A probabilistic approach to quantitatively assess the inhalation risk for airborne endotoxin in cotton textile workers

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ABSTRACT

Endotoxin, a component of gram-negative bacterial cell walls, is a proinflammatory agent that induces local and systemic inflammatory responses in normal subjects which can contribute to the risk of developing asthma and chronic obstructive lung diseases. A probabilistic approach linking models of exposure, internal dosimetry, and health effects were carried out to quantitatively assess the potential inhalation risk of airborne endotoxin for workers in cotton textile plants. Combining empirical data and modeling results, we show that the half-maximum effects of the endotoxin dose (ED50) were estimated to be 3.3×10^5 (95% confidence interval (CI): $1.9–14.7 \times 10^5$) endotoxin units (EU) for the blood C-reactive protein (CRP) concentration, 1.1×10^5 (95% CI: $0.6–1.7 \times 10^5$) EU for the blood polymorphonuclear neutrophil (PMN) count, and 1.5×10^5 (95% CI: $0.4–2.5 \times 10^5$) EU for the sputum PMN count. Our study offers a risk-management framework for discussing future establishment of limits for respiratory exposure to airborne endotoxin for workers in cotton textile plants.

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1. Introduction

Endotoxin is a component of the cell walls of gram-negative bacteria, and is known as lipopolysaccharide (LPS) in its pure form. The potent immune stimulatory capacity of endotoxin is mostly attributed to its lipid A moiety, which is highly conserved across different bacterial species [1]. Endotoxin is found in air and house dust, and occurs as a contaminant of organic dusts and aerosols in the environment. Therefore, it is a ubiquitous toxin potentially capable of affecting large numbers of people. In humans, acute exposure to endotoxin induces blood and lung inflammatory responses involving neutrophils and macrophages [2] and resulting in respiratory symptoms such as fever, shaking chills, and severe asthma [3]. Chronic exposure to endotoxin in the workplace such as the cotton textile industry and agricultural settings, in which airborne endotoxin levels are usually high, is related to the risk of developing nonatopic chronic obstructive pulmonary diseases [4,5]. However, other studies suggested that environmental exposure to endotoxin may protect against the development of allergic diseases [6–9]. In addition, there is very consistent epidemiologic evidence that there is an endotoxin dose-related reduction of lung cancer risk, and provocative evidence exists that risks for other cancers may be similarly reduced [21].

Textile factories are among the most studied occupational environments with the presence of endotoxin mostly due to the large quantity of biological materials used. Occupational exposure to cotton dust has long been associated with adverse respiratory effects and diminished lung function including byssinosis [10]. Many studies identified bacterial endotoxin, present in cotton dust, as a major causative agent contributing to adverse respiratory effects [4,11]. A recent 20-year follow-up cohort study of cotton textile workers in Shanghai, China, also found that chronic loss of lung function was more strongly associated with exposure to endotoxin than to cotton dust [5]. In the cotton textile industry, endotoxin concentrations are known to vary widely according to the stage of cotton processing. A meta-analysis using endotoxin measurements from cotton dust samples collected from different production stages within various cotton plants from different research groups found that the highest mean endotoxin levels occur in opening and carding operations (3780 and 3860 EU m^{-3}, respectively) [12].

Despite the potential risk which endotoxin poses to public health, there are currently no occupational exposure limits for endotoxin levels per se in place anywhere in the world. The purpose of this study was to use a probabilistic approach to quantitatively assess the potentially inhalation risk of airborne endotoxin for workers in cotton textile plants. Additionally, uncertainties resulting from the assessment were addressed.

2. Experimental

The probabilistic risk assessment framework in the present study was divided into four phases as shown in Fig. 1 and are described in detail in subsequent sections.

