger species, including humans (~80% in humans, 40% in rats, and 20% in mice).[1,64] Although both of these pathways are considered detoxifying, the glutathione pathway is faster but

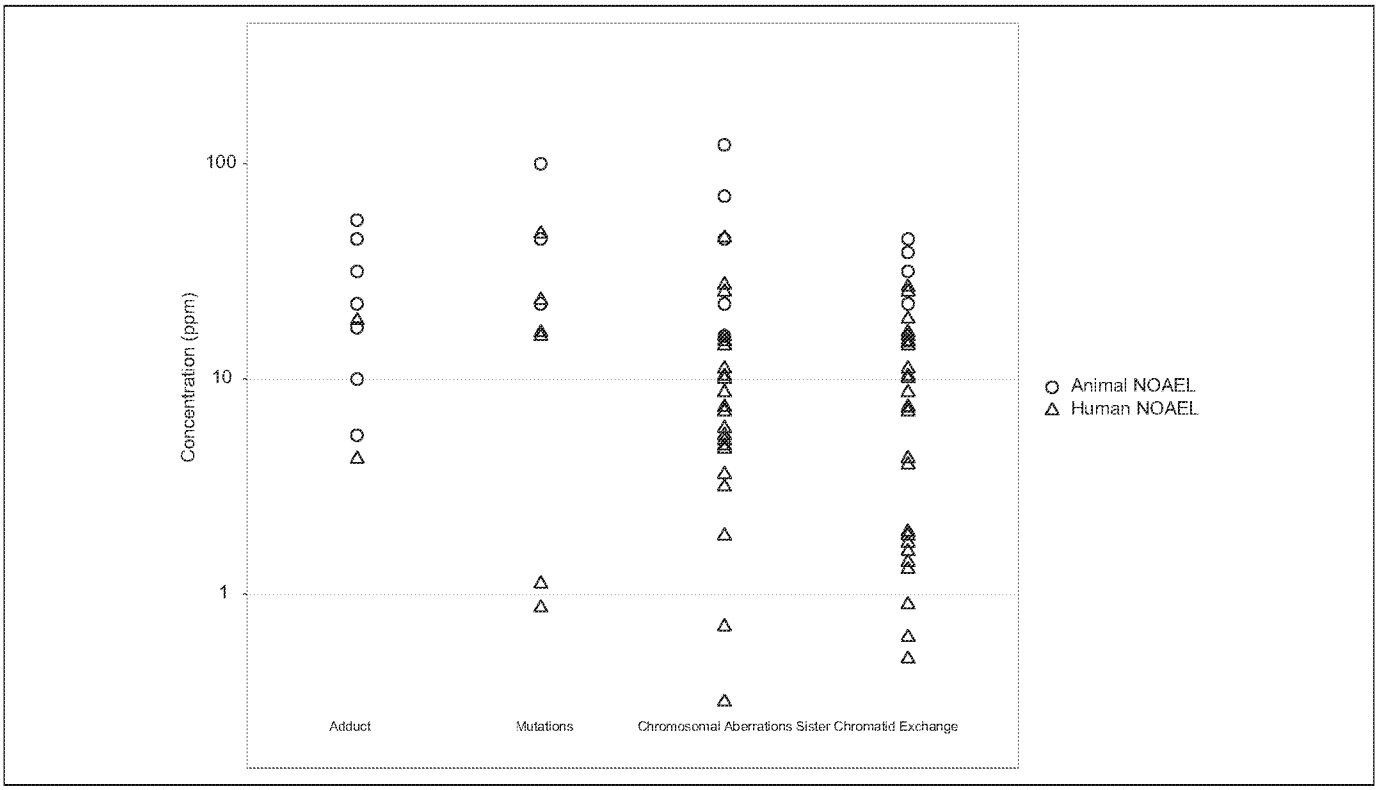

Figure 12. Human and laboratory animal responses to key events.

saturable, and mice have been shown to shift to slower hydrolysis at higher exposures.[1,62]

Specific laboratory animals generally have higher background cancer rates than humans for some tumor types. For example, background MNCL rates in Fisher rats from NTP studies approach 50%.[45,65]

Overall, the relative species differences in these various markers of exposure and effect for EtO for which data are available do not align with the orders of magnitude difference in cancer potency suggested by the USEPA-derived IUR from the epidemiology studies.

Discussion and Conclusions

Despite IARC's conclusion that "There is limited evidence in humans for a causal association of EtO with lymphatic and haematopoietic cancers . . . and breast cancer," and USEPA's acknowledging that the epidemiological evidence was "strong, but less than conclusive on its own," USEPA selected 2 epidemiological studies conducted by NIOSH as the basis for their derivation of the IUR for EtO. However, as demonstrated by our review and synthesis of the epidemiological evidence, occupational exposure to EtO was not clearly or consistently associated with the increased occurrence of breast cancers or LHM—or any cancer. In fact, one of the NIOSH studies demonstrated an anomalously statistically significant *deficit* of breast cancer among the least exposed workers, and no increase among more highly exposed workers. Similarly, fewer than expected LHM were observed in the lowest exposed group and no increase overall or among more highly exposed workers. Unfortunately, little consistency was found in the way study results were reported for specific LHM. Ideally, had results for at least major categories of LHM (eg, lymphomas, leukemias, myeloid malignancies, and perhaps their more common subtypes) been reported across more studies, a fuller evaluation might have been possible. Interpretation of risks associated with all LHM remains challenging unless the individual diseases comprising the group are evaluated.

Because further statistical analysis of "relative risk" designated the lowest exposed workers as the "referent" category, the groups of more highly exposed workers appeared to be at increased risk of breast cancers and LHM (specifically the subset described as "lymphoid cancers"). Although designating the least exposed members of a cohort as the referent constitutes a standard methodology in epidemiology, proper application requires verification that the group designated as the referent validly represents the background rate (ie, that unrelated to exposure) and does not have an unexplained (due to chance, bias, or possible biphasic effect) higher or lower rate of disease. In the USEPA risk assessment, the basic study data demonstrating no increased risk (and perhaps a "protective" effect among low exposure groups) appear to have been dropped in favor of the RR models recalibrated to the reduced risk of the referent groups.

The broader body of epidemiological studies demonstrates no increased cancer risks. We conclude that the epidemiological

evidence may not reach the level described by IARC as "limited" and certainly does not comport with USEPA's conclusion that the evidence was "strong" (and presumably positive). This alone may not call into question the classification of EtO as a known human carcinogen but also does not support it. The measures of association and dose–response analyses in Steenland et al[25] and Swaen et al[29] were heavily relied upon by the USEPA when they concluded that EtO was carcinogenic to humans, as both of these studies had adequate sample size, quantifiable measurements of EtO exposure, and sufficient follow-up time.[1] Steenland et al[25] examined many cancers and reported a significant increased risk of bone cancer and NHL for males in the highest exposure category. However, the other subtypes of lymphohematopoietic cancers were not significantly increased at any level of exposure and their use of the transformed log cumulative EtO exposure metric limits these results. Similar to Steenland et al,[25] Swaen et al[29] investigated the association between EtO exposure and many cancers but did not report a significantly increased risk of any cancer or with each increasing exposure category. Additionally, the study by Swaen et al[29] was limited to only men and had mixed exposures to other chemicals besides EtO.

Although we did not perform a new critical review of the animal toxicology studies on EtO and cancer, we did reconsider the animal studies identified in the USEPA review of EtO. Most of the study results were negative. This observation also is in striking contrast with USEPA's conclusion that there is "extensive evidence of carcinogenicity in laboratory animals, including lymphohematopoietic cancers in rats and mice and mammary carcinomas in mice following inhalation exposure." One study of leukemia in female F344 rats does provide results that include 2 doses above background[42]; however, this study was conducted in a species with an unusually high background rate of leukemia and increases uncertainty in its use for risk assessment. However, this remains the only study demonstrating a clear dose–response relationship. Interestingly, the dose–response function appears to be linear at the levels tested (ie, not precluding a threshold, given the consistently negative epidemiology studies). This further challenges the USEPA's use of a supralinear 2-slope dose–response function, albeit on the recalibrated epidemiological data.

Our review of the carcinogenic potential for EtO demonstrates the necessity of examining the evidence at the cellular level including an evaluation of the MOA and key events. Ethylene oxide is expected to be mutagenic and genotoxic in both humans and animals, but there is no evidence, based on evaluation of key events, that suggests animals and humans have highly different tumorigenic response rates (ie, no interspecies pharmacokinetic correction is needed) or response patterns. Evaluation of potential kinetic, dynamic, or metabolic differences between humans and laboratory animals did not identify significant differences that would explain or predict the drastic differences in toxicology- versus epidemiology-based IUR calculations.

Based on the USEPA's proposed genotoxic MOA, EtO at adequately high concentrations might be expected to increase cancer risk at some target tissues or organs. However, integrating this hypothesis with the negative epidemiological literature and animal toxicology evidence—which, at best, offers limited evidence of a carcinogenic response—aligns most closely with a classification of EtO as no more than "suggestive evidence of carcinogenic potential."[9]

Given that EtO is plausibly carcinogenic based on the most likely MOA, a quantitative risk assessment may be warranted. However, the evidentiary basis for the risk assessment becomes problematic, as does the selection of the most appropriate dose–response model. The extensive evaluation of candidate models performed by Steenland et al[24,25] resulted in the selection of a 2-stage spline model representing a steeply upward inclination followed by a segment with a more attenuated slope, which performed comparably well to a square root model. However, all of the models considered were "relative risk" models essentially recalibrated to the anomalously low-risk level (ie, deficit risk) documented among the lowest exposed workers used as the referent group. It is understandable how the first segment of the 2-stage spine model appeared to indicate a greater risk slope than across higher exposure groups: It represents the change in risk from a group with an anomalous deficit of cancers back up to the background risk.

Reasons why the least exposed groups demonstrated lower than expected cancer rates are intriguing. A similar pattern was seen in studies conducted by Marsh et al[66,67] on chloroprene exposure and risk of both lung and liver cancers, where overall slight deficits appeared to be driven by clear deficits in the lowest exposure group.[68] These observations raise important methodological questions regarding the underlying dose–response relationship and whether the risk deficits observed among the lowest exposure groups reflect a protective effect, chance, or some form of study bias. Considering that many epidemiologists assume that the cancer rate in the lowest exposure group (often without validating this assumption), the potential problem may be more widespread.

Given that the epidemiological evidence is negative (including the NIOSH studies), we recommend that a proper risk assessment validly cannot be based on the epidemiological findings. Furthermore, the integration of the different lines of evidence does not justify deviating from the USEPA's standard dose–response guidance, that is, a modeling approach using MOA and the best available evidence—which for EtO comes only from one possibly questionable study of leukemia in female F344 rats. Assuming this study was valid for quantitative risk assessment, due to high species–specific background rates of leukemia, the dose–response (at least across the specific doses studied) may follow a linear dose–response relationship. We conclude, based on a focused critical review, synthesis and integration of the published epidemiological and toxicological studies on the carcinogenicity of EtO—informed by consideration of the MOA—that the scientific basis for both IARC's and USEPA's classification of EtO as a known human carcinogen is not as strong as stated in their respective reviews. Further, the USEPA's derivation of the IUR for EtO using a 2-piece, supralinear dose–response model—giving rise to one

of the highest cancer potency estimates—appears not to be adequately justified based on the published literature and deviates from USEPA standard risk assessment guidance.

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Supplemental Material

Supplemental material for this article is available online.

Note

1. This reflects a summary rating for statistical analysis. For both Steenland et al[24] and Mikoczy et al,[35] relative risk analyses were performed using as the referent group the group with the lowest estimated cumulative exposure, without verifying that this group reflects the risk of the truly unexposed population. Because this category of workers demonstrated statistically significant deficits in breast cancer risk, bias was introduced when they were used as the referent group. In neither study was this identified as problematic or the subsequent relative risk analyses justified.

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Exhibit O

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Quantitative cancer risk assessment based on NIOSH and UCC epidemiological data for workers exposed to ethylene oxide

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ABSTRACT

The most recent epidemiological data on individual workers in the NIOSH and updated UCC occupational studies have been used to characterize the potential excess cancer risks of environmental exposure to ethylene oxide (EO). In addition to refined analyses of the separate cohorts, power has been increased by analyzing the combined cohorts. In previous SMR analyses of the separate studies and the present analyses of the updated and pooled studies of over 19,000 workers, none of the SMRs for any combination of the 12 cancer endpoints and six sub-cohorts analyzed were statistically significantly greater than one including the ones of greatest previous interest: leukemia, lymphohematopoietic tissue, lymphoid tumors, NHL, and breast cancer. In our study, no evidence of a positive cumulative exposure–response relationship was found. Fitted Cox proportional hazards models with cumulative EO exposure do not have statistically significant positive slopes. The lack of increasing trends was corroborated by categorical analyses. Cox model estimates of the concentrations corresponding to a 1-in-a-million extra environmental cancer risk are all greater than approximately 1 ppb and are more than 1500-fold greater than the 0.4 ppt estimate in the 2006 EPA draft IRIS risk assessment. The reasons for this difference are identified and discussed.
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1. Introduction

Ethylene oxide (EO), a high production volume chemical and a raw material/intermediate in the production of many materials, is a direct-acting alkylating agent and a low potency mutagen that has been shown to be a low potency carcinogen in animal models. In 2006, the U.S. EPA prepared a draft cancer risk assessment for ethylene oxide (EO) based on their analysis of grouped data from the National Institute for Occupational Safety and Health (NIOSH) hospital sterilant cohort mortality study (Steenland et al., 2004) and failed to utilize the Teta et al. (1993) UCC cohort mortality study data on manufacturing workers exposed to EO. The Ethylene Oxide Review Panel of the EPA Science Advisory Board met on January 18 and 19, 2007, and made several recommendations to EPA, with the expectation that the draft would be revised. Specifically, the Panel recommended that EPA consider all of the epidemiology data including the UCC data. The UCC study has recently been updated to now include an average follow up of 37 years and an average cumulative exposure of 67 ppm-years (Swaen et al., 2009). Also, the Panel unanimously recommended that the EPA develop risk models based on direct analysis of the individual exposure and cancer outcome data for the NIOSH cohort, rather than using published grouped data. We, therefore, analyzed the UCC and NIOSH individual data separately and also combined them in order to increase the statistical probability of detecting any increase in cancer associated with EO exposure, to examine dose–response patterns, and to calculate excess environmental cancer risk. The combined cohorts include more than 19,000 workers, with a significant fraction relatively highly exposed and with long follow up.

2. Methods

All analyses were based on two datasets: (1) the most current NIOSH mortality data of sterilant workers (Steenland et al., 2004) and (2) the most current UCC mortality data of EO chemical manufacturing workers (Swaen et al., 2009). These two selected datasets were used both separately and in a pooled fashion for analyses in four stages: (1) traditional standardized mortality ratio (SMR) analyses, (2) dose–response modeling using a continuous cumulative exposure metric, (3) dose–response modeling using a categorical cumulative exposure metric, and (4) excess risk characterization.

2.1. Datasets

Only three EO epidemiology studies include quantitative exposure estimates that could be linked to individual cohort members (Steenland et al., 2004; Swaen et al., 2009; Hagmar et al., 1995).

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The population studied in Hagmar et al. (1995), however, was too young and the follow up too short (median 11.8 years) to be useful for our purposes. Because of their size, extensive periods of follow up, and available exposure estimates at the individual level, the NIOSH and UCC mortality datasets have the requisite attributes to become the basis for dose–response modeling. We have discussed this issue in greater detail elsewhere (Teta et al., 1999).

In 1991, NIOSH published the results of a cohort mortality study with follow up through 1987 of male and female sterilant workers with potential for exposure to EO (Steenland et al., 1991). Using measurements of EO concentrations from 1976 to 1985, job-exposure matrices with concentrations corresponding to each job and calendar-year combination were developed. Retrospective exposure reconstruction to estimate exposures before 1976 were based on regression modeling of important correlates of exposure (Greife et al., 1988; Hornung et al., 1994). The workers in the NIOSH cohort were from 14 different plants. One of these plants did not have enough data to develop reliable exposure estimates and its workers were excluded from dose–response analyses. The NIOSH data were more recently updated to include follow up through the end of 1998, for an average follow up of 26 years (Steenland et al., 2004). The same job-exposure matrix used in the original cohort was used for the updated cohort. The workers active at the end of 1987 (the end of the original follow up period) were assumed to stay working on the same job until their end of employment. This assumption did not substantially affect the cumulative exposures to EO because concentrations after the mid-1980s, following reduction in the OSHA PEL and ACGIH TLV-TWA, were much lower than the concentrations in earlier years. After excluding workers from the plant with no exposure information and workers lost to follow up, 17,493 workers remained in the NIOSH dataset. The NIOSH dataset analyzed herein includes 9859 female, 7634 male, 13,761 white and 3732 non-white workers. The breakdown of workers by plant, race, and sex for the NIOSH data is given in Table S1 in Supplemental materials.

Greenberg and Ott (1990) conducted a cohort mortality study of Union Carbide workers assigned to EO using or producing units in three locations with follow up through 1978. Teta et al. (1993) updated the UCC study to include follow up through the end of 1988. More recently, Swaen et al. (2009) updated the UCC study to include follow up through the end of 2003, for an average follow up of 37 years. The UCC cohort consists of 2063 male EO workers employed sometime between January 1, 1940, and December 31, 1988. The EO concentrations (i.e., the job-exposure matrix) for the UCC cohort have been developed and used in other publications (e.g., Teta et al., 1999; Kirman et al., 2004) and are well-documented in Swaen et al. (2009). EO exposure estimates were made for the period between 1925, when EO production started at the South Charleston Plant, and 1988. After 1988 EO exposures were negligible compared with earlier exposure levels and were therefore not included in the cumulative exposure assessment. EO production was phased out in 1972. The exposure estimates rely on the qualitative categorization of EO producing and using departments by exposure level, developed by Greenberg and Ott (1990) and on quantitative estimates of average intensity by these department categories and by time period 1925–1988, developed by Teta et al. (1993).

Table 1 shows the distributions of the observed cumulative EO exposures (ppm-days) at the end of follow up among the NIOSH females, NIOSH males, and UCC males. Table 1 shows that the UCC males had generally higher cumulative EO exposures than the NIOSH males. Also, the NIOSH females had substantial albeit lower exposures. For example, the 90th, 75th, and 50th percentiles for UCC males are approximately twice as large as the values for NIOSH males, and the 90th, 75th, and 50th percentiles for NIOSH females are at least half as large as the values for NIOSH males.

Table 1
Distribution of the cumulative EO exposures (ppm-days) at the end of follow up among the workers.

Percentiles		NIOSH Females	NIOSH Males	UCC Males
100.0	Maximum	293,538	642,925	422,933
99.5		107,249	239,777	250,489
97.5		45,363	102,167	135,224
90.0		19,420	38,687	72,643
75.0	Third quartile	7178	12,160	28,119
50.0	Median	1767	2807	7364
25.0	First quartile	520	668	1876
10.0		166	134	391
2.5		45	31	68
0.5		17	14	14
0.0	Minimum	5.1	4.9	2.1

In the 2006 EPA draft assessment, EPA did not pool the NIOSH study with the UCC study available at that time, expressing concerns that the UCC study cohort may have had confounding exposures. (Confounding is not thought to be a concern in the NIOSH study as the use of other chemicals in this work environment is limited.) In order for confounding to explain the absence of an exposure–response relationship in the UCC EO data, a subpopulation with low EO exposure would have to be at increased risk due to some other chemical exposure(s). This was, in fact, examined in the past and workers producing ethylene chlorohydrin were identified as a low EO exposure group with elevated risk for leukemia, NHL and pancreatic cancer. This sub-cohort of 278 workers were excluded from the UCC EO cohort and their mortality experience was reported separately (Teta et al., 1993). They are also excluded from the Swaen et al. update. No other potential confounders have been identified. A recent review of the available data led to the conclusion that pooling these studies appears to be acceptable and that differences with respect to exposure estimation and possible confounding do not negate the validity of a pooled analysis (Delzell, Toxicology Forum in 2009).

2.2. Endpoints of interest

Hogstedt et al. (1979) reported a cluster of three cases of leukemia among female sterilant workers: one chronic myeloid leukemia, one acute myelogenetic leukemia and one Waldenstrom leukemia. A large number of EO worker cohort mortality studies and updates followed this first report; these included 12 different groups of workers (including numerous facilities, hospitals, and plants) and over 33,000 workers in five countries. These have been reviewed in a detailed meta-analysis (Shore et al., 1993) and in an update to this meta-analysis (Teta et al., 1999). Although there was no consistent pattern of cancer mortality excesses in these studies, we examined endpoints that have been suggested as being associated with EO exposure in one or more of these epidemiology studies; namely, cancers of the stomach, breast, and pancreas, CNS cancers (and specifically brain cancer), lymphohematopoietic tissue (LH) cancers including leukemia (and specifically myeloid and lymphocytic leukemia), non-Hodgkin's lymphoma (NHL), multiple myeloma, and "lymphoid" cancers (a grouping developed in Steenland et al. (2004) that included non-Hodgkin's lymphoma, multiple myeloma, and lymphocytic leukemia). There were only a total of six workers with deaths caused by Hodgkin's lymphoma and only seven workers with deaths caused by bone cancer. Because these numbers are too small for meaningful dose–response modeling, neither bone cancer nor Hodgkin's lymphoma was included among the endpoints of interest herein. The only other endpoints for which SMRs were calculated in Steenland et al. (2004) and Swaen et al. (2009) are prostate, lung, kidney,

Table 2
Number of worker deaths for each endpoint by study and sex for workers with exposure information.

Endpoint	NIOSH and UCC			NIOSH			UCC
	Total	Male	Female	Total	Male	Female	Male
Lymphohematopoietic tissue	101	64	37	74	37	37	27
Lymphoid tumors[a]	70	44	26	53	27	26	17
Non-Hodgkin's lymphoma	42	30	12	30	18	12	12
Multiple myeloma	16	7	9	13	4	9	3
Lymphocytic leukemia	12	7	5	10	5	5	2
Myeloid leukemia	17	10	7	10	3	7	7
Leukemia	36	21	15	25	10	15	11
Central nervous system	27	19	8	14	6	8	13
Malignant brain neoplasm	25	17	8	13	5	8	12
Breast	103	1	102	103	1	102	0
Pancreas cancer	51	34	17	36	19	17	15
Stomach cancer	34	21	13	24	11	13	10
All causes	3800	2517	1283	2749	1466	1283	1051
All workers	19,556	9697	9859	17,493	7634	9859	2063
% Deceased	19	26	13	16	19	13	51
Person-years	526,212	265,174	261,038	450,906	189,868	261,038	75,306
Average follow up (person-years)	26.9	27.3	26.5	25.8	24.9	26.5	36.5

[a] Lymphoid tumors are defined herein in the same manner as in Steenland et al. (2004); namely, non-Hodgkin's lymphoma, multiple myeloma, or lymphocytic leukemia.

and coronary heart disease—none of which had statistically significantly increased SMRs and have not been suggested as being associated with EO exposure.

Table 2 shows the number of workers that died with each of the 12 endpoints analyzed for each study, sex, and combination of sex and study. The UCC male cohort includes fewer workers than the NIOSH male and female cohorts. However, the UCC cohort is much older with an observation start date of 1940 and 10 years longer average length of follow up. As a consequence, the percentage of deceased workers in the UCC cohort (51%) is more than three times higher than the percentage of deceased workers in the NIOSH cohort (16%), resulting in comparable numbers of male deaths in the health outcomes of greatest interest. Although the UCC cohort has fewer workers than the NIOSH cohort, it is a much older cohort with substantial person-years at risk (see Table 2) at older ages and statistical power on its own, thereby increasing the power of the pooled analyses.

Table S2 in Supplemental materials shows the 12 cancer endpoints with the corresponding cause of death codes (ICD) and the calendar-year intervals for which the ICD codes were applicable.

