How Sensitive Is Safe? Risk-Based Targets for Ambient Monitoring of Pathogens

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***Abstract*—Biological agents present hazards at concentrations far below those of concern for most chemical agents. Detecting such low concentrations poses a great challenge to environmental monitoring systems. This study proposed a framework to address the questions of: 1) what level of risk would trigger the use of countermeasures and 2) what environmental sampling rates would be needed to detect the target risk level. In the first part, a decision model is developed to assess the costs and benefits of prophylactic antibiotic treatment for *Yersinia pestis* as a function of the risk of illness. A sensitivity analysis is then conducted to identify a threshold level of risk at which medical treatment of exposed individuals is justified. Risk levels of 1.5×10^{-4} are estimated to be sufficient to justify treatment. A dose-response function is developed to map these risk levels to delivered doses to individuals. Estimates are that an average dose of 1.8 organisms is sufficient to trigger medical treatment for an exposed population. A range of human breathing rates are used to estimate the environmental sampling rates required to detect air-phase concentrations corresponding to this dose over an 8-h exposure period. The environmental sampling rates for *Lassa virus* are two orders of magnitude greater than for *Yersinia pestis*, while those for *Bacillus anthracis* are an order of magnitude lower. These sampling rates represent idealized goals for the sensitivity of detector systems. By linking environmental sampling rates to risk-based goals for detection, this paper provides a framework for optimizing sensing systems.**

***Index Terms*—Dose response, microbial risk, pathogen, sensor.**

I. Introduction

PATHOGENIC microorganisms present risks at concentrations far below those of concern for most chemical agents. Developing a detector system that is sufficiently sensitive to detect these concentrations is a challenge. As a practical necessity, some level of environmental risk is considered acceptable. While detector systems need not be infinitely sensitive, ideally they would be capable of detecting the lowest level of risk att which some response becomes warranted. One would like to detect the concentration corresponding to the risk at which one would take some action, such as evacuating a public area or treating exposed individuals with antibiotics.

This paper describes a three-step procedure for the design of such an idealized detector system. First, decision analytic methods are used to identify the lowest level of risk at which a response is warranted. Second, a quantitative dose-response function is used to estimate doses associated with this risk level. In the third step, this dose is related to an environmental concentration, and sampling rates required to achieve this concentration are estimated.

The framework proposed here builds upon previous work that links infection risk to microbial concentrations [1]. This study extends the existing work by: 1) identifying environmental sampling rates needed to detect time-integrated concentrations of concern; 2) considering beta-Poisson dose response functions as well as the exponential dose-response functions addressed in previous work [1]; and 3) including decision analytic methods for the identification of an appropriate risk target for a sensor system.

This framework is applied to plague as an example analysis. Plague is an uncommon infectious disease of animals and humans caused by *Yersinia pestis* (*Y. pestis*) bacteria. *Y. pestis* is a Gram-negative bacterium, which is present in wild rodents and their fleas in many areas around the world, including most of the western United States. Plague is one of the most threatening and deadliest diseases in the world. It has been the cause of three pandemics, and has led to the deaths of millions of people, the devastation of cities and villages, and the collapse of governments and civilizations [2]. Small outbreaks of plague continue to occur throughout the world, and at least 2000 cases of plague are reported annually. At the present time, plague remains a serious problem for international public health, and its risk has been assessed using quantitative modeling approaches [3], [4].

Plague presents in three forms: bubonic, septicemic, and pneumonic. Among the three forms of plague, pneumonic plague is particularly dangerous, with an incubation period of 3 to 5 days and a mortality rate approaching 100% unless antibiotic treatment is initiated within 24 h of the onset of symptoms [5].

Because of the fast progression and high mortality of pneumonic plague, interest has been renewed recently in the possible use of *Y. pestis* as a biological weapon by terrorists. *Y. pestis* used in an aerosol attack could cause infection with the pneumonic form of plague being manifested 1 to 6 days after infection. Once people have the disease, the bacteria can spread to others who have close contact with them. Because of the delay between being exposed to the bacteria and becoming