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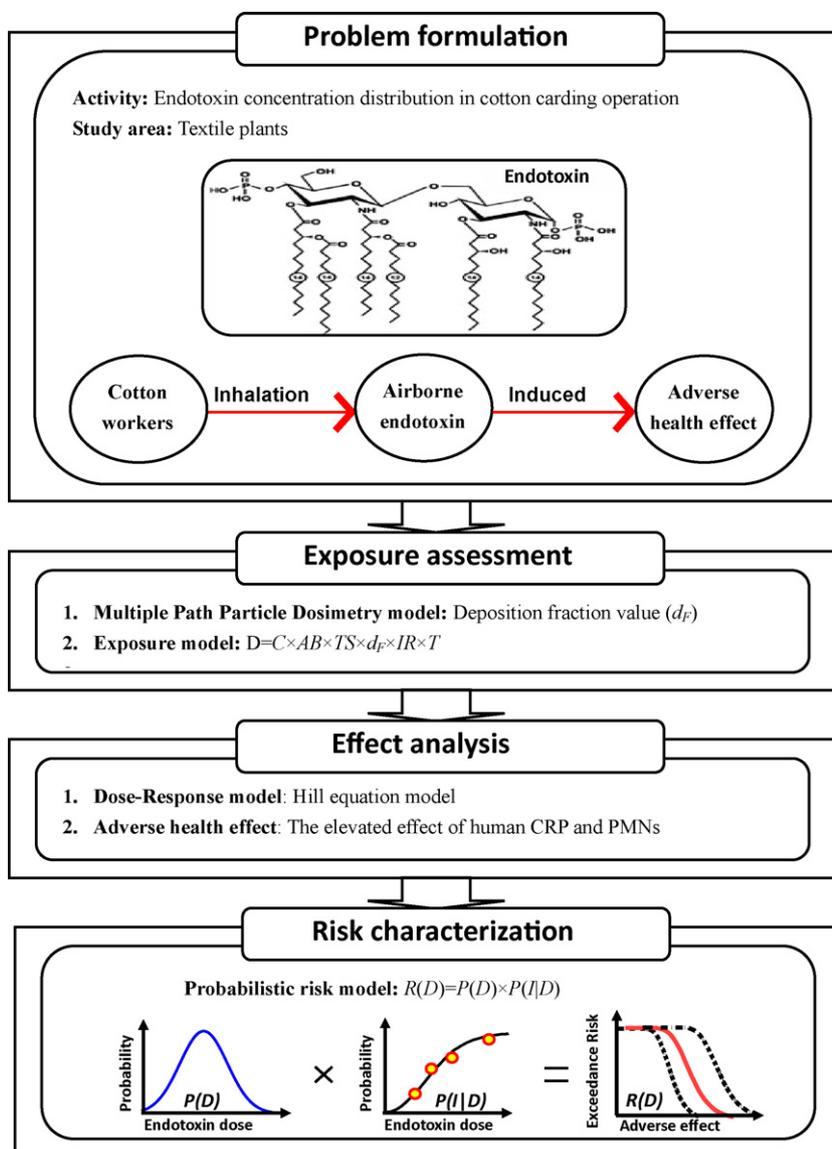
Fig. 1. Proposed probabilistic risk assessment framework to assess airborne endotoxin health risks in this study (modified from USEPA, 1992).

2.1. Problem formulation

Although cotton textile plants are among the most studied occupational environments which contain endotoxin, there are relatively few empirical data regarding airborne endotoxin concentrations associated with the particle size distribution. Therefore, we had to rely on a data reanalysis technique together with whatever empirical data were available. In the present study, airborne endotoxin concentrations and particle size distributions in cotton textile plants were obtained from published literature where available. Our study focused on airborne endotoxin exposure to workers in cotton textile plants in carding operations where the highest mean endotoxin levels ($3860\,EU\,m^{-3}$) are observed in most cotton textile plants [12]. The major database of adult human subjects exposed to various endotoxin concentrations was adopted from Michel et al. [13]. Information on particle size distributions and concentrations of airborne endotoxin was reanalyzed and optimally fitted to published data adopted from Olenchock et al. [14]. The conversion from nanograms (ng) to EU was based on the US Food and Drug Administration (FDA)'s sub-lot of the international standard, EC-6, that was assigned a potency of $10\,EU\,ng^{-1}$ [15]. Kolmogorov–Smirnov (K–S) statistics were used to optimize the goodness of fit of the distri-

bution of observed data using TableCurve 2D 5.01 (AISN Software, Mapleton, OR, USA).