2.3. Statistical analyses

SMRs were calculated in the standard manner as the ratio of observed to expected numbers of deaths. The expected values for the NIOSH and UCC cohorts were taken from Steenland et al. (2004) and Swaen et al. (2009), respectively. For the NIOSH cohort, life-table analyses were conducted using the NIOSH life-table program (Steenland et al., 1998), which allows for calculations of SMRs for 99 causes of death for the years 1960–1999. For the UCC cohort, the statistical analysis was performed by means of OCMAP (Marsh et al., 1998), a statistical program that includes subroutines specifically developed to analyze cohort studies based on a modified life-table procedure. Tables S3–S8 list calculations and values for the observed and expected numbers, the SMR, and a two-sided 95% confidence interval on the SMR.

For dose–response modeling, we fit Cox proportional hazards models with cumulative EO exposure (ppm-days) as the predictor variable to the data on individual exposures and cancer outcomes for each combination of 12 cancer mortality types of past interest and for six sub-cohorts (NIOSH males, UCC males, NIOSH and UCC males, NIOSH females, NIOSH males and females, and NIOSH and UCC males and females). The effect was modeled as a linear function of cumulative EO exposure (ppm-days) treated as a continuous variable. Age was the index variable used to identify the risk sets in the Cox regression. Because we found no covariates that were more than rarely statistically significant, no covariates (other than race for the NIOSH data) were included. The NIOSH dataset had workers classified as white (13,671), black (3105), Oriental (401), Hispanic (38), other (3), and unknown (185). The UCC dataset had the workers classified as white or Caucasian (1510), black (2), non-white (28), and unknown (523). The analyses of the NIOSH data were adjusted for race, but the analyses of the UCC data did not adjust for race because of the substantial uncertainty of the race classification. Each study and sex were fit separately as well as combined. In pooled analyses, study and sex were treated as covariates. Both lagged and unlagged analyses were conducted. The proportional hazards assumption in the Cox modeling herein was checked by testing for an interaction between the exposure metric and age in all combinations (69) of the 12 endpoints and six sub-cohorts analyzed. There was no statistically significant interaction (at the 5% significance level) in any of the 69 combinations using Wald's Test and only 2 out of 69 were significant using the likelihood ratio test.

Categorical dose–response analyses were added to augment the search for dose–response information beyond the log-linear model in the Cox proportional hazards models and to complement the categorical analyses in Steenland et al. (2004) and considered in EPA's 2006 draft assessment. Hazard rates (per person-year) at different exposure categories were compared to the hazard rate for the lowest exposure category. The dose range for each combination of study, sex, and endpoint was partitioned into five categories of the cumulative exposure to EO of the workers with the response, with approximately equal number of responses per category. The number of categories was five or fewer, defined in such a way that there would be at least two responses (deaths from the cause of interest) per category whenever the total number of deaths with the endpoint was more than three.

Following common U.S. EPA regulatory practice, we use the fitted Cox proportional hazards models to characterize excess environmental cancer risk. We incorporate the EPA (2005b) guideline's default age-dependent adjustment factors (ADAFs)[1] and computational procedures for age-dependent cumulative expo-

[1] *Abbreviations used:* ADAFs, age-dependent adjustment factors; EC, effective concentration; EO, ethylene oxide; EPA, U.S. Environmental Protection Agency; ICD, International Statistical Classification of Diseases and Related Health Problems; LEC, 95% lower confidence limit on the effective concentration; LH, lymphohematopoietic; MLE, maximum likelihood estimate; NIOSH, National Institute of Occupational Safety and Health; PoD, point of departure; RR, rate ratio; SMR, standardized mortality ratio; UCC, Union Carbide Corporation.

sures. These models estimate effective concentrations (ECs) corresponding to a 1-in-a-million excess environmental cancer risk. We contrast our analyses with that proposed by EPA (2006) based solely on grouped data for NIOSH males and one cancer mortality endpoint.

3. Results

3.1. SMR analyses

Steenland et al. (2004) and Swaen et al. (2009) present SMR analyses of the NIOSH and UCC cohorts, respectively, for several endpoints. Table 3 provides a consolidated overview of the SMRs for the six sub-cohorts. The details of the SMRs are in Tables S3–S8 in Supplemental materials. As discussed in Steenland et al. and Swaen et al., except for bone cancer, none of the SMRs were statistically significantly greater than one.

3.2. Dose–response modeling

Table 4 summarizes the findings with respect to the estimated slopes in the unlagged Cox proportional hazards models. (Lagged results were similar, e.g., see Table S10.) More details are given in the last column of Table S9 in Supplemental materials which shows the number of workers, number of deaths, maximum likelihood estimate (MLE) and standard error (SE) of the slope parameter multiplying cumulative EO exposure in the Cox proportional hazards model, and the slope's p-value for each of the 12 endpoints and for each analyzed combination of sex and study.

None of the dose–response models for the 12 endpoints and six sub-cohorts analyzed herein resulted in a statistically significant positive estimated slope. Also, as shown in Table 4 and as would be expected in the case of no dose–response relation, the maximum likelihood estimates of the slopes were approximately half positive and half negative. None of the estimated slopes that were positive were statistically significant, and none of the 12 endpoints had positive estimated slopes for all six sub-cohorts.

3.3. Categorical analyses

Cox proportional hazards models that treat cumulative EO exposure as a continuous variable indicated that there were no statistically significant increasing trends. The lack of increasing trends is corroborated by the categorical analyses.

Table 5 shows, for each combination of study, sex, and endpoint, the rate ratios that are statistically significantly different from zero at the 5% significance level. In Table S9 in Supplemental materials, there are five columns (one for each of the five or fewer categories) indicating the cumulative exposure interval (ppm-days), number of workers at risk, number of deaths, the estimated rate ratio, a two-sided 95% confidence interval on the rate ratio, and p-value for the rate ratio being non-zero.

There were statistically significant rate ratios only when the number of categories was five. All of the statistically significant categories had increased rates; none had decreased rates. There are nine cases in which the rate ratios (approximately 4%) are statistically significant at the 5% significance level. Most of these nine cases correspond to the highest dose range (the 5th category). The concentrations in these categories greatly exceed potential environmental levels and also exceed the OSHA PEL of 1 ppm TWA. There is no suggestion of a dose–response trend, in the sense that there is no case in which the rate ratio is statistically significant in the two highest categories, nor in any two consecutive categories. In addition, none of the slopes of the Cox proportional hazards models that were fit to the continuous exposure data indicated a statistically significant positive trend with increasing cumulative exposure to EO.

The results of the rate ratios presented herein cannot be directly compared with those given in Steenland et al. (2004) because they analyzed odds ratios instead of rate ratios and they used quartiles instead of quintiles. Also, the Steenland et al. odds ratios cannot be reproduced because they used a randomly selected subset of the risk set instead of the full risk set. (The full risk set is used herein in the standard Cox proportional hazards model.) However, the conclusions of the categorical analyses in Steenland et al. (all of which were based on cumulative exposure) are consistent with the conclusions drawn here for the NIOSH cohort.

3.4. Excess risk characterization

None of fitted Cox proportional hazards models herein for any of the 72 combinations of the 12 endpoints and the six sub-cohorts found statistically significant increases (statistically significant positive slopes) with increased cumulative EO exposure

Table 3
Standardized mortality ratios (SMRs).

Cause of death	NIOSH males and females and UCC males combined[a]	NIOSH and UCC combined: males[a]	NIOSH males and females combined[a,b]	NIOSH females[a,b]	NIOSH males[a,b]	UCC males[c]
All causes	0.89*	0.90*	0.90*	0.86*	0.94*	0.85*
All cancers	0.97	0.94	0.98	0.92	0.94	0.95
All hematopoietic	0.97	1.00	1.00	0.91	1.09	0.89
Non-Hodgkin's lymphoma	1.01	1.18	1.00	0.73	1.29	1.05
Hodgkin's lymphoma	0.92	1.13	1.24	0.47	1.83	0.00
Brain	0.85	0.98	0.59*	0.65	0.52	1.64
Leukemia	0.97	0.95	0.99	1.02	0.97	0.93
Pancreas	0.93	1.00	0.92	0.82	1.03	0.96
Stomach	1.06	0.93	1.07	1.34	0.87	1.02
Breast cancer	0.99	2.04	0.99	0.99	2.04	NA
Prostate	1.05	1.05	1.29	NA	1.29	0.81
Lung	0.99	0.96	1.05	1.05	1.05	0.86
Kidney	1.25	1.46	1.19	0.78	1.51	1.40
Bone	2.48	2.36	2.82**	2.04	3.51	1.37
Coronary heart disease	0.90*	0.94	0.92*	0.87*	1.04	0.86*

NA, not applicable.
[a] The NIOSH data includes all workers even those with no exposure information.
[b] From Table 1 of Steenland et al. (2004).
[c] From Table 2 of Swaen et al. (2009).
* SMR is statistically significantly less than one at the 5% significance level.
** SMR is statistically significantly greater than one at the 5% significance level.

Table 4
Slopes of estimated cancer-specific mortality rates with respect to cumulative exposure to EO: positive and negative non-statistically significant slopes and statistically significant negative slopes.[a]

Endpoint	Males			Females	Males and females	
	NIOSH	UCC	NIOSH and UCC	NIOSH	NIOSH	NIOSH and UCC
Lymphohematopoietic tissue	+ns	−ns	+ns	−ns	+ns	+ns
Lymphoid tumors	+ns	−ns	+ns	−ns	+ns	+ns
Non-Hodgkin's lymphoma (NHL)	+ns	−ns	+ns	−ns	+ns	+ns
Multiple myeloma	−ns	**−SS**	−ns	−ns	−ns	−ns
Lymphocytic leukemia	+ns	−ns	+ns	−ns	+ns	+ns
Myeloid leukemia	−ns	−ns	−ns	−ns	**−SS**	−ns
Leukemia	+ns	+ns	+ns	**−SS**	+ns	+ns
Central nervous system	−ns	**−SS**	**−SS**	+ns	−ns	−ns
Malignant brain neoplasm	−ns	**−SS**	−ns	+ns	−ns	−ns
Breast	−ns[b]	n/a	−ns	+ns	+ns	n/a
Pancreas cancer	−ns	+ns	−ns	+ns	−ns	−ns
Stomach cancer	−ns	+ns	+ns	−ns	−ns	+ns

n/a indicates that no males in UCC study had breast cancer.
[a] A positive sign (+ns) indicates that deaths increase (but not statistically significantly) with increases in the cumulative exposure to EO while a negative sign (−ns) indicates that deaths decrease (but not statistically significantly) with increases in the cumulative exposure to EO. −SS implies that the maximum likelihood estimate (MLE) of the parameter is statistically significantly less than zero at the 5% or 1% significance level.
[b] Result is based on only one breast cancer death in male NIOSH workers.

(lagged or unlagged) at the 5% significance level. Nevertheless, we used these same models and applied EPA's (2005a) guideline quantitative risk assessment procedures to characterize excess risk for a continuous lifetime exposure to a constant environmental concentration even though the positive slopes were not statistically significant.

Table 5
Categorical analysis: quintiles of cumulative EO exposure with statistically significantly increased response rates compared to the lowest quintile.[a,b,c]

Endpoint	Males			Females	Males & Females	
	NIOSH	UCC	NIOSH & UCC	NIOSH	NIOSH	NIOSH & UCC
Lymphohematopoietic Tissue						
Lymphoid Tumors						
Non-Hodgkin's Lymphoma (NHL)						
Multiple Myeloma						
Lymphocytic Leukemia						
Myeloid Leukemia						
Leukemia						
Central Nervous System						
Malignant Brain Neoplasm						
Breast						
Pancreas Cancer						
Stomach Cancer						

[a] A shaded cell indicates a cumulative EO exposure quintile in which there was a response rate statistically significantly greater than the response rate in the lowest (first) quintile. For example, for lymphohematopoietic tissue in the NIOSH male cohort, the 5th quintile of five quintiles (i.e., the interval with the highest cumulative exposures) had a response rate that was statistically significantly greater than the response rate in the lowest quintile at the 5% significance level.
[b] Every quantile for every combination of the 12 endpoints and the six sub-cohorts was evaluated. Blank cells for an endpoint-sub-cohort combination indicate that there no quantiles with statistically significantly increased response rates compared to the lowest quantile.
[c] Although all of the statistically significant response rates occurred when there were five cumulative exposure quantiles, a few cells had less than five quantiles because there were fewer than 10 responses (fewer than two responses for each of five quantiles).

Table 6
Maximum likelihood estimate (MLE) of the EC(1/Million): MLE of the environmental concentration in ppm corresponding to an extra risk of 0.000001.[a,b]

Endpoint	Males			Females	Males and females	
	NIOSH	UCC	NIOSH and UCC	NIOSH	NIOSH	NIOSH and UCC
Lymphohematopoietic tissue	0.0006		0.0010		0.0009	0.0019
Lymphoid tumors	0.0006		0.0010		0.0008	0.0015
Non-Hodgkin's lymphoma (NHL)	0.0012		0.0017		0.0015	0.0023
Multiple myeloma						
Lymphocytic leukemia	0.0013		0.0016		0.0019	0.0024
Myeloid leukemia						
Leukemia	0.0018	0.0116	0.0023		0.0078	0.0092
Central nervous system				0.0028		
Malignant brain neoplasm				0.0019		
Breast[c]				0.0007	0.0017	0.0017
Pancreas cancer		0.0012		0.0012		
Stomach cancer		0.0011	0.0034			0.0059

[a] Environmental concentration = (240 days/365 days) × (10 m^3/20 m^3) × occupational concentration.
[b] A blank cell implies that the estimated dose–response relationship was non-increasing.
[c] There were no males in the UCC cohort with a breast cancer mortality; hence, no dose–response modeling was done for the UCC cohort. There was one male in the NIOSH male cohort who had a breast cancer mortality; hence, dose–response modeling (albeit very uncertain) was done for the NIOSH male cohort.

Table 7
Lowest effective concentration [LEC(1/Million)]: 95% lower confidence limit on the environmental concentration in ppm corresponding to an extra risk of 0.000001.[a,b]

Endpoint	Males			Females	Males and females	
	NIOSH	UCC	NIOSH and UCC	NIOSH	NIOSH	NIOSH and UCC
Lymphohematopoietic tissue	0.0003	0.0006	0.0004	0.0004	0.0004	0.0005
Lymphoid tumors	0.0003	0.0011	0.0004	0.0003	0.0004	0.0005
Non-Hodgkin's lymphoma (NHL)	0.0006	0.0007	0.0007	0.0004	0.0008	0.0009
Multiple myeloma	0.0006	0.0001	0.0008	0.0004	0.0008	0.0012
Lymphocytic leukemia	0.0007	0.0001	0.0007	0.0003	0.0009	0.0009
Myeloid leukemia	0.0002	0.0014	0.0016	0.0005	0.0008	0.0025
Leukemia	0.0006	0.0005	0.0007	0.0007	0.0007	0.0009
Central nervous system	0.0003	0.0019	0.0030	0.0003	0.0005	0.0024
Malignant brain neoplasm	0.0002	0.0011	0.0014	0.0002	0.0004	0.0013
Breast[c]	0.0047		0.0047	0.0001	0.0003	0.0003
Pancreas cancer	0.0006	0.0003	0.0007	0.0003	0.0007	0.0008
Stomach cancer	0.0010	0.0006	0.0011	0.0006	0.0014	0.0016

[a] Environmental concentration = (240 days/365 days) × (10 m^3/20 m^3) × occupational concentration.
[b] A blank cell implies that the estimated dose–response relationship was non-increasing.
[c] There were no males in the UCC cohort with a breast cancer mortality; hence, no dose–response modeling was done for the UCC cohort. There was one male in the NIOSH male cohort who had a breast cancer mortality; hence, dose–response modeling (albeit very uncertain) was done for the NIOSH male cohort.

Tables 6 and 7 show the calculated effective concentrations (ECs) and the corresponding 95% lower confidence limits (LECs), respectively, for each of the 72 combinations for an extra risk of 1/Million by age 70 years. Values in analogous tables for extra risks of 1/100,000 and 1/10,000 were approximately linearly related to those in Tables 6 and 7. The ECs and LECs are environmental concentrations in ppm. For brevity, tabled values are for models without lags. The ECs and LECs incorporate the EPA (2005b) guideline's default age-dependent adjustment factors (ADAFs) and computational procedures for age-dependent cumulative exposures (see also Sielken and Valdez-Flores, 2009a). Tabled values are for mortality and do not attempt to calculate extra risks for incidence using mortality data and incorrect formulas (see also Sielken and Valdez-Flores, 2009b).

For regulatory purposes, it is important for ECs or, more generally, points of departure (PoDs), to be well within the range of observed exposures. Table 1 shows the distributions of the observed cumulative EO exposures (ppm-days) at the end of follow up among the NIOSH females, NIOSH males, and UCC males. Table S12 in Supplemental materials shows the corresponding general location of the estimated ECs within these observed distributions. Even for extra risks as low as 1/Million, the average ECs correspond to occupational exposures that are well within the range of observed worker exposures (>10th percentile for NIOSH males or females and >2.5th percentile for UCC males). This means that, for these data, a 1/Million extra risk is an appropriate risk level for a PoD. Furthermore, even though a "unit risk" can be calculated (specifically, unit risk = (1/Million)/[EC(1/Million)]), no low-dose extrapolation is necessary to characterize exposures with extra risks down to a *de minimis* level of 1/Million.

Although excess risks are sometimes calculated for greater than 70 years (e.g., 85 years), the authors do not believe that this is appropriate for these data. The estimated exposure–response models are based on worker exposures and not older age exposures; hence, calculating extra risks through age 85 years involves an extrapolation of the fitted models beyond the range of the data upon which they are based. Furthermore, this would not be a trivial extrapolation of the proportional hazards models because the background rates are much higher beyond age 70 than below age 70. For example, the US lymphohematopoietic (LH) cancer mortality rate at age 85 is approximately 2.5 times greater than that at age 70. There is no assurance that the exposure-dependent multiplier estimated for lower ages and lower background rates would be applicable to higher ages and much higher background rates. Extending the extra risk calculation to age 85, as was done in EPA 2006, involves considerable uncertainty and is scientifically unjustified.

Table 7 shows that the statistical procedures generating the LECs are insensitive to the observed data and the observed shape of the dose–response relationship (insensitive in the sense that

even those endpoint and sub-cohort combinations with negative estimates of the slope have LECs similar to the LECs for endpoint and sub-cohorts combinations with positive estimates of the slope). The LECs are roughly the same value regardless of the magnitude of the estimated slope and regardless of whether that slope is positive or negative. (Table 4 shows whether a slope is positive or negative; Table S9 in Supplemental materials lists the slope values.) Hence, the authors believe that LECs are a poor basis for risk-management decisions for EO and have focused on ECs herein.

4. Discussion

4.1. Appropriateness of pooled analysis

All of the Cox regression results included adjustments for potential heterogeneity among studies and/or across sexes. The data were stratified by study, sex, and race where applicable, and the background hazard rates were allowed to differ by stratum during the estimation of a common slope across strata.

Potential heterogeneity between dose–response models of different studies and pooled studies was tested using DerSimonian and Laird's Q Test (also known as Cochran's Test) which found no statistically significant differences at the 5% significance level (Cochran, 1954; DerSimonian and Laird, 1986; Takkouche et al., 1999). Because we had the individual worker data available and not just the summary results of the modeling, we also tested for potential heterogeneity among dose–response models of different studies using the more powerful likelihood ratio tests. Although there were some statistically significant differences among the endpoints with negative slopes using the likelihood ratio tests, there were no statistically significant heterogeneity among dose–response models for different studies for the endpoints with positive slopes.

Using likelihood ratio tests, there were statistically significant differences between dose–response models for different sexes for six endpoints (LH, lymphoid tumors, NHL, myeloid leukemia, CNS, and malignant brain neoplasms). In the NIOSH study, either both males and females had negative estimated slopes or one sex had a positive slope and the other sex had a negative slope (Table 4). Thus, it seems to be inappropriate to characterize the risks for females based on the analysis of males and vice versa. If an inference is to be made for both males and females combined, then the PoDs based on males and females combined and adjusted for differences between sexes seems most appropriate.

The NIOSH and UCC studies defined the cause of death categories similarly and both studies included exposure estimates at the individual worker level. This and the steps taken to account for potential confounding make it reasonable to use the PoDs based on the data pooled across studies for risk assessment.

As always, for any epidemiological study, if there is an underlying exposure–response relationship, random misclassification due to errors in exposure assessment, which can diminish risk estimates, is a possibility. However, because the estimated exposure–response relationships are being used to estimate extra cancer risk, despite the lack of statistical significance of the slopes and the absence of any pattern of increase with increasing cumulative EO exposure, any concern about that exposure uncertainty masking effects is reduced.

4.2. Comparison with Steenland et al. (2004) results for the NIOSH cohort

Steenland et al. conducted Cox regressions for breast cancer, LH cancers, and "lymphoid" cancers using a variety of exposure metrics (duration, average, maximum, cumulative, and log cumulative exposure) and both continuous and categorical exposure variables. For each of these combinations, a variety of lags were also examined (no lag, 5, 10, 15, 20 years). In Steenland et al. (2004), the only dose–response models that were reported to have statistically significant positive slopes for the given exposure metric were

(1) LH cancer mortality: males, log cumulative exposure model, and 15 year lag.
(2) Lymphoid cancer mortality: males, log cumulative exposure model, and 15 year lag.
(3) Breast cancer mortality: log cumulative exposure model and 20 year lag.

No results for the standard Cox proportional hazards model (i.e., the model with the logarithm of the hazard being a linear function of the cumulative EO exposure (either lagged or unlagged)) were reported as statistically significant.

In categorical analyses, Steenland et al. (2004) reported statistically significant increases for the same three endpoints but only in the highest exposure category.

The modeling results herein for the NIOSH cohort only partially agree with those presented by Steenland et al. (2004). They agree that there are no statistically significant increases in cancer mortality with cumulative exposure to EO using either lagged or unlagged data and the standard Cox proportional hazard model. The results also agree in the sense that for the endpoints for which Steenland et al. found increases (or decreases) we also found increases (or decreases) although the numerical values were slightly different.

The only "statistically significant" positive trends reported by Steenland et al. using Cox regression were not based on the standard Cox proportional hazard model but rather were based on a log cumulative exposure model which we do not believe is an appropriate model (see Section 4.3). Furthermore, the three "statistically significant" positive trends reported by Steenland et al. (i.e., for LH, lymphoid, and breast cancer) were for lagged exposures and are not statistically significant when statistical significance is evaluated using two degrees of freedom (one for the estimated slope parameter and one for the estimated lag). (We believe that Steenland et al. incorrectly used only one degree of freedom in their evaluation of statistical significance. Steenland et al. (2004) state that "...(5, 10, 15, and 20 year lags were tried)" and "In the results we present only the lagged model with the best fit to the data, as judged by the likelihood ratio test". As illustrated in Table S10 in Supplemental materials, the value of the likelihood used in the likelihood ratio test depends on both the lag and the slope. Because of this dependence and because both the lag and the slope are found in maximum likelihood searches and not just the slope, statistical significance should be evaluated using two degrees of freedom.)

As noted above, in Steenland et al. (2004), the three dose–response models that were reported to have statistically significant positive slopes involved lags. Table S10 in Supplemental materials shows the effect of different lags on the standard Cox proportional hazards model for these three endpoints. Table S10 shows the maximum likelihood estimate of the slope parameter, the standard error, and the deviance for each of the three endpoints and each lag period (0, 5, ..., 30 years). The results in Table S10 indicate that models with 0-lag exposures fit the LH cancer and lymphoid tumors better (i.e., have smaller deviances) than the models with cumulative EO exposure lagged 5, 10, ..., 30 years. Table S10 also shows that the models with lagged exposures fit the breast cancer data better than the model with 0-lag exposures. However, the improvements in the fit (decrease in the deviance) of the models with lagged exposures for breast cancer mortality are not statistically significant at the 5% significance level.

