Beyond Science and Decisions: From Issue Identification to Dose-Response Assessment: Summary of Preliminary Case Study: Health Risk Tradeoffs in Regulating Emissions of Ethylene Oxide (EtO) from Commercial Sterilization Plants

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Introduction

Science and Decisions: Advancing Risk Assessment (NAS, 2009) calls for increased utility of risk assessments and recommends that among other things, risk assessments should include estimates of the associated costs and any countervailing risks associated with the proposed mitigation options.

There are many ways in which the process of assessing and managing risk can lead to an increase in risk, similar to the concept of iatrogenic risk in medicine (risk "caused by the doctor"). Physicians must consider the side effects of their treatment decisions and the U.S. Environmental Protection Agency (EPA) should similarly consider the complete impact of its Integrated Risk Information System (IRIS) risk-assessments and how the use of the IRIS risk factors in managing environmental risk could lead to other potentially greater substitution risks.

The EPA completed a health assessment ethylene oxide (EtO) in 1985 as support for decision-making regarding possible regulation of EtO as a hazardous air pollutant (EPA, 1985). Subsequently, EtO was designated a hazardous air pollutant (HAP) under the 1990 Clean Air Act (CAA) due to increasing concerns regarding the adverse human health effects of EtO exposure. EPA's Office of Air and Radiation subsequently requested that the IRIS Program update the 1985 IRIS assessment for EtO. The IRIS Program began work on the EtO assessment in the early 2000s and completed it in December 2016 (84 Fed. Reg. 239, 2019).

The 2014 National Air Toxics Assessment (2014 NATA) used the EtO IRIS Inhalation Unit Risk (IUR) factor for the first time and the results were released in August 2018 (EPA, 2018). The 2014 NATA (EPA, 2018) identified EtO emissions as a potential concern in several areas across the country even though EtO had not been identified as a chemical of significant concern in previous NATAs. The elevated EtO risks resulted entirely because the IUR factor increased 30-fold based on the updated health assessment completed by the IRIS program in December 2016 (EPA, 2016). Additional investigation of NATA inputs and results led EPA to identify commercial sterilization facilities using EtO as a source category that contributes to some of these risks (84 Fed. Reg. 239, 2019). This led to more detailed evaluations of the potential health risks associated with emissions of EtO, primarily from sterilization plants. These evaluations have been based on 24-hour EtO concentrations either monitored by EPA, local health departments in coordination with EPA, or municipalities (GA EPD, 2019a, b, and c, CO APCD, 2018, CO DPHE, 2019, Lake County HDCHC, 2019 and 2020, IL EPA, 2019, GHD, 2019a and b). When these short-term sampling results and EPA's updated IUR factor were used to estimate theoretical cancer risks associated with long-term EtO exposure in ambient air, risks were above EPA's acceptable risk range of 1-in-1,000,000 to 1-in-10,000 in locations close to and distant from the sterilization plants.

Background

Commercial sterilization facilities use ethylene oxide (EtO) as a sterilant for heat- or moisture-sensitive materials and as a fumigant to control microorganisms or insects. The EtO Commercial Sterilization and Fumigation Operations source category covers the use of EtO as a sterilant and fumigant following the production of medical equipment and supplies, and in miscellaneous sterilization and fumigation operations at both major and area sources. Standards in 40 CFR part 63, subpart O regulate emissions of EtO from existing and new commercial sterilization operations using one ton of EtO per year or more (84 Fed. Reg. 239, 2019).

According to the Ethylene Oxide Sterilization Association (EOSA, 2018), EtO is used to sterilize more than 20 billion healthcare products each year in the U.S. alone, which represents more than 50% of the medical devices sterilized in the U.S. annually. Hundreds of thousands of medical, hospital, and laboratory processes rely on EtO to sterilize devices and equipment. For many medical devices, sterilization with EtO may be the only method that effectively sterilizes without damaging the device during the process. Medical devices made from certain polymers (plastic or resin), metals, or glass, or that have multiple layers of packaging or hard-to-reach places (for example, catheters) are frequently sterilized with EtO (FDA, 2019).

Although discovered as an effective sterilant decades ago, EtO has gained favor as a sterilization method in recent years because of its advantages over other technologies. The compatibility of EtO with a wide range of materials as well as its penetration properties compared with dry heat or steam, has made EtO sterilization the preferred sterilization method for most heat- and/or moisture-sensitive medical products. EtO sterilization has become particularly important since the single-use medical device market has grown and with medical devices supplied in customized kits for use in specific medical and surgical procedures. A major benefit of EtO is that it can be used to sterilize multiple medical instruments/devices simultaneously in these customized kits, which contain multiple instruments/supplies and often have multiple layers of packaging that are not easily penetrated by other sterilizing agents (Mendes, G, Brandão, T., and Silva, C., 2007). Pre-packaged central-line kits may contain up to 10 different medical devices, while surgical kits can have 20 to 50 different consumable items (e.g., gauze, swabs, sutures, scalpels, instruments and other implants/devices) (Richards *et al*., 2000; Crick *et al.*, 2008).

