

A microbial risk assessor's guide to Valley Fever (*Coccidioides* spp.): Case study and review of risk factors

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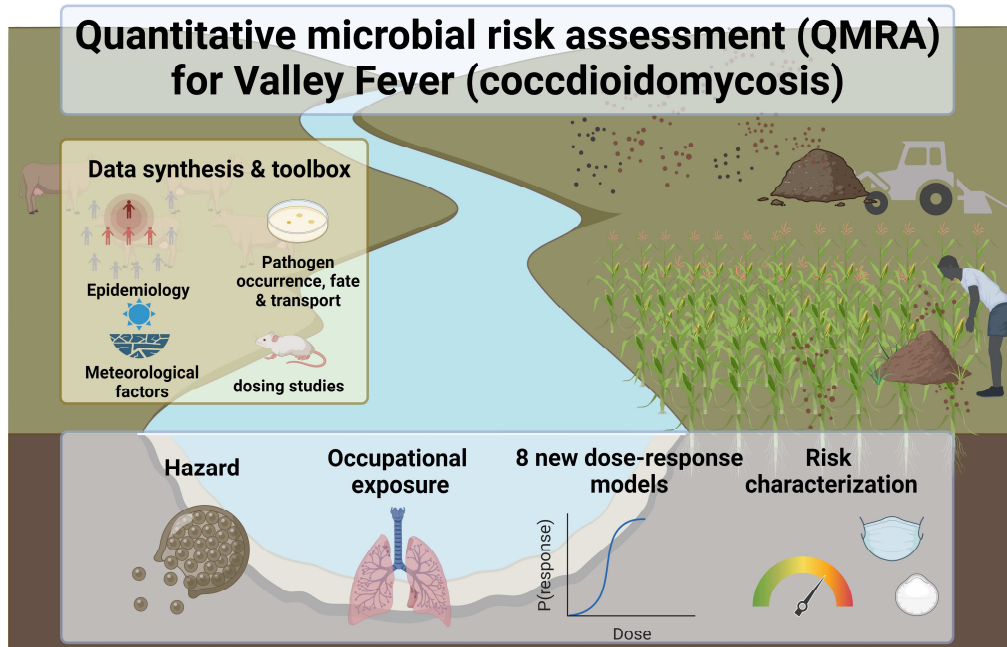
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GRAPHICAL ABSTRACT



ABSTRACT

Valley Fever is a respiratory disease caused by inhalation of arthroconidia, a type of spore produced by fungi within the genus *Coccidioides* spp. which are found in dry, hot ecosystems of the Western Hemisphere. A quantitative microbial risk assessment (QMRA) for the disease has not yet been performed due to a lack of dose-response models and a scarcity of quantitative occurrence data from environmental samples. A literature review was performed to gather data on experimental animal dosing studies, environmental occurrence, human disease outbreaks, and meteorological associations. As a result, a risk framework is presented with information for parameterizing QMRA models for *Coccidioides* spp., with eight new dose-response models proposed. A probabilistic QMRA was conducted for a Southwestern US agricultural case study, evaluating eight scenarios related to farming occupational exposures. Median daily workday risks for developing Valley Fever ranged from 2.53×10^{-7} (planting by hand while wearing an N95 facemask) to 1.33×10^{-3} (machine harvesting while not wearing a facemask). The literature review and QMRA synthesis confirmed that exposure to aerosolized arthroconidia has the potential to result in high attack rates but highlighted that the mechanistic relationships between environmental conditions and disease remain poorly understood. Recommendations for Valley Fever risk assessment research needs in order to reduce disease risks are discussed, including interventions for farmers.