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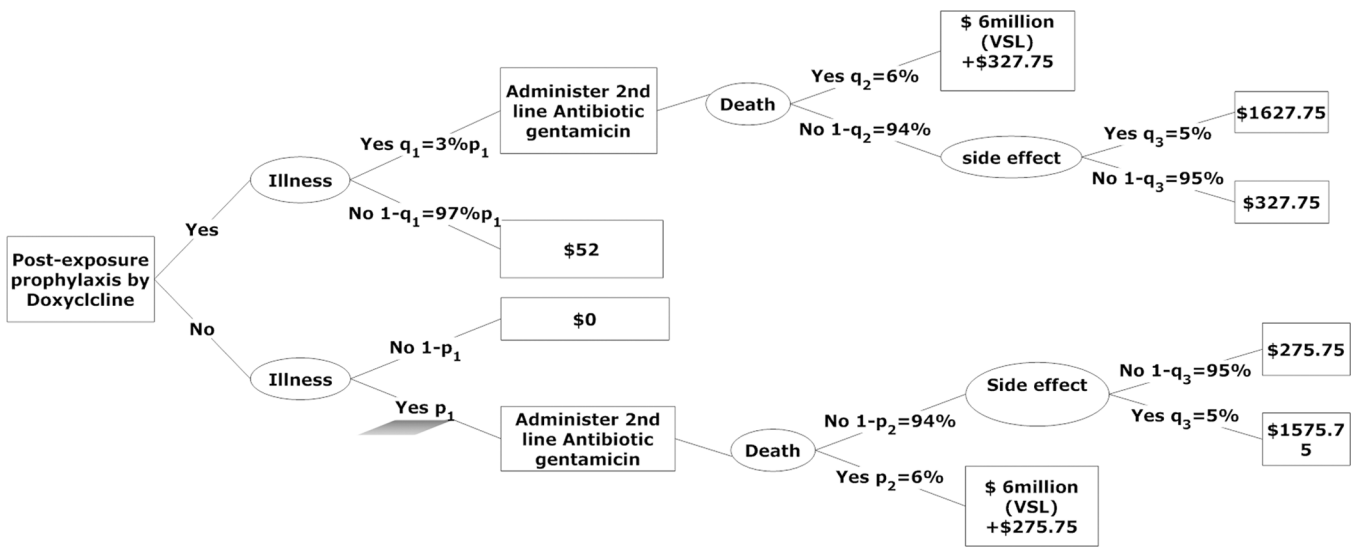

Fig. 1. Decision tree. q_1 is the probability of illness after prophylaxis; p_1 (underscored with shadow) is the probability of illness without prophylaxis, which is the target risk to be identified; q_2 and p_2 are the probabilities of death of patients treated with second line antibiotic; q_3 is the probability of side effects, and VSL is the value of statistical life.

sick, people could travel over a large area before becoming contagious and possibly infecting others. Controlling the disease would then be more difficult. A bioweapon carrying *Y. pestis* is possible because the bacterium occurs in nature, and could be isolated and grown in quantity in a laboratory. Even so, manufacturing an effective weapon using *Y. pestis* would require advanced knowledge and technology.

Currently, there is no available vaccine for plague in the U.S. Antibiotics are the cornerstone of plague treatment. There are a limited number of antibiotics with demonstrated efficacy for the treatment of plague in human [5]. Gentamicin and tetracyclines have been used with success [6]. For the treatment of pneumonic plague, doxycycline, streptomycin, chloramphenicol, and the tetracyclines have demonstrated efficacy [7].

The first step of this framework, the identification of a risk level at which response is warranted, is a complex societal choice. The second and third steps are relatively straightforward calculations. While space permits the first step to be demonstrated for only a single pathogen, the second and third steps are demonstrated for three potential bioterrorism agents for which new quantitative dose-response information has recently become available in the technical literature: *Y. Pestis*, *Lassa virus*, and *Bacillus anthracis* (*B. anthracis*).

II. Method

A. Scenario and Decision Tree

The first step of the framework, identifying a risk level at which response is warranted, was applied to a scenario in which an individual has been exposed to a low level of aerosolized *Y. pestis*. The exposure is sufficiently low that it is unlikely that the individual will become ill even if not treated. Thus, it is not clear that the expense and risk of side effects from treatment are justified. This scenario is represented by a decision tree with two options: apply a first line antibiotic immediately as postexposure prophylaxis, or wait until symptoms are manifest at which point one would apply a second line antibiotic. Fig. 1 shows this decision tree. The box on the left-hand side of the diagram indicates the decision to be made, the circles indicate uncertain future events, and the branches indicate possible outcomes.