1. **Provide a few sentences summarizing the method illustrated by the preliminary case study.**

This preliminary case study represents a "health-risk tradeoff" analysis intended to provide a screening-level method for comparing theoretical environmental cancer risks based on regulatory risk factors and unintended risks created by regulating those risks.

2. **Describe the problem formulation(s) the case study is designed to address.**

In using EPA's revised EtO IUR factor to estimate the potential health impacts from EtO levels modeled for and monitored near sterilization plants, regulators and local communities focused on the direct benefit of decreased use of EtO as a sterilizing agent, or in some cases essentially banning

its use (i.e., reduction in theoretical cancer risk), but the countervailing risk of increased healthcare-associated infections (HAIs) has not been adequately considered. Although a scenario involving a complete ban on the use of EtO to sterilize medical devices/supplies may seem extreme, it is not entirely unlikely. In 2019, the Illinois EPA issued a Seal Order preventing a sterilization plant in a suburb of Chicago from commencing any new sterilization cycles using EtO (Illinois.gov, 2019), which was followed by a company decision not to reopen the plant seven months later (WBBM, 2019). Amid heightened concerns over elevated cancer risks in other communities near sterilization plants, similar actions are being requested. If EtO were banned, an increase in HAIs is anticipated because prepackaged procedure/surgical kits would likely become unavailable due to lack of a suitable alternative sterilizing agent that does not damage device materials and is capable of penetrating the multiple layers of packaging typical of these kits.

Studies demonstrate that opening individually wrapped/enclosed medical supplies/instruments introduces a possible source of contamination of the surgical set-up or sterile procedure field and repeated opening compounds the potential for contamination (Crick, *et al.*, 2008; Smith *et al.*, 2009). This preliminary case study compares theoretical cancer risk estimates from exposure to EtO concentrations in ambient air near medical equipment sterilization plants[1] and the countervailing increase in the risk of HAIs that are expected if EtO becomes unavailable for sterilization of multiple instruments simultaneously in procedure/surgical kits.

Estimation of Theoretical Cancer Risks

The estimation of theoretical cancer risks associated with EtO exposure near sterilization plants relies on EPA's 2016 EtO IUR factor (EPA, 2016), as well as an alternative Draft EtO IUR factor developed by the Texas Commission on Environmental Quality (TCEQ, 2019). The TCEQ's Draft IUR factor is several orders of magnitude lower than EPA's IUR factor. the TCEQ's Draft IUR factor is based on the same occupational cohort dataset used by EPA in deriving its IUR factor in which workers were exposed to EtO concentrations for decades that are thousands of times higher than levels of EtO detected in ambient air today. The primary difference in the two values is in the choice of dose-response models chosen for extrapolating from high EtO concentrations in the worker study to the relatively low levels found in ambient air today. EPA chose a supra-linear model instead of using the more conventional linear model that the TCEQ used. TCEQ demonstrated that EPA's model significantly over-predicted the number of cancers observed in the worker cohort (TCEQ, 2019). The TCEQ's Draft IUR factor is considered to represent the more scientifically-defensible value.

Although several sterilization plants, one chemical company and several municipalities conducted their own ambient EtO monitoring, only 24-hour sampling results collected by EPA or local health departments in coordination with EPA or local air pollution control departments were used to estimate cancer risk associated with exposure to EtO in ambient air. This decision was made because final quality assured/quality controlled (QA/QCed) monitoring datasets from those sources are readily accessible on government websites. Some of the EtO monitoring results used in this analysis were collected after additional pollution controls were installed at sterilization

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[1] Data were collected in Illinois near one specialty chemical plant.

plants, but no data collected after closure of a facility were used (i.e., after February 15, 2019 in Willowbrook Illinois).

Because all of the available EtO sampling results represent 24-hour samples that were collected over a few days or months, which are not appropriate for use in evaluating long-term exposure, all of the EtO data were utilized together as a single dataset for estimating an overall 95% Upper Confidence Limit (UCL) using EPA's ProUCL Version 5.1. These data represented more than 750 data points that were collected from different locations (Village of Willowbrook, IL, Lake County, IL, Covington GA, Smyrna GA, and Lakewood Co) between August 2018 and December 2019. The EtO UCL recommended by ProUCL was 1.2 $\mu g.m^3$ (95% KM (Chebyshev) UCL) and was assumed to represent a reasonably conservative estimate of long-term EtO concentrations near sterilization plants in the U.S. The ProUCL input (monitored EtO concentrations) and output (estimated 95% UCLs) files are provided as **Attachment 1**.

Theoretical estimated cancer risks using both EPA's 2016 and TCEQ's Draft IUR factor for EtO are summarized in **Table 1** (*see* Preliminary Results), along with estimated HAI risks, the calculation of which is discussed in the following section.