2.2. Exposure assessment

Predicting the amount of particles deposited in the human lung following exposure to airborne particulate matter (PM) is the first step toward evaluating the risks associated with exposure to airborne pollutants. In addition, establishing an approximate aerodynamic particle size distribution for airborne endotoxin is an important factor in determining endotoxin toxicity and its health effects. To obtain actual internal doses of PM-bound endotoxin through the inhalation pathway, multiple-path particle dosimetry (MPPD) [16] and exposure (modified from Chio et al. [17]) models were applied. First, the MPPD model was applied to estimate the deposition fraction (d_F) of various particle sizes inhaled into the different lung regions. The size-dependent d_F is the model output using a polydispersive condition of the environmental setting with a particle size range of 0.01–$10\,\mu m$ as the major model input. For the output of the MPPD model, the human lung was divided into three major regions: the head, tracheobronchial (TB), and pulmonary (P) regions. The summed value of the deposition

Table 1
Parameters used in the multiple-path particle dosimetry (MPPD) and exposure models.

Model parameter	Value
MPPD model	
1. Lung morphometry	
Number of segments	24 (default)
Total lung capacity (TLC)	5564 ml (default)
Functional residual capacity (FRC)	3300 ml (default)
Upper respiratory tract (URT) volume	50 ml (default)
2. Breathing parameters and times	
Breathing frequency	$12 \, min^{-1}$ (default)
Tidal volume	625 ml (default)
Nasopharyngeal dead space	50 ml (default)
3. Particle size range	0.01–10 μm
Exposure model	
Air breathing rate (for light excise)[a]	$1.31 \pm 0.14 \, m^3 \, h^{-1}$
Time spent	$8 \, h \, d^{-1}$
Exposure duration	$260 \, d \, year^{-1}$

[a] Adapted from ICRP66 (ICRT, 1994).

fractions in the head, TB, and P regions is presented as the total. Parameters of lung morphometry, and breathing parameters and times were input into the MPPD model; otherwise we used default values [16]. The model was set for the human scenario, and the default value of the number of segments of the human lung was 24. The other default parameters for lung morphometry such as total lung capacity (TLC), functional residual capacity (FRC), and upper respiratory tract (URT) volume were set to 5564, 3300, and 50 ml, respectively. The breathing frequency was $12 \, min^{-1}$, and the tidal volume and nasopharyngeal dead space were 625 and 50 ml, respectively (Table 1). Second, we reconstructed the mass-basis dosimetric exposure model using the following equation:

$$D = C \times AB \times TS \times d_F \times IR \times T \tag{1}$$

where D is the mass-based cumulative dose of inhaled endotoxin (EU), C is the mass concentration of PM-bound endotoxin (EU m^{-3}), AB is the volume of air breathed (m^3 h^{-1}), TS is the time spent in a cotton textile plant (h d^{-1}), d_F is the deposition fraction deposited in different human lung regions according to the MPPD model, IR is the interchange ratio of alveolar ventilation to the blood flow rate (0.7931, dimensionless), and T is the exposure time (d year^{-1}). We treated the PM-bound endotoxin concentration, C, and AB (1.31 ± 0.14 m^3 h^{-1}) [18] probabilistically, and they both had lognormal distributions. Other deterministic parameters of TS and T in the model were set to 8 h d^{-1}, and 260 d year^{-1}, respectively (Table 1). Parameters used in the MPPD and exposure models are summarized in Table 1.

2.3. Effect assessment

Administration of reference endotoxin to humans is an important means of studying inflammation *in vivo*. *In vivo* studies based on dose–response data are used to describe relationships of inflammatory responses to different doses of endotoxin in healthy human subjects [13]. Studies showed that in normal human subjects, the response to inhaled LPS is dose-related, with the most sensitive markers of LPS-induced inflammation being the blood C-reactive protein (CRP) concentration, the blood polymorphonuclear neutrophil (PMN) count with the level of activation, and the sputum PMN count [13]. Therefore, in the present study, the blood CRP concentration, the blood PMN count, and the sputum PMN count were selected as endpoints for the endotoxin responses because (i) CRP is one of the acute-phase proteins that increases during systemic inflammation which has been used as an inflammatory marker [1]; (ii) the elevated effects of the PMN count were shown to mainly

cause a neutrophil-dominated inflammatory response [1]; and (iii) the sputum PMN count is used to assess the bronchial inflammatory response [13].