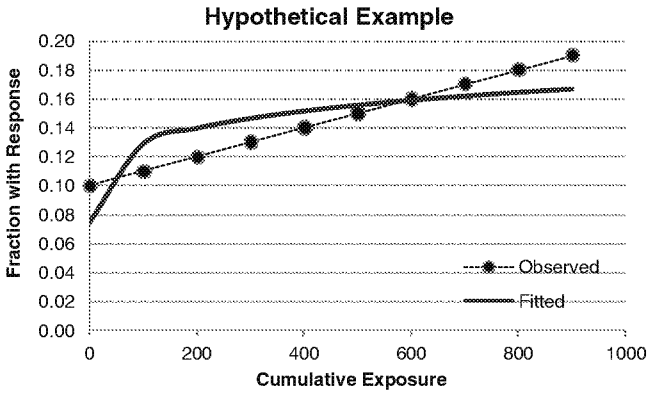

Fig. 1. Inappropriate supralinear fit when the observed data follow a linear relationship with cumulative exposure and there are equal numbers of observed person-years in each of 10 exposure intervals.

4.3. Inappropriateness of log cumulative exposure models

The "log cumulative exposure" model applied in Steenland et al. (2003, 2004) involves more than just a change in dose scale. Our concerns with the log cumulative exposure model are with the model itself and not necessarily just its use with respect to EO. Our primary concerns are (1) inappropriate supralinear fits when the observed data follow a linear or sublinear relationship with cumulative exposure; (2) the biological plausibility of supralinear models with either infinite slopes at zero or slopes at very low doses that are much greater than the slopes at slightly larger doses; (3) replacing ln(cumulative exposure) by ln(epsilon + cumulative exposure) where epsilon is arbitrarily chosen to be 1.0 or some smaller constant, and the arbitrary choice of epsilon resulting in an arbitrary choice of the slope at zero and an arbitrary choice of the low-dose behavior of the fitted model; (4) even when supralinearity is seemingly suggested by the observed data, the supralinearity may be the result of an artifact such as using an inappropriate dose metric (e.g., administered dose instead of delivered dose) or exposure misclassification; (5) the amount of forced supralinearity being arbitrarily determined by the choice of exposure scale (for example, $\mu g/m^3$-years, mg/m^3-years, or g/m^3-years); and (6) the shape of the fitted model not changing substantially with changes in the observed data especially at the low to middle exposure levels.

The Cox proportional hazards model incorporating log cumulative exposure in Steenland et al. (2004) has the following general form:

$$\text{Fraction response at cumulative exposure } X = \text{Beta0} \times \exp[\text{Beta1} \times \ln(1+X)] = \text{Beta0} \times [1+X]^{\text{Beta1}},$$

where the parameters Beta0 (the background response rate) and Beta1 (the power) are restricted to non-negative values. The form of this model forces the fitted dose–response model to be supralinear regardless of the observed response data. Fig. 1 provides a simple hypothetical example illustrating the inappropriateness of the model.

Another way to understand the forced supralinearity (Beta1 < 1.0) is as follows. The general model above can be rewritten in terms of rate ratios (RRs) as

$$(\text{Fraction response at cumulative exposure } X)/\text{Beta0} = \text{RR} = [1+X]^{\text{Beta1}}.$$

RRs are of concern when they exceed 1 but rarely are they very large, say greater than 10. However, cumulative exposure (ppm-days or ppm-years) can easily be in the 100s or the 1000s or larger. For example, the only way that an RR can be less than 10, if $X = 1000$, is for Beta1 to be substantially less than 1 (in fact, Beta1 has to be less than or equal to ln(10)/ln(1001) = 0.3333) in which case the model is forced to be supralinear.

Table S11 in Supplemental materials indicates that the fit (maximum likelihood) varies depending upon the exposure scale used in the log cumulative exposure model (i.e., ppm-days, ppm-years, ppb-days, and ppb-years). Table S11 also illustrates that the Cox proportional hazard model with the slope parameter multiplying cumulative EO exposure fits the data better than any of these four alternative log cumulative exposure models in more than 55% of the combinations of 12 endpoints and six sub-cohorts analyzed.

4.4. Comparison with EPA 2006 draft risk characterization

The EPA 2006 draft assessment shows an LEC(1/100) of 0.00608 ppm for 85 years for LH which is equivalent to 0.014 ppm for 70 years using their life-table calculator. Table S13 in Supplemental materials shows the ratio of the LECs for an extra risk of 1/100 from our Cox proportional hazards modeling to that 0.014 ppm. The average ratio ranges between 100 and 300 depending on the sub-cohort. Although the authors would disagree with the appropriateness of using an LEC(1/100) as a PoD for EO, the magnitude of the ratios in Table S13 in Supplemental materials indicate the impact of how the exposure–response modeling and excess risk characterization is carried out.

More important than the comparison of LEC(1/100)s, even the smallest EC(1/Million) in Table 6 (namely, 0.0006 ppm or 600 ppt) is more than 1500 times larger than the 2006 EPA value for the lifetime chronic EO exposure level corresponding to an increased risk of 1/Million. EPA's 2006 draft value is 0.0007 $\mu g/m^3$ which is equivalent to 0.00038 ppb (using 1 ppb EO = 1.83 $\mu g/m^3$) or approximately 0.4 ppt. The 0.0006 ppm = 0.6 ppb = 600 ppt divided by 0.4 ppt is 1500. The breakdown of the source of the difference is approximately as follows:

(1) 150-fold for our Cox proportional hazards modeling of specific data for individual workers versus EPA's draft linear modeling of summary odds ratios, and our evaluation of mortality versus EPA's evaluation of incidence.
(2) 1.6-fold for our direct evaluation of extra risks of 1/Million instead of EPA's linear extrapolation below an extra risk of 1/100.
(3) 2-fold for our use of ECs versus EPA's reliance on LECs.
(4) 2.3-fold for our assessing extra risk at age 70 instead of EPA's 85 years.
(5) 1.66-fold for correctly implementing EPA's (2005b) guidelines for ADAFs.

If these differences were independent (which they are not), they would have compounded to more than 1800 ($150 \times 1.6 \times 2 \times 2.3 \times 1.66 > 1800$).

Some of the differences between our risk characterizations and those in the EPA 2006 draft assessment are a matter of EPA policy such as the use of LECs rather than ECs and the use of 70 years instead of 85 years.

5. Conclusions

In the analyses of the NIOSH cohort, the updated UCC cohort, and the pooled studies of over 19,000 workers, none of the SMRs for any combination of the 12 cancer endpoints and six sub-cohorts analyzed were statistically significantly greater than one

including the ones of greatest previous interest: leukemia, lymphohematopoietic tissue, lymphoid tumors, NHL, and breast cancer.

The analyses presented herein fit Cox proportional hazards models with cumulative EO exposure (ppm-days) as the linear predictor to six sub-cohorts (NIOSH males, UCC males, NIOSH and UCC males, NIOSH females, NIOSH males and females, and NIOSH and UCC males and females). None of these models found statistically significant increases in any of the 12 cancer mortality types with increased cumulative EO exposure at the 5% significance level. Furthermore, if "any increases" are evaluated instead of just "statistically significant increases," then none of the endpoints had an increase for every sub-cohort. Thus, there was not even a consistent indication among the six sub-cohorts of the direction of an effect.

As in Steenland et al. (2004) and Swaen et al. (2009), the Cox proportional hazards models presented here with cumulative EO exposure treated as a continuous variable and the linear predictor indicate that there are no increasing trends in the hazard rates with increasing cumulative EO exposure. The lack of increasing trends is corroborated by categorical analyses which compared the hazard rates at different quintiles to the hazard rate at the lowest quintile.

Our Cox proportional hazards modeling based on individual worker data and cumulative EO exposure as a continuous exposure metric yields substantially different estimates of risks than EPA's models based on summary odds ratios in their 2006 draft assessment. Our modeling estimates of ECs in Table 6 corresponding to a 1-in-a-million excess environmental cancer risk are more than 1500-fold greater than the 0.4 ppt in EPA's 2006 draft IRIS risk assessment.

There is no statistically significant heterogeneity between the dose–response models of the two studies and the dose–response model of the pooled studies. Combining studies increases power. For males, the estimates of the EC(1/Million) for endpoints with a positive slope based on the pooled data across studies and including an adjustment for potential differences between studies range from approximately 0.001 to 0.003 ppm and average approximately 0.002 ppm. The same range and average applies to females in the NIOSH study. However, the endpoints with positive slopes for females have negative slopes for males, and the endpoints with positive slopes for males have negative slopes for females. An EC(1/Million) of 0.001 ppm (1 ppb or 1.83 $\mu g/m^3$) corresponds to a potency value of approximately 5×10^{-7} per $\mu g/m^3$.

Because the statistical procedures generating the LECs are insensitive to the observed data and the observed shape of the dose–response relationship, and because the estimates of the EC (1/Million) are based on human data and are well within the heart of the observed epidemiological exposure data, the EC (1/Million), ranging between 0.001 and 0.003 ppm, is an appropriate point of departure for risk characterization of EO.

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The epidemiological data for the updated UCC study were obtained under a November 19, 2008, confidentiality agreement between Union Carbide Corporation and Sielken & Associates Consulting, Inc.

Dr. Sielken gave a related presentation entitled "Use of Pooled Epidemiology Data in Quantitative Risk Assessment" at the Toxicology Forum on July 15, 2009.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.yrtph.2009.10.001.

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Exhibit P

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REVIEW

Ethylene oxide and risk of lympho-hematopoietic cancer and breast cancer: a systematic literature review and meta-analysis

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Abstract

Purpose To conduct a systematic literature review and meta-analysis of studies of lympho-hematopoietic cancers (LHC) and breast cancer risk among persons occupationally exposed to ethylene oxide (EO).

Methods We performed a literature search for articles available in PubMed and Web of Science databases to identify literature and subsequently systematically searched the reference lists of identified studies, published review papers and meta-analyses, as well as relevant government or regulatory documents. We qualitatively reviewed 30 studies and conducted meta-analyses on 13 studies. Pooled risk estimates were calculated using random effects models, stratifying by occupational group, cancer type and decade of publication.

Results The overall meta-relative risks (meta-RRs) for LHC and breast cancer, respectively, were 1.48 (95% CI 1.07–2.05) and 0.97 (95% CI 0.80–1.18). The meta-RR's for LHC among EO production and EO sterilization workers were 1.46 (95% CI 0.85–2.50) and 1.07 (95% CI 0.87–1.30), respectively. We observed higher risks of LHC in the earlier published studies, compared to the later studies, and the meta-RR's for the 1980s, 1990s, 2000s, and the 2010s, respectively, were 3.87 (95% CI 1.87–8.01), 1.38 (95% CI 0.85–2.25), 1.05 (95% CI 0.84–1.31), and 1.19 (95% CI 0.80–1.77).

Conclusions The most informative epidemiology studies, which were published in the 2000s and 2010s, do not support the conclusion that exposure to EO is associated with an increased risk of LHC or breast cancer.

Keywords Epidemiology · Ethylene oxide · Occupational exposure · Meta-analysis · Lymphohematopoietic cancers · Breast cancer

Introduction

Ethylene oxide (EO, CAS no.: 75-21-8) is a highly reactive chemical produced in large volumes. EO is used primarily as an intermediate in the production of several industrial chemicals, and derivatives of EO are commonly used in several industries, including plastics, polyester fibers, detergents and ethylene glycol antifreeze. EO is also used as a fumigant or insecticide for use in certain agricultural products and as a sterilant for medical equipment and supplies. A very small proportion (0.05%) of the annual production of EO is used as a sterilizing agent or fumigant or insecticide (Dever et al. 2004).

Two primary sources of occupational exposure to EO are from production facilities (via the older chlorohydrin process or the direct oxidation process) and sterilization operations. Workers involved in the sterilization of medical equipment and in the direct oxidation process are predominately exposed to EO. Through the chlorohydrin method of EO production, exposure may be: (1) solely to EO (and the raw material ethylene chlorohydrin) if conducted in a separate unit from the one producing ethylene chlorohydrin, or (2) to EO and associated chemicals if production of ethylene chlorohydrin and EO occurs in the same unit (NTP 2015).

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The current permissible exposure limit for EO is an 8-h time-weighted average (8-h TWA) of 1 ppm (OSHA 2018).

The National Toxicology Program (NTP) classifies EO as *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans, including epidemiological studies and studies on mechanisms of carcinogenesis (NTP 2015). Notably, NTP's definition of *sufficient evidence of carcinogenicity from studies in humans* groups together traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question (NTP 2016).

Epidemiological studies, reviews, and evaluations of the carcinogenicity of EO made by the US Environmental Protection Agency (EPA) and the International Agency for Research on Cancer (IARC) note the inconsistency between the toxicological and epidemiological evidence. IARC's (2008) classification of EO as carcinogenic in humans (Group 1) was based on a combination of mechanistic data and sufficient evidence for carcinogenicity in experimental animals, but the evidence for carcinogenicity in humans was assessed as limited (IARC 2008). At the 2010 EO Working Group meeting, IARC reaffirmed the Group 1 classification for EO via: (1) limited evidence in humans for a causal association of EO with lympho-hematopoietic cancers (LHCs) (specifically lymphoid tumors, i.e., non-Hodgkin lymphoma (NHL), multiple myeloma and chronic lymphocytic leukemia), and breast cancer; (2) sufficient evidence of carcinogenicity in experimental animals, and (3) strong evidence of a genotoxic mechanism (IARC 2012).

The EPA's Integrated Risk Information System (IRIS) final report, Evaluation of the Inhalation Carcinogenicity of Ethylene Oxide, characterized EO as carcinogenic by the inhalation route of exposures based on the "total weight of the evidence," including: (1) "strong, but less than conclusive on its own, epidemiological evidence of lympho-hematopoietic cancers and breast cancer" in EO exposed workers; (2) "extensive evidence of carcinogenicity in laboratory animals, including LHCs in rats and mice and mammary carcinomas in mice following inhalation exposure"; (3) "clear evidence that EO is genotoxic and sufficient weight of evidence to support a mutagenic mode of action for EO carcinogenicity", and (4) "strong evidence that the key precursor events are anticipated to occur in humans and progress to tumors, including evidence of chromosome damage in humans exposed to EO" (USEPA 2016, p. 1–1, 1–2). The focus of the IRIS summary evaluation was on a specific subset of the epidemiological literature, and no attempt was made to evaluate the epidemiological evidence collectively. Furthermore, a peer-reviewed summary of the IRIS evaluation considered the observations of LHC in both males and females as well as female breast cancer to be the strongest evidence of EO's carcinogenicity in humans (Jinot et al. 2018).

The aim of the current systematic review and meta-analysis is to provide an evaluation of the available epidemiological evidence regarding the risk of LHCs and breast cancer as a result of occupational exposure to EO, and to determine whether the epidemiological evidence is supportive of a causal association.

Methods

Literature search

We conducted this study using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Moher et al. 2009) and the Meta-analysis of Observational Studies in Epidemiology (Stroup et al. 2000) guidelines. Two systematic literature searches were conducted using the National Center for Biotechnology Information's (NCBI) PubMed and the Institute for Scientific Information's Web of Science search engines to identify published articles available from 1946 to March 2018. The following operators were used for our literature search: (ethylene oxide) AND (cancer epidemiology). Additionally, in order to identify relevant articles that may not have been captured in the primary literature search, all references in the EO evaluation by IARC (2012) were obtained and the bibliographies of all articles identified in our literature review were systematically searched. All abstracts and articles were reviewed by at least two authors to determine if the inclusion criteria were met.

Studies were selected for the meta-analysis based on the following criteria:

1. Only studies published in English were considered for inclusion.
2. Human subject epidemiological studies (case–control and cohort studies) were considered for inclusion and descriptive epidemiological studies (case reports and case series) were excluded.
3. The health endpoint(s) of interest were defined as LHC or breast cancer.
4. Only occupational exposures to EO occurring during the production or manufacturing of EO or the use of EO during sterilization processes were considered for inclusion.
5. For any exposure group assessed multiple times, only the most recent evaluation with the longest follow-up time was included in the meta-analysis.
6. Studies that reported effect estimates or provided enough information to calculate an effect estimate were considered for inclusion.

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The following data were extracted for all studies that met the aforementioned inclusion criteria: first author, publication year, study design, study location, cancer type [all LHC combined, LHC subcategories (including myeloma, leukemia, NHL and Hodgkin's disease) or breast cancer], occupational group (EO production vs. EO sterilization), sex of the exposed subjects, number of cases, and effect estimate [odds ratio (OR), risk ratio (RR), standardized incidence ratio (SIR), or standardized mortality ratio (SMR)] and corresponding confidence intervals (CIs).

Meta-analysis

We performed meta-analyses to calculate pooled effect estimates, stratifying for: (1) type of cancer, (2) occupational groups, (3) type of cancer within occupational groups, and (4) decade of publication. Four of the studies that met our inclusion criteria did not provide effect estimates for all of the endpoints of interest, therefore, we manually calculated crude (unadjusted) effect estimates and/or corresponding confidence intervals (CIs) using the data provided (Hogstedt 1988; Norman et al. 1995; Olsen et al. 1997; Steenland et al. 2004). The appendix provides technical details of the data extraction and calculations performed to generate effect estimates for the aforementioned studies. Additionally, in order to reflect the improved quality and informativeness of recently published studies, we conducted time period analyses that stratified overall effect estimates for all lympho-hematopoietic cancers (all LHC) by the four decades of publication (1980s, 1990s, 2000s, 2010s). Detailed decade of publication analyses were not performed for the individual LHC subcategories or for breast cancer due to the limited number of effect estimates. In our decade of publication analysis for all LHC, we included in the respective period of publication the earlier reports of studies that were subsequently updated and published in later decades. If there was a cohort with two studies in a given decade, the study with the longest follow-up and/or the larger case ascertainment was chosen for that decade. We also included in the respective decade of publication only the updated findings of studies that were published in previous decades. This was done by subtracting out the observed and expected numbers of deaths or cases that were reported in the earlier updates and computing a revised risk estimate (SMR or SIR).

Upon extraction or derivation of effect estimates and/or CIs, fixed effects models were performed on the aforementioned stratifications and the I^2 statistic was used to assess the potential for heterogeneity. Heterogeneity is defined as variation in study results greater than what is expected by chance and exists when the true effects being evaluated differ between studies (Higgins and Thompson 2002; Rothman et al. 2008). Significant heterogeneity was defined as an $I^2 > 75\%$ and a p value of < 0.05; borderline heterogeneity was defined as an I^2 between 25 and 75% and a p value of 0.05–0.20; and homogeneity was defined as an $I^2 < 25\%$ and a p value of > 0.20 (Higgins et al. 2003; Higgins and Thompson 2002). If the I^2 statistic was rejected ($p < 0.05$), DerSimonian and Laird random effects models were then fit to determine an overall effect estimate for EO exposure (DerSimonian and Laird 1986; Elwood 2007a, b). The meta-analyses results are reported as a meta-relative risk (meta-RR), with the corresponding 95% CIs.

Begg's rank correlation method and Egger's weighted regression method were utilized to assess the potential for publication bias (Begg and Mazumdar 1994; Egger et al. 1997). Additionally, funnel plots were generated to visually evaluate the potential for bias by plotting all LHC categories by decade of publication effect estimates on a log scale against the standard error, which was used as a measure of study size. All statistical analyses were performed using StataMP 14 (StataCorp LP, College Station, TX, USA).

Results

Literature search

The PubMed and Web of Science literature searches, unpublished data, as well as the references from the IARC monographs resulted in 106 unique articles to consider for the evaluation of EO exposure and cancer (Fig. 1). Ninety-five studies were excluded from the meta-analysis because they were: review papers or commentaries ($n = 22$), the predominant exposures were not specific to EO ($n = 19$), focused on biomarker endpoints ($n = 17$), the health outcomes were not LHC or breast cancer ($n = 8$), not epidemiological in nature ($n = 14$), there was insufficient information to estimate risk ($n = 1$), or the study populations had been evaluated multiple times ($n = 14$). An additional analysis conducted by Divine (1990) was identified through Teta et al.'s (1999) previously published EO meta-analysis. Although this study was unpublished, we acquired it from Dr. Teta for inclusion in the updated review and meta-analysis presented here. Overall, 13 studies met the inclusion criteria, of which four studies reported effect estimates for both LHC and breast cancer (Norman et al. 1995; Coggon et al. 2004; Steenland et al. 2004; Mikoczy et al. 2011), eight studies reported effect estimates for only LHCs (Hogstedt 1988; Divine 1990; Kiesselbach et al. 1990; Bisanti et al. 1993; Swaen et al. 1996, 2009; Olsen et al. 1997; Kiran et al. 2010), and one study reported effect estimates only for breast cancer (Steenland et al. 2003). Of note, studies that reported zero cases for a respective health outcome were not included in the statistical portion of the meta-analysis.

