Risk-Based Selection of Respirators Against Infectious Aerosols: Application to Anthrax Spores

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This article presents two methods for estimating infection risk among individuals wearing air-purifying respirators against airborne pathogens, with the overall aim of selecting appropriate respiratory protection. Necessary data inputs are the parameters for the ambient pathogen concentration distribution, the respirator penetration distribution, and the infectious dose distribution, along with the breathing rate, duration of a respirator use period, and the number of use periods. The first method assumes that the pathogen does not exhibit a cumulative dose effect, whereas the second accounts for a cumulative dose effect. The methods are illustrated with hypothetical scenarios involving Bacillus anthracis *(anthrax) spores. Available data suggest that anthrax spores would exhibit a cumulative dose effect for multiple exposures occurring close in time, as would likely affect personnel responding to a bioterrorist release. The analysis shows that failure to account for a cumulative dose effect when present leads to underestimating infection risk. Three types of air-purifying respirators are compared for their predicted efficacy in reducing the risk of inhalation anthrax. Although uncertainty analyses are not performed, a general conclusion is that a full-facepiece powered air-purifying respirator would be the best air-purifying device for responding to an anthrax spore release. Because such respirators would not prevent all personnel from inhaling an infectious dose, it would be advisable for users not previously vaccinated against anthrax to receive post-exposure prophylactic therapy.*

Strategies for selecting respiratory protection against airborne chemicals are well established.[1–3] When choosing an air-purifying respirator, one should consider the chemical's physical nature, the air-purifying medium's efficiency in removing the chemical, the chemical's airborne concentration outside the respirator (C_o), the degree of leakage of contaminated air into the respirator, and the chemical's target concentration in inspired air. The two greatest sources of uncertainty are the values of C_o and the chemical's overall fractional penetration (P) into the respirator, which is due primarily to inward leakage around the respirator's sealing perimeter. Although the selection process has numerous steps, the overall idea is simple—one chooses a respirator that will keep the inspired concentration at or below the chemical's permissible exposure limit.

Across an individual's respirator use periods, there can be substantial variability in C_o,[4,5] and in P.[6,7] Across a cohort of respirator users, there can be variability in average C_o levels[5] and average P values.[7,8] In the past, interindividual variability has not been appropriately considered in analyzing respirator efficacy data and in assigning nominal levels of protection for respirator classes.[8,9] The Occupational Safety and Health Administration (OSHA) is presently deciding how to account for these sources of variability in its respirator-related rulemaking.[10]

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Selecting a respirator against an infectious aerosol is still more complex, because there are no regulatory limits for the number of organisms that may be inhaled or for infection risk. Further, when estimating the risk of infection or morbidity among an exposed cohort, there may be substantial interindividual variability in susceptibility. Recommendations from public health agencies for respirator use against Hantavirus[11] and *Mycobacterium tuberculosis*[12] have been based on expert opinion and not on quantitative risk analysis. More recently, a strategy was offered that was applicable to a broad array of infectious aerosols, but it also constituted a qualitative approach involving unspecified criteria for acceptable risk.[13] For *M. tuberculosis* exposure in health care settings one of us has previously described a risk-based method for selecting respiratory protection.[14,15] Our purpose here is to begin to develop a general framework that permits quantitative risk estimates and identifies necessary data inputs and sources of uncertainty. We illustrate the approach for *Bacillus anthracis*, the etiologic agent of anthrax, in part because there exist better published dose-response data for *B. anthracis* than for other airborne pathogens.

In the past, inhalation anthrax was a recognized hazard among certain agricultural and manufacturing occupations,[16] although there have been no reported work-related cases for several decades in the United States. Unfortunately, *B. anthracis* is the leading candidate agent for bioterrorism by means of aerosolization of spores,[17] and there has been little discussion of the type of respirator appropriate for emergency response personnel. A pressure-demand supplied air respirator (eg, a self-contained breathing apparatus) is the best choice, but we speculate that a minority of response personnel would be equipped and trained to use such devices. For a large domestic bioterrorist incident, it seems likely that many responders would wear air-purifying respirators and that most would not be vaccinated against anthrax. In considering respirator use against *B. anthracis*, we first summarize pertinent information on anthrax and then describe the computation of infection risk for an individual respirator wearer and for a cohort of wearers. For convenience, we hereafter refer to viable spores of *B. anthracis* as anthrax spores.

Inhalation Anthrax

Bacillus anthracis is an aerobic rod-shaped bacterium that causes three forms of human disease: (1) inhalation anthrax, which follows spore deposition in the alveolar region and germination in lymph nodes; (2) cutaneous anthrax, which follows spore entry into injured skin and germination in skin tissue; and (3) gastrointestinal anthrax, which follows spore ingestion and germination in the gastrointestinal tract. In the United States, cutaneous anthrax is now the only naturally occurring form. The pathogenesis of inhalation anthrax has been well described,[16–19] but we note some aspects relevant to respiratory protection.

Spores deposited in the alveolar region are phagocytized by macrophages, which cross the alveolar membrane and are carried by draining lymphatic channels to the mediastinal lymph nodes. Spores in the lymph nodes can survive and germinate as long as 100 days later.[17,20] Furthermore, clearance of spores from the alveolar region is not rapid. Experiments with radiolabeled *B. subtilis* spores, which are physically similar to anthrax spores, found that essentially 100% of the spores that deposited in the alveolar region of guinea pigs following an acute inhalation exposure were still present 24 hours later.[21] These data suggest that the number of spores in the alveolar region and the draining mediastinal lymph nodes can accumulate over a series of exposure periods that occur within several days.

Appendix 1 summarizes data from two dose-response studies of inhalation anthrax in monkeys and guinea pigs.[22,23] In both studies, death was the outcome scored and the dose-response distribution was modeled as lognormal. To our knowledge, no data exist on the lethal inhalation dose distribution in humans. The US Defense Intelligence Agency estimated the human geometric mean (GM) or median lethal inhalation dose to be 8000 to 10,000 spores, although the provenance of this estimate was not provided.[24] For the hypothetical exposure scenarios used in this article, we assume that the median lethal inhalation dose is 10,000 spores and the geometric standard deviation (GSD) is 3. The latter value is within the GSD range observed for laboratory animals exposed to respirable anthrax spores.

Individual Infection Risk

Because an individual may have multiple periods of respirator use, all which contribute to infection risk, it is necessary to consider how infection risk accumulates. Computing the cumulative risk requires specifying: (1) the infectious inhalation dose, B (#); (2) the air concentrations of the infectious agent, C_o (#/m^3); (3) the user's respirator penetration values, P(0 – 1); (4) the user's breathing rate Q_v (m^3/hr); (5) the duration of a respirator use period, T (hr); and (6) the anticipated number of respirator use periods, M. We recognize that such complete information will seldom be available. For this discussion, different infectious dose values and exposure scenarios are considered, and a number of default assumptions are employed. More specific information can be incorporated if available.