A three-parameter Hill equation model was used to optimally fit the published data to reconstruct dose–response profiles by taking into account the effects of endotoxin as:

$$E = \frac{E_{max}}{(1 + (ED50/D)^n)} \tag{2}$$

where D is the cumulative endotoxin dose (EU), E_{max} is the maximum dose effect, ED50 is the specific dose that causes an equal effect of half that of the E_{max}, and n is a slope factor referred to as the Hill coefficient which determines the overall shape of the curve. The Hill coefficient is a measure of cooperativity of the ligand binding to the enzyme or receptor. A coefficient of 1 indicates completely independent binding, regardless of how many additional ligands are already bound. Numbers >1 indicate positive cooperativity, while numbers <1 indicate negative cooperativity.

2.4. Risk characterization

Risk characterization is the phase of risk assessment where the results of exposure and quantitative effect assessments are integrated to provide an estimate that quantifies the magnitude of individual risks. In the present study, it entailed combining the exposures, measured as the endotoxin dose in the human lung pulmonary region, with the quantitative dose–response relationship between endotoxin doses and associated clinical and inflammatory mediator responses determined from experimental studies. This resulted in a joint probability function (JPF) or an exceedance risk (ER) profile, which describes the probability of exceeding the concentration associated with a particular degree of effect. A graphical display of the JPF also provides a means of assessing how alterations in ambient concentrations of endotoxin affect the risk assessment. This can be expressed mathematically as a probabilistic risk profile as:

$$R(D) = P(D) \times P(E|D) \tag{3}$$

where $R(D)$ is the risk at a specific dose, D, $P(D)$ is the probability of having an internal tissue dose, D, and $P(E|D)$ is the conditional probability of an adverse effect, given the internal dose, D, in a specific target tissue.

2.5. Uncertainty analysis

Uncertainty is a key component of risk assessment. Uncertainty arises from estimations of both the exposure and effects. In order to quantify this uncertainty and its impact on the risk estimates, a Monte Carlo (MC) simulation that included input distributions for the parameters of the derived dose–response function as well as for the estimated exposure parameters was performed. Ten thousand MC simulations were performed, and the 95% confidence interval (CI) for the expected risk was determined on the basis of the 2.5th and 97.5th quantiles of the simulation results. A risk curve was generated from the cumulative distribution of the simulation outcomes. The statistical analyses and simulations were implemented using Crystal Ball software (version 2000.2, Professional Edition, Decisioneering, Denver, CO, USA).

3. Results

3.1. Exposure assessment

Fig. 2 depicts the different particle size ranges of airborne PM-bound endotoxin concentrations in cotton textile plants during
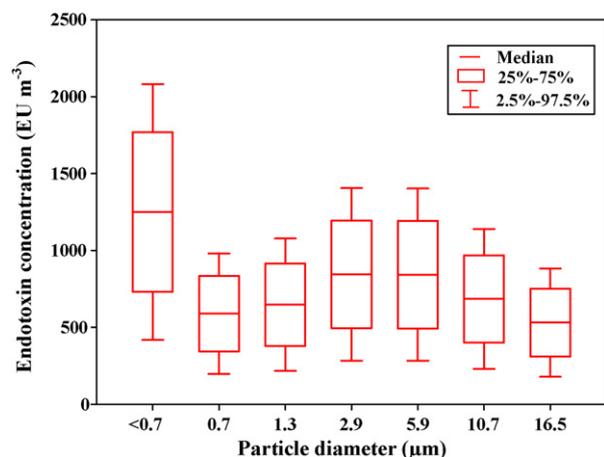
Fig. 2. Box and whisker diagrams of different particle size ranges of airborne particulate matter-bound endotoxin concentrations in textile plants during carding operations. The box indicates the range of the 25–75-percentiles, whereas the whisker shows the range of the 95% confidence interval.

carding operations. The smallest particle size (<0.7 μm) contained the highest endotoxin concentration (1239.9 EU m^{-3}, 95% CI: 264.1–2215.7 EU m^{-3}). High endotoxin concentrations were also observed at particle sizes of 2.9 and 5.9 μm with 837.5 (95% CI: 264.1–2215.7) and 835.9 EU m^{-3} (95% CI: 178.1–1493.7), respectively. This suggests that airborne endotoxin is readily inhaled deeply into the lung.