Keywords: Valley fever, *Coccidioidomycosis*, *Coccidioides*, *C. immitis*, *C. posadasii*
meteorological factors, weather, climate

1. INTRODUCTION

Coccidioidomycosis, also known as Valley Fever, is an infection caused by fungi within the genus *Coccidioides*, which contains the species *C. immitis* and *C. posadasii* (Nguyen et al., 2013). *C. immitis* has historically been endemic to the California Central Valley and *C. posadasii* to central and southern Arizona, as well as parts of Central and South America (McCotter et al., 2019). The perceived endemic range of coccidioidomycosis is likely expanding northward due to the interacting effects of climate change, susceptible population movement, revised reporting and testing practices, and land use changes (Seagle et al., 2021). In 2019, 20,003 cases of Valley Fever were reported in the United States, the majority of which (97%) were reported in Arizona and California (CDC, 2021a). Infection can be difficult to diagnose due to lack of widespread testing, lack of general disease knowledge, and symptoms that mimic common pathogens (Williams & Chiller, 2022). Any case numbers presented are therefore likely an underestimate due to underreporting of asymptomatic and mild cases, or misdiagnosis (Benedict et al., 2019). Estimated annual costs due to Valley Fever in the US are \$3.9 billion when considering broader aspects of economic valuation such as annual medical costs, lost income, and economic welfare losses for Valley Fever (Gorris et al., 2021).

Typical symptoms of *Coccidioides* infection range from mild flu-like symptoms to pneumonia, dissemination from the lungs to other organs, and in extreme cases, death (CDC, 2021a). For many, symptoms of coccidioidomycosis resolve on their own, but for those who seek medical treatment common antifungal medications such as fluconazole are often prescribed (Ampel, 2015; Thompson et al., 2019). Most people infected with Valley Fever recover, with 5-10% of patients developing long-term lung infections (CDC, 2021b). In Arizona there were 11,489 reported cases of coccidioidomycosis resulting in 862 hospitalizations, 102 deaths, and over \$84 million spent in direct medical costs in 2021 (AZDHS, 2021). Increasing incidence of the disease in the Southwestern United States in recent decades has been attributed to environmental conditions, soil disturbances due to human activity, and expanding populations in affected areas (Crum, 2022).

In its soil-dwelling, saprotrophic life stage, *Coccidioides* spp. exist as filamentous hyphae, which are composed of arthroconidia (a type of spore) separated by thin-walled, brittle cells which promptly break apart when soil is disturbed, releasing arthroconidia. Once released, arthroconidia are readily aerosolized and able to be transported large distances through the air depending on meteorological conditions (Kollath, Miller, et al., 2019). Coccidioidomycosis most often occurs after the inhalation of arthroconidia (CDC, 2021a), and infection by secondary transmission from person-to-person is not known to occur (Converse et al., 1962).

Epidemiological studies identify soil disturbances as the major cause of point outbreaks (Heaney et al., 2021). Soil properties that govern the survival of *Coccidioides* spp. in its natural habitat include pH, soil moisture, organic matter, electroconductivity, and salinity (Elconin et al., 1964). Soils throughout the Southwestern United States are heterogeneous and therefore it is difficult to identify the “hot spots” of *Coccidioides* spp. (Dobos et al., 2021).

Agriculture is a major economic driver in the Southwestern US, especially Arizona and California, due to suitability for growing crops year-round, with at least 19,000 farms in operation over 26 million acres across Arizona (USDA, 2021). Agricultural work presents potentially increased risks of exposure and infection from *Coccidioides* spp., due to the close working proximity to soil and long working hours (Lupolt et al., 2022). Latino populations have been identified as having an increased risk for infection, possibly due to majority presence as agricultural workers in US endemic regions (Heaney et al., 2021). Some sources indicate that previous infection leaves most individuals with some degree of lifelong immunity, indicating high potential for an effective vaccine (Hung et al., 2019; Wouters, 2023)