The Infectious Inhalation Dose

The infectious inhalation dose is the number of organisms that must be inhaled over a relevant period to cause host infection. For two reasons, the relevant period for anthrax spores is taken as several days. First,

previously cited laboratory data indicate that physically similar spores that deposit in the alveolar region are only slowly removed.[21] Therefore, the number of spores deposited in the lungs can increase across respirator use periods that are close in time and build to a level exceeding an infectious deposited dose. Second, we speculate that the response to a bioterrorist incident would not involve any individual wearing a respirator beyond several days.

The above paragraph draws a distinction between the inhaled and deposited doses. Not all inhaled organisms deposit in the lungs, and only those that deposit can infect the host. Ideally, the deposition fraction as well as the total number of organisms inhaled should be specified. However, experiments on the infectious dose of anthrax spores did not determine the number that deposited. Instead, animals were exposed for known time periods to known spore concentrations. Using the estimated breathing rate of the animals, the investigators reported estimated inhalation doses (total spores inhaled). In general, an infectious dose is not the same as a lethal dose, but we treat inhalation anthrax as leading to certain death absent medical intervention. This is a reasonable assumption, given the high mortality rate historically associated with inhalation anthrax,[16] and it also permits interpreting reported data on lethal inhalation doses as data on infectious inhalation doses.

The infectious inhalation dose as defined here is a deterministic rather than probabilistic quantity. For example, if B = 10,000 anthrax spores for an individual, infection occurs with certainty if the inhaled dose equals or exceeds 10,000. Variability pertains to the distribution of infectious inhalation doses across a cohort of individuals. An alternative model offered for airborne infections[25] and for gastrointestinal tract infections[26] is that only one organism is necessary to initiate host infection but that each organism has a small, independent probability of success in initiating infection. For example, if N anthrax spores are inhaled, and if each spore has independent success probability r, infection occurs with probability equal to $1 - (1 - r)^N$. The latter model usually assumes no variability across individuals in susceptibility to infection. For the estimated human median lethal inhalation dose of 10,000 anthrax spores, the corresponding $r = 6.9 \times 10^{-5}$.

We are not aware of analyses for airborne pathogens that have compared the deterministic and probabilistic models. Further, the notion of eventually overwhelming a host's defense mechanisms with a sufficiently high pathogen dose seems more biologically plausible than each organism's having a small "success" probability on the order of 10^{-5}. For these reasons, we assume that the infectious inhalation dose is a deterministic quantity, but we note that it is possible to account for the alternative model.

The Distributions of C_o and P Values

C_o is defined as a constant airborne concentration of infectious organisms over a T-hr interval, where T is the duration of a respirator use period. Each organism need not be carried on a separate particle. For an individual, C_o is assumed to be lognormally distributed across respirator use periods. Given the overall lack of sampling data for infectious aerosols, there is no strong justification for assuming any specific distribution for C_o. However, occupational aerosol exposure concentrations are usually well described by lognormal distributions,[4] so it is reasonable to invoke that distribution here. P is similarly defined as a constant T-hr respirator penetration value and is reasonably assumed to be lognormally distributed and independent of the C_o values.[8,9] In a strict sense, P cannot be a lognormal variable because fractional penetration cannot exceed one. However, for the types of respirators considered, there is a negligible probability associated with $P > 1$.

Breathing Rate and Exposure Duration

For simplicity, a respirator user's breathing rate is assumed to be constant, and for the anthrax application, $Q_v = 1.75$ m^3/hr. The latter value corresponds to a medium work rate[1] and is higher than the typical assumption of breathing at 1.0 m^3/hr, which corresponds to a light work rate. It seems reasonable that an emergency responder's activities would be more rigorous than "light" work and that the individual would be under considerable stress. For simplicity, it is assumed that each respirator use period is the same duration. For the anthrax application, T = 2 hr is taken as a reasonable value.

Cumulative Risk With No Cumulative Dose Effect

The lack of a cumulative dose effect signifies that an infectious inhalation dose must be received during a single respirator use period and cannot accumulate across periods. For example, if an individual has an infectious inhalation dose B = 10,000, and if 10,000 or more organisms are inhaled during one T-hr exposure period, infection occurs. On the other hand, if 9000 organisms are inhaled during one respirator use period and 9000 are inhaled during the next period, infection does not occur. The lack of a cumulative dose effect is unrealistic when two or more respirator use periods are close in time, and it is almost certainly invalid for exposure to anthrax spores occurring over 1 to several days. Rather, this scenario is offered primarily as a contrast to the situation in which the dose can accumulate. However, the lack of a cumulative dose effect would pertain to multiple respirator use periods that are far removed in time, such that no viable organisms that had deposited

during previous exposures are likely to remain.

Let q_i denote the probability of not being infected during the i^{th} respirator use period, and let M denote the number of periods. The cumulative infection risk over M periods, R_M, is:

$$R_M = 1 - \prod_{i=1}^{M} q_i. \qquad (1)$$

If the q_i are independent and identically distributed random variables across the M periods, the cumulative infection risk is given by:

$$R_M = 1 - (E[q])^M, \qquad (2)$$

where E[q] denotes the expected value of the random variable q_i. E[q] is related to C_o, P, Q_v, and T in the following manner. The inhalation dose during a single respirator use period, D (# organisms), is:

$$D = C_o \cdot P \cdot Q_v \cdot T. \qquad (3)$$

Let GM[C_o] and GSD[C_o] denote the GM and GSD, respectively, of the lognormal distribution of C_o. Let GM[P] and GSD[P] denote the GM and GSD, respectively, of the lognormal distribution of respirator penetration values. If C_o and P are independent, and if Q_v and T are constants, the distribution of inhaled doses D across respirator use periods is also lognormal with:

$$GM[D] = GM[C_o] \cdot GM[P] \cdot Q_v \cdot T. \qquad (4)$$

$$GSD[D] \qquad (5)$$

$$= \exp\left(\sqrt{\ln^2 GSD[C_o] + \ln^2 GSD[P]}\right).$$

The probability that D does not exceed the infectious inhalation dose B corresponds to E[q], and is given by:

$$E[q] = \Phi\left(z = \frac{\ln B - \ln GM[D]}{\ln GSD[D]}\right), \qquad (6)$$

where $\Phi(z)$ is the cumulative standard normal distribution function evaluated for the argument z. Values for $\Phi(z)$ are tabled in most every statistics text.