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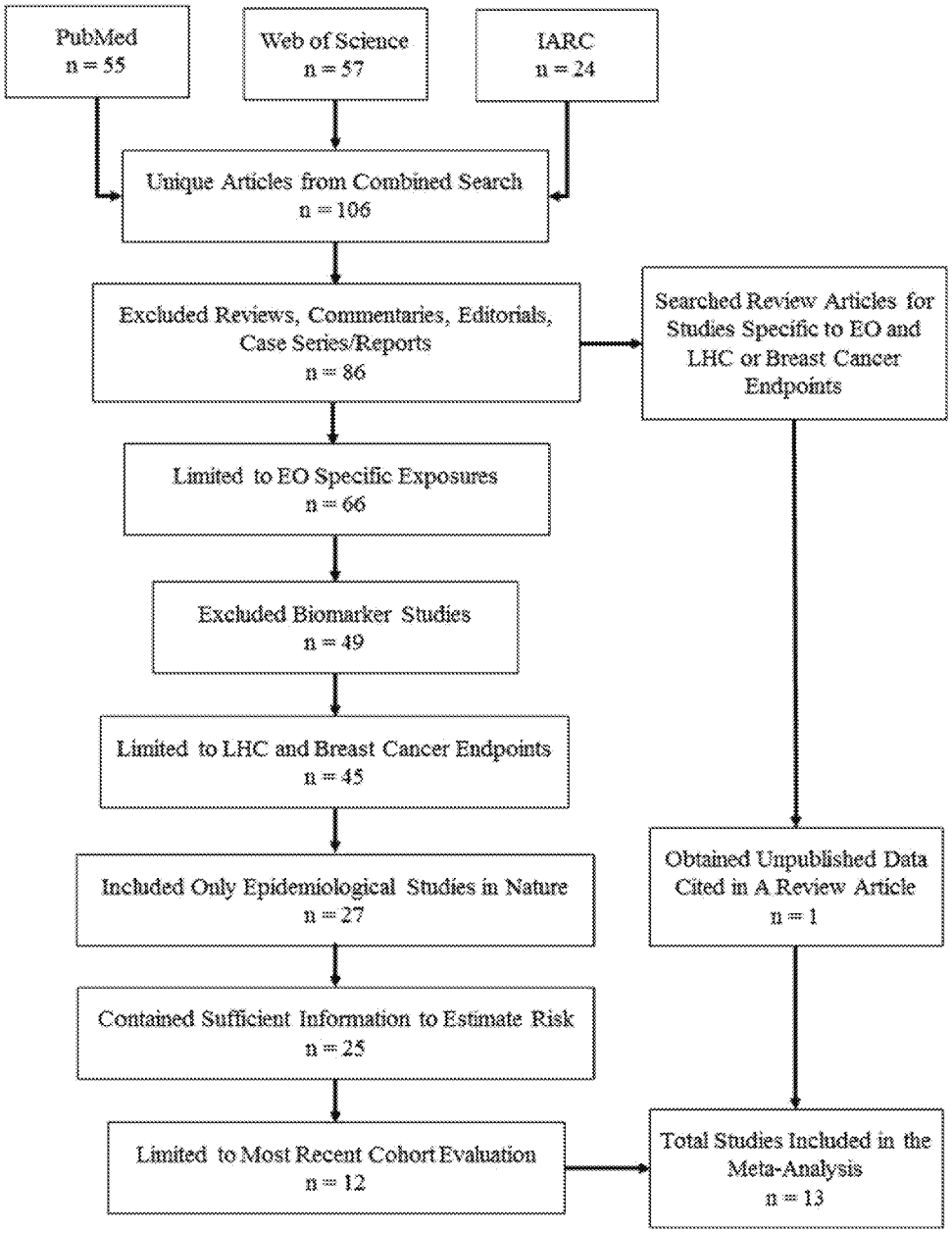

Fig. 1 Flow diagram of studies included in the meta-analysis

Qualitative evaluation of the epidemiological evidence

As specified by our inclusion criteria, the current analysis is focused on occupational exposures to EO and health outcomes of LHC and breast cancer. Many of the studies reviewed here provided data on EO exposure and cancers from other sites (e.g., stomach, brain, pancreas); however, the data were generally sparse and provided no consistent evidence of an association with EO exposure for any cancer site. IARC (

Lympho-hematopoietic cancers

Prompted by the earlier reports of EO mutagenicity and genotoxicity (Ehrenberg and Gustafsson

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Table 1 Summary of key characteristics, results, and methodological limitations of studies of the risk of lympho-hematopoietic cancer and breast cancer from occupational exposure to ethylene oxide in production and sterilization industries

Study	LHCs	Breast cancer	Methodological limitations[a]							
	Total number of subjects (sex)	Total number of subjects (sex)	Small cohort size < 5000 or no. cases < 100	< 10 total observed cases/ deaths for some outcome categories	Insufficient cohort follow-up (< 90%) or case–control participation (< 60%)	Low EO exposures[b]	Lack of individual EO exposure data	Lack of quantitative exposure–response analysis	Presence of co-exposures	Lack of latency or lagged exposure analysis
Hogstedt (1988)	709 (539 M; 170 F)	NA	●	●	?	○	●	●	●	●
Divine (1990)	767 (M)	NA	●	●	○	●	●	●	?	●
Kiesselbach et al. (1990)	2658 (M)	NA	●	●	○	?	●	●	●	●
Bisanti et al. (1993)	1971 (M)	NA	●	●	○	?	●	●	●	o
Norman et al. (1995)	1132 (204 M; 928 F)	1132 (204 M; 928 F)	●	●	●	○	●	●	○	●
Swaen et al. (1996)	10 cases (M) 200 controls (M)	NA	●	○	?	●	○	○	●	●
Olsen et al. (1997)	1361 (M)	NA	●	●	○	?	●	●	●	●
Steenland et al. (2003)	NA	7576 (F)	○	○	●	○	○	○	○	○
Coggon et al. (2004)	2876 (1864 M; 1012 F)	1012 (F)	●	●	○	○	●	●	●	●
Steenland et al. (2004)	18,235 (45% M; 55% F)	9908 (F)	○	○	○	○	○	○	○	○
Swaen et al. (2009)	2063 (M)	NA	●	●	○	○	○	○	●	●
Kiran et al. (2010)	2347 cases (1314 M; 1033 F) 2463 controls (1321 M; 1142 F)	NA	○	●	○	○	○	○	●	●
Mikoczy et al. (2011)	2171 (1309 M; 862 F)	2171 (1309 M; 862 F)	●	●	○	●	○	○	○	○

NA not applicable, *M* male, *F* female

[a]The cut points used for the quantitative characteristics are indicated in the column headings unless otherwise specified

[b]Low EO exposure designation for each group was determined by exposures below the current OSHA TWA limit of 1 ppm or cumulative exposures below 45 ppm-years for all exposure categories

○Absence of characteristic

●Presence of characteristic

?Unable to evaluate due to absence of reported information

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and other chemicals in a chlorohydrin production facility followed from 1961 to 1977 (Hogstedt et al. 1979b). These were later combined with a third cohort of workers exposed to EO in a direct oxidation production facility and updated through 1983 for incidence and 1985 for mortality (Hogstedt et al. 1986; Hogstedt 1988). At the hospital equipment sterilization plant, sampling for EO was conducted in 1977 and the mean estimated exposure was approximately 20 ppm (peak: not given) in the sterilization room and 2–70 ppm in the storage hall (peak, 150 ppm) (Hogstedt et al. 1986). Specific to production facility that produced EO by the chlorohydrin process, Hogstedt et al. (1979b) provided "rough estimates of exposure levels" to EO from 1941 to 1947 and from the 1950s to 1963, respectively, which were "probably below" 14 ppm[1] (peak: 722 ppm) and approximately 6–28 ppm (peak, 722 ppm). Although EO production ceased at the facility in 1963, EO was still used in manufacturing various products, and random workplace samples taken in the 1970s measured concentrations ranging from 0.6 to 6 ppm with "occasional" higher values (Hogstedt et al. 1979b). In the plant that produced EO by direct oxidation, the average 8-h TWA concentration of EO was 1–8 ppm (peak: 333–1000 ppm) from 1963 to 1976 and 0.4–2 ppm (peak: 333–1000 ppm) from 1977 to 1982 (Hogstedt et al. 1986). Although exposure to EO was calculated from air samples, the most recent follow-up of these three cohorts qualitatively evaluated EO exposure by duration of employment categories (1–9 years, ≥ 10 years, and all years) (Hogstedt 1988). The combined analysis of 709 production and sterilization workers from the three facilities revealed statistically significant elevated mortality risks for all LHC and leukemia, although no trends were observed by length of employment.

The elevated risks suggested by the first epidemiological cohort studies prompted cohort studies of EO workers in the US (Morgan et al. 1981) and Europe (Thiess et al. 1981) to be published in the early 1980s. Morgan et al. (1981), which was later updated by Divine (1990), conducted a mortality study from 1955 to 1985 of production workers with potential exposure to EO at a Texas chemical plant. The chemical plant produced EO by the chlorohydrin process from 1948 to 1964 and by direct oxidation beginning as early as 1958 (Divine 1990). An industrial hygiene survey was conducted at this plant in 1977 and all samples that were taken in production areas were less than 10 ppm EO (Morgan et al. 1981). The study authors attributed the low levels of EO throughout the plant to engineering controls and precautionary measures intended to reduce potential exposures to workers.

In the US, there have been numerous evaluations of EO-exposed workers from three Union Carbide Corporation (UCC) facilities in West Virginia (Benson and Teta 1993; Greenberg et al. 1990; Swaen et al. 2009; Teta et al. 1993). Environmental monitoring data for EO was routinely collected at in EO using/producing department at one UCC facility beginning in 1976 and subsequent exposures were < 1 ppm as an 8-h TWA, although there were measurements as high as 66 ppm (Greenberg et al. 1990; Teta et al. 1993). It was estimated that the 8-h TWA concentration of EO in the 1960s ranged from 3 to 20 ppm in direct oxidation units and that the levels were higher in the units producing EO by the chlorohydrin process (Teta et al. 1993).

In a follow-up of Greenberg et al. (1990), Benson and Teta (1993) conducted a mortality follow-up from 1940 to 1988 among a subset of 278 workers from the chlorohydrin unit who intermittently used and handled EO in small volumes. A three-fold statistically significant excess of LHC was observed but the study authors attributed this finding to by-products in the production of ethylene chlorohydrin (Benson and Teta 1993). Additionally, Teta et al. (1999) conducted a follow-up during the same time period of 1896 men employed in departments using or producing EO, excluding the chlorohydrin workers that were included in Benson and Teta (1993). This was only the second US cohort study to include EO exposure estimates for individual workers, albeit relatively crudely, along with a quantitative evaluation of EO exposure–response using both external and internal comparisons. There were not statistically significant excess of deaths observed due to any lymphatic and hematopoietic tissue cancers and there were no statistically significant trends for leukemia by cumulative duration of assignments in EO departments. Subsequently, Swaen et al. (2009) conducted an update of the cohort and a total of 2063 men who were employed between 1940 and 1980 were observed for mortality through 2003. The authors used historical measurements in comparable facilities as well as exposure monitoring data in the relevant facility to estimate individual EO exposures. Despite relatively high past EO exposures and extensive follow-up, the study authors found no elevated mortality for LHC cancers, or any indication of an exposure–response relationship with cumulative exposure to EO (Swaen et al. 2009).

Subsequently, other smaller and less informative studies were conducted in the US. For example, Norman et al. (1995) conducted a cancer incidence study of mostly females (928 vs. 204 males) employed in a medical sterilizing plant from 1974 to 1980 and observed only one case of leukemia by 1987. During this time period, EO exposure monitoring was intermittent. Three, 2-h samples were taken in 1980 and the 8-h TWA exposure to EO for sterilizer operators ranged from 50 to 200 ppm, although corrective action was taken to lower exposures and subsequent samples ranged

[1] For the purposes of consistency, values that were reported in mg/m^3 were converted to ppm, assuming that 1 ppm = 1.8 mg/m^3.

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from 5 to 20 ppm. Additionally, Olsen et al. (1997) conducted a cohort mortality study of 1361 males who worked in ethylene and propylene chlorohydrin production facilities located in Texas, Louisiana, and Michigan from 1940 to 1992. In contrast to Union Carbide, the production of these two products occurred within the EO production units at all four plants. No data were reported on exposure levels. The study authors found a small, non-statistically significant 1.29-fold excess for LHC.

Several other studies conducted in Europe were small and subject to many limitations. In the UK, Coggon et al. (2004) reported an update of an earlier cohort mortality study (Gardner et al. 1989) of 1864 male and 1012 female workers from a variety of EO exposure scenarios: three EO production facilities (two using both chlorohydrin and direct oxidation processes), one facility that used EO as an intermediate for other chemicals, and eight hospitals that used EO in sterilizing units. All of the chemical companies produced or used ethylene oxide beginning in the 1950s and the hospitals had sterilizing units since the 1960s. Industrial hygiene data were available beginning in 1977 and it was reported that subsequent 8-h TWA exposures to EO were less than 5 ppm for "almost all jobs" and less than 1 ppm "in many" jobs. Additionally, it was reported that occasional peaks of exposure occurred up to several hundred ppm as a result of operating difficulties in chemical plants and during the loading and unloading of sterilizers in hospitals. Gardner et al. (1989) believed that there were higher average EO exposures in earlier years and that peak exposures above the odor threshold of 700 ppm had been reported by manufacturers at the hospitals. Mortality was slightly increased, although not statistically significant for Hodgkin's disease and NHLs, multiple myeloma and leukemia. This study was limited by small numbers of observed deaths, lack of individual EO exposure data, presence of co-exposures and lack of latency analysis.

In Germany, Kiesselbach et al. (1990) conducted an updated cohort mortality study of 2658 males from eight chemical companies in Germany that were exposed to EO through production or maintenance activities for at least 12 months between 1928 and 1981. Some of the subjects were part of an earlier study by Thiess et al. (1981) and were exposed to numerous chemicals in addition to EO. Kiesselbach et al. (1990) found no excess risk from overall LHCs or from leukemia. However, this study was limited because exposure information was only available for 67.2% of the cohort and categorized into three qualitative levels: weak, medium and strong exposure.

A subsequent Italian cohort mortality study was conducted by Bisanti et al. (1993) of 1971 male chemical workers licensed to handle EO for at least 1 year between 1938 and 1948. There were two categories of workers: those who had a license for all toxic chemicals ($n = 1971$) and those who had a license for only EO ($n = 637$). Among the 637 workers that were only licensed to handle EO, statistically significant excess risks for the all LHCs and lymphosarcoma/reticulosarcoma were observed, while there was an increased, although non-significant, risk for leukemia (Bisanti et al. 1993). This study did not have quantitative exposure information, had insufficient follow-up time (only 4% of EO licensed workers were deceased), and it is likely that these workers had co-exposures to other carcinogenic chemicals (Bisanti et al. 1993).

Hagmar et al. (1991, 1995) assessed cancer incidence among 2170 Swedish workers (861 male, 1309 female) in two medical sterilizing plants from 1972 and 1976 to 1990. No statistically significant excesses were observed for overall LHCs or any subtypes, regardless of whether an induction latency period was applied or not. Sterilization operations began in the first plant in 1970, during which exposures were estimated to be as high as 40 ppm, and air monitoring demonstrated that exposures continuously decreased to < 0.2–0.75 ppm in 1985–1986 (Hagmar et al. 1991, 1995). In the second plant, sterilization operations began in 1964, during which estimated exposures ranged from < 0.2 to 75 ppm, although subsequent monitoring showed a continuous decrease in exposure to < 0.2–0.5 ppm in 1985 and 1986 (Hagmar et al. 1991, 1995). Although this study included EO exposure estimates for individual workers, it was limited by short follow-up time and low EO exposures among a large percentage of workers, lessening its usefulness for evaluating EO-related cancer risks.

In Belgium, Swaen et al. (1996), performed a nested case–control study of Hodgkin's disease among workers at a large chemical plant to evaluate a suspected cluster of ten cases exposed to EO between 1966 and 1992. For all subjects, occupational exposures were identified and categorized by work history and process, medical records, and industrial hygiene data. The study authors reported a statistically significant association for benzene, ammonia, sodium hydroxide, oleum and EO, but the interpretation of these findings are constrained by the exclusion of inactive workers and the presence of many other chemical exposures. Further dose–response analyses were conducted for EO but failed to provide support for a causal relationship. Into the 2000s, Kardos et al. (2003) evaluated causes of death during 1987–1999 among 299 female workers from a pediatric clinic in Hungary where EO was used as a sterilant. No individual monitoring data was available for review. One case of lymphoid leukemia was observed, although no quantitative information (i.e., leukemia-specific risk estimates or expected number of cases to calculate a risk estimate) was available regarding EO exposure risks.

Returning to the US, as part of an earlier quantitative risk assessment for EO, Teta et al. (1999) conducted an update of the meta-analysis conducted by Shore et al. (1993) that

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included leukemia and NHL findings from many of the studies reviewed above. The authors found no statistically significantly elevated meta-SMRs for these categories and no evidence of overall trends in relation to duration or intensity of EO exposure or latency.

Arguably, the most scientifically sound and informative epidemiological study of EO-related cancer risk was a NIOSH cohort mortality study that followed 18,235 employees (45% male, 55% female) at 14 facilities where EO was used to sterilize medical supplies and spices from 1987 to 1998 (Stayner et al. 1993; Steenland et al. 1991, 2004). Wong and Trent (1993) essentially published a duplication of the study conducted by Steenland et al. (1991), but with far more limitations that the initial study, and thus will not be reviewed for the purposes of this paper (Steenland and Stayner 1993). Steenland et al. (1991) reported that the average 8-h TWA exposures to EO from 1976 to 1985 were 4.3 ppm and 2.0 ppm, respectively, for sterilizer operators and for other exposed workers (i.e., production, maintenance, warehouse, and laboratory workers). Furthermore, Stayner et al. (1993) reported that the average exposure to EO for all exposed workers was 5.5 ppm and ranged from 0.05 to 77.2 ppm. In the most recent report with mortality follow-up through 1998 (Steenland et al. 2004), industrial hygiene measurements and historical data regarding process changes at the plants were used to assess the exposure of each individual worker and the categories of exposure were: > 0–1199 ppm-days; 1200–3679 ppm-days; 3680–13,499 ppm-days; and 13,500+ ppm-days. Steenland et al. (2004) found no statistically significant excesses in males or females combined for all LHCs, including Hodgkin's disease, NHL, multiple myeloma and leukemia, when analyses were conducted using no lag and a 10-year lag. The 10-year lag model resulted in a statistically significant 2.37-fold risk for NHL among males only in the highest EO exposure category (≥ 13,500 ppm-days), based on 8 deaths. Furthermore, internal analyses found statistically significant exposure–response relationships in males only between log cumulative EO exposure (using a 15-year lag) for all LHCs combined and the subcategory "lymphoid cell line tumors" (NHL, multiple myeloma and lymphocytic leukemia). No positive trends were found in males or females for the EO exposure metrics, duration of exposure, peak exposure, average exposure or cumulative exposure. The sex-specificity of the exposure–response findings, which were limited to the transformed metric log cumulative exposure, weaken the overall evidence for EO as a risk factor for LHC. This weakened evidence was also noted by the authors (Steenland et al. 2004). Notably, the NIOSH studies had none of the limitations we considered in Table 1. The relative strengths of the NIOSH studies were also noted by IARC, which gave the greatest weight to the findings of this study when assessing the balance of the epidemiological evidence on EO (IARC 2012).

As part of a quantitative risk assessment for EO, Valdez-Flores et al. (2010) combined primary data from the NIOSH (Steenland et al. 2004) and UCC cohorts (Swaen et al. 2009). In separate and combined gender-specific external mortality comparisons, the authors found no statistically significant excesses for all LHCs, including the subcategories Hodgkin's disease and NHL. Internal exposure–response analyses of LHC overall and several subtypes (lymphoid tumors, NHL, multiple myeloma, lymphocytic leukemia, myeloid leukemia and leukemia) found no positive trends relative to cumulative EO exposure with and without lags for any of six cohort/gender combinations examined. Valdez-Flores et al. (2010) also challenged Steenland et al.'s (2004) use of the log cumulative EO exposure metric describing several interpretational issues related to the apparent supra-linear exposure–response relationship resulting from the log-transformed EO exposure scale. In the present meta-analysis, Swaen et al. (2009) and Steenland et al. (2004) were used and Valdez-Flores et al. (2010) was excluded.

Two epidemiology studies of LHC in relation to EO exposure were published after the 2010 IARC evaluation (Kiran et al. 2010; Mikoczy et al. 2011), and each is associated with several methodological limitations. Kiran et al. (2010) described a population-based and hospital-based case–control study of 2347 lymphoma cases diagnosed between 1998 and 2004 and 2463 controls from six European countries [part of European EPILYMPH Study (Besson et al. 2006)]. These authors defined lymphoma (all types) according to the World Health Organization classification and found an overall, non-statistically significant 1.3-fold increased risk for persons ever exposed to EO (versus never exposed). We note that the risk estimate for lymphoma as reported by these authors for all lymphoma types was included in the presented meta-analysis for all LHCs. The highest risk, though not statistically significant, was reported for chronic lymphocytic leukemia (OR 2.0; 95% CI 0.8–4.7). Additionally, intensity and frequency of exposure to EO were categorized into unknown exposure, low exposure, medium exposure, and high exposure and then used to calculate an individual's cumulative exposure score. Subgroup analyses of lymphoma subtype by cumulative exposure found several statistically significantly elevated ORs, however interpretation is limited by the population-based and hospital-based case–control design, very low EO exposure frequency in cases/controls (1.3%/1.1%), differential case/control participation (88%/52%), small numbers of cases/controls in subgroup analyses and reliance of self-reported socio-demographic and work history data. We note that small numbers of cases and limited covariate data were limitations inherent in many of the case–control and cohort studies reviewed.

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Mikoczy et al. (2011) reported a 16-year mortality and cancer incidence update of the Hagmar et al. (1991, 1995) cohort of Swedish sterilant workers employed before 1986 and reviewed in detail above. The authors found small, non-statistically significant elevations in mortality and cancer incidence for LHC and some subtypes that decreased with additional follow-up time. Exposure–response analyses using external and internal comparisons provided no evidence of increasing LHC risk with increasing cumulative EO exposure. Although having estimates of individual worker exposures to EO and exposure–response analyses, the Mikoczy et al. (2011) study was limited by small numbers of observed cases and deaths, insufficient follow-up and relatively low cumulative EO exposures.

Breast cancer

As seen in Table 1, several previously discussed studies also provided data on the association between EO exposure and breast cancer (Coggon et al. 2004; Mikoczy et al. 2011; Norman et al. 1995; Steenland et al. 2003, 2004). The UK cohort mortality study reported by Coggon et al. (2004) found no overall excess in breast cancer; while the Norman et al. (1995) US cohort incidence study (and assuming follow-up through 1985) found a statistically significant 2.55-fold overall excess in the most recent follow-up of the cohort. The Hungarian cohort study by Kardos et al. (2003) was uninformative regarding breast cancer risks related to EO because the authors only reported three breast cancer deaths, but did not provide the expected number of deaths by cancer endpoint.

As with LHC, the most informative epidemiological study of breast cancer risk in relation to EO was the large U.S. NIOSH cohort mortality study (Steenland et al. 2004) that included a nested breast cancer incidence study of 7576 females employed in commercial EO sterilization facilities from the 1940s to the 1980s (Steenland et al. 2003). The mortality study revealed no overall excess for breast cancer, but internal exposure–response analyses found a statistically significant positive trend for breast cancer using the log of cumulative EO exposure with a 20-year lag (Steenland et al. 2004). This pattern of findings was repeated in the incidence study, which found no overall excess in breast cancer among the total cohort. However, the authors caution that due to under-ascertainment of cases the reported SIRs underestimate risk. An analysis of an internal nested case–control study of subjects with complete cancer ascertainment data found evidence of an exposure–response relationship with log cumulative EO exposure using a 15-year lag. The authors caution against over-interpreting the positive exposure–response because the trend analysis may have been biased due to increased breast cancer rates among women who were more highly exposed because of longer durations of employment. Steady employment may have led to more cancer screenings because of insurance coverage (Steenland et al. 2003). The methodological issues raised by Valdez-Flores et al. (2010) and discussed above regarding the log-transformed EO exposure scale in the mortality study also apply to the breast cancer incidence analyses.

The Mikoczy et al. (2011) study, an update of the Swedish cohort incidence study, also provides information on breast cancer in relation to EO exposure. The authors found overall deficits in breast cancer cases and deaths compared to the regional Swedish population with and without consideration of a 15-year induction period. Internal analyses of cumulative EO exposure in relation to breast cancer incidence revealed statistically significant elevated incidence rate ratios (IRRs) in the two highest categories (IRR = 2.76 and 3.55, respectively) compared to the baseline category of low-exposed workers (defined as 50% of workers with cumulative exposures less than the median). This finding led to the authors' conclusion of a positive-exposure relationship with EO and breast cancer, which in turn has been interpreted by others as lending support for a causal association (e.g., USEPA 2014).