To assess the risk of exposure to pathogenic microorganisms, the process of quantitative microbial risk assessment (QMRA) can be used. A QMRA includes hazard identification, exposure assessment, dose-response, and risk characterization (Haas et al., 2014). After an index pathogen is identified based on the goal of the assessment (e.g., to understand risk drivers of Valley Fever) and information from epidemiological literature, pathogen fate and transport is assessed for a particular exposure scenario to calculate a dose, or number of pathogens arriving at a target organ. The probability of an adverse outcome given the pathogen dose is calculated using a dose-response relationship, and contributions to variability and uncertainty are typically assessed via a simulation that can inform management interventions. There is a major gap in available research which uses QMRA to assess the risks posed by fungal pathogens due to lack of published dose-response relationships and complexities surrounding quantification of viable fungal organisms during various stages of their life cycle (Haas, 2015), especially as climate change is projected to increase the geographic scope and severity of fungal infections (Nnadi & Carter, 2021; van Rhijn & Bromley, 2021). One previous risk analysis has been performed for bioaerosols including *C. immitis* for road construction workers to inform selection of appropriate personal protective equipment (PPE) (Nicas & Hubbard, 2002). The few other fungal risk evaluations for occupational populations indicate that inhalation risks are of concern (Akpeimeh, 2019; Nicas, 2018b; Nicas & Hubbard, 2002). Fungi have been highlighted as a key gap for QMRA (Haas, 2015; Weiskerger & Brandão, 2020).

The objectives of this work are therefore to (1) propose a QMRA approach for *Coccidioides* spp. via a case study on the risk of coccidioidomycosis posed to a group of agricultural workers; (2) aggregate existing literature on risk assessment inputs for *Coccidioides* spp. to parameterize the QMRA model and for use by the broader QMRA modeling community; (2) perform a systematic literature review to develop new dose-response models for *Coccidioides* spp.; (3) evaluate risk drivers by comparing QMRA scenarios regarding personal protective equipment usage and dose-response variables; and (5) evaluate information available for “reality checking” the proposed QMRA model by reviewing outbreaks and meteorological factor relationships.

2. METHODS

2.1 Exposure models. *Coccidioides* spp. arthroconidia were modelled as the primary hazard, as the infectivity of *Coccidioides* spp. is dependent on the release of arthroconidia from segmented, soil-dwelling hyphae which aerosolize prior to being deposited into the lungs of a host to form spherules and replicate (Akram & Koirala, 2023; Malo et al., 2014). Aerosolization can occur from natural effects including wind or animal activities that disturb the soil, as well as from human activities like farming. The population of focus for this QMRA was agricultural workers with no known prior exposure to the pathogen, i.e., those without existing immunity. Exposure scenarios were explored for (1) planting by hand and (2) harvesting using a machine with no dust containment device (e.g., containment cabin). The effect of PPE in the form of masks was investigated as they are designed to reduce the number of aerosols inhaled (i.e., removal efficiency). PPE scenarios were considered including (1) no mask; (2) wearing a cotton mask; (3) wearing a surgical mask; and (4) wearing an N95 mask. Thus, eight total scenarios are examined in our exposure analysis (**Table 1**). **Equation 1** describes the dose of arthroconidia inhaled and subsequently deposited into the lungs.

$$Dose = E * f * B * \frac{1h}{60min} t (C_{soil} * A + b) \quad (1)$$

Where E = mask efficiency, defined as a 1- fraction of respirable particles $<5 \mu m$ removed [dimensionless]; f = lung deposition efficiency [dimensionless]; B = the breathing rate for a worker [m^3/h]; t = exposure time, i.e. duration of a worker shift [h/day]; C_{soil} = the concentration of the arthroconidia in soil [arthroconidia / g soil]; A = the ratio of soil containing arthroconidia aerosolized by a farming activity [g soil aerosolized / m^3 air (activity-specific)]; and b =

background airborne concentration of arthroconidia [arthroconidia /m³ air] (**Table 2**). A Monte Carlo analysis was conducted using distributions for each variable in **Equation 1**, which are summarized in **Table 2**. Monte Carlo analysis was conducted using R v.4.2.2. Sensitivity analysis was evaluated using bivariate Spearman rank correlations.