Cumulative Risk With a Cumulative Dose Effect

Again consider that C_o and P are independent and lognormally distributed across respirator use periods, that Q_v and T are constants, but that the inhalation dose (strictly, the deposited dose) can accumulate across respirator use periods close in time. Let S_M denote the sum of the inhalation doses over M consecutive respirator use periods, or:

$$S_M = \sum_{i=1}^{M} D_i, \qquad (7)$$

where D_i is the inhaled dose for the i^{th} respirator use period and is a lognormal variable with parameters defined by equations 4 and 5. Although D_i is a lognormal variable, the sum S_M is not. For $M > 30$, S_M is well approximated as a normal variable, with mean and variance equal to M-fold the mean and variance of D, respectively. For $M \leq 10$, as will be considered for anthrax spores, the normal approximation can be poor. In the alternative, the distribution of S_M can be determined by Monte Carlo simulation, which also permits finding the proportion of S_M values that equal or exceed the infectious inhalation dose B. This proportion corresponds to R_M, the cumulative infection risk over M respirator use periods.

For Monte Carlo simulation of the S_M distribution, the GMs and GSDs of the lognormal C_o and P distributions are specified, along with values for Q_v and T. For a given round of simulation, a C_o value is randomly drawn from the C_o distribution, a P value is randomly drawn from the P distribution, and the corresponding D value is computed by equation 3. This procedure is repeated M times, and the sum of the D values equals S_M. At least 50,000 rounds of simulation are performed to obtain a stable distribution of S_M values. The following example for anthrax spores illustrates the method and compares the R_M value that accounts for a cumulative dose effect with the R_M value obtained by equation 2 that does not account for a cumulative dose effect.

A Hypothetical Example for Anthrax Spores

Consider an individual who is subjected to a distribution of C_o values for anthrax spores with GM[C_o] = 21,900 per m^3, and GSD[C_o] = 3. This corresponds to an average C_o value of 40,000 per m^3, and substantial period-to-period variability (%CV = 150%). Assume that the individual wears a negative-pressure, full-facepiece air-purifying respirator equipped with high-efficiency (now termed Type N100) filters and experiences a distribution of penetration values with GM[P] = 0.0064, and GSD[P] = 2. For this individual, only 5% of P values exceed 0.02, such that the device meets the criterion for adequate performance of this respirator class.[2] Assume that Q_v = 1.75 m^3/hr and T = 2 hr, that the individual's infectious inhalation dose is B = 10,000 spores, and that the individual has not been vaccinated against anthrax.

Figure 1 is a histogram depiction of the distribution of individual D values that could be experienced, for which GM[D] = 490 spores and GSD[D] = 3.67. The percent of D values exceeding 10,000 is 1.0%, which signifies that E[q] in equation 6 is 0.99. If this individual has eight respirator use periods over the course of several days, the cumulative anthrax infection risk, according to equation 2, is: $R_8 = 1 - (0.99)^8 = 0.077$.

In contrast, Fig. 2 is a histogram of the distribution of S_8 values, where S_8 is the sum of eight random D values received over the course of several days. The distribution of D corresponds to that in Fig. 1. The percent of S_8 values exceeding 10,000 is 30%, so: $R_8 = 0.30$. The latter cumulative risk, which accounts for a cumulative dose effect, is approximately 4-fold greater than

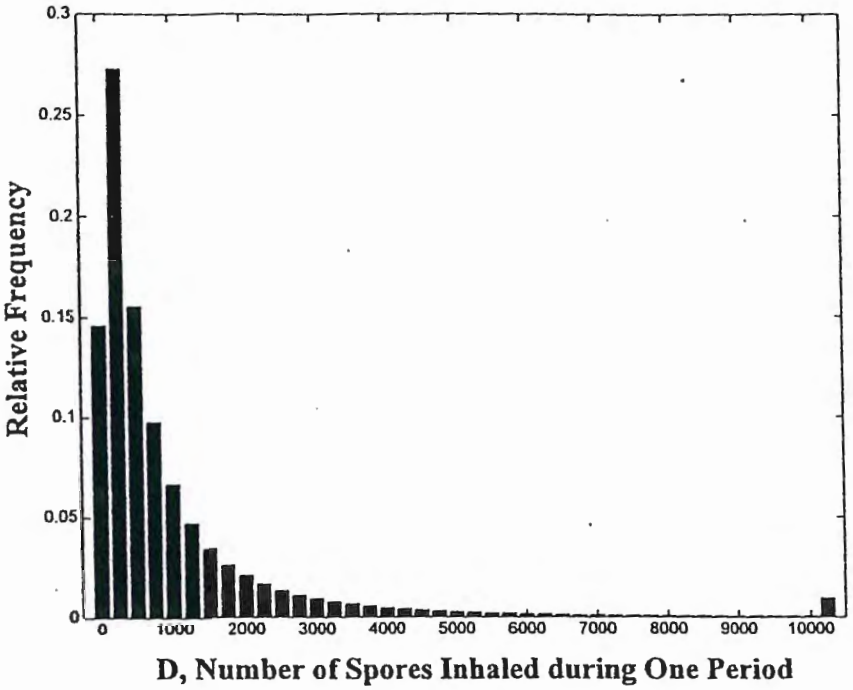

Fig. 1. The lognormal distribution of inhaled doses of anthrax spores for a single respirator use period, D, given use of an air-purifying full-facepiece respirator with APF = 0.02 against an expected airborne spore concentration of 40,000 per m^3. The parameters are GM[D] = 490 spores and GSD[D] = 3.67. One percent of the D distribution exceeds 10,000 spores.

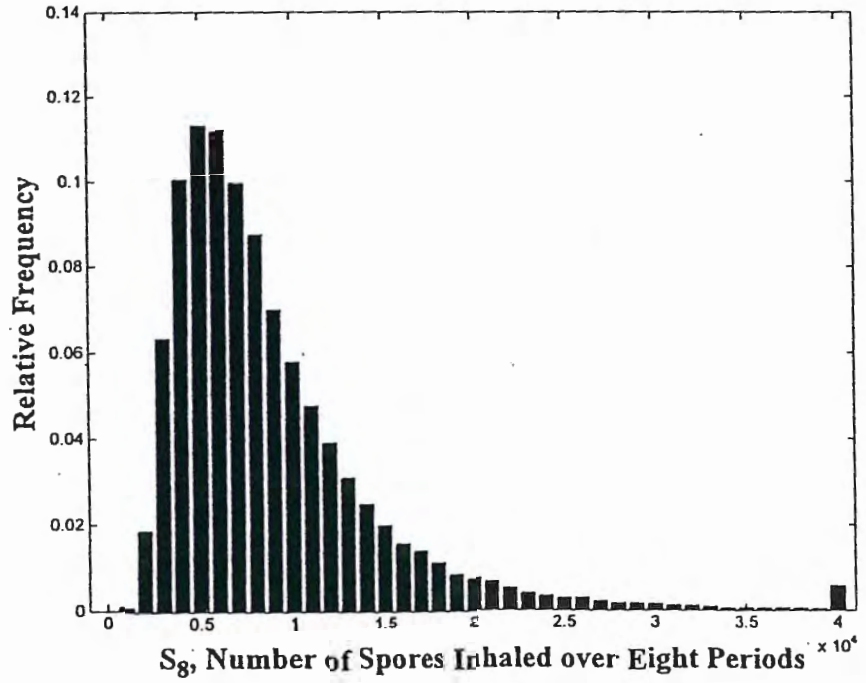

Fig. 2. The distribution of cumulative inhaled doses of anthrax spores over eight respirator use periods, S_8, given the use of an air-purifying full-facepiece respirator with APF = 0.02. The inhaled dose for a single respirator use period is drawn from the D distribution in Fig. 1. Thirty percent of the S_8 distribution exceeds 10,000 spores.