The validity of the Mikoczy et al. (2011) finding and conclusion can be challenged, however, on the basis of several methodological issues. First, the greater than two-fold *relative* excesses in breast cancer incidence risk in the two highest cumulative EO exposure categories were ensured by an inordinately large, statistically significant 48% *deficit* in breast cancer incidence in the baseline category. The inordinately low baseline SIR for breast cancer is puzzling given that regional rates were used in the external comparisons and that there was no apparent problem with under-ascertainment of breast cancer cases. The healthy worker effect is also not a reasonable explanation for the low baseline breast cancer rate (Gridley et al. 1999). It appears that for unknown reasons, the baseline group used by Mikoczy et al. (2011) differs from the highest two cumulative EO exposure groups on factors other than EO exposure that may be related to breast cancer. Second, cumulative EO exposure levels in the Mikoczy et al. (2011) study were very low relative to both the UCC cohort (Swaen et al. 2009) and NIOSH breast cancer cohort incidence study (Steenland et al. 2003). For example, in the Mikoczy et al. (2011) study the median cumulative EO exposure values of workers in both the second and third cumulative EO exposure categories (0.17 and 0.39 ppm-years, respectively) fall well within the *lowest* non-baseline cumulative EO exposure category (> 0 to < 2.34 ppm-years) used in the NIOSH study (with no exposure lag as in Mikoczy et al. (2011). In this category, Steenland et al. (2003), using internal comparisons, found a deficit in breast cancer cases compared with the strikingly disparate, statistically significant 2.76- and 3.55-fold excesses reported by Mikoczy et al. (2011) for workers

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Table 2 Studies of occupational exposure to ethylene oxide in production and sterilization industries and the risk of lympho-hematopoietic cancer and breast cancer

Study	Study population	Previous evaluations	Exposure assessment	Deceased (%)	Cancer endpoint[a] (ICD revision: ICD code)	Cases (sex)	Exposure type	Effect estimate	95% CI
Hogstedt (1988)	Sterilizers and production workers in three industries, Sweden	Hogstedt et al. (1979a, b, 1986)	Duration of employment	12	Blood and lymphatic (ICD-8: 200-209)	9 (M + F)	Sterilization + production	SMR = 4.59	2.10–8.72[b c]
					Leukemia (ICD-8: 204-207)	7 (M + F)		SMR = 9.21	3.70–18.98[c]
Divine (1990)	Production workers at a Texas chemical plant, USA	Morgan et al. (1981)	Reviewed work histories and included jobs on production units, maintenance, QC lab, and engineers	11.2	All lymphopoietic (ICD-8: 200-209)	3 (M)	Production	SMR = 1.01	0.20–2.96[b]
					Hodgkin disease (ICD-8: 203)	3 (M)		SMR = 8.34	1.68–24.38
					Leukemia (ICD-8: 204-207)	0		SMR = 0	0–3.28[d]
					Other lymphatic tissue (ICD-8: 202, 203, 208)	0		SMR = 0	0–4.04[d]
Kiesselbach et al. (1990)	EO exposed workers at 8 chemical plants, Germany	Thiess et al. (1981)	Job task from company records	10.1	Lymphatic and hematopoietic tissue (ICD-9: 200-208)	5 (M)	Production	SMR = 1.00	0.32–2.34[b]
					Leukemia (ICD-9: 204-208)	2 (M)		SMR = 0.85	0.10–3.07
Bisanti et al. (1993)	Chemical workers licensed to handle EO and other toxic chemicals, Italy	–	Only included chemical workers licensed to handle EO	11.9	All hematopoietic (ICD-9: 200-208)	5 (M)	Production	SMR = 7.00	2.27–16.37[b]
					Leukemia–aleukemia (ICD-9: 204-208)	2 (M)		SMR = 6.50	0.79–23.49
Norman et al. (1995)	Sterilizers of medical equipment and supplies that were assembled at a New York plant, USA	–	EO was the only major process chemical used and historical records suggest widespread exposure	NA	Breast (ICD revision/codes: NR)	8 (F)	Sterilization	SMR = 2.55	1.31–4.98
					All LHC (ICD revision/codes: NR)	2 (M + F)		SMR = 3.19	0.48–21.22[b e]
					Multiple myeloma (ICD revision/codes: NR)	1 (F)		SMR = 5.56	0.14–30.95[c]
					Leukemia (ICD revision/codes: NR)	1 (M + F)		SMR = 1.85	0.05–10.32[c]

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Table 2 (continued)

Study	Study population	Previous evaluations	Exposure assessment	Deceased (%)	Cancer endpoint[a] (ICD revision: ICD code)	Cases (sex)	Exposure type	Effect estimate	95% CI
Swaen et al. (1996)	EO exposed workers at a large chemical production plant, Belgium	–	Industrial hygiene data from the facility, work histories, and processing categories	NA	Hodgkin's disease (ICD revision NR: 201)	3 (M)	Production	OR = 8.5	1.4–39.9
Olsen et al. (1997)	Production workers (chlorohydrin process) from four production plants, USA	–	NR	22	Lymphopoietic and hematopoietic (ICD-8: 200-209)	10 (M)	Production	SMR = 1.29	0.62–2.38[b]
					Hodgkin's disease (ICD-8: 201)	2 (M)		SMR = 2.86	0.35–10.32[c]
					Leukemia and aleukemia (ICD-8: 204-207)	2 (M)		SMR = 0.67	0.08–2.42
Steenland et al.—incidence (2003)	Sterilization workers at 14 plants, USA	–	IH measurements and historical data regarding process changes	18	Breast (ICD-9: 174, 233)	230 (F)	Sterilization	RR = 0.89	0.78–1.01
Coggon et al. (2004)	Sterilization workers at eight hospitals and production workers at three manufacturing facilities, England and Wales	Gardner et al. (1989)	Environmental and personal monitoring with TWA exposure < 5 ppm for almost all jobs, peaks up to several hundred ppm	19.6	Breast (ICD-9: 174)	11 (F)	Sterilization	SMR = 0.84	0.42–1.51
					All LHC (ICD-9: 200-208)	12 (M + F)	Production	SMR = 1.53	0.79–2.95[b e]
						5 (M + F)	Sterilization	SMR = 1.51	0.51–4.53[b e]
						17 (M + F)	All	SMR = 1.33	0.78–2.27[b e]
					Non-Hodgkin's lymphoma (ICD-9: 200, 202)	4 (M + F)	Production	SMR = 1.38	0.38–3.53
						3 (M + F)	Sterilization	SMR = 1.59	0.33–4.66
						7 (M + F)	All	SMR = 1.46	0.59–3.02
					Hodgkin's disease (ICD-9: 201)	1 (M + F)	Production	SMR = 1.40	0.04–7.82
						1 (M + F)	Sterilization	SMR = 2.98	0.08–16.62
						2 (M + F)	All	SMR = 1.91	0.23–6.89
					Multiple myeloma (ICD-9: 203.0)	3 (M + F)	Production	SMR = 2.03	0.42–5.94
						0	Sterilization	SMR = 0	0–3.57[d]
						3 (M + F)	All	SMR = 1.20	0.25–3.49
					Leukemia (ICD-9: 204-208)	4 (M + F)	Production	SMR = 1.41	0.39–3.62
						1 (M + F)	Sterilization	SMR = 0.55	0.01–3.06
						5 (M + F)	All	SMR = 1.08	0.35–2.51

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Table 2 (continued)

Study	Study population	Previous evaluations	Exposure assessment	Deceased (%)	Cancer endpoint[a] (ICD revision: ICD code)	Cases (sex)	Exposure type	Effect estimate	95% CI
Steenland et al.—mortality (2004)	Sterilization workers at 14 plants, USA	Steenland et al. (1991) and Stayner et al. (1993)	IH measurements and historical data regarding process changes	15.6	Breast (ICD-9: 174)	103 (F)	Sterilization	SMR = 0.99	0.84–1.17
					All hematopoietic (ICD-9: 200-208)	79 (M + F)		SMR = 1.00	0.79–1.24[b]
					Non-Hodgkin's lymphoma (ICD-9: 200, 202)	31 (M + F)		SMR = 1.00	0.72–1.35
					Hodgkin's disease (ICD-9: 201)	6 (M + F)		SMR = 1.24	0.53–2.43
					Myeloma (ICD-9: 203)	13 (M + F)		SMR = 0.92	0.51–1.53[c]
					Leukemia (ICD-9: 204-208)	29 (M + F)		SMR = 0.99	0.71–1.36
Swaen et al. (2009)	Workers at EO production plants, USA	Greenberg et al. (1990) and Teta et al. (1993)	Exposure estimates were based on environmental monitoring data	50.8	All lymphatic and hematopoietic (ICD revision/codes: NR)	27 (M)	Production	SMR = 0.89	0.59–1.29[b]
					Non-Hodgkin lymphoma (ICD revision/codes: NR)	12 (M)		SMR = 1.05	0.54–1.83
					Hodgkin disease (ICD revision/codes: NR)	0		SMR = 0	0–2.22[d]
					Leukemia (ICD revision/codes: NR)	11 (M)		SMR = 0.93	0.47–1.67
Kiran et al. (2010)	EO exposed workers in 6 European countries (Czech Republic, France, Germany, Italy, Ireland, Spain)	–	Exposures were assessed retrospectively by industrial hygienists based on information obtained survey responses	NA	Lymphoma (ICD revision/codes: NR)	31 (M + F)	NR	OR = 1.3	0.7–2.1[b]

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Table 2 (continued)

Study	Study population	Previous evaluations	Exposure assessment	Deceased (%)	Cancer endpoint[a] (ICD revision: ICD code)	Cases (sex)	Exposure type	Effect estimate	95% CI
Mikoczy et al. (2011)	Workers at two disposable medical equipment production facilities, Sweden	Hagmar et al. (1991, 1995)	Industrial hygiene data and work histories were used to develop job specific exposure matrices	7.9	Breast (ICD-7: 170)	41 (F)	Sterilization	SIR = 0.81	0.58–1.09
					Lympho-hematopoietic (ICD-7: 200-209)	18 (M + F)		SIR = 1.25	0.74–1.98[b]
					Non-Hodgkin's lymphoma (ICD-7: 200, 202)	9 (M + F)		SIR = 1.44	0.66–2.73
					Hodgkin's lymphoma (ICD-7: 201)	1 (M + F)		SIR = 0.76	0.02–4.25
					Multiple myeloma (ICD-7: 203)	2 (M + F)		SIR = 0.96	0.12–3.47
					Leukemia (ICD-7: 204-205)	5 (M + F)		SIR = 1.40	0.45–3.26

NA not applicable, *NR* not reported in text, *M* male, *F* female, *ICD* International Classification of Diseases, *CI* confidence interval, *SMR* standardized mortality ratio, *SIR* standardized incidence ratio, *OR* odds ratio, *RR* relative risk

[a]Cancer endpoint as described in each respective study

[b]Effect estimate used in the "all LHC" analysis

[c]Crude effect estimates and/or 95% CIs were calculated from the raw data provided in the study. Technical details provided in online supplementary appendix

[d]Cancer endpoints that had a reported number of 0 cases were included in the table for reference but were not included in the meta-analysis

[e]Effect estimates were combined together using DerSimonian and Laird random effects models

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Table 3 Random effects analysis by cancer type and occupational group

Cancer type	All effect estimates			EO production/use[a]			EO sterilization[a]		
	N^b	Meta-RR	95% CI	N^b	Meta-RR	95% CI	N^b	Meta-RR	95% CI
Breast	5	0.97	0.80–1.18	–	–	–	5	0.97	0.80–1.18
All LHC	11[c d]	1.48	1.07–2.05	6[d]	1.46	0.85–2.50	4[d]	1.07	0.87–1.30
Leukemia	9[d]	1.62	0.87–3.01	5[d]	1.21	0.66–2.21	4[d]	1.03	0.76–1.39
NHL	4[d]	1.09	0.85–1.40	2[d]	1.12	0.65–1.90	3[d]	1.08	0.82–1.43
Myeloma	4[d]	1.01	0.63–1.63	1[d e]	2.03	0.42–5.94	3	0.99	0.59–1.65
Hodgkin's disease	6[d]	2.76	1.21–6.27	4[d]	5.36	2.31–12.44	3[d]	1.27	0.63–2.58

N number of studies, *Meta-RR* meta-relative risk, *CI* confidence interval, *LHC* lympho-hematopoietic cancer

[a]With the exception of the effect estimates reported in Kiran et al. (2010) and Hogstedt (1988), the effect estimates could be classified by occupational group

[b]Total number of effect estimates per category

[c]Nine studies provided effect estimates for all LHC combined. In two instances (Coggon et al. 2004; Norman et al. 1995), effect estimates for individual blood and lymphatic malignancies were combined using DerSimonian and Laird random effects models to determine a combined LHC effect estimate

[d]Coggon et al. (2004) provided an overall effect estimate for workers from both chemical manufacturing and sterilization facilities, which was used in the overall analysis, as well as effect estimates by occupational group, which was used in the occupational group sub-analysis

[e]As reported, Coggon et al. (2004) was the sole study for this category

with similar levels of cumulative EO exposure. This marked contrast provides further support that the non-baseline IRRs reported by Mikoczy et al. (2011) were inflated by the inordinately low baseline breast cancer rates.

Meta-analysis

Thirteen studies were identified for use in the meta-analysis of LHC and breast cancer, which constituted 11 effect estimates categorized as all LHC, nine effect estimates for leukemia, four effect estimates for NHL, four effect estimates for myeloma, six effect estimates for Hodgkin's disease, and five effect estimates for breast cancer (Table 2). Analysis by cancer type demonstrated significant heterogeneity for leukemia ($I^2 = 74.6\%$; p value < 0.05), breast cancer ($I^2 = 62.2\%$; p value < 0.05), and all LHC ($I^2 = 68.9\%$; p value < 0.05), borderline heterogeneity for Hodgkin's disease ($I^2 = 45.6\%$; p value $= 0.101$), and homogeneity for myeloma ($I^2 = 0\%$; p value $= 0.634$) and NHL ($I^2 = 0\%$; p value $= 0.708$) (data not shown). Therefore, to account for the almost universal heterogeneity demonstrated across the studies, we present results from our random effects models exclusively.

Overall analysis by cancer type

Table 3 presents results of the random effects meta-analyses models and corresponding 95% CIs, for all effect estimates by LHC cancer type and LHC cancer type within occupational groups. The meta-RRs for the all LHC and Hodgkin's disease categories, respectively, were statistically significantly elevated at 1.48 (95% CI 1.07–2.05) and 2.76 (95% CI 1.21–6.27). Slight to moderate excess risks, although not statistically significant, were observed for leukemia, NHL, and myeloma. Based on five effect estimates, the meta-RR for breast cancer revealed no evidence of an elevated risk (0.97; 95% CI 0.80–1.18).

Analysis by occupational group and cancer type

Within the EO production/using group, there were slightly elevated meta-RRs, although not statistically significant for all LHC (1.46; 95% CI 0.85–2.50), leukemia (1.21; 95% CI 0.66–2.21), NHL (1.12; 95% CI 0.65–1.90), and myeloma (2.03; 95% CI 0.42–5.94). However, EO producers and users had a statistically significantly increased risk for Hodgkin's disease (meta-RR = 5.36; 95% CI 2.31–12.44). No cases of breast cancer were reported in the EO production group. Additionally, the meta-RRs for the EO sterilization group were close to the null value and not statistically significant for breast cancer, all LHC, and LHC subcategories.

Analysis by decade of publication

Overall, the decade analysis (Fig. 2) demonstrated statistically significant borderline heterogeneity with an I^2 of 59.6% (p value = 0.002), although heterogeneity improved from an I^2 of 61.3% (p value = 0.012) in the 1990s to an I^2 of 0% (p values ≥ 0.563) in both the 2000s and 2010s. When effect estimates were stratified by decade, there was nearly a four-fold and statistically significantly increased risk for all LHC in papers published in the 1980s (meta-RR = 3.87; 95% CI 1.87–8.01) and an elevated, although

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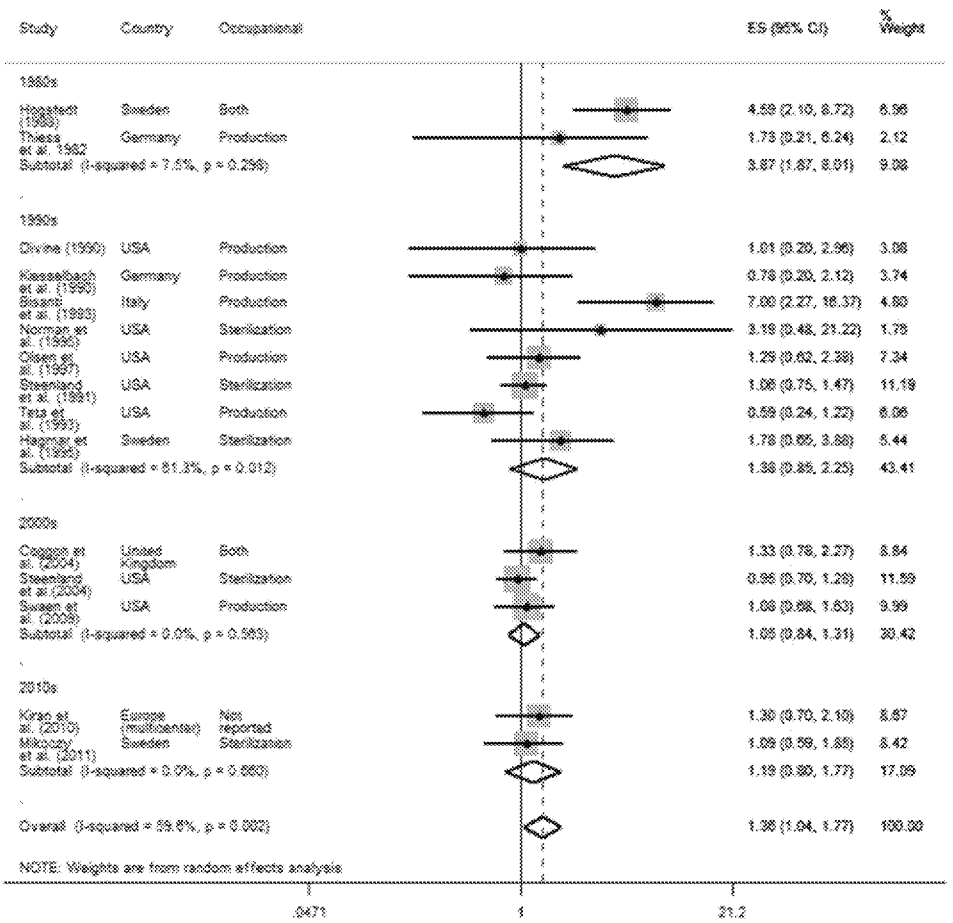

Fig. 2 Forest plot of random effects model of all LHC by decade of publication

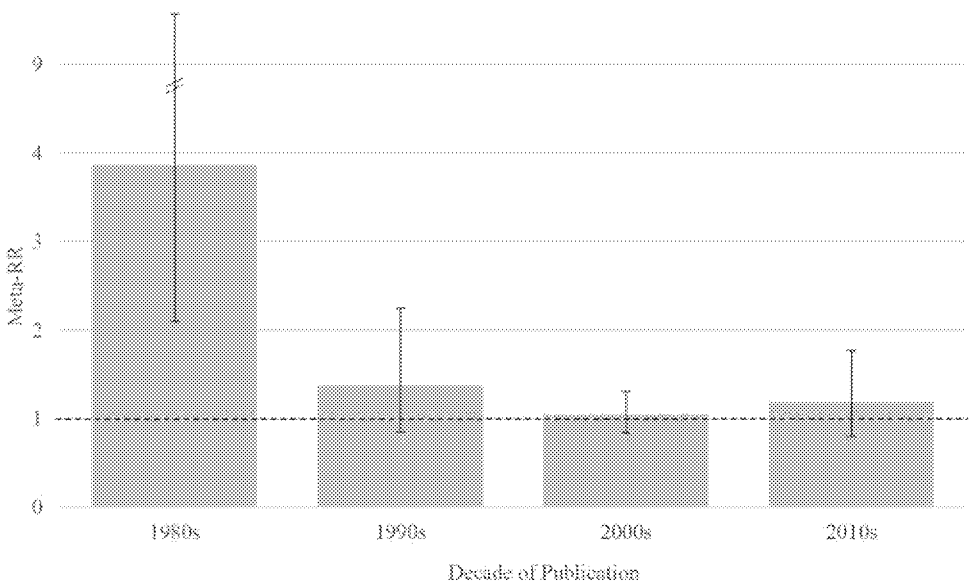

Fig. 3 Time-trend analysis by decade of publication for all LHC

non-significant, meta-RR of 1.38 (95% CI 0.85–2.25) in the 1990s. In contrast to the results for the 1980s and 1990s, we found a near-baseline-level risk for all LHC in the papers published in the 2000s (meta-RR = 1.05; 95% CI 0.84–1.31) and a small, non-statistically significantly elevated risk in the 2010s (meta-RR = 1.19; 95% CI 0.80–1.77).

Moreover, the precision of the meta-RRs calculated across decade increased markedly in studies conducted in

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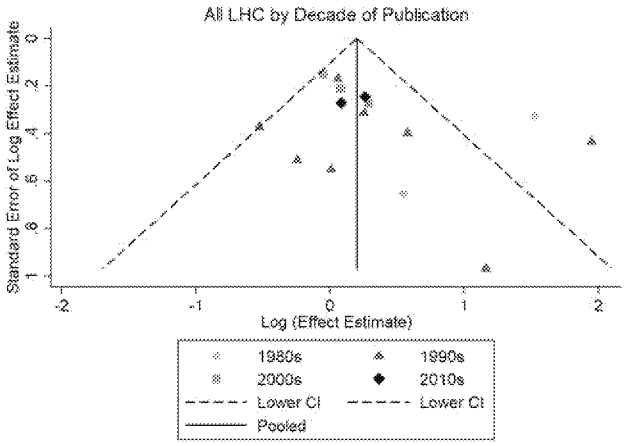

Fig. 4 Funnel plot of all LHC effect estimates by decade of publication

the 2000s and 2010s compared to those conducted in the 1980s and 1990s. Figure

Evaluation of publication bias for LHC studies

To evaluate the publication bias for LHC studies, a funnel plot was generated for all LHC effect estimates by decade of publication (Fig.

=0.13), but the Begg's test was borderline statistically significant ($p=0.048$), results consistent with the visual representation shown in the funnel plot. The plot suggests that effect estimates that demonstrated an absence of LHC risk may have been underrepresented in studies conducted in the 1980s and 1990s, and that the studies published in the earlier decades were associated with less precision due to small size or otherwise poor study quality (Table

Sensitivity analysis for leukemia studies

A time period analysis (pre- and post-2000s) for leukemia was conducted to evaluate potential sources of heterogeneity (Fig.

=1.01; 95% CI 0.77–1.32). Heterogeneity was observed in the pre-2000s ($I^2=66.6\%$; $p<0.05$) but not in the post-2000s ($I^2=0\%$; $p=0.916$). We also performed a time period analysis excluding Hogstedt (

2

of 73.6% ($p<0.001$) to an I^2 of 0% ($p=0.596$) (results not shown).

Discussion

Since a systematic review and risk assessment was published by Teta et al. (

Overall findings for LHC

Accounting for the latest updates of the cohort studies reviewed, only the early Swedish (Hogstedt

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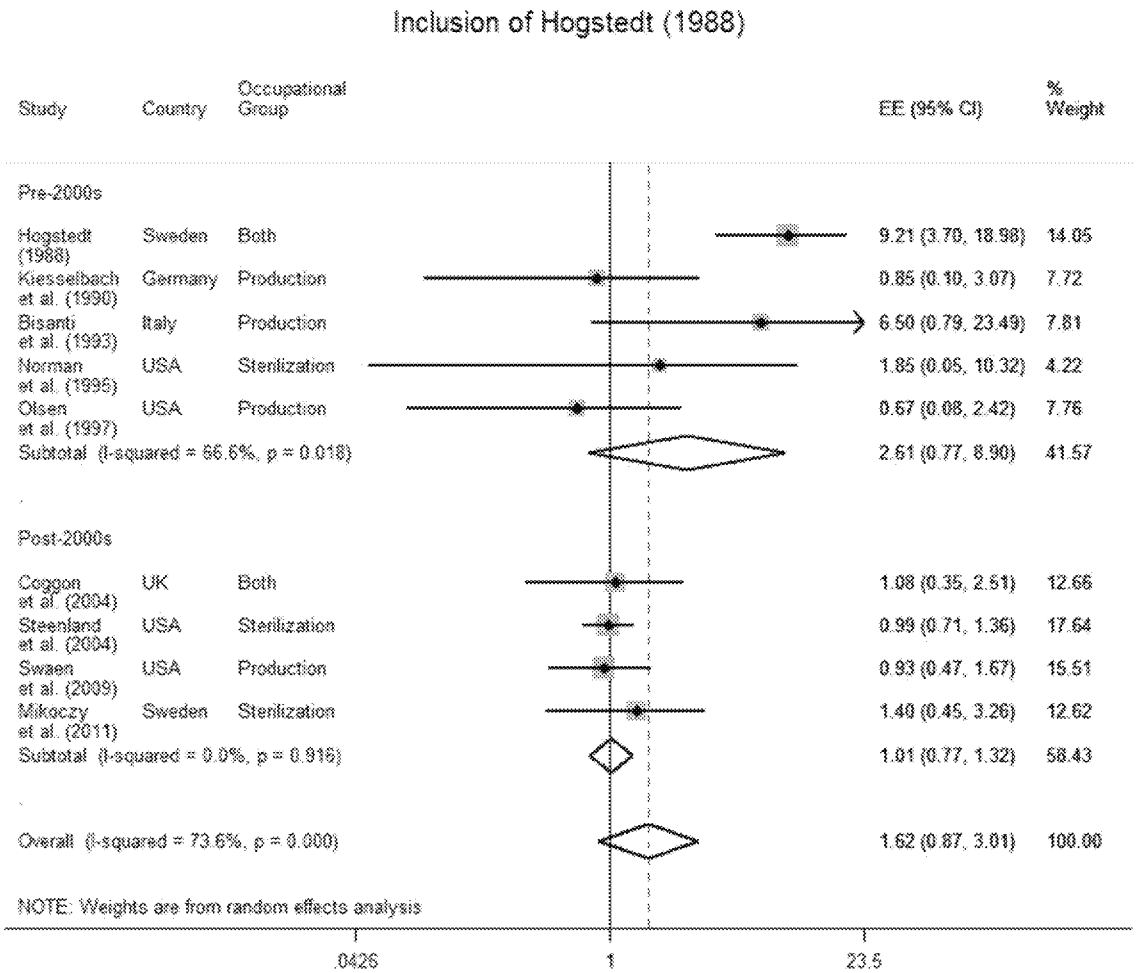

Fig. 5 Forest plot of random effects model of leukemia by pre- and post-2000s time periods

gender-specific and limited to the transformed metric log cumulative EO exposure, which weakened the overall evidence for EO as a risk factor for LHC. The overall findings from the NIOSH study was equivalent to the null (SMR = 1.00; 95% CI 0.79–1.24). To a lesser extent, the UCC cohort study (Swaen et al.