The top branch of the decision tree shows the immediate postexposure prophylaxis option. The probability of illness (indicated by q_1) is the probability that the exposure is sufficient to cause illness (p_1) multiplied by the probability that the first line antibiotic fails to prevent the illness. The probability of the first line antibiotic failing is estimated as 3% based on the literature [8]. If the individual does become ill, the second line antibiotic will be applied, which has 6% probability of failure (q_2) [8]. Individuals not falling ill due to infection have a 5% chance of experiencing a side effect (q_3) due to antibiotic treatment (allergic reactions, colitis, etc.).

In the other option, shown on the bottom branch of the decision tree, the first line antibiotic is not applied initially. If the exposed individual subsequently becomes ill, he or she will be treated with the second line antibiotic. Thus, the second line antibiotic is applied in both options if needed. If the individual survives, potential side effects are also taken into consideration.

Doxycycline is selected as first line antibiotic. It is regarded as the least toxic of the tetracyclines with a long serum half-life ($\sim$18 h), which reduces the frequency of administration. Doxycycline has been widely used, and is well characterized with regard to long periods of administration as a prophylactic antibiotic and for treating atypical pneumonias [7]. Also, doxycycline is inexpensive and can be given orally, making it the first choice for mass postexposure prophylaxis. Gentamicin is attractive as an effective treatment because it is readily available and can be used intravenously in a single daily dose. It is likely a better choice for those patients in later stages of infection [6]. Therefore, gentamicin is used as a second line antibiotic in this project.

TABLE I
DATA REFERENCE CITED BY DECISION TREE

Parameter	Value	Reference
Probability of failure of second-line antibiotic (q_2 and p_2)	6%	Mwengee et al. [8]
Probability of failure of first-line antibiotic (q_1/p_1)	3%	Mwengee et al. [8]
Cost of doxycycline prophylaxis	$2	Keyes [9], Brouilard et al. [10]
Cost of gentamicin	$225.75	Keyes [9],
Cost of prescription	$50	Philadelphia Local hospital
Value of statistical life	$6,000,000	Viscusi & Aldy [11]
Side effect of antibiotics	$1300	Fowler et al. [12]
Probability of side effect (q_3)	5%	Fowler et al. [12]

TABLE II
SUMMARY OF THE DOSE-RESPONSE DATA

Average dose (inhaled organisms)	Deaths/exposed
1.4×10^2	0/8
5.8×10^2	1/19
1.5×10^3	1/21
5.8×10^3	4/15
2.3×10^4	19/33
6.3×10^4	21/25
2.0×10^5	32/33
5.0×10^5	12/14
1.5×10^6	12/14

B. Exponential Dose-Response Model for Y. Pestis Infection

The decision tree analysis described before identified the threshold value of risk for antibiotic treatment. The next step is to identify the human dose associated with this risk level. Data from the animal dose response study of Speck and Wolochow [13] are used as the basis for this estimate, because this study used a host animal similar to humans (a primate species), and the exposure pathway is the pathway of interest here (inhalation). Speck and Wolochow exposed 2.2–4.9 kg *rhesus* monkeys to an aerosol suspension of *Y. pestis* in a cloud chamber outfitted with a Wells-type atomizer. Dose-response data from the study are presented in Table II. The animal subjects did not receive antibiotic treatment, and in such cases, the risk of death and illness are approximately equal due to the high mortality of untreated plague. However, the risk estimates based on the animal mortality data are interpreted as predicting illness for a human population that would receive antibiotic treatment.

Exponential and beta-Poisson models, which are widely used microbial dose-response functions [14], were evaluated for fitting the dataset in Table II. The equations for exponential and beta-Poisson models are shown as (1) and (2), respectively, as

$$P(d) = 1 - e^{-rd} \tag{1}$$

$$P(d) = 1 - \left[1 + \frac{d}{N_{50}} \times \left(2^{\frac{1}{\alpha}} - 1\right)\right]^{-\alpha} \tag{2}$$

where d is dose, r, N_{50}, and α are parameters to be estimated from the data. Maximum-likelihood estimation, (MLE) as described by Haas *et al.* [14], was implemented in the *R* programming language to fit these models to the dose-response data presented in Table II.