the cumulative risk that does not account for a cumulative dose effect (0.30/0.077). Figure 3 compares these two cumulative risks for M = 1 – 10 respirator use periods. The R_M value based on the S_M distribution is shown by the diamonds. The R_M value based on equation 2 is shown by the circles. Both R_M values increase as M increases, as does the absolute difference between the respective cumulative risks. The overall meaning of Fig. 3 is the following. Given a series of exposure periods close in time, failure to account for a cumulative dose effect when present, as likely pertains to anthrax spores, can lead to seriously underestimating a respirator wearer's infection risk.

The intent of the above example is not to claim that, in general, an emergency responder will be exposed to variable anthrax spore levels with an average value of 40,000 per m^3 while wearing a negative-pressure, full-facepiece air-purifying respirator equipped with high-efficiency filters. The average C_o level could be lower or higher, and a different type of respirator might be worn. Figure 4 shows R_8 based on the distribution of S_8 values over average C_o levels ranging from 0 to 10^5 per m^3, with GSD[C_o] = 3, for an individual whose infectious inhalation dose value is 10,000 spores. Four levels of respiratory protection are examined. Each level corresponds to an assigned penetration factor (APF), defined as the penetration value expected to be exceeded during 5% of respirator use periods. For each distribution of respirator penetration values, GSD[P] = 2. The definition and derivation of the APF are briefly discussed in Appendix 2.

The APF = 0.1 corresponds to a negative-pressure, half-facepiece air-purifying respirator. The APF = 0.02 corresponds to a negative-pressure, full-facepiece air-purifying respirator, according to the ranking system of the National Institute for Occupational Safety and Health (NIOSH); this was the APF value assumed in Figs. 1 through 3. The APF = 0.01 corresponds to a negative-pressure, full-facepiece air-purifying respirator, according to the ranking system of the American National Standards Institute (ANSI) Z88.2 Committee.[3] The APF = 0.001 corresponds to a full-facepiece

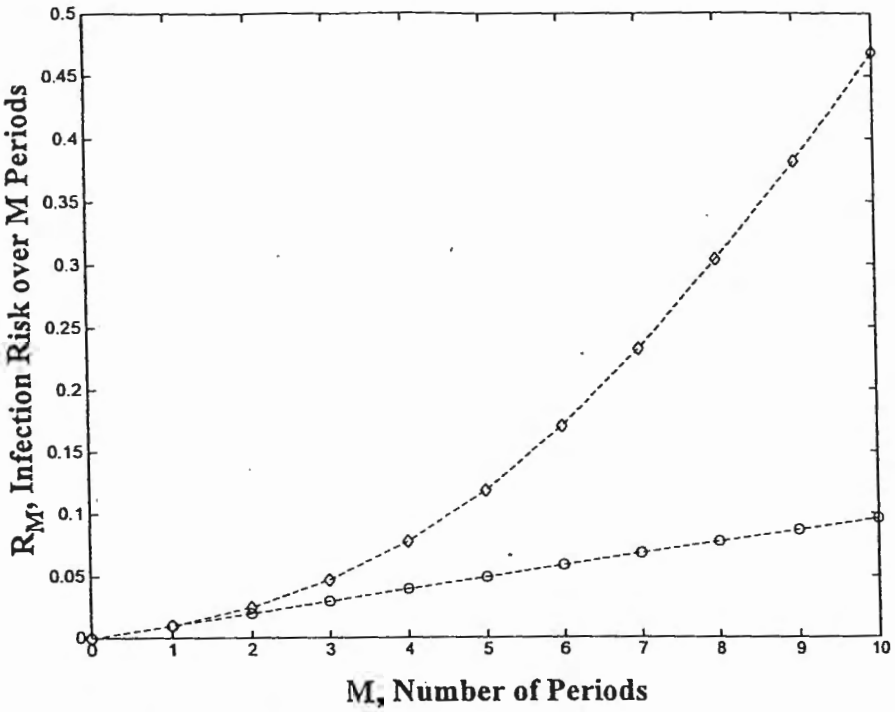

Fig. 3. An individual's cumulative risk of anthrax infection over M respirator use periods, R_M, given use of an air-purifying full-facepiece respirator with APF = 0.02. The inhaled dose for a single respirator use period is drawn from the D distribution in Fig. 1. The individual has an infectious inhalation dose of 10,000 spores. The line marked with diamonds assumes a cumulative dose effect for exposures occurring within several days. The line marked with circles does not assume a cumulative dose effect.

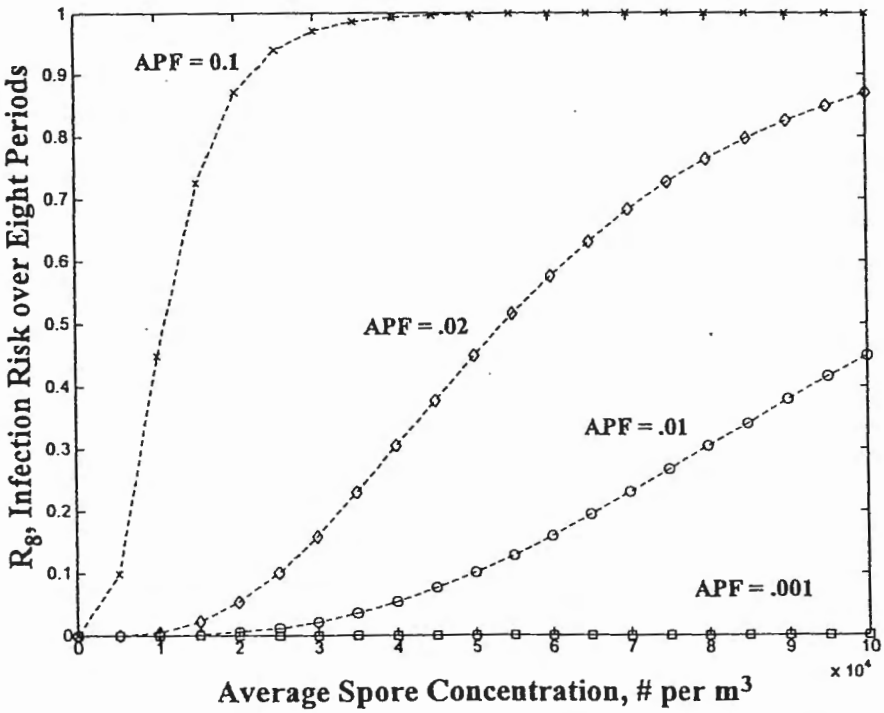

Fig. 4. An individual's cumulative risk of anthrax infection over eight respirator use periods, R_8, for different average spore concentrations up to 10^5 per m^3, and for different levels of respiratory protection (APFs of 0.1, 0.02, 0.01, 0.001). The individual has an infectious inhalation dose of 10,000 spores. The R_8 values are based on a cumulative dose effect for exposures occurring within several days.