<u>Estimation of HAI Risks</u>

Disease transmission resulting in infection requires a chain of events and circumstances including a microorganism that is pathogenic to humans, the presence of the pathogen in the environment, survival of the pathogen, a portal of entry into the potential host, a sufficiently large dose/inoculum, and failure of the human host's immune system to prevent infection (i.e., a susceptible host). Each of these events represent an independent step in the chain and must occur in the proper sequence. Infection will be prevented if any step in the sequence fails to occur. Therefore, research on the probabilities for each of these events (or a range of probabilities) was conducted and infection risks were then calculated by multiplying the independent probabilities of each event to estimate a compound probability of infection (Rutala and Weber, 2007).

The conduct of a microbial risk assessment can generally be contemplated in the context of the standard risk assessment paradigm, as follows:

1) Hazard Identification - effects of microbes on the population
2) Toxicity Assessment – virulence (similar to mechanism of toxicity), infectious dose (similar to RfD), dose response (similar to cancer potency factor), infectivity (how frequently it spreads among hosts), or probability of progression from colonization to infection
3) Exposure Assessment – occurrence in the environment and transmission from the environment to a host
4) Risk Characterization – comparison of an exposure level to the infectious dose or calculation of the probability of infection

Estimates of and assumptions about the probability of the independent occurrences in the chain of events that must take place for infection to occur are discussed in the context of the risk assessment paradigm below.

<u>Hazard Identification</u>: Hazard identification involves identifying both the microbial agent and spectrum of clinical outcomes associated with a specific microorganism.

Spectrum of Clinical Outcomes
The spectrum of clinical outcomes from HAIs range from asymptomatic infections to death (Haas, Rose, and Gerba, 1999). Infection risk estimates for microorganisms capable of causing infectious disease in humans has generally relied on outbreak data to assess human health outcomes and indicator microorganisms for assessing the potential for contamination.

The National Healthcare Safety Network (NHSN) is the nation's most widely used HAI tracking system (CDC, 2019). The NHSN tracks risk-adjusted rates that account for differences in patient case mix for the following medical device-related HAIs:

- Central line-associated bloodstream infections (CLABSIs)
- Catheter-associated urinary tract infections (CAUTIs)
- Ventilator-associated events (VAEs)

The NHSN also tracks procedure-associated data on Surgical site infections (SSIs).

The data are voluntarily reported to the NHSN by a subset of Acute Care Hospitals (ACHs) and Critical Access Hospitals (CAHs). CLABSIs and CAUTIs are also voluntarily reported by Inpatient Rehabilitation Facilities (IRFs). This risk assessment uses 2018 NHSN data. The NHSN device-associated HAI database represents a high-quality dataset that is updated annually and 2018 is the most recent year for which data are available. However, only the increased risk of developing CLABSIs and SSIs expected if EtO becomes unavailable are estimated in this assessment. The risk assessment will be updated with estimates for CAUTIs and VAEs following receipt of input on the proposed case study methods from the peer review panel. The 2018 CLABSI and SSI rates used in the risk assessment are provided in **Tables A** and **B** of **Attachment 2**.

Pathogens that Cause CLABSIs and SSIs
Some resources indicate that Coagulase negative Staphylococcus (CoNS) is the most common bacteria found on medical devices and the most frequent cause of HAIs (Piette and Verschraegen, 2009; Becker, Heilmann, and Peters, G., 2014), while others indicate that *Staphylococcus aureus* (*S. aureus*) is the most commonly found bacteria (Smith *et al*., 2009; Percival, Suleman, Vuotto, and Donelli, 2015). The pathogens most often associated with CLABSIs and SSIs and the percentage of these infection caused by specific bacteria is provided in **Tables A** and **B** of **Attachment 2**.

<u>Toxicity Assessment</u>: There is a high risk of infection if surgical instruments, cardiac or urinary catheters, implants, or other medical devices/supplies that enter sterile body cavities are contaminated by microorganisms (Rutala and Weber, 2007). In microbial risk assessments, it is generally assumed that a single microorganism can initiate infection (i.e., no threshold) (Cornforth *et al*., 2015), partly because the exact relationship between inoculum size (i.e., dose)

and the probability of infection is unclear for most microorganisms. Therefore, this risk assessment assumes that *any* microbial contamination of medical supplies or devices that enter sterile tissue or the vascular system poses some risk of infection.

No type of inserted or implanted foreign body has ever failed to be colonized by CoNS, with *S. epidermidis* as the leading cause of CoNS device-related HAIs. Broken skin and the respiratory or urinary tract can become asymptomatically colonized with many bacteria. Colonized patients may subsequently develop clinical infection, but this does not always occur (Coello *et al*., 1997; Roghmann, *et al*, 1997; Mossad, *et al*., 1997). One explanation for why colonization by pathogens does not necessarily progress to full-blown infection is that humans naturally carry many of the bacteria associated with device-related HAIs on their skin and mucous membranes.[2] Despite the multifactorial nature of bacterial carriage, pathogenesis, and host vulnerability, observed probabilities of progression from colonization to CLABSIs and SSIs were obtained from the scientific literature for several bacteria responsible for HAIs. Those probabilities are provided in **Tables A** and **B** of **Attachment 2**.