We further determined the particle deposition fraction in different lung regions. Fig. 3 shows that the deposition fraction for the particle size range between 0.01 and 0.5 μm was dominated by losses in the head and tracheobronchial regions, whereas the deposition fraction for particle sizes >0.5 μm increased in these regions. On the other hand, the particle deposition fraction of the pulmonary region had a bimodal distribution in the size ranges of 1.0–3.0 and 0.01–0.03 μm, respectively. It is noted that nanoparticles (<0.1 μm) and fine particles (0.1–2.5 μm) could easily deposit on the pulmonary region, yet coarse particles had a higher probability of being deposited in the head and tracheobronchial regions. We adopted size-specific deposition fraction (d_F) values of 0.0595, 0.0545, 0.0629, 0.0881, 0.0776, 0.0332, and 0.0262 deposited on the tracheobronchial region for particle sizes of <0.7, 0.7, 1.3, 2.9, 5.9, 10.7, and 16.5 μm from the model outputs, whereas d_F values of 0.0806, 0.0790, 0.1256, 0.1917, 0.0690, 0.0054, and 0.0014,
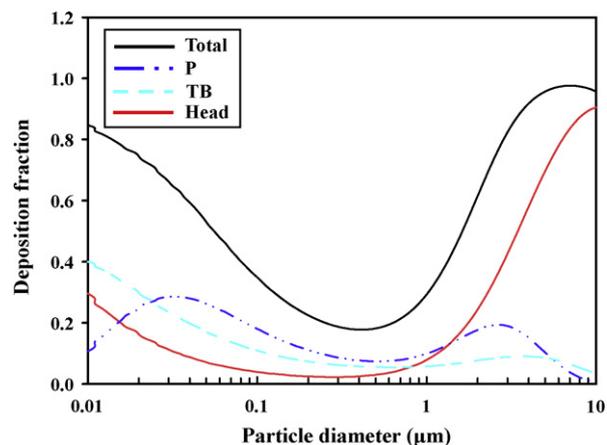
Fig. 3. Size-dependent deposition fractions estimated in different human lung regions. TB and P respectively represent the tracheobronchial and pulmonary regions of the human lung. "Total" denotes the summation of the Head, TB, and P.
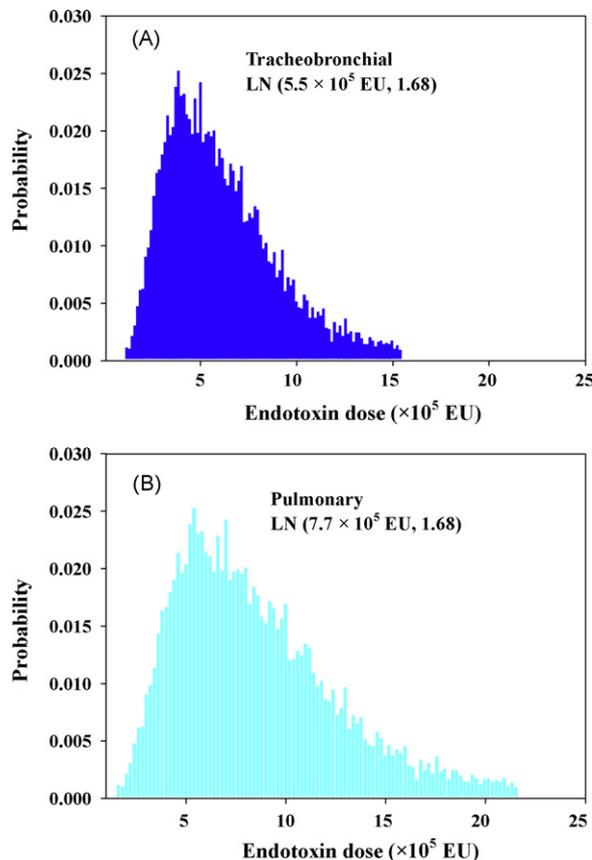
Fig. 4. Estimated endotoxin doses in human (A) tracheobronchial and (B) pulmonary regions for workers in cotton textile plants. LN (gm, gsd) denotes a lognormal distribution with the geometric mean and standard deviation.

respectively, were deposited in pulmonary regions for the above sizes.