Time-trend and sensitivity analysis for LHC

The epidemiological evidence of the risk for human cancer from EO used in the IARC evaluation came from 12 cohort studies of exposed workers in the US and Europe, employed in chemical plants where EO was produced or used, or in facilities where EO was used as a sterilizing agent (IARC

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all epidemiological evidence for the potential human carcinogenicity of EO was available to IARC at their Working Group meeting in 2010 and most of this evidence relates to LHC (IARC 2012).

As we show in Tables 1 and 2, the earlier epidemiological studies of EO were limited by factors such as small population size and/or observed number of cases or deaths (ten studies). These limitations can lead to low statistical power to detect important excess LHC risks, or in the case of studies reporting statistically significant results, imprecise risk estimates. Other limitations include insufficient follow-up or case–control participation rates (two studies), low EO exposure potential (three studies), lack of individual exposure data or exposure–response analysis (seven studies), inconsistencies in histopathological classification of diagnoses over time (variation between ICD 7–9 and ICD 10 (mortality) codes as well as ICDO (incidence) codes across time), with four studies not reporting classification), as well as the lack of latency analysis (not a major issue with LHC in general). Perhaps the key methodological issue of the earlier studies was the inability to account for residual confounding by factors including co-exposure to other chemicals (nine and eight studies, respectively). However, determining which occupational and/or non-occupational factors are potential confounding factors is difficult given the absence of knowledge on known risk factors for LHC.

Our qualitative findings regarding methodological limitations over time were corroborated in our meta-analyses of all LHC conducted by decade of publication. When stratified by decade of publication, the effect estimates from studies published in the 2000s and 2010s were homogeneous, whereas effect estimates from studies published in the 1990s revealed borderline heterogeneity. As for the 1990s, borderline heterogeneity may exist due to the nature of the decade categorization (this decade had the most studies when stratified), as well as in part due to the variation in disease inclusion over time.

While relatively few studies were conducted within each decade, our decade-specific meta-analyses revealed a clear pattern of increasing study quality (as measured by precision) and decreasing LHC risk with increasing decade from the 1980s to the 2010s. This pattern was observed across all studies combined and within studies of EO production or EO sterilization workers. For example, meta-RRs for LHC from all studies published in the 2000 and 2010s are about four times lower than the effect estimate reported by Hogstedt (1988). This observed trend over time could be due to improved disease diagnostic accuracy and/or improved study quality including larger study sizes and better adjustment for potential confounding factors and other study biases.

The results of our sensitivity analysis of LHC cancers confirmed our observation that the older studies, particularly those of Hogstedt (1988) and Swaen et al. (1996), are indeed inherently different from the more recent and updated evaluations of EO-exposed cohorts. In addition, our funnel plot evaluation of potential publication bias revealed that studies showing an absence of LHC risk among EO exposed populations may have been underrepresented in studies conducted in the 1980s and 1990s.

Thus, based on our meta-analyses by decade of publication, our sensitivity analysis of LHC cancers and our funnel plot evaluation of publication bias, the most accurate and meaningful information regarding breast cancer and LHC risks comes from studies published in the 2000s and 2010s. These more recent and more informative studies do not support the conclusion that exposure to EO during production or use in sterilization processes is associated with an increased risk of breast cancer or LHC.

Overall findings for breast cancer

With the exception of the large and informative NIOSH (Steenland et al. 2003, 2004) study and the methodologically problematic Swedish study (Mikoczy et al. 2011), none of the available studies found two-fold or greater elevated relative risks for breast cancer, although some studies reported risks greater than 1.0 but less than 2.0. However, similar to the LHC results, the NIOSH findings, which revealed no overall excess for breast cancer, were limited to the exposure–response analyses using the log-transformed EO exposure metric and were questioned by the authors due to their inconsistency across the other EO metrics considered and potential case over-ascertainment in the higher exposure categories. As discussed above, due to the questionable validity of the positive EO exposure–response of Mikoczy et al. (2011), these findings add little weight to the overall evidence for EO exposure and breast cancer.

Although based on a limited number of effect estimates ($n = 5$), our meta-analysis found no evidence of an elevated risk for breast cancer among workers exposed to EO during sterilization processes (meta-RR = 0.97; 95% CI 0.80–1.18) (no effect estimates were available for EO production workers). As noted with studies evaluating LHC risks, the largest effect estimate for breast cancer were observed in a relatively imprecise and uninformative study published in the 1990s (Norman et al. 1995).

Overall findings for other cancer endpoints

In addition to the findings presented for all LHC and breast cancer, we note that no statistically significant increased risks of cancer were observed for in either exposure group for NHL, leukaemia, or multiple myeloma. Furthermore, the presented meta-RRs for these cancer endpoints are overestimated. As shown in Table 2, several studies reported zero cases for these disease endpoints. To err on the side of

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conservatism, we excluded such risk estimates from the presented meta-analysis. Had these risk estimates been included in the meta-analyses, the overall level of risk would have been further reduced for these endpoints.

Future directions

Future opportunities of exploring the association between occupational exposure to EO and risk of specific lymphoma subtypes might be afforded by pooled analyses of international lymphoma studies such as the International Lymphoma Epidemiology Consortium. Further evaluation of the association between EO exposure and breast cancer should consider the possible interactions between potential risk factors, including possible exposures early in life and during breast gland development, as well as the large diversity of breast cancer itself.

Conclusions

Based on our analysis, the most accurate and meaningful information regarding breast cancer and LHC risks in relation to EO exposure comes from epidemiology studies published in the 2000s and 2010s. These more recent and more informative studies do not support the conclusion that exposure to EO during production or use in sterilization processes is associated with an increased risk of LHC. Evaluations of workers exposed during sterilization processes do not support the conclusion that EO exposure is associated with an increased risk of breast cancer.

Acknowledgements The authors thank Dr. Jane Teta for providing data from the unpublished Divine (1990) study and for her helpful comments on the draft manuscript.

Author contributions GMM developed the idea for the manuscript, assisted with the biostatistical approach to the analysis, and was responsible for the overall quality of work. KAK reviewed the literature and confirmed the inclusion and exclusion of various studies, drafted text, created figures, and assisted with conducting the analyses. ASR reviewed the literature and confirmed the inclusion and exclusion of various studies, drafted text, and assisted with conducting the analyses. EAB reviewed the literature and confirmed the inclusion and exclusion of various studies, drafted text, assisted with conducting the analyses, and created figures. SMB reviewed the literature and confirmed the inclusion and exclusion of various studies, drafted text, and created figures.

Funding Earlier work on this commentary was performed under a consulting agreement between GM and the American Chemistry Council (ACC). Later work including the meta- analysis and preparation of this manuscript was performed under a consulting agreement between Cardno ChemRisk and the ACC.

Compliance with ethical standards

Conflict of interest The financial sponsor ACC was given the opportunity to review and comment on the draft manuscript, but the study design, the synthesis of findings, the conclusions drawn and the preparation of the manuscript are the exclusive professional work product of the authors, and may not necessarily be those of Cardno ChemRisk or ACC. GM performed part of this work as a private consultant and part as Consulting Senior Science Advisor for Epidemiology at Cardno ChemRisk. In addition to his role as a consultant, GM is Professor of Biostatistics and Director and Founder of the Center for Occupational Biostatistics and Epidemiology at the University of Pittsburgh, Graduate School of Public Health. For more than 42 years, GM has directed or co-directed epidemiological research on the potential carcinogenicity of numerous chemical agents. SB, KK, EB and AR are epidemiologists at Cardno ChemRisk with experience in environmental and occupational health research.

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Message

From: Branning, Amy [Branning.Amy@epa.gov]
Sent: 6/29/2021 3:35:39 PM
To: Witt, Jon [Witt.Jon@epa.gov]
Subject: FW: amicus brief on commercial sterilizers
Attachments: LPS-#288705-v1-New_Mexico_v__Sterigenics_Amicus_FINAL_Version_to_NM_for_Filing (AutoRecovered).pdf

Hi Jonathan:

I meant to include you when I sent the brief to Kelly and Amy (attached below).

Thank you so much for your help in analyzing the factual statements in the parties' briefs.

Amy Huang Branning
EPA Office of General Counsel
phone: (202) 564-1744
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From: Branning, Amy
Sent: Tuesday, June 29, 2021 11:22 AM
To: Rimer, Kelly <Rimer.Kelly@epa.gov>; Vasu, Amy <Vasu.Amy@epa.gov>
Cc: Anderson, Lea <anderson.lea@epa.gov>; Versace, Paul <Versace.Paul@epa.gov>
Subject: amicus brief on commercial sterilizers

LPS-#288705-v1...
(AutoRecovered)...

Hi Kelly and Amy:

Sorry I have been on the phone since 8:30 am this morning. Here is the amicus brief I mentioned during our 8:30 am call. The brief describes IRIS and NATA. As a quick background (which Kelly already knows), New Mexico Attorney General has brought suit against the Steregenic facility in New Mexico relying on the new IRIS value for EtO and the NATA released in 2018. The court in that case asked that EPA file an amicus brief to discuss issues in that suit. Ex. 5 AC/DP

Ex. 5 AC/DP

Thank you.

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STATE OF NEW MEXICO
COUNTY OF DOÑA ANA
THIRD JUDICIAL DISTRICT COURT

THE STATE OF NEW MEXICO, EX REL. HECTOR BALDERAS, ATTORNEY GENERAL,

Plaintiff,

v.

STERIGENICS U.S., LLC, SOTERA HEALTH HOLDINGS, LLC, SOTERA HEALTH LLC, AND SOTERA HEALTH COMPANY,

Defendants.

No. D-307-CV-2020-2629

(Judge Beyer)

UNITED STATES' AMICUS CURIAE BRIEF

On April 14, 2021, Plaintiff the State of New Mexico filed an Emergency Motion for Temporary Restraining Order and Preliminary Injunction. This brief is filed in response to the Court's April 22, 2021 order. In its order, the Court asks the United States Environmental Protection Agency (EPA) to provide its views on the issues raised in Plaintiff's motion, including the impact of the doctrine of primary jurisdiction with respect to EPA. With respect to EPA's role, there is no basis in the Clean Air Act, federal regulatory law or in ongoing actions by EPA for this Court to invoke the doctrine of primary jurisdiction to stay or dismiss this action. Additionally, we note that the parties have cited EPA-generated documents in this action, and we clarify the typical function of those documents in the background section below. The United States, in

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this brief, does not address the applicability of primary jurisdiction with respect to the role of the New Mexico Environmental Department.

INTERESTS OF THE UNITED STATES

The Environmental Protection Agency administers the Clean Air Act in cooperation with the States. The Clean Air Act is founded on the principle of "cooperative federalism" and envisions a robust role for the States in administering the Clean Air Act. It preserves the application of State tort law. As set forth in this brief, the Environmental Protection Agency has engaged in certain regulatory activities with respect to ethylene oxide, the pollutant at issue in this case. The United States files this brief at the Court's request to clarify the applicable statutory and regulatory framework under federal law and the scope of relevant EPA activities. This filing is limited to addressing applicable provisions of federal law and ongoing federal actions that may be relevant to the Court's decision in this case; and the United States ordinarily does not address issues of state law.

BACKGROUND

I. Statutory and Regulatory Background

A. The Clean Air Act

The Clean Air Act (CAA), 42 U.S.C. §§ 7401-7671q, sets up a comprehensive program for control of air pollution through a system of shared federal and state responsibility. Hazardous air pollutants are "pollutants which present, or may present . . . a threat of adverse human health effects . . . or adverse environmental effects whether through ambient concentrations, bioaccumulation, deposition, or otherwise." 42 U.S.C. § 7412(b)(2). The 1990 CAA Amendments established a two-phase approach to control

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emissions of hazardous air pollutants. EPA's role is prescribed by statute. The first phase involves EPA setting technology-based emission standards. *Id.* § 7412(d). The second phase requires EPA to determine whether the residual risks that remain warrant more stringent standards. *Id.* § 7412(f). The idea is to set limits that, as an initial matter, require all sources in a category to at least clean up their emissions to the level that their best performing peers have shown can be achieved. *See* 42 U.S.C. § 7412(d)(3). The second phase then returns to a risk-based analysis – which occurs within eight years after initial standards are promulgated – and requires EPA to consider whether residual risks remain that warrant more stringent standards. *Id.* § 7412(f).

CAA section 112(b)(1) lists pollutants to be regulated within industrial source categories. 42 U.S.C. § 7412(b)(1). Ethylene oxide is a listed hazardous pollutant. *Id.* Section 112(c)(1) requires EPA to publish a list of categories of sources emitting listed hazardous air pollutants. *Id.* § 7412(c)(1). A "category" of sources is a group of sources having common features (such as boilers, or coal-fired power plants), suggesting they should be regulated in the same way.

B. EPA's Nationwide Regulation of Ethylene Oxide Commercial Sterilization Facilities

On July 16, 1992, EPA published a list of major and area sources (the source category list) that required the promulgation of section 112 standards. 57 Fed. Reg. 31,576. Ethylene oxide commercial sterilization and fumigation operations were one of the listed categories. *Id.* EPA first published hazardous air pollutant standards for these commercial sterilization facilities more than twenty-five years ago. *See* 59 Fed. Reg. 62,585 (Dec. 4, 1994). As part of this regulatory process, EPA set major source

and area source standards for those facilities. *See Id.* at 62,586. The current ethylene oxide emission standards are available at 40 C.F.R. part 63, subpart O.

The process of ethylene oxide sterilization typically occurs in a sterilization chamber, from which there are three major emission points: (1) the sterilization chamber vent; (2) the aeration room vent; and (3) the chamber exhaust vent. 84 Fed. Reg. 67,892. The sterilization chamber vent evacuates ethylene oxide from the sterilization chamber following sterilization, fumigation, and any subsequent gas washes. *Id.* The aeration room vent evacuates ethylene oxide from the aeration room (where sterilized materials off-gas in a facilitated environment following sterilization). *Id.* The chamber exhaust vent evacuates ethylene oxide-laden air from the sterilization chamber after the chamber door is opened for product unloading following the completion of sterilization and associated gas washes. *Id.* In the initial 1994 regulation of ethylene oxide sterilization facilities, EPA regulated all three major emission points. Those regulations were later revised due, in part, to a series of explosions at sterilization facilities. *See* 84 Fed. Reg. 67,892. As a result of those revisions, EPA's regulations currently require no controls for emissions from the chamber exhaust vent. *See* 40 C.F.R. part 63, subpart O.

Ethylene oxide emissions can occur from sources other than the aeration room vent, sterilization chamber vent, or the chamber exhaust vent – such emissions are considered "fugitive emissions."[1] EPA, to date, has not set standards for fugitive

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[1] Fugitive emissions are emissions that could not reasonably pass through a stack, chimney, vent, or other functionally equivalent opening. *See* 40 C.F.R. §§ 70.2, 71.2 (defining "fugitive emissions" under CAA Title V). For purposes of regulation of ethylene oxide, fugitive emissions are considered to be "those

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emissions from ethylene oxide commercial sterilization facilities. 84 Fed. Reg. 67,892. In 2019, however, EPA issued an advanced notice of proposed rulemaking that solicited information to aid in potential future revisions to ethylene oxide emission standards for commercial sterilization facilities. *Id.* at 67,889.

Potential revisions being considered include developing control measures for fugitive emissions as well as promulgating additional safety measures for chamber exhaust vents, and other improvements. *Id.* Since 2019, EPA has issued a questionnaire to nine companies with commercial sterilization facilities, including Sotera Health, under section 114 of the CAA. *See EPA Proposes Info. Collection Request for Ethylene Oxide Commercial Sterilization Facilities,* U.S. EPA (June 5, 2020) https://www.epa.gov/hazardous-air-pollutants-ethylene-oxide/ethylene-oxide-updates. The questionnaire was intended to help EPA better understand ethylene oxide emission sources, measurement and monitoring techniques, and available control technologies. EPA has also initiated a proposed information collection request to gather the same information from companies that did not receive the initial questionnaire. *See* 86 Fed. Reg. 24,862 (May 10, 2021, proposed information collection request); 85 Fed. Reg. 35,931 (June 12, 2020, proposed information collection request). This regulatory process is ongoing.

C. EPA's delegation of authority to New Mexico

Congress, in the Clean Air Act, recognizes that air pollution and control is the "primary responsibility of States and local governments." 42 U.S.C. § 7401(a)(3).

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emissions which are not routed to an existing pollution control device." 84 Fed. Reg. 67,894.

Section 112(l) of the CAA and 40 C.F.R. part 63, subpart E authorize EPA to delegate authority for the implementation and enforcement of emission standards for hazardous air pollutants to a state that satisfies the statutory and regulatory requirements in subpart E. 42 U.S.C. § 7412(l); 40 C.F.R. § 63.12(b) (addressing EPA's authority to delegate administration of hazardous air pollutant standards).

EPA has delegated to New Mexico the authority to administer the state's program implementing specified new source performance standards and national emission standards for hazardous air pollutants. 83 Fed. Reg. 46,107 (Sept. 12, 2018). This delegation includes authority to administer standards for ethylene oxide sterilizers. 83 Fed. Reg. 46,112 (showing the delegation status in New Mexico for part 63 standards).

Permits in New Mexico are issued pursuant to New Mexico's Air Quality Control Act and regulations adopted pursuant to that act, including title 20, chapter 2, pts. 72, 77, 78 and 82 of the New Mexico Administrative Code (establishing New Mexico's new source performance standard program and New Mexico's program for national emission standards for hazardous air pollutants). Pursuant to those provisions, and potentially others, New Mexico administers CAA programs relevant to the facility at issue in this case.

II. Factual Background

A. Permitting and allegations concerning the Santa Teresa Facility

Defendants Sterigenics U.S. LLC, Sotera Health Holdings, LLC, Sotera Health LLC, and Sotera Health Company (collectively, Defendants) own and operate an

industrial sterilization and fumigation facility in Santa Teresa, New Mexico.[2] Complaint ¶ 3. At this facility, Defendants use substantial quantities of ethylene oxide. Complaint ¶ 6.

The Santa Teresa facility operates under an Air Quality Bureau New Source Review permit issued by the New Mexico Environment Department. *See* Sterigenics Air Quality Permit, attached as Ex. A to Declaration of Steve Ortiz, Dkt. 14-1 in Civil Action No. 2:20-cv-01355-KG-KRS. This is a "permanently applicable" permit issued in response to a prior modification of the Sterigenics facility. *See* Permit §§ A101-102. While the Sterigenics facility permit addresses some forms of ethylene oxide emissions, it does not address fugitive emissions (though this is not surprising because, as noted above, EPA has not, to date, established fugitive emission standards for ethylene oxide from commercial sterilization facilities). *See* Sterigenics Air Quality Permit.

In this action, New Mexico alleges that Defendants have caused "substantial unreported, uncontrolled releases" of ethylene oxide. Complaint ¶ 19. Allegedly, these uncontrolled releases are due to lax oversight of Defendants' operation, including leaving open sterilization chamber doors, improperly washing equipment, and causing delivery of sterilized products that were off-gassing during the delivery process. *Id.* New Mexico also alleges that mechanical failures and breakdowns led to additional uncontrolled emissions of ethylene oxide. Complaint ¶ 20. All of New Mexico's claims are state-law based tort claims, and are based on alleged harms associated with ethylene oxide emissions. Complaint ¶¶ 53-222. New Mexico has not alleged any

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[2] This factual summary is based on factual allegations contained in New Mexico's complaint. The United States has not independently verified the accuracy of those allegations.

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federal claims and has not asserted claims based on a violation of the state-issued permit.

B. EPA's Integrated Risk Information System and National Air Toxics Assessment

Both Plaintiff and Defendants cite to an assessment of ethylene oxide carcinogenicity released in 2016 by EPA's Integrated Risk Information System (IRIS). Additionally, the parties cite to EPA's 2014 National Air Toxics Assessment.

EPA's IRIS program identifies and characterizes health hazards posed by chemicals found in the environment. *See Basic Info. About the Integrated Risk Info. Sys.,* U.S. EPA, https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system (last visited June 17, 2021). To the extent that any information presented in its 2016 evaluation of ethylene oxide may be relevant to this action, we note that the EPA assessment focuses generally on potential hazards posed by the substance itself, and not to any factors associated with any individual facility or risk to the population near any specific facility.

EPA's 2014 National Air Toxics Assessment (NATA) was developed as a screening tool for state, local, and tribal air pollution control agencies. *See NATA Overview*, U.S. EPA, https://www.epa.gov/national-air-toxics-assessment/nata-overview (last visited June 17, 2021). This tool helps those agencies identify likely emission sources for pollutants and identify areas that they may wish to study further. *Id.* More localized studies are often needed to better characterize local-level risk. *Id.* The 2014 NATA includes a map application that allows users to display risks, emissions, and other NATA data on a map. A user's guide to the mapping application is available at https://gispub.epa.gov/NATA/2014NATAmapappuserguide.pdf. While useful as a

screening tool, NATA has limitations. *See NATA Limitations*, U.S. EPA, https://www.epa.gov/national-air-toxics-assessment/nata-limitations (listing limitations including data availability) (last visited June 17, 2021).

When EPA becomes aware of a data gap, the agency issues a "NATA Emissions Update," a document that provides a list of some of the issues that either were not addressed during the review of a prior assessment or were not known at the time of a prior assessment. Known data gaps in 2014 NATA have been periodically acknowledged, most recently in a document listing known changes to emissions that occurred after 2014 and prior to July 28, 2020. *See* Ex. M to Sterigenics Preliminary Injunction Opposition. EPA notes in that document that the Santa Teresa facility installed a control device for ethylene oxide between 2014 and 2016.

On March 31, 2020, EPA's Office of the Inspector General issued a Management Alert, which called on EPA to provide information to 25 communities that NATA identified as potentially having the highest risk from ethylene oxide emissions. *See Ethylene Oxide: Technical Reviews and Outreach to Potentially Affected Communities Status Report for Sterigenics – Santa Teresa, NM,* Attached as Ex. L to Sterigenics Preliminary Injunction Opposition. In response to that Management Alert, EPA noted that it believed the Office of the Inspector General "erroneously included the Sterigenics Santa Teresa Facility in its list of facilities for follow-up." *Id.* EPA explained that NATA estimated risks based on 2014 emissions data but that more current emissions data would result in changes in the estimate of risk associated with the Santa Teresa facility. *Id.* EPA noted that it had learned that the Santa Teresa facility installed a pollution control device that reduced ethylene oxide emissions from 2014 levels, and that this

emissions reduction would be expected to reduce risk. *Id.* EPA did not, however, conclude that the data indicates that additional investigation would be inappropriate.