HAIs are the 10th leading cause of death in the U.S. (AST, 2019). CLABSIs make up about 12% of all HAIs (O'Grady *et al*., 2011), while SSIs make up about 20% of HAIs (Anderson *et al*., 2014). Mortality ratios, representing the observed fraction of patients that contract a CLABSI or SSI who die from it, were also obtained from the literature and are presented in **Tables A** and **B** of **Attachment 2**.

Exposure Assessment: In microbial risk assessments, exposure assessment often takes the form of pathogen occurrence and prevalence (how often specific microbes are found) or the distribution of microorganisms in space over time. Although there is no shortage of sources of infectious agents in hospital and clinical settings, concentrations of these organisms in the medium in direct contact with patients (e.g., medical equipment/devices) are rarely known (Haas, Rose, and Gerba, 1999).

Pathogen Occurrence and Distribution in the Environment
The most common sources of pathogens associated with HAIs include the patients themselves, medical equipment or devices, the hospital environment, health care personnel, contaminated drugs, and contaminated food.

Healthcare workers are a primary source of bacterial contamination of medical supplies/devices (Smith *et al*., 2009). Many microorganisms can survive for long periods of time on environmental surfaces in hospitals and clinics, making inanimate surfaces an important source of healthcare worker hand contamination (Bhalla, *et al*., 2004; Kramer, Schwebke, and Kampf, 2006; Ahmed, *et al*., 2019). Although wearing gloves during patient care is generally associated with a reduction in hand contamination, gloved hands of healthcare workers also showed significant bacterial colonization (Pittet, *et al*., 1999). Even when there is no direct patient contact, touching contaminated hospital surfaces can result in the acquisition of pathogens on healthcare worker's gloved and ungloved hands (Kleinpell, Munro, and Giuliano, 2008; Bhalla, *et al*., 2004). For example, studies have

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[2] All humans are colonized with *S. Epidermis* (the most prevalent species in CoNS). Massey, Horsburgh, Lina, and Höök, 2006.

shown vancomycin-resistant *Enterococcus* and methicillin-resistant *S. aureas* (MRSA) contaminated gloved hands nearly half of the time after healthcare workers touched the bed rails or bedside tables of colonized patients. *Acinetobacter, Klebsiella*, and *Enterobacter* have also been detected on the gloved hands of healthcare workers. In fact, cultures were positive for one or more pathogens that cause HAIs more than 50% of the time (Bhalla, *et al.*, 2004). Contamination of ungloved hands with low levels of pathogenic microorganisms also occurs more than 50% of the time, even from surfaces in rooms that had been terminally cleaned after patient discharge (Kleinpell, Munro, and Giuliano, 2008). Healthcare workers have also been observed to change gloves only 16% of the time between patient interactions (Pittet, *et al.*, 1999).

Pathogen Transmission from Medical Devices to Patients
According to one review, more than 90% of HAIs are associated with medical devices. In addition to providing a portal of entry for microbial colonization or infection, medical devices facilitate transfer of pathogens from one part of the patient's body to another, from healthcare worker-to-patient, or from patient-to-healthcare worker-to-patient (Kleinpell, Munro, and Giuliano, 2008).

Based on the above discussion of pathogen occurrence and distribution in the healthcare environment, the probability that a healthcare workers' gloves may be contaminated is substantial. In this risk assessment, it was conservatively assumed that that all healthcare workers wear gloves but that the probability that those gloves are contaminated is a 50% and that contaminated gloves are not changed 85% of the time between activities (*see* **Tables A** and **B** of **Attachment 2**).

The possibility that healthcare staff carry human pathogens on their gloves up to 42% of the time (i.e., 50% [glove contamination] x 85% [failure to change gloves between activities]) has grave implications for the potential contamination of medical supplies/devices. Two studies located in the scientific literature (Crick, *et al.*, 2008; Smith *et al.*, 2009) hypothesized a potential increased risk of infection associated with the practice of using individually packaged medical supplies/devices (orthopedic screws in both studies). However, estimating the degree of clinical risk associated with the practice of opening individually packaged medical supplies/devices is difficult. Smith and colleagues reported that the act of opening the packets yielded bacterial growth in 7/50 cases, although microorganisms were not cultured from the devices themselves but rather from the packet opening process (i.e., the package was opened by a gloved scrub nurse over a petri dish after removing the inner packet from an outer packet that had been previously opened by an ungloved circulating nurse via accepted aseptic technique). Therefore, the bacterial growth in this study represent the result of bacterial scattering due to the opening of individually wrapped supplies/devices. The Crick *et al.* (2008) study, which used similar aseptic technique for transferring individually-packaged screws to the sterile field and packet opening reported a 1% chance of contaminating medical devices/supplies with each individual package opened. If at any time the nurses felt that contamination may have occurred, the sample was removed from the trial, as would occur during a normal surgery. At the conclusion of the first stage involving 100 individually packaged screws,

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contamination was identified in one sample, which showed a streaky distribution of the ultraviolet cream used to identify contamination on the outer rim of the inside packaging (i.e., not on the screw itself). The authors concluded that this was consistent with the inside packaging contacting the outer packet, which had been touched before the removal of the inside packet.