C. Environmental Detection

Ideally, a negative response from a sensor should indicate that the risk is below levels where a response is warranted. Thus, the detector must be capable of detecting environmental concentrations that produce the dose (obtained according to Section II-B) corresponding to the risk level at which action is warranted (estimated in Section II-A). In this study, it is assumed that an air filtration device is used to concentrate the sample. The flow rate of the concentration device must be sufficiently larger than the human respiration rate that the detector is more likely to encounter sufficient numbers of pathogens to detect than the humans are likely to encounter sufficient numbers of pathogens to become ill. Thus, in this conceptual study, a single design parameter is consider, the sampler flow rate, Q. Example calculations were made for three pathogens: *Y. Pestis*, *Lassa virus,* and *B. anthracis* using recently estimated quantitative dose-response functions.

At low-dose range, a first-order Taylor series can be used to approximate both the exponential and the beta-Poisson dose-response functions [15].

For the exponential dose-response model

$$\text{risk} = r\ \text{Dose}. \tag{3}$$

For the beta-Poisson dose-response model

$$\text{risk} = \frac{\alpha}{\beta}\ \text{Dose} \tag{4}$$

where r and $\alpha/\beta(\beta = N_{50}/[2^{(1/\alpha)} - 1])$ are risk coefficients in exponential and beta-Poisson model, and Dose refers to inhalation dose, which is the integral of aerosol concentration (C), fraction of viable organisms (D_i) and breathing rate (Inh) over sampling time (t_s)

$$\text{Dose} = \int_0^{t_s} \text{Inh}\, C D_i dt. \tag{5}$$

The number of pathogens captured by a sampling device (A_s) is the integral of the sampler flow rate (Q), the capture efficiency (e), fraction of detectable organisms (D_d), and the aerosol concentration (C):

$$A_s = \int_0^{t_s} QeCD_d dt. \tag{6}$$

Linking (5) and (6) provides an estimate of human dose as a function of number of pathogens detected

$$\text{Dose} = \text{Inh}\frac{D_i}{D_d}\frac{A_s}{Qe}. \tag{7}$$

Substituting (3) and solving for the design parameter Q yields

$$Q = \frac{r\text{Inh}}{\text{risk}}\frac{D_i}{D_d}\frac{A_s}{\text{e}}. \tag{8}$$

The efficiency at which the sampler collects pathogens is estimated as 0.74 [16].

One method to estimate the required flow rate of the sampler is to assume that the number of organisms must be equal to the detection limit of whatever sensor is used to identify the pathogen

$$Q_{\mathrm{DL}} = \frac{r\mathrm{Inh}}{\mathrm{risk}} \frac{D_i}{D_d} \frac{DL}{\mathrm{e}} \tag{9}$$

where *DL* is the sensor detection limit and Q_{DL} is the required sampler flow rate estimated based on this process. In this study, a value of 15 is used for DL based on estimates of the sensitivity of PCR-based detection systems [1].

While the approach described earlier ensures that *on average,* the pathogen will be detected at the risk level of concern, it does not account for sampling variability, i.e., those situations due to random variability, the number of organisms captured by the detector is below the long-term average. A second method to estimate the required flow rate of the sampler uses classical statistics to account for sampling variability. In this approach, the pathogens are assumed to be randomly distributed in the air. Thus, counts at the detector follow a Poisson distribution. The probability of successfully identifying the pathogen is

$$P = 1 - \sum_{x=0}^{\mathrm{DL}-1} \frac{e^{A_s}(A_s)^x}{x!}. \tag{10}$$

If we assume that a negative result from the sampler must demonstrate with 95% confidence that the pathogen concentration is below the risk level of concern, then one finds another target value for A_s, which is 22 organisms, based on a detection level of 15. This higher value of A_s can then be used with (7) to estimate a required sampling rate, denoted by $\mathrm{Q_p} \cdot Q_p$ is larger than Q_{DL} and provides better protection, as it limits the probability that sampling variability will result in failure to detect the pathogen.