DISCUSSION

Despite the name, the doctrine of primary jurisdiction does not involve jurisdictional questions, but prudential considerations. *Syntek Semiconductor Co., Ltd. v. Microchip Technology Inc.*, 307 F.3d 775, 780 (9th Cir. 2002). It is a common law doctrine used to coordinate administrative and judicial decision making. *Mashpee Tribe v. New Seabury Corp.*, 592 F.2d 575, 580 (1st Cir. 1979). Thus, when a court and an agency have concurrent jurisdiction and "the agency has expertise of a specific sort, a court may grant the agency primary jurisdiction to decide the issue under its enabling statute, before the court becomes involved." § 15:94. Primary jurisdiction, O'Reilly, Administrative Rulemaking (2021 ed.). Primary jurisdiction allows a court to stay further proceedings, or dismiss a case, so as to give parties an opportunity to seek an administrative ruling. *Reiter v. Cooper*, 507 U.S. 258, 268 (1993) (recognizing court's ability to stay a cause pursuant to doctrine of primary jurisdiction); *Astiana v. Hain Celestial Grp., Inc.*, 783 F.3d 753, 761 (9th Cir. 2015) (recognizing court's ability to dismiss pursuant to doctrine of primary jurisdiction). The doctrine should be invoked sparingly, as it often results in "added expense and delay." *Mississippi Power & Light Co. v. United Gas Pipeline Co.*, 532 F.2d 412, 419 (5th Cir. 1976). Not every case that implicates the expertise of federal agencies warrants invocation of primary jurisdiction. Rather, the doctrine is reserved for a "limited set of circumstances" that "requires resolution of an issue of first impression, or of a particularly complicated issue that Congress has committed to a regulatory agency." *Clark v. Time Warner Cable*, 523

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F.3d 1110, 1114 (9th Cir. 2008) (quoting *Brown v. MCI WorldCom Network Servs.*, 277 F.3d 1166, 1172 (9th Cir. 2002)).

While there is no "fixed formula" governing application of the doctrine, in general, the factors that courts evaluate include (1) whether the issue is a question within an agency's particular field of expertise, (2) whether the issue is particularly within the agency's discretion, (3) whether there is a substantial risk of inconsistent rulings, and (4) whether a prior application to the appropriate agency has been made. *See, e.g.*, *United States v. Western Pacific Railroad Co.*, 352 U.S. 59, 62–63 (1956); *Raritan Baykeeper v. NL Indus., Inc.*, 660 F.3d 686, 691 (3d Cir. 2011).

There is no pending or completed action by EPA that points to application of the doctrine to the instant case based on any of these factors. First, the legal questions at issue in this case are primarily questions of New Mexico state law, and EPA has no particular expertise regarding New Mexico tort law. In *United States v. Western Pacific*, the Supreme Court examined whether, in order to effectuate the statutory purposes of the Interstate Commerce Act, a reviewing court was required to allow the Interstate Commerce Commission to construe a tariff issue before that same issue was addressed by a reviewing court. 352 U.S. at 65. The Supreme Court focused on whether the particular expertise of the agency was vital to inform the legal question (involving tariff construction and the reasonableness of a tariff imposed on a shipper) presented to the Court of Claims. Concluding that knowledge of "intricate facts" about the transportation sector was necessary to interpret the meaning of the key term at issue in that case and that the Interstate Commerce Commission had the necessary knowledge, the Supreme Court held that the tariff issues involved in this case were initially matters for the

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Interstate Commerce Commission to determine. *Western Pacific*, 352 U.S. at 66-69. There is no parallel here.

New Mexico tort law forms the basis of New Mexico's claim here. These questions of state law will be applied to a factual scenario that involves details that will be clarified through discovery. The question of whether Plaintiff can prove that Defendants' emissions caused a harm that is actionable under state nuisance law can be fully addressed by the parties to the action and is a question that can readily be resolved by this Court. EPA does not have any unique expertise necessary to resolve those factual issues. Rather, such actions are standard fare for state trial courts and clearly fall "within the conventional competence of th[ose] courts." *See Nader v. Allegheny Airlines, Inc.*, 426 U.S. 290, 305–06 (1976) (in an ordinary fraud action against an airline, expertise of the Civil Aeronautics Board, which had concurrent jurisdiction, was not likely to be helpful); *Baykeeper*, 660 F.3d at 691 (state environmental agency's general expertise in environmental matters did not support court's "abdicat[ion of] its responsibility" where Congress had authorized judicial actions over the subject matter of the suit).

With respect to the second factor, EPA does not have "particular" discretion over a New Mexico tort action – in fact EPA has no statutory role to play in such an action. Even if the underlying issue were construed to be fundamentally tied to the enforcement of CAA emission control standards for stationary sources, it is clear that Congress did not provide EPA with "particular" discretion or exclusive control over that subject matter. *See generally Baykeeper*, 660 F.3d at 691–92 (recognizing that, where a state environmental agency may have general discretion over environmental matters, it did

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not have "particular" discretion where courts had authority to enforce the federal statutes at issue). Instead, Congress expressly preserved the right of states to take concurrent action. A savings clause of the Clean Air Act captioned "Retention of State Authority" provides:

> Except as otherwise provided ... nothing in this chapter shall preclude or deny the right of any State or political subdivision thereof to adopt or enforce (1) any standard or limitation respecting emissions of air pollutants or (2) any requirement respecting control or abatement of air pollution....

42 U.S.C. § 7416. Consistent with that statutory provision, EPA's regulations recognize that states may adopt air emission standards, limitations, provisions or regulations that are more stringent than federal standards, under specified circumstances. 40 C.F.R. § 63.12(a). Congress contemplated that states would have an independent role to play in controlling air pollution. *See Merrick v. Diageo Americas Supply, Inc.*, 805 F.3d 685, 690-93 (6th Cir. 2015) (concluding that the Clean Air Act did not preempt state common-law claims); *Bell v. Cheswick Generating Station*, 734 F.3d 188, 194-197 (3d Cir. 2013) (same); *Her Majesty the Queen in Right of the Province of Ontario v. Detroit*, 874 F.2d 332 (6th Cir.1989) (holding that the Clean Air Act did not preempt suit under state Environmental Protection Act). Additionally, both EPA and New Mexico have concurrent authority to enforce violations of standards and permits issued by the state under delegated CAA programs. *See* 83 Fed. Reg. 46,107 (delegating to New Mexico authority for implementation and enforcement of relevant emission standards). Finally, Congress contemplated a structure that would allow state and citizen actors to litigate such questions in trial-level courts across the country. 42 U.S.C. § 7604 (citizen suit enforcement provision). Accordingly, EPA lacks "particular" or exclusive discretion over the issues presented in this state nuisance action.

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The third factor also weighs against an exercise of primary jurisdiction. "The court in its discretion may defer to an administrative agency in the interests of judicial economy, where the agency is in a better position to fully develop a record of the grievance." *McDowell v. Napolitano*, 895 P.2d 218, 222 (N.M. S. Ct. 1995). Here, however, EPA is not currently engaged in an administrative or judicial enforcement action against Sterigenics with respect to its New Mexico facility and, accordingly, EPA is in no better position to develop the factual record relevant to New Mexico's claims than the parties already before the Court. Additionally, EPA cannot be compelled to file such an action. *Heckler v. Chaney*, 470 U.S. 821 (1985) (recognizing that an agency's decision not to take an enforcement action is not subject to judicial review). Put another way, there are no EPA enforcement actions that could generate rulings that are inconsistent with the rulings of this Court.

With respect to the fourth factor, there has been no "application" to EPA to assess the particular facts of this case. As mentioned in the prior paragraph, EPA has not commenced an administrative or judicial enforcement action with respect to Sterigenics's Santa Teresa facility. Although EPA has issued an advanced notice that it is collecting information in support of a future rule that, if finalized as proposed, could set nationwide regulations for fugitive emissions from ethylene oxide sterilization facilities like the facility at issue in this case, 84 Fed. Reg. 67,889, that ongoing EPA rulemaking process provides no basis for applying the doctrine of primary jurisdiction to this case.

EPA's rulemaking process is still underway, and it could be some time before a final rule is issued. Once issued, that rule might be very different from the proposed

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rule. Even if a final rule were issued that provided emission standards for fugitive emissions from stationary sources such as Sterigenics's plant, nothing that will occur in the pending state nuisance action will interfere with, impede or otherwise affect EPA's ability to fulfill its regulatory obligations under the CAA.

For the reasons discussed above, with respect to EPA's role, there is no basis in the Clean Air Act, federal regulatory law or ongoing actions by EPA for this Court to invoke the doctrine of primary jurisdiction to stay or dismiss this action.

Respectfully Submitted,

FRED FEDERICI
Acting United States Attorney

/s/ Manuel Lucero June 25, 2021
MANUEL LUCERO
Assistant United States Attorney
P.O. Box 607
Albuquerque, NM 87103
(505)224-1467
manny.lucero@usdoj.gov

JEAN E. WILLIAMS
Acting Assistant Attorney General
Environment and Natural Resources Division
U.S. Department of Justice

Dated: June 25, 2021

s/ Matthew R. Oakes
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CERTIFICATE OF SERVICE

I hereby certify that I electronically filed the foregoing *United States' Amicus Curiae Brief* with the Clerk of Court using the Court's electronic filing system.

Dated: June 25, 2021 *s/ Matthew R. Oakes*

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Message

From: Casso, Ruben [Casso.Ruben@epa.gov]
Sent: 6/30/2021 12:20:13 PM
To: Bremer, Kristen [Bremer.Kristen@epa.gov]; Vasu, Amy [Vasu.Amy@epa.gov]
CC: Witt, Jon [Witt.Jon@epa.gov]
Subject: FW: Albuquerque Journal: Judge halts 'uncontrolled' emissions at NM plant

From: Casso, Ruben
Sent: Wednesday, June 30, 2021 7:17 AM
To: Robinson, Jeffrey <Robinson.Jeffrey@epa.gov>; Verhalen, Frances <verhalen.frances@epa.gov>
Cc: Schoellkopf, Lynde <Schoellkopf.Lynde@epa.gov>
Subject: Albuquerque Journal: Judge halts 'uncontrolled' emissions at NM plant

https://www.abqjournal.com/2404806/judge-orders-halt-to-uncontrolled-emissions-at-nm-medical-plant.html

Judge halts 'uncontrolled' emissions at NM plant

BY DAN MCKAY / JOURNAL STAFF WRITER
Published: Tuesday, June 29th, 2021 at 6:31pm
Updated: Tuesday, June 29th, 2021 at 11:15pm

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The Attorney General Complex, named after former AG Paul Bardacke, sits in Santa Fe, not far from the Capitol. Attorney General Hector Balderas has filed an environmental lawsuit against a Santa Teresa plant that sterilizes medical equipment, generating national interest. (Eddie Moore/Albuquerque Journal)

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SANTA FE – The uncontrolled emission of an air pollutant in southern New Mexico is endangering public health and contributing to the risk of cancer in nearby communities, a state judge found Tuesday.

In a four-page order, District Judge Marci Beyer granted a preliminary injunction prohibiting a medical plant in Santa Teresa from allowing uncontrolled emissions of ethylene oxide as it sterilizes medical equipment used in surgeries throughout the United States.

She directed Sterigenics, the company operating the plant, to ensure shipping bays and doors are closed when not in use. Beyer also called for a monitoring program to ensure emissions are limited.

Her order comes after state Attorney General Hector Balderas accused Sterigenics of subverting control technologies in place at the plant by opening shipping bays and doors to release excess gas. His lawsuit accuses the defendants of creating a public nuisance.

“We are grateful the Court considered the risks to New Mexican families and agreed that immediate action must be taken to protect our communities with the rule of law,” Balderas said in a written statement Tuesday.

The case has attracted national attention.

The U.S. Chamber of Commerce and industry groups have warned that any interruption to the plant’s work could strain medical supplies across the state and country.

Supporters of the plant estimate it sterilizes 2.5 million surgical kits, preoperative skin products and other medical devices a day.

A shutdown of the supply would be “catastrophic,” the New Mexico Hospital Association said in a letter to Gov. Michelle Lujan Grisham, who isn’t a party to the lawsuit.

In court filings, Sterigenics says it already closes shipping bays and doors when they’re not in use and that the attorney general presented no evidence that its emissions have harmed the public.

Furthermore, the company says, the plant faces strict oversight by federal and state agencies and is in compliance with air quality regulations.

Judge Beyer, however, found Tuesday that uncontrolled emissions of ethylene oxide pose “an imminent and substantial endangerment to the public health and welfare of residents in Santa Teresa and nearby communities, including a significant risk of cancer, and has resulted in substantial deterioration of air quality.”

Her order prohibits Sterigenics from allowing ethylene oxide to escape without processing or filtration.

She said evidence in the record demonstrates that uncontrolled emissions of ethylene oxide continue to occur and that there are significantly elevated levels of the pollutant in the atmosphere.

Balderas' office filed the lawsuit in December on behalf of the state of New Mexico, seeking damages and other relief.

The plant is about 2 miles from schools, churches and neighborhoods, according to the complaint, and residents of the census tract that includes Santa Teresa have a cancer risk far exceeding the national average.

The Santa Teresa plant is about 6 miles from the border with Mexico and has operated since 1989.

Message

From: Casso, Ruben [Casso.Ruben@epa.gov]
Sent: 1/24/2022 3:28:14 PM
To: Vasu, Amy [Vasu.Amy@epa.gov]
CC: Witt, Jon [Witt.Jon@epa.gov]
Subject: FW: [EXTERNAL] RE: [EXT] Stergenics NM State case update
Attachments: Declaration of Kenny Sullivan re Negative Pressure system sufficient to prevent fugitive emissions.pdf

---

From: Schoellkopf, Lynde <Schoellkopf.Lynde@epa.gov>
Sent: Monday, January 24, 2022 9:24 AM
To: Casso, Ruben <Casso.Ruben@epa.gov>
Subject: FW: [EXTERNAL] RE: [EXT]

From: Jacqueline Ortiz <jortiz@nmag.gov>
Sent: Friday, January 21, 2022 3:37 PM
To: Schoellkopf, Lynde <Schoellkopf.Lynde@epa.gov>; Baizel, Bruce, NMENV <Bruce.Baizel@state.nm.us>
Cc: Cholla Khoury <ckhoury@nmag.gov>
Subject: RE: [EXTERNAL] RE: [EXT]

Hi Lynde,

Attached is a new filing in the Sterigenics case today.

Regards,

Jackie

From: Jacqueline Ortiz <jortiz@nmag.gov>
Sent: Tuesday, January 18, 2022 9:15 AM
To: 'Schoellkopf, Lynde' <Schoellkopf.Lynde@epa.gov>; 'Baizel, Bruce, NMENV' <Bruce.Baizel@state.nm.us>
Cc: Cholla Khoury <ckhoury@nmag.gov>
Subject: RE: [EXTERNAL] RE: [EXT]

Hi Lynde,

Yes, I am and of course. Attached is the order denying the defendants' motions to dismiss and their Report Concerning Its Installation of the Negative Pressure System.

Please let me know if there's anything else I can send your way. I'm happy to help.

Regards,

Jackie

From: Schoellkopf, Lynde <Schoellkopf.Lynde@epa.gov>
Sent: Tuesday, January 18, 2022 7:38 AM

To: Baizel, Bruce, NMENV <Bruce.Baizel@state.nm.us>; Jacqueline Ortiz <jortiz@nmag.gov>
Cc: Cholla Khoury <ckhoury@nmag.gov>
Subject: RE: [EXTERNAL] RE: [EXT]

Good Morning Jacqueline,
I hope you are still the correct contact to receive updates on the Sterigenics, Santa Teresa Facility, state court litigation matter. Our Headquarters counterparts have asked for an update in the cases as there may have been a recent order from the court or some kind of report filed in the matter? Any attachments that you can easily send so that I can share would be most appreciated. Apologies again for having to lean on you all – I really wish our Westlaw account allowed us access to state court matters!
Many Thanks,
Lynde

From: Baizel, Bruce, NMENV <Bruce.Baizel@state.nm.us>
Sent: Tuesday, November 02, 2021 10:42 AM
To: Jacqueline Ortiz <jortiz@nmag.gov>; Schoellkopf, Lynde <Schoellkopf.Lynde@epa.gov>
Cc: Cholla Khoury <ckhoury@nmag.gov>
Subject: RE: [EXTERNAL] RE: [EXT]

Thank you for responding, Jackie.

Bruce

From: Jacqueline Ortiz <jortiz@nmag.gov>
Sent: Tuesday, November 2, 2021 9:37 AM
To: Schoellkopf.Lynde@epa.gov
Cc: Cholla Khoury <ckhoury@nmag.gov>; Baizel, Bruce, NMENV <Bruce.Baizel@state.nm.us>
Subject: [EXTERNAL] RE: [EXT]

CAUTION: This email originated outside of our organization. Exercise caution prior to clicking on links or opening attachments.

Good morning,

I'm one of the attorneys working on the Sterigenics matter. Cholla asked me to reach out to you to provide an update on this case.

By the June 2021 injunction order, the parties were required to meet and confer to discuss an appropriate protocol to monitor Sterigenics' compliance with the injunction order. Unfortunately, we weren't able to agree on a protocol and on October 28, we had a hearing at which we presented several options for monitoring for the Judge to decide.

Also on October 28, the Judge heard arguments on the defendants two motions to dismiss. One motion to dismissed was based on lack of jurisdiction. For that motion, the judge stayed a hearing on the motion until we were allowed to do jurisdictional discovery (the discovery is out, we're meeting and conferring and anticipate a motion to compel soon). The second motion was for failure to state a claim. The judge denied that motion. I'm attaching a copy of the proposed order we submitted to the judge yesterday. Please let me know if you'd like copies of the briefing on these two motions.

I'm attaching their proposed monitoring protocol that they filed. Since the judge did not request that we file the protocols, we did not file ours, but I'm happy to set up a call to talk about our proposals if you'd like.

Please let me know if you'd like any further information or if you'd like to discuss any of this further.

Regards,

Jackie

Jacqueline N. Ortiz, Esq.
Assistant Attorney General, Consumer and Environmental Protection Division
New Mexico Attorney General's Office
P.O. Drawer 1508
Santa Fe, NM 87504
(505)717-3570 (office)
(505)318-1050 (fax)

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From: Khoury, Cholla <ckhoury@nmag.gov>
Sent: Monday, November 1, 2021 3:02 PM
To: Jackie Ortiz <jortiz@nmag.gov>
Subject: Fwd: [EXT]

Can you please provide an update to EPA?

---------- Forwarded message ---------
From: **Schoellkopf, Lynde** <Schoellkopf.Lynde@epa.gov>
Date: Mon, Nov 1, 2021 at 11:39 AM
Subject: RE: [EXT]
To: Baizel, Bruce, NMENV <Bruce.Baizel@state.nm.us>, Khoury, Cholla <ckhoury@nmag.gov>
Cc: McGuire, James <McGuire.James@epa.gov>, Andrews, Suzanne <Andrews.Suzanne@epa.gov>

Good Afternoon Bruce and Cholla,

I am reaching out to you all to check on the status of the NM Santa Teresa facility/Sterigenics state EtO matter that was filed in the 3rd Judicial District Ct. Our Office of Air & Radiation in Washington D.C. has asked Region 6 for any updates in the case (recent filings). If you have any information that you could please share with us – much appreciated!! The last filing we saw was a June 2021 injunction (attached) where the company was to file an air monitoring protocol for fugitive emissions. I am wondering if there has been movement on that front? Many thanks for any updates that we can share with our Office of Air counterparts.

Lynde Schoellkopf

From: Baizel, Bruce, NMENV <Bruce.Baizel@state.nm.us>
Sent: Tuesday, May 04, 2021 11:15 AM
To: Khoury, Cholla <ckhoury@nmag.gov>; Schoellkopf, Lynde <Schoellkopf.Lynde@epa.gov>
Cc: McGuire, James <McGuire.James@epa.gov>
Subject: RE: [EXT]

Thank you for providing those to EPA, Cholla. Would you copy me please when they are sent?

Thank you

Bruce

From: Khoury, Cholla <ckhoury@nmag.gov>
Sent: Tuesday, May 4, 2021 9:18 AM
To: Schoellkopf, Lynde <Schoellkopf.Lynde@epa.gov>
Cc: McGuire, James <McGuire.James@epa.gov>; Baizel, Bruce, NMENV <Bruce.Baizel@state.nm.us>
Subject: Re: [EXT]

Good morning,

I will have my office send you the pleadings/docket in this matter, at which point we would be happy to discuss further.

Thanks,

Cholla

On Mon, May 3, 2021 at 11:46 AM Schoellkopf, Lynde <Schoellkopf.Lynde@epa.gov> wrote:

> Good Afternoon,
>
> I serve as the Branch Chief for ORC's Multimedia Counseling Division. To date, our section has not received any information on the state case. This could be a symptom of office closure, delays in mail, etc. Unfortunately, we also do not have access to PACER or access to state law matters on Westlaw. To get caught up and to best determine when/where/how EPA has been brought into the matter – I am hoping there is

someone from your respective offices that could please send the entire state case file (pleadings, filings, etc.). That will help determine a path forward and better understand where any correspondence may have been mailed. I am a bit surprised to see that EPA is subject to an order to file an amicus brief and the timing of such – if you all have been in touch with someone from our Headquarters office on the matter, please let us know. I will need to coordinate with our Office of General Counsel who typically has the lead on litigation matters in coordination with DOJ – but here were are not in the typical Petitioner/Respondent context. Thank you in advance for any assistance and information you can provide.

Lynde Schoellkopf

Lynde Schoellkopf | US EPA Region 6 | Office of Regional Counsel | Multimedia Counseling | 1201 Elm Street, Suite 500 | Dallas, Texas 75270 | phone: w: (214) 665-7359/c: (469) 597-0603

From: McGuire, James <McGuire.James@epa.gov>
Sent: Monday, May 03, 2021 12:33 PM
To: Baizel, Bruce, NMENV <Bruce.Baizel@state.nm.us>
Cc: Khoury, Cholla <ckhoury@nmag.gov>; Schoellkopf, Lynde <Schoellkopf.Lynde@epa.gov>
Subject: RE: [EXT]

Thanks Bruce and Cholla. Lynde Schoellkopf is lead on this for EPA Region 6 so I am copying her as well.

Thanks,

James McGuire

Regional Counsel, EPA Region 6

214-665-6560

From: Baizel, Bruce, NMENV <Bruce.Baizel@state.nm.us>
Sent: Monday, May 3, 2021 11:59 AM
To: McGuire, James <McGuire.James@epa.gov>
Cc: Khoury, Cholla <ckhoury@nmag.gov>
Subject: RE: [EXT]

You are welcome. Cholla Khoury, copied here, would be the appropriate contact at the NM AG's office. I am the appropriate point of contact here at NMED.

Bruce

From: McGuire, James <McGuire.James@epa.gov>
Sent: Monday, May 3, 2021 10:50 AM
To: Baizel, Bruce, NMENV <Bruce.Baizel@state.nm.us>
Subject: RE: [EXT]

Received, many thanks Bruce! Is there a case attorney at NMED or NM AG's office we could use as an appropriate point of contact?

Thanks,

James McGuire

Regional Counsel, EPA Region 6

214-665-6560

From: Baizel, Bruce, NMENV <Bruce.Baizel@state.nm.us>
Sent: Monday, May 3, 2021 11:47 AM
To: McGuire, James <McGuire.James@epa.gov>
Subject: RE: [EXT]

Here is the order, James. 45 days from April 22. Let me know if you need the pleadings to see the issues. I think in part this stems from the question of assertion of primary jurisdiction, or not.

Bruce

From: McGuire, James <McGuire.James@epa.gov>
Sent: Monday, May 3, 2021 10:31 AM
To: Baizel, Bruce, NMENV <Bruce.Baizel@state.nm.us>
Subject: RE: [EXT]

Great, I am in a meeting right now that should wrap up in the next 10-15 minutes. What is the best number to reach you at?

Thanks,

James McGuire

Regional Counsel, EPA Region 6

214-665-6560

From: Baizel, Bruce, NMENV <Bruce.Baizel@state.nm.us>
Sent: Monday, May 3, 2021 11:29 AM
To: McGuire, James <McGuire.James@epa.gov>
Subject: RE: [EXT]

Morning James

Yes, this morning is unscheduled so I am able to talk.