Although neither of the two studies described above assessed the health implications of the contamination, they confirmed occult contamination of medical device packaging. Based on these studies, it was assumed that the probability of contaminating a medical device is 1% per individual package opened. Central line kits typically contain around 10 items (sterile mask, cap, gloves, full drape, disinfectants, lines, needles, syringes, and often guidelines or a checklist) (Silow-Carroll and Edwards, 2011), while specialized surgical procedure kits may contain 20 to 50 individual items (Richards *et al*., 2000; Crick *et al*., 2008; Stockert and Langerman, 2014; Van Meter and Adam, 2016). Based on this information, it was assumed that 10 individual packages are opened during central-line insertion and that 20 individual packages were opened during surgery to estimate the risk of CLABSIs and SSIs, respectively.

Risk Characterization: The scientific literature was searched for information on increased HAIs resulting from contamination of medical devices/supplies by healthcare staff required to open individually wrapped sterile medical supplies versus scenarios in which procedure/surgical kits were used. Although several studies demonstrated decreased rates of infection associated with overall infection control programs, none focused exclusively on infection decreases from use of procedure/surgical trays/kits, although many acknowledged that their use reduced surgery time and mistakes and likely reduced infection rates (Fenik *et al*., 2013; Allen *et al*., 2014). One study evaluated use of traditional vs. single-use instrumentation trays on SSIs and concluded that since there was no difference in procedure time between the groups, the observed 93% decrease in infection rate was likely due to decreased risk of contamination when using single-use trays, which reduced the number of instrument trays that needed to be opened during surgery by 5 or 6. The traditional equipment comparison group included surgeries in which 6–12 trays of instruments were required to be opened for each surgery (Siegel, Patel, Milshteyn, Buzas, *et al*., 2015).

An algorithm was constructed to estimate the increased risk of medical device-related HAIs expected if EtO becomes unavailable for sterilization of procedure/surgical kits. The algorithm is intended to consider the independent probabilities of a series of occurrences in the chain of events important for development of infection (e.g., presence of microorganism that is pathogenic to humans in the environment, survival of the pathogen, a portal of entry into the potential host, and a susceptible host). The algorithm is presented below:

$$Risk = \sum \left(IR \; x \; P_{microorg \; x,y,z..} \; x \; P_{Inf} \; x \; P_{glove \; contam} \; x \; P_{glove \; chan} \quad P_{\frac{MD \; contam}{pkg}} \; x \; \# \frac{items}{pkg} \right)$$

Where:

Risk	=	Risk of contracting a device-related HAI
IR	=	Annual NHSN CLABSIs or SSIs from ACHs + CAHs + IRFs
$P_{microorg}$	=	Probability of infection caused by specific microorganism
P_{inf}	=	Probability that microbe colonization progresses to infection
$P_{glove \; contam}$	=	Probability that healthcare workers' gloves are contaminated
$P_{glove \; contam}$	=	Probability that healthcare workers' gloves are changed between activities
$P_{MD \; contam/pkg}$	=	Probability of contaminating medical device with each package opened
# items/pkg	=	Number of medical supply/device packages opened

Estimated infection risks are summarized in **Table 1**. **Tables A** and **B of Attachment 2** shows the calculations.

To estimate the increased number of CLABSI and SSI-associated mortalities, the risk of CLABSIs and SSIs were multiplied by the mortality ratios for CLABSIs and SSIs, respectively. The mortality ratio represents the fraction of patients that contract a CLABSI or SSI who die from it. Estimated mortality risks are summarized in **Table 2**. To estimate the increase in the number of deaths expected to occur (annually) from CLABSIs and SSIs, the risk of death from CLABSIs and SSIs were multiplied by the annual number of central line insertions and surgeries (in patient only) in the U.S. (O'Grady, *et al*., 2011; McGee and Gould, 2003; Steiner, *et al*. 2018). The number of central line insertions and surgeries are provided in **Tables A** and **B of Attachment 2**, as are the mortality calculations.

Preliminary Results

Efforts to reduce environmental risks from exposure to contaminants present in ambient air often neglect the possibility that measures to reduce the target risk may introduce or enhance countervailing risks. If EtO, which is currently used to sterilize more than 20 billion healthcare products each year in the U.S. alone (i.e., more than 50% of medical devices sterilized in the U.S. annually) becomes unavailable for use in sterilizing medical procedure and surgical kits, there would likely be a an increase in HAIs and deaths associated with HAIs. The increase in risk is expected to arise from a change in the current practice of sterilizing procedure/surgical kits containing 10 to 50 different items simultaneously to sterilizing medical/surgical supplies and instruments individually. Studies show that the very act of opening medical supplies and surgical instruments/devices that are individually wrapped/enclosed increases the risk of device contamination and that the risk is compounded with each package opened (Crick, *et al.*, 2008; Smith *et al.*, 2009).