III. Results and Discussion

A. Threshold of Risk

The expected values for prophylaxis and without prophylaxis shown in Fig. 1 were compared to obtain the risk of infection (p_1) at which the expected values of the two options were equal.

$$\begin{aligned} &\mathrm{E[prophylaxis]} \\ &\quad = \mathrm{E\,[no\ prophylaxis]} \end{aligned} \tag{11}$$

$$\begin{aligned} &\mathrm{E\,[prophylaxis]} \\ &\quad = (\text{cost of doxycycline} + \text{cost of prescription}) \\ &\qquad + q_1 \times (\text{cost of gentamicin} + \text{cost of prescription}) \\ &\qquad + q_1 \times q_2 \times \text{value of statistical life} \\ &\qquad + q_1 \times (1 - q_2) \times q_3 \times \text{ cost of side effect} \end{aligned} \tag{12}$$

$$\begin{aligned} &\mathrm{E\,[no\ prophylaxis]} \\ &\quad = p_1 \times (\text{cost of gentamicin} + \text{cost of prescription}) \\ &\qquad + p_1 \times p_2 \times \text{value of statistical life} \\ &\qquad + p_1 \times (1 - p_2) \times q_3 \times \text{ cost of side effect.} \end{aligned} \tag{13}$$

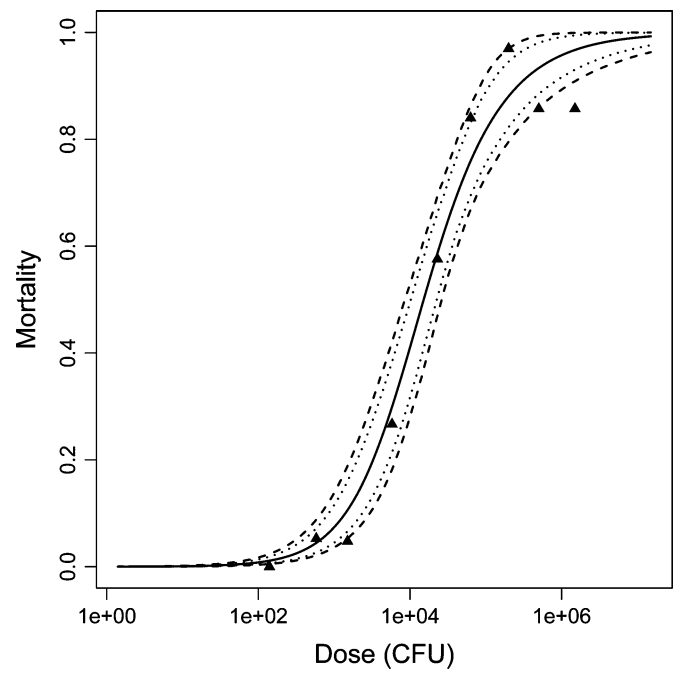

Fig. 2. Best fit model for dose response of *Yersinia pestis* infection. (——) best fit model, (· · · · ·) 95% confidence, (– – –) 99% confidence, and (▲) dose-response data [13].

TABLE III
Risk Level and Corresponding Dose

Risk Level	Dose (organisms)
LD_{50}	15166
LD_{10}	1403
LD_1	124
Target (1.5×10^{-4})	1.84

Substituting the data in Table I into (12) and (13) yields a threshold for risk (p_1) equal to 1.5×10^{-4}. At risks above this level, the response (administering the first-line antibiotic) is warranted for an expected value decision maker. At risks below this level, no immediate action is preferred, and thus detection by a sensor system would yield no benefit as it would not trigger any response.

B. Threshold of Dose

Fig. 2 shows that the beta-Poisson dose-response model is the best fit model for the set of pooled animal data (Table II) with the optimal parameters $\alpha = 0.652 \mathrm{and} N_{50} = 15166$. The $\mathrm{LD}_1, \mathrm{LD}_{10}, \mathrm{LD}_{50}$ (the doses required to produce a lethal response in 1%, 10%, or 50% of the subjects), and the critical dose associated with the target risk were listed in Table III. The sensitivity of the estimates on inclusion of different dose levels was tested by excluding the highest or lowest dose (Table II) from the analysis, and the resulting risk target dose estimates within $\pm 25\%$ range (data not shown) indicates no overly large influence exerted by various dose levels.