We first reanalyzed the published data of airborne endotoxin measurements in cotton textile plants during carding operations and then incorporated them into the MPPD model to estimate the endotoxin concentrations in the tracheobronchial and pulmonary regions. Fig. 4 shows the probability profiles for the predicted particulate deposition fractions of the endotoxin dose in the tracheobronchial and pulmonary regions. The results indicated a higher endotoxin dose distribution of LN (7.7 × 10^5 EU, 1.68) in the pulmonary region, whereas in the tracheobronchial region, an endotoxin dose distribution of LN (5.5 × 10^5 EU, 1.68) was estimated.

3.2. Effect assessment

The Hill model was employed to describe the dose–response profile based on data of inflammatory responses to increasing doses of inhaled LPS in normal human subjects [13]. The reconstructed dose–response profiles were implemented using the TableCurve 2D package which provides an adequate fit for the experimental data [13] of inhaled endotoxin on changes in the blood CRP concentration ($r^2 = 0.87$) (Fig. 5A), the elevated blood PMN count ($r^2 = 0.98$) (Fig. 5B), and the elevated sputum PMN count ($r^2 = 0.82$) (Fig. 5C). ED50 values were estimated to be 3.3 × 10^5, 1.1 × 10^5, and 1.5 × 10^5 EU, for changes in the blood CRP concentration (95% CI: 1.9–4.7 × 10^5 EU), the elevated blood PMN count (95% CI: 0.6–1.7 × 10^5 EU), and the elevated PMN count (95% CI: 0.4–2.5 × 10^5 EU), respectively. The fitted Hill coefficients (n) were estimated to be 1.26 for the change in blood CRP concentration, 1.30 for the elevated blood PMN count, and 0.72 for the elevated sputum PMN count.
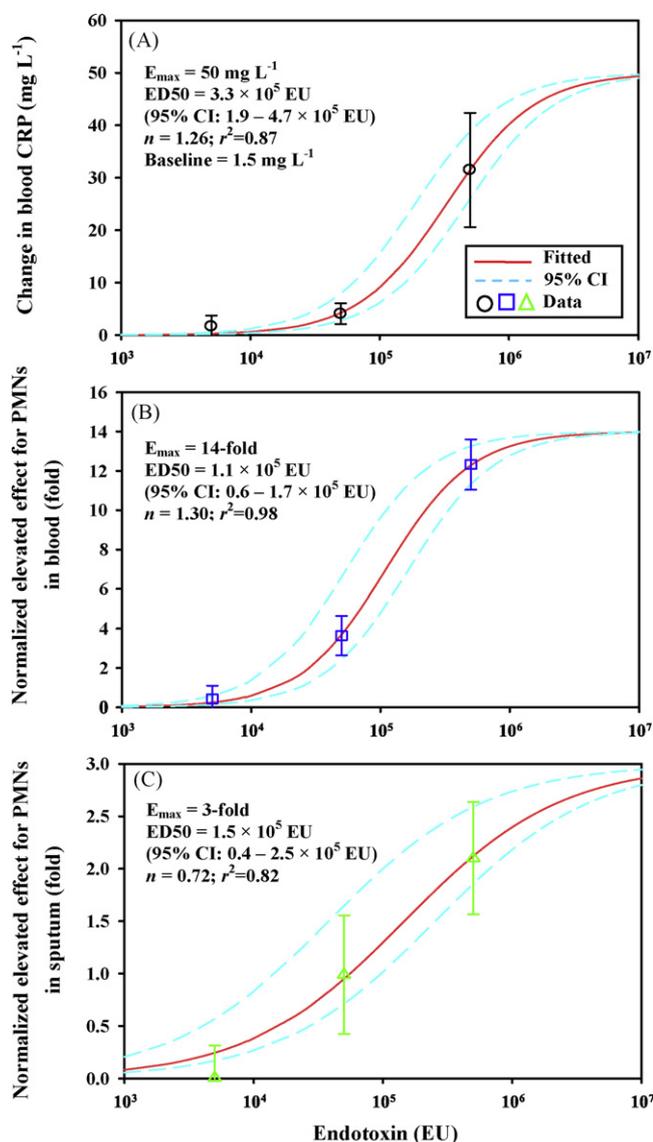
Fig. 5. Reconstructed dose–response profiles of the change in the blood C-reactive protein (CRP) concentration (A), and the normalized elevated (B) blood polymorphonuclear PMN count and (C) sputum PMN count after exposure to various airborne endotoxin levels.