Table 1 provides a side-by-side comparison of the estimated increase in the risk of infection from two categories of HAIs (CLABSIs, SSIs) and the theoretical cancer risks potentially posed by exposure to EtO concentrations monitored near sterilization plants in the U.S. The infection risks were estimated under the presumption that EtO is no longer available for use in sterilizing procedure/surgical kits and the environmental risks were estimated under the presumption that EtO remains available for this use.

Table 1: Comparison of Annual Estimated HAI Risks and Theoretical Lifetime Cancer Risks

HAI Risks			Cancer Risks from Environmental Exposure	
CLABSI	SSI	TOTAL	EPA IUR Factor	TCEQ IUR Factor
5×10^{-6}	8×10^{-5}	8×10^{-5}	6×10^{-3}	2×10^{-6}

As shown in **Table 1**, although the estimated risk of HAIs is less than the theoretical cancer risks using EPA's IUR factor, it is considerably greater than cancer risks estimated using TCEQ's Draft IUR factor, which is considered to represent a more scientifically-defensible value. However, only two categories of potential HAIs reported to NHSN were estimated. The other two categories of HAIs tracked by NHSN (Catheter-Associated Urinary Tract Infections or CAUTI and Ventilator-Associated Events or VAE) are also expected to increase if EtO becomes unavailable. CAUTIs represent approximately 40% of HAIs, with significant consequences for morbidity and mortality (Haque, Sartelli, McKimm, and Bakar, 2018) and ventilator-associated pneumonia causes about 22% of HAIs (Beckers, 2014). If risks for these other HAI categories are estimated, it is expected that the disparity in the risk of HAIs and the theoretical cancer risks would be even greater. These results clearly indicate that one risk would be substituted for another if EtO became unavailable for use as a sterilizing agent.

The estimated increase in the risk of CLABSI and SSI-related deaths, as well as the total number of deaths expected to result from HAIs annually are presented in **Table 2**.

Table 2: Risk of Death and Total Number of Deaths from CLABSIs and SSIs

RISK OF DEATH FROM INFECTION			TOTAL No. DEATHS ANNUALLY		
CLABSI	SSI	TOTAL	CLABSI	SSI	TOTAL
6×10^{-7}	1×10^{-4}	1×10^{-4}	3	1,106	1,109

Table 2 makes it clear that, even though the risk of infection may be considered less serious than developing cancer, these estimated risks are not trivial as they are expected to result in thousands of deaths each year.

3. **Comment on whether the method is general enough to be used directly, or if it can be extrapolated, for application to other chemicals and/or problem formulations. Please explain why or why not.**

Traditional risk assessment methods usually only consider one driver and/or hazard at a time, but compound probability estimation is generalizable to other health-related problems. However, numerous difficulties were encountered while performing this health-risk tradeoff analysis. The risk of developing a HAI represents the sub-acute risk associated with a single procedure, while theoretical cancer risks are assumed to accrue over a lifetime (70 years) of repeated exposures. It could be argued that most people only have one serious procedure (e.g., central line insertion) but many people have more than one surgery over a lifetime. Therefore, HAI risks cannot necessarily be considered lifetime risks. For this reason, theoretical cancer risks and the risk of developing a HAI may not be directly comparable. In addition, although most would likely consider developing cancer more serious than developing a HAI, **Table 2** demonstrates that the estimated increase in HAIs if EtO became unavailable would result in many deaths every year and are, therefore, not trivial. In addition, the estimated cancer risks represent the theoretical probability of developing cancer, not dying from it. An attempt to estimate the number of people that would be expected to die from breast or lymphohematopoietic cancer associated with exposure to EtO near sterilization plants was not attempted. Although the estimates could be made, it would be an uncertain estimate at best and, amid the heightened level of concern in communities where sterilization plants are located, if made, the estimates would very likely be mis-used.

4. **Discuss the overall strengths and weaknesses of the method.**

The quantitative analysis discussed in the previous section provides some indication of the effect of an EtO ban on the risk of several HAIs. However, data and methodological limitations precluded a more comprehensive risk-trade-off analysis. Significant factors that precluded a more complete analysis were: 1) lack of information on the probability of colonization progressing to full-blown infection for most microorganisms that cause HAIs; and 2) limited quantitative information on the risk of contaminating medical devices associated with increased handling (i.e., with each individually packaged item opened). Although one study reported the increased risk associated with opening each individually packaged orthopedic screw (Crick *et al*., 2009), other items are likely to be packaged differently (e.g., with an outer cardboard box, or tray), resulting in a different probability of contaminating the device while opening. Progression from colonization to infection is likely the weakest input in the equation proposed for estimating HAI risks. In a few cases (CoNS colonization of blood versus CoNS-associated bacteremia) colonization data for the infected area was located, but in many cases, the only data on progression from colonization to infection referred to commensal colonization.