C. Environmental Sampling Rate

Substituting the parameters obtained earlier for *Y. pestis* and those from literature for *Lassa virus* and *B. anthracis*,

TABLE IV
FLOW RATE BASED ON DIFFERENT PATHOGENS AND RISK LEVEL (Q_p IN BOLD TYPE PROVIDES 95% CONFIDENCE THAT RISK TARGET IS ACHIEVED)

Risk level	Organism	risk coefficient	Source of r	Q_l (l/min)	Q_p (l/min)
1.5×10^{-4}	*Yersinia pestis**	$\alpha/\beta=8.15\times10^{-5}$	This study	81.5	**1.19×10^{2}**
10^{-4}	*Yersinia pestis**	$\alpha/\beta=8.15\times10^{-5}$	This study	1.22×10^{2}	**1.78×10^{2}**
10^{-4}	*Lassa virus*	r=0.039	[17]	5.85×10^{4}	**8.54×10^{4}**
10^{-4}	*Bacillus anthracis**	$r=7.15\times10^{-5}$	[3, 18]	1.07×10^{1}	**1.57×10^{1}**
10^{-5}	*Yersinia pestis**	$\alpha/\beta=8.15\times10^{-5}$	This study	1.22×10^{3}	**1.78×10^{3}**
10^{-5}	*Lassa virus*	r=0.039	[17]	5.85×10^{5}	**8.54×10^{5}**
10^{-5}	*Bacillus anthracis**	$r=7.15\times10^{-5}$	[3, 18]	1.07×10^{2}	**1.57×10^{2}**
10^{-6}	*Yersinia pestis**	$\alpha/\beta=8.15\times10^{-5}$	This study	1.22×10^{4}	**1.78×10^{4}**
10^{-6}	*Lassa virus*	r=0.039	[17]	5.85×10^{6}	**8.54×10^{5}**
10^{-6}	*Bacillus anthracis**	$r=7.15\times10^{-5}$	[3, 18]	1.07×10^{2}	**1.57×10^{2}**

* Risk coefficient for *Bacillus anthracis* and *Y. pestis* are based on mortality risk while that of *Lassa virus* is based on infection risk

Table IV summarizes estimated flow rates required to detect different pathogens and risk levels. In calculating these values, we assume the following.

1) All organisms have the ability to launch an infection process (conservative protection), and that the detector is sensitive to all the pathogens captured, which leads D_{i} and D_d to be 1.
2) Dose is calculated based on a human inhalation rate of 8 l/min, and the assumption that the sampling time is the same as that of the human exposure time.

Based on the risk level of concern for *Y. Pestis* of 1.5×10^{-4}, the sensor's sampler should take in 81.5 l air per minute to detect the average environmental concentration corresponding to this risk level. The required sampling rate rises to 119 l/min if one desires 95% confidence that the risk level of concern will be detected. Table IV also provides estimated sensor flow rates based on various risk level for two other pathogens with potential to be used as bioterrorism agents, *Lassa virus* and *B. anthracis*.

These sampling rates assume that the sampling period and the exposure period are identical. In reality, the exposure period may be briefer (the individual moves out of the affected area before the sampling is completed), in which case these sampling rates would be conservative (health protective). If the sampler is to be operated for a shorter time than the potential exposure period, then greater sensitivity would be required. This appears to argue for continuous sampling or longer sampling periods to the extent feasible.

The estimated sampling rates are high, but might be attainable, especially with multiple samplers. It should also be noted that these are the maximum sensitivity desired. Less sensitive detectors may be very valuable in detecting larger releases. These results may also inform the interpretation of sampling results. For sensor systems that do not achieve these sampling rates, some response may be warranted even when sampling results are negative, if there is other evidence of a release, such as a threat. However, the willingness of decision makers to order costly response actions in the face of negative sampling results may be problematic.

This analysis is intended primarily to outline a framework for how sensor systems may be informed by risk assessment. In particular, it shows how decision analytic approaches and quantitative dose-response models may be used to inform environmental sampling rates. While quantitative dose-response models for bioterrorism agents of concern are becoming available in the literature, applying these dose response models involves two key assumptions. The first is that the model fit to nonhuman animals can be applied to humans. The second is that the high dose risks observed in the study can be extrapolated to lower doses. The models used here have a mechanistic basis that supports their use at low doses [19], [14]. Nevertheless, validating these models at low doses is infeasible due to the large number of animal test subjects that would be required. While risk management decisions must often be made in the face of challenges, such as those that cannot be feasibly resolved with available scientific methods [20], the uncertainties introduced by such assumptions should be acknowledged. Finally, one must note that risk levels at which response actions are taken are not informed solely by decision analytic studies such as this, but also by public perceptions and preferences, which would need to be taken into account in how a sensor system is designed and how the results are interpreted.

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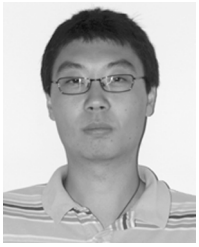

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