3.3. Risk characterization

Risk curves for endotoxin-induced inflammatory responses (the change in the blood CRP concentration, the elevated blood PMN count, and the elevated sputum PMN count) were generated to reveal the expected risk in the lung tracheobronchial and pulmonary regions for workers in cotton textile plants (Fig. 6). The plotted probabilities, calculated from the outcome of the MC simulation followed a JPF as shown by Eq. (3) describing the exceedance cumulative distribution functions (CDFs) associated with the dose–response relationship (Fig. 5), by taking into account the uncertainty in estimating the risk (Fig. 6). Fig. 6A indicates that the change in the blood CRP concentration was estimated to be 37.3 (95% CI: 32.6–42.8) mg L^{-1} compared to healthy normal subjects at a 50% probability (with an exceedance risk (ER) of 50). Fig. 6B shows that the elevation in blood PMNs was estimated to be 13.0 (95% CI: 12.3–13.6)-fold compared to normal healthy subjects at an ER50, whereas the ER50 value for the sputum PMN elevation effect was estimated to be 2.2 (95% CI: 1.9–2.6)-fold (Fig. 6C).
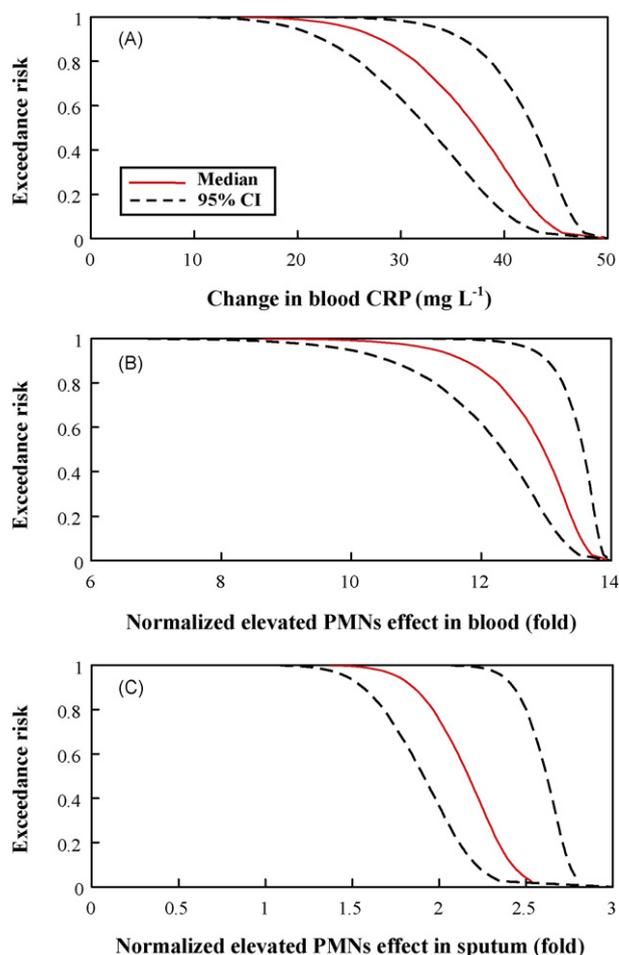
Fig. 6. Risk profiles of (A) the change in blood C-reactive protein (CRP) concentration, (B) the normalized elevated blood polymorphonuclear neutrophil (PMN) count and (C) sputum PMN count after exposure to airborne endotoxin levels for workers in cotton textile plants.