Another weakness of the approach is that risks were only estimated for two of the four HAI categories that are reported to the NHSN (i.e., CLABSIs and SSIs). Since CAUTIs represent approximately 40% and ventilator-associated pneumonia is responsible for another 22% of HAIs (Beckers, 2014), the infection risks estimated in this risk assessment are no doubt underestimated. There are several other sources of underestimation in this risk assessment. For example, data on the probability of progressing from colonization to infection was not located in the scientific

literature for four and five of the nine microorganisms known to cause CLABSIs and SSIs, respectively.

It is generally believed that the NHSN database underestimates the risk of HAIs. NHSN data are voluntarily reported; therefore, it may be the case that the facilities reporting infection rates to the NHSN have better infection prevention and control programs, which may result in underestimates of the true infection rates. In addition, the number of SSIs is likely to be underestimated because approximately 50% of SSIs only become evident after discharge (Mangram *et al*., 1997). The SSIs reported to NHSN are those detected during the same admission as the surgical procedure or upon readmission to the same facility. Yet another source of potential underestimation is that the nurses that took part in the Crick *et al*. (2008) study (the source of increased risk of contamination with each package opened) were highly experienced (average surgery experience of ~18 years) and the participants were informed of the purpose of the study. This study may underestimate the probability of contaminating the orthopedic screws or other devices in real-world surgical scenarios both because real-world surgeries would likely involve a wider range of nurse experience levels and the nurses involved in those surgeries may not be as careful not to contaminate medical devices as the nurses in Crick *et al*. study who knew that they were being surveilled. The authors of the Crick *et al* study also lamented that the rate of contamination might have been even higher if all of the non-sterile areas of the packaging had been labelled with ultraviolet dye.

Finally, a more detailed evaluation of trade-offs would have used full distributions of probabilities for the required precursor events.

HOW THIS ASSESSMENT ADDRESSES ISSUES RAISED IN SCIENCE & DECISIONS

Science and Decisions (NAS, 2009) suggests that questions about the risks posed by industrial processes could be better answered by considering risk-risk tradeoffs than by studying risks in isolation. This preliminary case study evaluates the implications of a ban on the use of EtO to sterilize medical equipment/supplies on the countervailing risk of CLABSIs and SSIs.

A. Describe the dose-response relationship in the dose range relevant to human exposure?

The dose-response relationship between the inoculum size and the probability of infection is unclear for most, if not all, microorganisms. A controversial topic in microbial risk assessment is the potential for a single microorganism to initiate infection (i.e., lack of threshold). This is known as the "independent action hypothesis" and it is the underlying basis for microbial risk assessments conducted by various national and international health organizations (Cornforth *et al*., 2015). Since the exact relationship between inoculum size (i.e., dose) and the probability of infection or death (i.e., response) is not known, this risk assessment assumes that *any* microbial contamination of medical supplies or devices that enter sterile tissue or the vascular system poses some risk of infection.

Despite its importance in predicting and managing microbial risks, experimental support for the "independent action hypothesis" in bacterial pathogens is indirect at best. As a result, risk assessments, such as this one, which assume that assume that a single microorganism is capable

of initiating infection may overestimate infection risk at low doses (Cornforth *et al.*, 2015). Although, it has been reported that dose-response data may support the "independent action hypothesis"[3], it should be kept in mind that many factors can mask a response threshold in observational data. Detecting thresholds at the population level is difficult because if the "true" exposure-response has a threshold, then errors and uncertainties associated with the exposure measurements will tend to "smear out" or blur the threshold in the modeled dose-response relationship, giving the misleading appearance of a smooth biological gradient (i.e., suggesting that there is no threshold or change in slope of the line) (Rhomberg, *et al.*, 2011).

B. Address human variability and sensitive populations?

Patients with diminished immunocompetence, the elderly and the young are more susceptible to developing HAIs for the same reasons that they are susceptible to common infections. However, because the NHSN infection rates are reported by women and children's hospitals, neonatal intensive care units (NICUs), veteran's hospitals, general hospitals, military hospitals, intensive care units (ICUs) and oncology hospitals, these sensitive populations should be built into the dataset.

C. Address background exposures or responses?

EtO is ubiquitous in ambient air. A relatively recent study conducted by EPA (March 2019), which characterized background EtO concentrations (in areas not influenced by emissions from sterilization plants) in 17 cities in nine states demonstrated that EtO levels between 0.2 and 0.4 $\mu g/m^3$ are found across the country (EPA, 2019).

D. Address incorporation of existing biological understanding of the likely mode of action?

Colonization of the polymer surface of medical devices by formation of a multilayered biofilm is the critical factor in the pathogenesis of medical device-related HAIs caused by the bacteria that are the focus of this risk assessment. Once a biofilm has formed, single cells or cell agglomerates can dissociate from the biofilm and disseminate via the bloodstream to start colonization and biofilm formation at a different site (Becker, Heilmann, and Peters, 2014). Broken skin and the respiratory or urinary tract can become asymptomatically colonized with many bacteria and colonized patients may subsequently develop clinical infection. However, this does not always occur (Coello *et al.*, 1997; Roghmann, *et al*, 1997; Mossad, *et al.*, 1997). One explanation for this phenomenon is that humans naturally carry many of the bacteria associated with device-related HAIs on their skin and in mucous membranes.[4] However, it is also clear that host defenses (immunity) play a critical role in determining which individuals develop infections or more severe infections and this interferes with estimating infectious doses.