powered air-purifying respirator (PAPR), according to the ranking system of the ANSI Z88.2 Committee. It is assumed that all respirators are equipped with high-efficiency filters. Two items are noted. First, a PAPR blows filtered air into the facepiece and, during inhalation, is thought to maintain a positive pressure inside the facepiece relative to ambient air. In contrast, during inhalation, the pressure inside the facepiece of a negative-pressure respirator is always negative relative to ambient air. Second, the NIOSH and ANSI Z88.2 APF ranking systems agree for the negative-pressure, half-facepiece air-purifying respirator but do not agree for the negative-pressure, full-facepiece air-purifying respirator and for the full-facepiece PAPR. In general, OSHA enforcement policy relies on the NIOSH APF rankings.

As shown in Fig. 4, a negative-pressure, half-facepiece respirator (the APF = 0.1 line marked by x's) offers little protection over the posited range of average C_o values, given M = 8 respirator use periods by an unvaccinated individual for whom B = 10,000 spores. The negative-pressure, full-facepiece respirator (the APF = 0.02 line marked by diamonds, and the APF = 0.01 line marked by circles) offers much better protection but still permits a substantial infection risk for average C_o levels > 20,000 per m^3. In contrast, the full-facepiece PAPR (the APF = 0.001 line marked by squares) limits infection risk to near zero; for the highest average C_o level of 10^5 per m^3, R_8 = 0.0005 (0.05%).

Cohort Infection Risk

Estimating the proportion of a cohort infected over M respirator use periods, denoted CR_M, is more complex. In essence, for each cohort member one specifies the distributions of C_o and P, the infectious inhalation dose B, and the values of Q_v and T, and estimates the cumulative infection risk R_M by one of the methods previously outlined. The mean of the individual R_M values equals CR_M. If Q_v and T are constant

across individuals and time, the cohort analysis should still account for interindividual variability in B, in mean penetration values, and in mean C_o levels. The following discussion considers variability in B and provides a hypothetical illustration involving inhalation anthrax. To keep the cohort analysis succinct, methods of accounting for interindividual variability in mean penetration values and mean C_o levels are not presented. It happens that for a fixed proportion of cohort-aggregated penetration values greater than the APF, interindividual variability in mean penetration values slightly reduces CR_M relative to no interindividual variability. For a fixed proportion of cohort-aggregated C_o levels above a given value, interindividual variability in mean C_o levels has a similar effect.

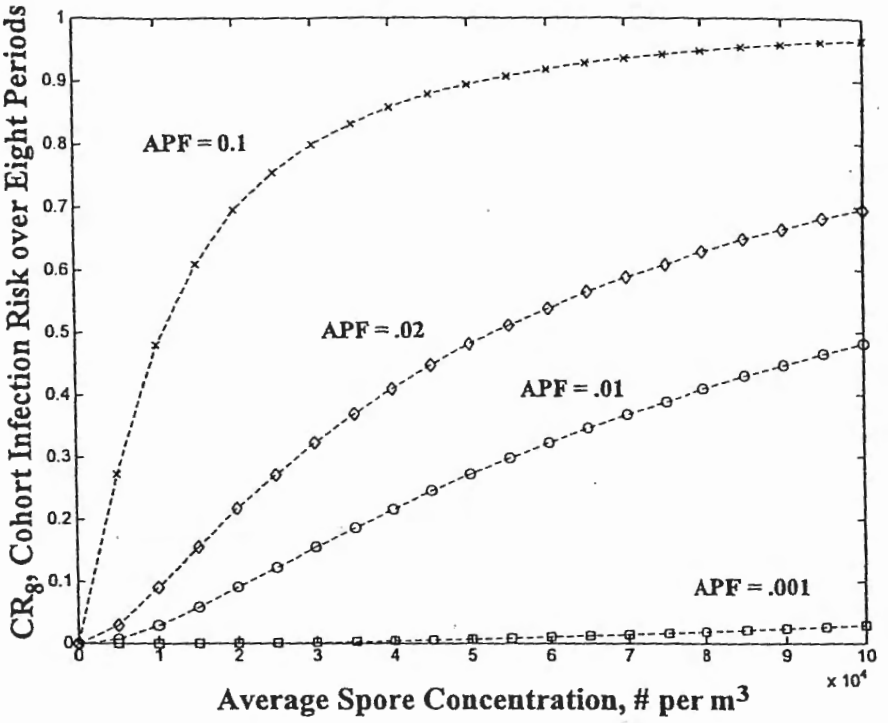

Fig. 5. The cohort cumulative risk of anthrax infection over eight respirator use periods, CR_8, for different average spore concentrations up to 10^5 per m^3, and for different levels of respiratory protection (APFs of 0.1, 0.02, 0.01, 0.001). Infectious inhalation doses among cohort members are lognormally distributed with GM[B] = 10,000 spores and GSD[B] = 3. The CR_8 values are based on a cumulative dose effect for exposures occurring within several days.

Variability in the Infectious Inhalation Dose With a Cumulative Dose Effect

Assume that every individual experiences the same respective lognormal distribution of C_o and P but that B varies lognormally across individuals. We are not aware of a strong a priori reason to treat the B distribution as lognormal, in general, but for anthrax spores the lognormal model has been used historically. After specifying GM[B] and GSD[B], one creates a set of N equal-probability intervals of B values. For example, if N = 1000, each interval encompasses 0.1% of the B distribution. The bottom limit of the first interval is zero; the upper limit of the last interval is infinite in theory but is set to a suitably large value. Assume that the pathogen exhibits a cumulative dose effect across exposure periods close in time and that every individual has M respirator use periods. A distribution of at least 50,000 S_M values is generated by Monte Carlo simulation, as previously described. For each interval of B, the proportion of the S_M distribution that exceeds the interval's upper limit is found, and this proportion is multiplied by the probability encompassed by the interval. Given N intervals, the probability factor is 1/N. In general:

$$CR_M = \sum_{j=1}^{N} \Pr[S_M > B_{max,j}] \times \frac{1}{N}, \quad (8)$$

where $B_{max,j}$ is the upper limit of the j^{th} interval of B values. Equation 8 slightly underestimates CR_M, because the S_M values are compared with the highest B value in each interval. N = 1000 is adequate for GSD[B] ≤ 3, although more intervals can be used.