Table 2 summarizes the exposure exceeding thresholds for the probabilities of inflammatory responses with selected endpoints (elevated blood CRP concentration, blood PMN count, and sputum PMN count) at risk levels of 0.1 and 0.5 for workers exposed to airborne endotoxin in cotton textile plants during carding operations. As the CRP is one of the acute-phase proteins that increase during systemic inflammation, it is used as an inflammatory marker. Additionally, it was suggested that testing CRP levels in the blood may be an additional way to assess cardiovascular disease risk [1]. The American Heart Association has suggested that a serum CRP level of >3.0 mg L^{-1} implies a high risk for cardiovascular disease [19]. Therefore, we used a blood CRP concentration of 3.0 mg L^{-1} as the critical endotoxin concentration (2.1 × 10^4 EU) with a potential risk of endotoxin exposure. Our analysis thus indirectly indicated that airborne endotoxin in cotton textile plants may pose significant potential risks to workers.

Table 2
Potential median responses with 95% confidence intervals (CIs) for three selected effects at 10% and 50% exceedance risks (ERs) for cotton textile workers.

	ER10	ER50
Blood CRP (mg L^{-1})[a]	43.5 (40.5–46.6)	37.3 (32.6–42.8)
Blood PMNs (fold)[a]	13.5 (13.2–13.8)	13.0 (12.3–13.6)
Sputum PMNs (fold)	2.4 (2.2–2.8)	2.2 (1.9–2.6)

[a] CRP and PMNs represent C-reactive protein and polymorphonuclear neutrophils, respectively.

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4. Discussion

In this study, we present an approach which links a model of exposure, internal dosimetry, and health effects to estimate the potential risks to human health of long-term exposure to airborne endotoxin for workers in cotton textile plants. Three major findings are presented in our study: (i) the ED50 of the endotoxin concentration was estimated to be 3.3×10^5 (95% CI: $1.9–14.7 \times 10^5$) EU for an increase in blood CRP concentration, 1.1×10^5 (95% CI: $0.6–1.7 \times 10^5$) EU for elevation of the blood PMN count, and 1.5×10^5 (95% CI: $0.4–2.5 \times 10^5$) EU for elevation of the sputum PMN count; (ii) airborne endotoxin in cotton textile plants may pose significant potential risks to workers; and (iii) the exposure risk curves are pivotal results for current public policy.

There is no consensus on endotoxin's 'no observed effect levels' (NOELs), as health endpoints have been described to range from 50 to several hundred EU m^{-3} [20]. A health-based exposure limit of 50 EU m^{-3} was proposed in the Netherlands by the Dutch Health Council [20]. However, introduction of an endotoxin exposure safety level is compounded by numerous problems, such as discrepancies in extraction and analysis of endotoxin samples and inter-individual variations in inhalation responses. Hence, there is controversy surrounding the precise exposure limit to endotoxin that should be implemented in order to achieve optimal disease prevention. Our proposed probabilistic approach for quantitatively assessing the potential inhalation risk of airborne endotoxin may compensate for the discrepancy in the NOEL by using a scientifically based framework for assessing the risk of airborne endotoxin that may be present either indoors or outdoors.

We believe that a probabilistic risk-based framework, probability distributions, and risk profiles, as presented in Fig. 6, are effective scientific assessments of airborne endotoxin exposure for workers in cotton textile plants. To the best of our knowledge, this risk-based framework for endotoxin exposure has not been used until now. We recognized limitations in each of our data sources and model assumptions, particularly the inherent problem of uncertainty and variability of the data sources. Additionally, we used default, or simplifying, assumptions where data were missing or of poor quality in the MPPD and exposure models which may have introduced uncertainty into the final predictions of ambient concentrations, exposure, and risk. Although the suitability and effectiveness of approaches for presenting uncertain results are context dependent, we believe that such probabilistic methods are valuable for communicating an accurate view of current scientific knowledge to those seeking information for decision-making. The probabilistic framework and approaches presented in this study produce general conclusions that are more robust than estimates made with a limited set of scenarios or without probabilistic presentations of outcomes. Therefore, our present study offers a risk-management framework for discussing future establishment of limits for respiratory exposure to airborne endotoxin.

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