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[3] In most cases, exponential or beta models provide a significantly better fit over the lognormal model. Haas, Rose, and Gerba, 1999.

[4] All humans are colonized with *S. Epidermis* (the most prevalent species in CoNS). Massey, Horsburgh, Lina, and Höök, 2006.

E. Address other extrapolations, if relevant – insufficient data, including duration extrapolations, interspecies extrapolation?

N/A

F. Address uncertainty?

Although banning EtO as a sterilizing agent may lower EtO exposures in the relatively small populations living and working in the immediate vicinity of sterilization plants, it is expected that this action would only have a limited impact on overall EtO exposures because EtO is ubiquitous in the environment. EtO has many sources other than sterilization facilities, such as automobile exhaust, cigarette smoke, food, consumer products, etc. On the other hand, if EtO use in sterilizing medical equipment/devices were banned, the much more tangible risk of HAIs could increase across the entire U.S. Therefore, this case study illustrates risk-transformation in which the countervailing risk causes different negative outcomes (HAIs instead of cancer) in a different population (in patients undergoing medical procedures across the U.S. as opposed to the much smaller populations that live and work near sterilization plants).

It is generally accepted that most infectious disease tracking systems greatly underestimate the risk of HAIs (Haas, Rose, and Gerba, 1999), and the NHSN is no exception. Much of the data on microbial occurrence are gathered using insensitive analytical methods that give poor recovery efficiencies. As a result, there may be appreciable health risks associated with concentrations of microbes that are lower than can be measured by current methods. Microbial occurrence is measured in doses that are routinely used to count microbes in the laboratory (Haas, Rose, and Gerba, 1999). Bacteria are usually measured as colony-forming units (CFUs). This means that viable but non-culturable are <u>not </u>counted, which could result in underestimation. This is a limitation for estimating exposure dose.

Additional information on the virulence or infectivity of microbes and host susceptibility is needed to reduce the uncertainty in estimating microbial risks. Although mechanisms of pathogenicity are known for some microbes, little is known about the virulence factors of many. Potential changes in the virulence of microbes that may occur because of treatment are also likely to be important. Exposure risks may be affected, not only by host status, but also by the physical state of the microorganisms in the environment, with aggregation (biofilm formation) affording protection to the microbes and increasing their persistence on surfaces. Furthermore, biofilms can also contain large numbers of microorganisms, which results in higher potential exposure doses. This may significantly affect the exposure outcome (the dose-response relationship and the effects end point) and thus influence the magnitude and type of health risk (infection, illness, and death) (Sobsey *et al.*, 1993).

Secondary spread of infectious diseases is a unique feature of microbial risks that has no parallel in chemical risks (Sobsey et al., 1993) that is not addressed in this case study. Another source of uncertainty in this case study is that the fraction of infections caused by specific microorganisms varied widely across studies. Finally, the risk of CAUTIs and VAEs were not estimated in this risk assessment due to time constraints.

G. **Allow the calculation of risk (probability of response for the endpoint of interest) in the exposed human population?**

Risks were estimated for the endpoints of interest in the exposed human population, but lack of information on the probability of colonization progressing to infection for most of the microorganisms involved in HAIs substantially limited the comprehensiveness of the method used in this case study.

H. **Work practically? If the method still requires development, how close is it to practical implementation?**

This method requires additional development, which is why it is presented as a preliminary case study for the panel's consideration. The lack of data for progression from colonization to infection for many of the microorganisms involved in HAIs is notable. In addition, sources of current information on the number of central-line insertions and surgeries performed annually were not located but are believed to exist. Additional sources from which to obtain these data need to be identified. It is also unclear if <u>all</u> relevant inputs to the equation for estimating HAI risk were identified/included and, therefore, the algorithm used may need additional development. Identification of areas for additional development of the case study and/or method by the Panel would be greatly appreciated.

QUESTIONS FOR THE PANEL

1. Is the Panel aware of databases or resources for more current information on the annual number of central-line insertions, surgeries, urinary catheter insertions, and ventilator events?
2. Since the NHSN infection rates are risk-adjusted for patient characteristics, is there any need to include the probability that patients are young, of advanced age, or immunocompromised?
3. Is the Panel aware of additional resources for data on progression from colonization to infection for the microorganisms involved in HAIs?
4. For many of the bacteria considered, the only data on progression from colonization to infection referred to commensal colonization. Is it scientifically defensible to use the probability of infection in patients naturally colonized with a bacterium as a surrogate for the probability that colonization of a central-line insertion site or surgical site wound will progress to CLABSI or SSI?
5. Studies located in the literature that used NHSN data focused on years in the distant past (e.g., 2006, 2008) as opposed to using the most recent NHSN, even though the NHSN is updated annually. Is there any reason not to use the most recent data?

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