Variability in the Infectious Inhalation Dose With No Cumulative Dose Effect

Assume that every individual experiences the same respective lognormal distribution of C_o and P, that B varies lognormally across individuals, that every individual has M respirator use periods, and that the pathogen does not exhibit a cumulative dose effect. The approximate value of E[q] is found for cohort members in small intervals of B, the corresponding values of R_M are found by equation 2, and the mean R_M value is computed. More specifically, one creates N equal-probability intervals for B. For each interval, the proportion of the D distribution less than the interval's upper limit is found by means of equation 6. This proportion is raised to the M^{th} power and subtracted from 1, using equation 2, to provide the R_M value for individuals in that interval of B. The R_M values are multiplied by the probability encompassed in the interval 1/N and are summed. In general,

$$CR_M = \sum_{j=1}^{N} (1 - (\Pr[D < B_{max,j}])^M) \times \frac{1}{N}, \quad (9)$$

where $B_{max,j}$ is the upper limit of the j^{th} interval of B values, and $Pr[D < B_{max,j}]$ is the approximate value of E[q] in that interval. Equation 9 slightly underestimates CR_M because the D values are compared with the highest B value in each interval, although one can improve the estimate by increasing N.

A Hypothetical Example for Anthrax Spores

Assume that GM[B] = 10,000 spores and GSD[B] = 3. Again, the GM corresponds to the human median lethal inhalation dose estimated by the US Defense Intelligence Agency, and the GSD is within the range of values observed for laboratory animals exposed to respirable anthrax spores. Assume that every individual has M = 8 respirator use periods. Given that anthrax spores exhibit a cumulative dose effect, Fig. 5 shows CR_8 based on the distribution of S_8 values over average C_o levels ranging from 0 to 10^5 per m^3, with GSD[C_o] = 3. Four levels of respiratory protection are again considered, with GSD[P] = 2. Fig. 5 is analogous to Fig. 4, except that the former depicts cumulative risk for a cohort and the latter depicts cumulative risk for an individual whose infectious inhalation dose is 10,000 spores. The half-facepiece respirator (the APF = 0.1 line marked by x's) and the full-facepiece respirator (the APF = 0.02 line marked by diamonds and the APF = 0.01 line marked by circles) permit a substantial cohort infection risk, even at low-average C_o levels. The full-facepiece PAPR is the most effective device, but CR_8 = 0.029 (ie, 2.9% of respirators users become infected) at the highest average C_o level of 10^5 per m^3.

If the cumulative dose effect is ignored, Fig. 6 shows estimated CR_8 values based on the distribution of D for: (1) average C_o levels ranging from 0 to 10^5 per m^3, with GSD[C_o] = 3; (2) four levels of respiratory protection with GSD[P] = 2; (3) a lognormal distribution of infectious inhalation doses with GM[B] = 10,000 and GSD[B] = 3; and (4) N = 1000. Figure 6 is analogous to Fig. 5, except that the former does not account for a cumulative dose effect and the latter does. For each level of respiratory protection at each average C_o level, the CR_8 value in Fig. 6 is lower than that in Fig. 5, which is similar to the result observed in Fig. 3 for an individual. For example, for a full-facepiece PAPR worn at the highest average C_o level of 10^5 per m^3, CR_8 = 0.0094 in Fig. 6 compared with CR_8 = 0.029 in Fig. 5. Therefore, failure to account for a cumulative dose effect when present, as likely pertains to anthrax spores, leads to underestimating the cumulative infection risk for a cohort of respirator users.

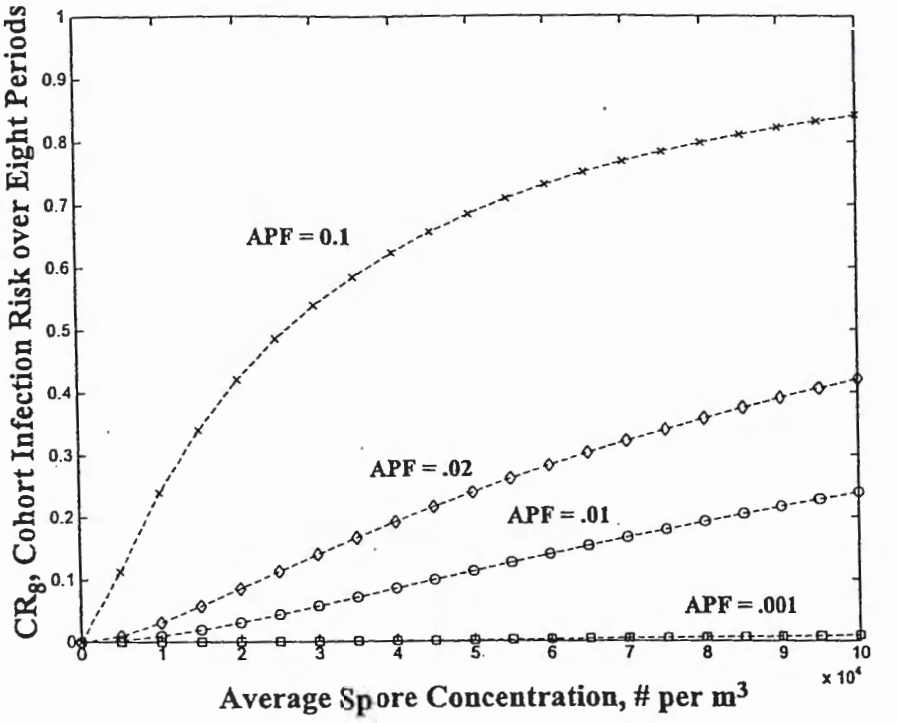

Fig. 6. The cohort cumulative risk of anthrax infection over eight respirator use periods, CR_8, for different average spore concentrations up to 10^5 per m^3, and for different levels of respiratory protection (APFs of 0.1, 0.02, 0.01, 0.001). Infectious inhalation doses among cohort members are lognormally distributed with GM[B] = 10,000 spores and GSD[B] = 3. The CR_8 values assume that there is no cumulative dose effect for exposures occurring close in time.