Bruce

From: McGuire, James <McGuire.James@epa.gov>
Sent: Monday, May 3, 2021 10:24 AM
To: Baizel, Bruce, NMENV <Bruce.Baizel@state.nm.us>
Subject: [EXT]

Bruce-

Do you have a minute today? I have a quick question for you.

Thanks,

James McGuire

Regional Counsel

U.S. Environmental Protection Agency, Region 6

1201 Elm Street, Suite 500

Dallas, Texas 75270-2102

214-665-6560

--

Cholla Khoury, CIPP/US
Director, Consumer and Environmental Protection Division

New Mexico Attorney General's Office
408 Galisteo Street
Santa Fe, NM 87501
(505)490-4052 (office)

(505)231-3483 (cell)

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--

Cholla Khoury, CIPP/US
Director, Consumer and Environmental Protection Division
Interim Director, Litigation Division
New Mexico Attorney General's Office
408 Galisteo Street
Santa Fe, NM 87501
(505)490-4052 (office)
(505)231-3483 (cell)

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1/21/2022 2:14 PM

STATE OF NEW MEXICO
COUNTY OF DOÑA ANA
THIRD JUDICIAL DISTRICT COURT

THE STATE OF NEW MEXICO, EX REL. HECTOR BALDERAS, ATTORNEY GENERAL,	)	
	)	No. D-307-CV-2020-02629
Plaintiff,	)	
v.	)	
STERIGENICS U.S., LLC, SOTERA HEALTH HOLDINGS, LLC, SOTERA HEALTH LLC, AND SOTERA HEALTH COMPANY,	)	
Defendants.	)	

NOTICE OF FILING DECLARATION OF KENNY SULLIVAN, P.E.

Pursuant to Paragraph 7 of the Court's December 20, 2021 Order, Sterigenics U.S., LLC files the Declaration of Kenny Sullivan, P.E., confirming that a negative pressure system is an accepted and reliable method of preventing uncontrolled emissions of ethylene oxide from a facility.

[signature on following page]

ED_013218_00002933-00001

This 21st day of January, 2022.

MODRALL, SPERLING, ROEHL, HARRIS
& SISK, P.A.

By:*/s/ Jeremy K. Harrison*
Alex C. Walker (awalker@modrall.com)
Tiffany L. Roach Martin (tlr@modrall.com)
Jeremy K. Harrison (jkh@modrall.com)
Post Office Box 2168
500 Fourth Street NW, Suite 1000
Albuquerque, New Mexico 87103-2168
Telephone: 505.848.1800
Attorneys for Sterigenics U.S., LLC

ALSTON & BIRD LLP
W. Clay Massey (clay.massey@alston.com)
Admission pro hac vice
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Admission pro hac vice
1201 West Peachtree Street
Atlanta, GA 30309
Telephone: 404.881.7000
Attorneys for Sterigenics U.S., LLC

WE HEREBY CERTIFY that a true and correct copy of the foregoing was submitted through the Odyssey Electronic Filing System for filing and service to all counsel of record this 21st day of January 2022.

MODRALL, SPERLING, ROEHL, HARRIS
& SISK, P.A.

By: */s/ Jeremy K. Harrison*
Jeremy K. Harrison

ED_013218_00002933-00002

STATE OF NEW MEXICO
COUNTY OF DOÑA ANA
THIRD JUDICIAL DISTRICT COURT

THE STATE OF NEW MEXICO, EX REL. HECTOR BALDERAS, ATTORNEY GENERAL,	)	
	)	No. D-307-CV-2020-02629
Plaintiff,	)	
v.	)	
STERIGENICS U.S., LLC, SOTERA HEALTH HOLDINGS, LLC, SOTERA HEALTH LLC, AND SOTERA HEALTH COMPANY,	)	
Defendants.	)	

DECLARATION OF KENNY SULLIVAN, P.E.

I, Kenny Sullivan, declare as follows:

1. I am a Project Engineer at Clean Air Engineering (CleanAir), an environmental source emission testing and consulting firm. I am over 18 years of age, of sound mind, and under no legal disability.

2. The facts set forth herein are based upon my expertise and personal knowledge of air emission testing and measurement, including that of ethylene oxide (EO) and negative pressure systems. If called to testify about these facts, I could and would do so competently and under oath.

Qualifications

3. For nearly fifty (50) years, CleanAir has provided respective clients environmental testing and consulting services. For multiple decades, CleanAir has provided source emission testing, monitoring, and laboratory analysis for a vast range of pollutants regulated under the jurisdiction of Title 40 of the Code of Federal Regulations (Title 40 CFR).

4. CleanAir is an American Society for Testing and Materials (ASTM) accredited air emission testing body. CleanAir is certified by the American Association for Laboratory Accreditation (A2LA) and Stack Testing Accreditation Council (STAC) to perform testing activities in compliance with ASTM. CleanAir is also accredited in accordance with the recognized International Standard ISO/IEC 17025 for technical competence in the field of environmental testing.

5. I am licensed by the state of Illinois as an environmental Professional Engineer (P.E.). I am certified as a Qualified Stack Testing Individual (QSTI) in promulgated test method Groups I through IV, which includes methodology in the measurement of EO, volumetric flow rate, and pollutant destruction efficiency.

6. I have been employed by CleanAir since June of 2009. I have experience in the execution of Environmental Protection Agency (EPA) promulgated methodology and measurement of volatile organic compounds

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(VOCs), which EO is classified as per the EPA, since the start of my employment at CleanAir.

7. Since 2014, my responsibility at CleanAir has been project engineer. As a project engineer, I am responsible for every aspect of a procured test project. This includes protocol development, consulting, planning, test execution, and reporting. Since becoming a project engineer for CleanAir, I have managed projects including the testing and measurement of VOCs, negative pressure systems, and VOC capture and destruction efficiency.

8. Since 2019, I have been project engineer for several projects including the testing and measurement of EO, negative pressure systems, and EO removal and destruction efficiency. During this time, in addition to the standard project engineer responsibilities, I have aided and consulted in negative pressure system design, I have been responsible for the execution of an innovative measurement device designed for higher precision measurement of EO, and I have collaborated directly with EPA regulators and administrators for compliance and best practice methodology in the measurement of EO.

9. For EO and negative pressure system projects, I have tested the removal or destruction efficiency of control devices used in negative pressure systems. I have

also assessed the effectiveness of installed negative pressure systems and determined capture efficiencies.

Negative Pressure Systems

10. Definitions:

    a. *affected area* – Any zone or enclosure within a facility which has the potential to create ambient or workspace exposure to a VOC, in this case EO.

    b. *fugitive emissions* – Emissions from a facility which are not collected by a capture system and are released to the atmosphere.

    c. *natural draft openings (NDOs)* – Any permanent opening in the enclosure that remains open during operation of the facility and is not connected to a duct in which a fan is installed. Examples of NDOs would be open windows, louvers, spaces under doors, and atmospheric vents.

    d. *makeup air* – Air forced into the affected area by means of fan/blower or any other air flow inducing device. Makeup air is utilized to aid in the control of air pressure in the affected area and to ensure fresh air is routinely cycled into the affected area.

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e. *face velocity* – The calculated rate, typically in feet per minute, of air flow through NDOs into or out of an affected area.

f. *control device* – Equipment that removes or eliminates certain compounds or groups of compounds (e.g., EO, VOCs) from the air through any manner of chemical and/or physical processes such as incineration, adsorption, absorption, and filtration, including but not limited to a dry bed system.

g. *negative pressure system* – A network of ducts, blowers/fans, hoods, louvers, vents, dampers, and control devices installed in and around the confines of an affected area with the goal of achieving 100% capture of fugitive emissions.

11. The basic premise of a negative pressure system is the following: If all air flow across the confines of an affected area is *into* the affected area, and all air flow inside the affected area is contained and ducted to a control device, then there are zero fugitive emissions. Emissions originating from inside the affected area are then considered 100% captured.

12. Negative pressure in the affected area is attained by drawing more air from the affected area into the negative pressure system than is being forced into the affected area via makeup air – thus, thinking in terms of 'in must equal out,' the

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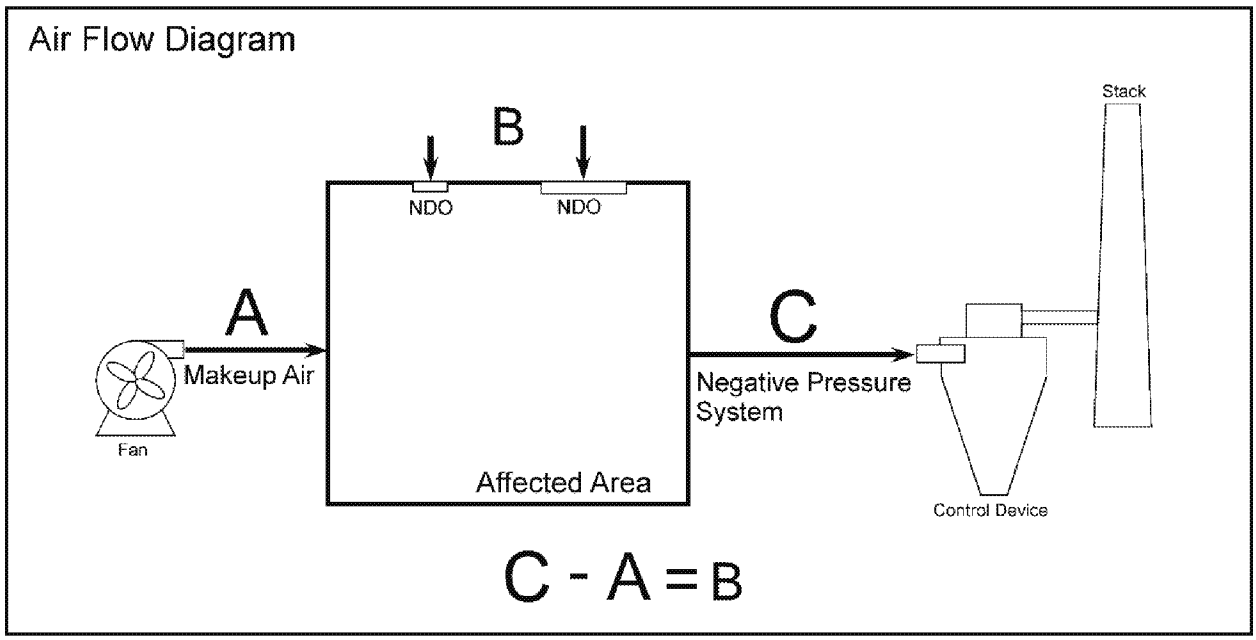
balance of air flow is drawn *into* the affected area through the NDOs, as depicted in the air flow diagram below.



13. If air flow being drawn into the negative pressure system (C) is greater than the makeup air (A), then the face velocity through NDOs (B) is considered positive, and the affected area is considered to be under negative pressure.

14. For the negative pressure system, components are designed so air flow through all NDOs is *into* the affected area and routed to a control device. The negative pressure system is designed so that the air pressure inside the affected area is negative relative to its immediate exterior surroundings. This means air outside the confines of the affected area, under higher pressure, will be drawn into the affected area instead of air inside of the affected area being allowed to emanate out

of the affected area. This inward air flow and negative pressure differential are maintained continuously for the duration of production.

Acceptability and Reliability of a Negative Pressure System

15. A negative pressure system is an accepted and reliable method of preventing uncontrolled EO emissions, i.e. fugitive emissions, from a facility. A negative pressure system is capable of effectively capturing 100% of EO fugitive emissions within the affected area of a facility.

I verify under penalty of perjury that the foregoing is true and correct.

Executed on January 20, 2022.

Kenny Sullivan, P.E.

ED_013218_00002933-00009

Appointment

From: Witt, Jon [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=EA00BC6F645B438682026A77A8D4267C-WITT, JONAT]
Sent: 5/18/2021 1:09:10 PM
To: Rimer, Kelly [Rimer.Kelly@epa.gov]

Subject: Sterigenics New Mexico
Attachments: 2021-04-14 Emergency Mtn ISO Request for TRO and Prelim Injunc.pdf; 2021-04-17 Sterigenics Brief in Opp to Pltf's Emergency Mtn for TRO and Prelim Injunc.pdf; Sterigenics.amicus.April22.pdf
Location: Microsoft Teams Meeting

Start: 5/18/2021 7:30:00 PM
End: 5/18/2021 8:00:00 PM
Show Time As: Tentative

Required Attendees: Rimer, Kelly

Following up from this morning. Depending on how OAR wants to proceed, we may need to come up with some text for an amicus briefing

---

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Appointment

From: Witt, Jon [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=EA00BC6F645B438682026A77A8D4267C-WITT, JONAT]
Sent: 5/18/2021 1:27:27 PM
To: Rimer, Kelly [Rimer.Kelly@epa.gov]

Subject: Sterigenics New Mexico
Attachments: 2021-04-14 Emergency Mtn ISO Request for TRO and Prelim Injunc.pdf; 2021-04-17 Sterigenics Brief in Opp to Pltf's Emergency Mtn for TRO and Prelim Injunc.pdf; Sterigenics.amicus.April22.pdf
Location: Microsoft Teams Meeting

Start: 5/26/2021 1:30:00 PM
End: 5/26/2021 2:00:00 PM
Show Time As: Tentative

Required Attendees: Rimer, Kelly

Following up 5/18. Depending on how OAR wants to proceed, we may need to come up with some text for an amicus briefing

---

Microsoft Teams meeting

Join on your computer or mobile app
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Ex. 6 Personal Privacy (PP) United States, Raleigh
Phone Conference ID: Ex. 6 Personal Privacy (PP)
Find a local number | Reset PIN

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Message

From: Witt, Jon [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=EA00BC6F645B438682026A77A8D4267C-WITT, JONAT]
Sent: 6/15/2021 3:48:24 PM
To: Anderson, Lea [anderson.lea@epa.gov]; Shrager, Brian [Shrager.Brian@epa.gov]
Subject: RE: A couple more Sterigenics follow up questions

Ex. 5 Deliberative Process (DP)

From: Anderson, Lea <anderson.lea@epa.gov>
Sent: Tuesday, June 15, 2021 11:35 AM
To: Witt, Jon <Witt.Jon@epa.gov>; Shrager, Brian <Shrager.Brian@epa.gov>
Subject: RE: A couple more Sterigenics follow up questions

Ex. 5 Deliberative Process (DP)

Lea Anderson
(202) 564-5571

From: Witt, Jon <Witt.Jon@epa.gov>
Sent: Tuesday, June 15, 2021 11:10 AM
To: Shrager, Brian <Shrager.Brian@epa.gov>; Anderson, Lea <anderson.lea@epa.gov>
Subject: RE: A couple more Sterigenics follow up questions

Ex. 5 Deliberative Process (DP)

From: Shrager, Brian <Shrager.Brian@epa.gov>
Sent: Monday, June 14, 2021 11:16 PM
To: Anderson, Lea <anderson.lea@epa.gov>; Witt, Jon <Witt.Jon@epa.gov>
Subject: RE: A couple more Sterigenics follow up questions

I'm unsure of the facts regarding this facility. Jonathan? I'll be out of the office until Thursday.

Thanks!

Brian

From: Anderson, Lea <anderson.lea@epa.gov>
Sent: Monday, June 14, 2021 4:43 PM

To: Shrager, Brian <Shrager.Brian@epa.gov>; Witt, Jon <Witt.Jon@epa.gov>
Subject: RE: A couple more Sterigenics follow up questions

Jon or Brian,

If you could take a look at the paragraph below and let me know if it's accurate. The last two sentences in particular are not clear to me – Ex. 5 Deliberative Process (DP)

Ex. 5 Deliberative Process (DP)

Lea Anderson
(202) 564-5571

From: Oakes, Matthew (ENRD) <Matthew.Oakes@usdoj.gov>
Sent: Monday, June 14, 2021 3:13 PM
To: Anderson, Lea <anderson.lea@epa.gov>
Subject: A couple more Sterigenics follow up questions

Ex. 5 AC/AWP/DP

Ex. 5 AC/AWP/DP

From: Anderson, Lea <anderson.lea@epa.gov>
Sent: Monday, June 14, 2021 11:19 AM
To: Oakes, Matthew (ENRD) <Matthew.Oakes@usdoj.gov>; Marks, Matthew <Marks.Matthew@epa.gov>
Cc: Harvey, Judy (ENRD) <Judith.Harvey@usdoj.gov>; Branning, Amy <Branning.Amy@epa.gov>; Srinivasan, Gautam <Srinivasan.Gautam@epa.gov>; Witt, Jon <Witt.Jon@epa.gov>
Subject: RE: LPS-#288438-v1-New_Mexico_v_Sterigenics_Amicus_Brief_June_7.docx

Ex. 5 AC/AWP/DP

From: Oakes, Matthew (ENRD) <Matthew.Oakes@usdoj.gov>
Sent: Monday, June 14, 2021 11:03 AM
To: Anderson, Lea <anderson.lea@epa.gov>; Marks, Matthew <Marks.Matthew@epa.gov>
Cc: Harvey, Judy (ENRD) <Judith.Harvey@usdoj.gov>; Branning, Amy <Branning.Amy@epa.gov>; Srinivasan, Gautam <Srinivasan.Gautam@epa.gov>
Subject: RE: LPS-#288438-v1-New_Mexico_v_Sterigenics_Amicus_Brief_June_7.docx

Ex. 5 AC/AWP/DP

-Matt

From: Anderson, Lea <anderson.lea@epa.gov>
Sent: Monday, June 14, 2021 9:37 AM
To: Oakes, Matthew (ENRD) <Matthew.Oakes@usdoj.gov>; Marks, Matthew <Marks.Matthew@epa.gov>
Cc: Harvey, Judy (ENRD) <Judith.Harvey@usdoj.gov>; Branning, Amy <Branning.Amy@epa.gov>; Srinivasan, Gautam <Srinivasan.Gautam@epa.gov>
Subject: RE: LPS-#288438-v1-New_Mexico_v_Sterigenics_Amicus_Brief_June_7.docx

Ex. 5 AC/AWP/DP

From: Oakes, Matthew (ENRD) <Matthew.Oakes@usdoj.gov>
Sent: Saturday, June 12, 2021 10:26 AM
To: Marks, Matthew <Marks.Matthew@epa.gov>
Cc: Anderson, Lea <anderson.lea@epa.gov>; Harvey, Judy (ENRD) <Judith.Harvey@usdoj.gov>; Branning, Amy <Branning.Amy@epa.gov>; Srinivasan, Gautam <Srinivasan.Gautam@epa.gov>
Subject: RE: LPS-#288438-v1-New_Mexico_v_Sterigenics_Amicus_Brief_June_7.docx

Ex. 5 AC/AWP/DP

From: Marks, Matthew <Marks.Matthew@epa.gov>
Sent: Saturday, June 12, 2021 8:26 AM

To: Oakes, Matthew (ENRD) <Matthew.Oakes@usdoj.gov>
Cc: Anderson, Lea <anderson.lea@epa.gov>; Harvey, Judy (ENRD) <Judith.Harvey@usdoj.gov>; Branning, Amy <Branning.Amy@epa.gov>; Srinivasan, Gautam <Srinivasan.Gautam@epa.gov>
Subject: Re: LPS-#288438-v1-New_Mexico_v_Sterigenics_Amicus_Brief_June_7.docx

Ex. 5 AC/AWP/DP

Matthew C. Marks
Deputy Associate General Counsel
Air and Radiation Law Office
Office of General Counsel
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460
T: 202-564-3276
E: marks.matthew@epa.gov

On Jun 11, 2021, at 8:25 PM, Oakes, Matthew (ENRD) <Matthew.Oakes@usdoj.gov> wrote:

Ex. 5 AC/AWP/DP

Ex. 5 AC/AWP/DP

From: Anderson, Lea <anderson.lea@epa.gov>
Sent: Friday, June 11, 2021 6:37 PM
To: Oakes, Matthew (ENRD) <Matthew.Oakes@usdoj.gov>; Branning, Amy <Branning.Amy@epa.gov>
Cc: Srinivasan, Gautam <Srinivasan.Gautam@epa.gov>; Marks, Matthew <Marks.Matthew@epa.gov>
Subject: RE: LPS-#288438-v1-New_Mexico_v_Sterigenics_Amicus_Brief_June_7.docx

HI Matt,

Ex. 5 AC/AWP/DP

Ex. 5 AC/AWP/DP

Lea Anderson
(202) 564-5571

From: Oakes, Matthew (ENRD) <Matthew.Oakes@usdoj.gov>
Sent: Wednesday, June 09, 2021 12:46 PM
To: Branning, Amy <Branning.Amy@epa.gov>
Cc: Srinivasan, Gautam <Srinivasan.Gautam@epa.gov>; Anderson, Lea <anderson.lea@epa.gov>
Subject: RE: LPS-#288438-v1-New_Mexico_v_Sterigenics_Amicus_Brief_June_7.docx

Ex. 5 AC/AWP/DP

From: Branning, Amy <Branning.Amy@epa.gov>
Sent: Wednesday, June 9, 2021 12:15 PM
To: Oakes, Matthew (ENRD) <Matthew.Oakes@usdoj.gov>
Cc: Srinivasan, Gautam <Srinivasan.Gautam@epa.gov>; Anderson, Lea <anderson.lea@epa.gov>
Subject: FW: LPS-#288438-v1-New_Mexico_v_Sterigenics_Amicus_Brief_June_7.docx

Hi Matt:

Thank you for sending the draft brief.

First of all, please include Lea Anderson in your emails re. this. She is the practice group leader for section 112 NESHAP. Ex. 6 Personal Privacy (PP)

Ex. 5 AC/AWP/DP

Amy Huang Branning
EPA Office of General Counsel
phone: (202) 564-1744
fax: (202) 564-5603 or (202) 564-0070

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From: Oakes, Matthew (ENRD) <Matthew.Oakes@usdoj.gov>
Sent: Wednesday, June 09, 2021 10:42 AM
To: Branning, Amy <Branning.Amy@epa.gov>; Schoellkopf, Lynde <Schoellkopf.Lynde@epa.gov>;

Harvey, Judy (ENRD) <Judith.Harvey@usdoj.gov>; Srinivasan, Gautam <Srinivasan.Gautam@epa.gov>; Witt, Jon <Witt.Jon@epa.gov>
Cc: Thomas.Carroll@USDOJ.GOV; Purdy, Angeline (ENRD) <angeline.purdy@usdoj.gov>; Long, Kenneth (ENRD) <Kenneth.Long@usdoj.gov>; Thomas Ballantine <thomas.ballantine@usdoj.gov>
Subject: LPS-#288438-v1-New_Mexico_v_Sterigenics_Amicus_Brief_June_7.docx

Hi Everyone,

I've attached a preliminary draft of the Sterigenics amicus brief for your review. Ex. 5 AC/AWP/DP

Ex. 5 AC/AWP/DP

Message

From: Witt, Jon [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=EA00BC6F645B438682026A77A8D4267C-WITT, JONAT]
Sent: 6/15/2021 8:40:52 PM
To: Anderson, Lea [anderson.lea@epa.gov]
Subject: RE: New Mexico: facility-specific assessments

Ex. 5 AC/AWP what we said in the ANPRM (84 FR 67893):

"NATA is the Agency's nationwide air toxics screening tool, designed to help the EPA and state, local, and tribal air agencies identify areas, pollutants, or types of sources for further examination."

Ex. 5 AC/AWP

From: Anderson, Lea <anderson.lea@epa.gov>
Sent: Tuesday, June 15, 2021 1:59 PM
To: Witt, Jon <Witt.Jon@epa.gov>
Subject: New Mexico: facility-specific assessments

Ex. 5 AC/AWP

Lea Anderson | Assistant General Counsel for the Air Toxics, Consumer Products and Indoor Air Group |
US EPA | Office of General Counsel | Air and Radiation Law Office | phone: (202) 564-5571