Discussion

The risk assessment methods described in this article involve three key assumptions: the infectious dose is deterministic, the inhaled dose is independent and identically distributed across respirator use periods, and continuous probability distributions are appropriate descriptors for infectious and inhaled doses. The methods also require data inputs that would almost always be uncertain. Before addressing these issues, we argue that the explicit assumptions and data requirements represent a strength rather than weakness of the overall approach. Identifying assumptions such as the deterministic nature of the infectious dose permits critical examination of the biological basis of infection and disease and consideration of plausible alternatives. Specifying essential inputs such as the distributional form and parameters of a cohort's respirator penetration distribution prompts the risk assessor to gather the best information available and provides a framework for uncertainty analysis. The defined nature of the method leads to repeatable risk estimates,

given the same input data. The alternative expert opinion method involves the subjective judgments of one or more experts, is often poorly documented, and tends to produce categorical risk estimates such as low, medium, or high. Because the method is highly personal and usually ill defined, a different group of experts given the same data and charged with the same task can arrive at a substantially different risk estimate.

A Deterministic Versus Probabilistic Infectious Dose

Treating the infectious dose as a deterministic quantity is not contraindicated by any published analysis, but a probabilistic interpretation can be accommodated. To briefly explain, consider equation 6, which relates E[q], the probability of not being infected during a random period, to the random inhaled dose D and a deterministic infectious inhaled dose B. In a simple probabilistic infectious dose model:

$$E[q] = \sum_{\text{all } d} (1 - r)^d \cdot \Pr[D = d], \quad (10)$$

where r is an organism's success probability of initiating infection, and D is explicitly modeled as a discrete random variable. The probabilistic model obviates consideration of cumulative risk based on the S_M distribution, because there is no cumulative dose effect per se. Instead, R_M would always be computed by equation 2, where E[q] is defined by equation 10. At the cohort level, interindividual variability in susceptibility could be modeled by a distribution of r across individuals, although how this distribution would be specified is uncertain.

Independent and Identically Distributed Inhaled Doses

Equation 2 for R_M, and the simulation procedure described for generating the S_M distribution to estimate CR_M, assumed that the random inhaled dose D for each respirator use period was independent of D for all other periods and had the same distribution across periods. This assumption greatly simplifies the estimation process but is not essential. That is, for each respirator use period, one might specify a unique distribution of D (likely involving a unique C_o distribution), and a deterministic function describing how the expected D value changes with time (likely involving a decreasing average C_o level). To estimate R_M, one would determine q for each respirator use period and use equation 1. To estimate CR_M, in effect, one would draw a random D value from a series of M unique D distributions, compute the sum S_M, and repeat the process numerous times to create the S_M distribution. This procedure is not computationally difficult, but specifying a function for the expected D value versus time would require new assumptions.

Continuous Versus Discrete Distributions

The analysis implicitly assumed that inhaled doses and infectious doses are large integer values, such that continuous probability distributions are appropriate for describing them. Continuity is a valid assumption for anthrax spores that have a median lethal inhalation dose on the order of 10,000. However, some pathogens, such as *M. tuberculosis*, have estimated infectious inhalation doses on the order of 1 to 10, and plausible inhaled dose values might also be small integers, in which case discrete probability distributions must be applied.[15]

Anthrax

Respirator selection against aerosolized anthrax spores depends on the desired confidence in the risk estimates and the degree of infection risk deemed acceptable. Specifying an acceptable risk value and a desired level of confidence involves considerations beyond the scope of this article. Further, because we are not familiar with bioterrorism scenarios involving anthrax spores, nor with the type of emergency response anticipated, we cannot offer typical values for the variables C_o, T, and M on which to base an uncertainty analysis. However, the procedure for a given scenario and a given value M can be outlined as follows. One would make best estimates of the parameters for B, C_o, P, Q_v, and T and posit distributions of these parameters. For example, the anticipated average C_o level is 10^5 spores per m^3, but the true value may be described by a triangular distribution centered on this best estimate. For a given round of simulation, one draws a set of parameters from the respective posited distributions and proceeds with the risk computation as before. By performing many rounds of such simulations, one creates an "uncertainty" distribution of risk estimates for the scenario. A given percentile of this distribution corresponds to a degree of "confidence" in the risk estimate; for example, if the 95th percentile risk estimate is 0.02, then one can be 95% confident that infection risk is less than 0.02.

Absent such an analysis, we conclude that, in general, a full-facepiece PAPR would be the air-purifying respirator of choice for responding to a bioterrorist incident involving anthrax spores. We base this conclusion on the previous hypothetical scenarios that incorporated plausible values for B, C_o, P, Q_v, T, and M. We considered average C_o levels up to 10^5 spores per m^3, but it is reasonable to believe that the average C_o level could be much higher during the initial aerosol release phase. For example, assume that just 1 g of dry spore material can be released into the ventilation system of a large auditorium of volume 2.5×10^5 m^3 (100 m × 100 m × 25 m). If a spore is treated as a cylinder 1 μm in length and 0.5 μm in diameter with density equal to 1 g/cm^3, one spore has 2×10^{-13} g mass, and 1 g of dry spore material contains 5×10^{12} spores. If one assumes a rapid release into

well-mixed air in the auditorium, the initial spore concentration would be 2×10^7 spores per m^3.

Conclusions

This article develops methods for estimating infection risk among individuals wearing air-purifying respirators against airborne pathogens. Necessary data inputs are the parameters for the ambient pathogen concentration distribution, the respirator penetration distribution, and the infectious dose distribution, as well as the breathing rate, duration of a respirator use period, and the number of use periods. The methods are illustrated with hypothetical scenarios involving anthrax spores. Although uncertainty analyses for scenarios involving a bioterrorist release of anthrax spores were not performed, our general conclusion is that a full-facepiece PAPR would be the air-purifying respirator of choice for responding to such an incident. Because use of PAPRs would still permit an appreciable degree of infection risk (see Fig. 5), it would be advisable for PAPR users not previously vaccinated against anthrax to receive post-exposure prophylactic antibiotic therapy and, perhaps, vaccination.[17] It should not be assumed that PAPR use would prevent all personnel from inhaling an infectious dose.

Acknowledgment

This research was funded by National Institute for Occupational Safety and Health/ Centers for Disease Control grant no. 1 R01 OH03570-01. The ideas expressed are solely the authors' and do not necessarily represent the views of the funding agency.

Appendix 1: Inhalation Anthrax Dose-Response Studies

In the first study, *Macacus rhesus* monkeys and guinea pigs were acutely exposed to aerosolized anthrax spores (Vollum M36 strain) carried by particles of different diameters.[22] Among monkeys exposed to "single spores" (presumably 1 μm in length), the estimated GM or median lethal inhalation dose was 54,000 spores, and the GSD was 2.1. For spores carried on particles with a median diameter of 12 μm, the estimated GM lethal inhalation dose was 640,000 spores and the GSD was 7.2. Among guinea pigs exposed to "single spores," the estimated GM lethal inhalation dose was 51,000 spores and the GSD was 3. For spores carried on particles with a median diameter of 12 μm, the estimated GM lethal inhalation dose was 8,600,000 spores and the GSD was 6.3. As shown for guinea pigs in Table 1, the GM lethal inhalation dose was similar for "single spores" and spores carried on particles with median diameters of 3.5 μm and 4.5 μm. Because particles with aerodynamic diameters <5 μm primarily deposit in the alveolar region, and particles with aerodynamic diameters >10 μm primarily deposit in the upper respiratory tract, these data are generally interpreted to mean that inhalation anthrax requires the alveolar deposition of 1- to 5-μm particles carrying spores. However, the investigators observed that monkeys exposed to 12-μm particles carrying spores often developed "a localized infection beginning somewhere in the head" that led to death, and they concluded that infection could also be initiated in the upper respiratory tract, albeit at a much higher dose.

TABLE 1
Estimated Geometric Mean (GM) and Geometric Standard Deviation (GSD) of the Lognormal Distribution of Lethal Inhalation Doses of *Bacillus anthracis* Spores in Two Large Dose-Response Studies

Animal	Particle Size	GM (Median) Lethal Inhalation Dose	GSD	Reference
Rhesus monkeys	"Single spores"	54,000	2.06	22
	12 μm	640,000	7.16	22
Guinea pigs	"Single spores"	51,000	2.95	22
	3.5 μm	55,000	2.57	22
	4.5 μm	61,000	6.22	22
	8 μm	5,700,000	2.48	22
	12 μm	8,600,000	6.31	22
Cynomolgus monkeys	<5 μm	4,100	31	23

In the second study, cynomolgus monkeys were acutely exposed to aerosolized anthrax spores (strain not identified) carried by particles with diameters primarily <5 μm.[23] Based on a compilation of results involving 1236 monkeys, the estimated GM lethal inhalation dose was 4100 spores and the GSD was 31. The latter value represents tremendous variability in the distribution of lethal inhalation doses (ie, percent coefficient of variation = 36,400%), and it is inconsistent with the GSD value of 2.1 observed for rhesus monkeys exposed to "single spores" and with GSD values of 2.6 to 6.2 observed for guinea pigs exposed to spores carried by particles with diameters <4.5 μm (Table 1). Furthermore, these laboratory dose-response data are somewhat inconsistent with results from a field study in which cynomolgus monkeys were exposed to anthrax spore aerosols generated by an operation in a goat hair mill.[27] Groups of monkeys were exposed for multiple days to airborne spores released at a picking machine. The spores were captured by a ventilation hood and delivered to a special chamber housing the monkeys; chamber air was sampled to determine the concentration of spores in particles with diameters <5 μm. On the basis of the reported inhalation doses over the initial days of three experiments, the observed fatality rates were considerably lower than predicted. For example, in one experiment, 28 monkeys were exposed for 3 consecutive days to an estimated cumulative inhalation dose of

950 spores. Based on a GM lethal inhalation dose of 4100 and GSD = 31, about 9 or 10 of 28 monkeys (≈34%) should have died of inhalation anthrax, whereas only 2/28 (7%) died.

Appendix 2: The Assigned Penetration Factor

In the early 1980s, researchers began examining respirator performance in workplace settings. A typical study involved measuring penetration values experienced during several respirator use periods by multiple users; for example, in a NIOSH study on PAPRs, four P values were measured for each of 12 users.[6] However, the analysis applied to the data did not account for interindividual variability in the user mean penetration value $\bar{P}$. Instead, the data were simply aggregated, and the 95th percentile of the aggregate P values was estimated; further, it was proposed that the respirator's APF be equated with the 95th percentile estimate.[6] This analytical approach is reflected in the NIOSH and ANSI Z88.2 APF ranking systems. The intended meaning in both systems is that the APF is the maximum penetration value that would be experienced by 95% of properly fitted and trained respirator users. Interestingly, the intended meaning is incorrect, given the aggregate statistical derivation of the APF.[9] That is, if every user experienced the same distribution of P values, the APF would represent every user's 95th percentile P value. On the other hand, if users differed in their $\bar{P}$ values, the APF would have no clear meaning other than being the 95th percentile of P values aggregated across all wearers.

Some published respirator penetration data sets fit a lognormal random effects model summarized as follows: individual $\bar{P}$ values vary lognormally across wearers, but each wearer has a lognormal P distribution with the same GSD[P] value.[7–9] According to this construct, although only 5% of cohort-aggregated P values exceed X (the 95th percentile value equated with the APF), a higher percentage of wearers will experience more than 5% of P values greater than X. To illustrate, consider the full-facepiece PAPR with APF = 0.001 according to ANSI Z88.2. Assume that each within-wearer P distribution has GSD[P] = 2 and that the lognormal $\bar{P}$ distribution has GM[$\bar{P}$] = 0.00034 and GSD[$\bar{P}$] = 1.5. It can be shown that GM[P_{TOTAL}] = 0.00027 and GSD[P_{TOTAL}] = 2.23, where P_{TOTAL} denotes the total or aggregate distribution, and that only 5% of the cohort's P values exceed 0.001, in which case the APF criterion is satisfied. Note that GSD[$\bar{P}$] = 1.5 represents a small-to-moderate degree of interindividual variability in $\bar{P}$ (%CV = 42%) and is within the range of observed values.[7,8] More importantly, it can be shown that 33% of wearers in this cohort have more than 5% of their P values exceeding 0.001.

We note that the term APF as used in the respirator literature denotes the assigned "protection" factor rather than the assigned "penetration" factor, where the protection factor is an integer equal to the inverse of the penetration value. For example, an assigned penetration factor of 0.01 corresponds to an assigned protection factor of 100 (1/0.01). We choose to speak in terms of penetration values rather than protection factors, because inspired pathogen concentrations and doses are directly related to penetration values and inversely related to protection factor values.

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Personal Locators

The belief that it should be easy to find anyone, anywhere, at any time with a few pushes of a button has caught on with the advent of the Global Positioning System. People imagine a miniature device, attached to one's person, that reports one's whereabouts almost instantaneously. Add the highly practical need to find missing persons promptly, and the personal locator system (PLS) industry is born. Systems of this nature. . .are being tested throughout the world. Some. . .are already deployed in Japan. The service alone can be sold by cellular companies, which base it on their wireless infrastructure.

In Japan, location services are now commercially available to 72% of the nation's population. . . . Initially designed to support the mentally handicapped, PLS services have expanded to serve children, the elderly, tourist groups, and security patrols. They may also be used to track valuables and recover stolen vehicles.

From Koshima H. and Hoshen J. Personal Locator Services Emerge. *IEEE Spectrum,* 2000;37(2):41–48.