2.2. Aggregation of existing literature on risk inputs for *Coccidioides* spp. To parameterize the model in equation 1, a literature review was conducted using PubMed and Web of Science for exposure, dose-response, and risk characterization information described below using keywords such as ("coccidioid*" OR "coccidiomycosis" OR "coccidia" OR "valley fever") AND ("soil" OR "water" OR "air" OR "dust" OR "farming" OR "agriculture" OR "exposure"). Due to a general lack of dose-response information for fungal microorganisms (Haas, 2015), we chose to conduct a systematic literature review for this variable only.

2.3 Dose-response. A keyword search was performed in PubMed and Web of Science on 11/02/22 to acquire experimental animal data for use in dose-response modelling using keywords "((coccidioides spefcies) or (Coccidioides spp.) or (Coccidioides posadasii) or (C.posadasii) or (Coccidioides immitis) or (C. immitis) or (coccidioidomycosis) or (valley fever) or (San Joaquin valley fever)) AND (dose) AND ((aerosol infection) or (aerosol exposure) or (respiratory exposure) or (intranasal) or (intratracheal) or (intraperitoneal) or (intravenous) or (intracerebral) or (intradermal) or (intracardiac) or (in vivo) or (experimental illness) or (experimental challenge) or (model) or (inoculation) or (experimental infection) or (infectious dose))". 1,206 records returned through the searches were imported into Zotero for review. Abstracts were screened by two reviewers for relevance to the inclusion criteria and full texts of 121 studies were obtained on this basis and further reviewed for relevant data extraction. Most studies excluded during abstract review indicated that they had no experimental exposure to *Coccidioides* spp. arthroconidia. Inclusion criteria for assessing data for dose-response modeling appropriateness were (Haas et al., 2014; Hamilton et al., 2017):

- Number of organisms in the dosing inoculum was quantified;
- Criteria for a positive endpoint was stated and monitored for;
- Number of subjects administered the inoculum and experiencing the endpoint (illness, infection, death) was defined and quantal (i.e., number of subjects presenting with an endpoint, divided by the total number of subjects);
- Dosing method and exposure route defined (intravenous, oral, intratracheal, etc.);
- Strain and/or source of inoculum was defined; and
- One or more intermediate responses were observed (not all 0% or 100% infected).

While articles were initially screened based on any defined exposure route, data from studies were split into two categories for further analysis: one which generally matched the modelled human exposure route (i.e., inhalation, intranasal, or intratracheal experimental animal exposure to simulate human respiratory exposure); and another which included exposure routes unlikely to be applicable to respiratory exposure (i.e., intraperitoneal, subcutaneous, intravenous, etc.) Two biologically plausible, commonly applied dose-response models in QMRA analysis were used for fit testing based on a Poisson distributed dose and binomial probability of infection (Haas et al., 1999, 2014). A Cochran-Armitage test of trend was performed for individual datasets to determine if model fitting was appropriate with maximum likelihood estimation (MLE) to minimize the deviance of the model and bootstrapping using the exponential or Beta-Poisson dose-response models (Equations 2 and 3, respectively) as described elsewhere (Hamilton et al., 2017).

$$P(response) = 1 - e^{-k*dose} \quad (2)$$

$$P(response) = 1 - \left(1 + \frac{dose^{\left(\frac{1}{2\alpha}-1\right)}}{N_{50}} \right)^{-\alpha} \quad (3)$$

Individual model fit was evaluated using the minimized deviance compared to a 95% confidence value from chi-square distribution with degrees of freedom set equal to the number of dose groups from the study minus the number of parameters per model. As data with an endpoint of animal infection was sparse compared to data with an endpoint of animal death, and measurements of infection were generally described as unreliable or imprecise across the studies due to available testing methods for infection, our dose-response model considers animal death as a proxy for severe illness in humans, a method used in other dose-response models with similar limitations (Watanabe et al., 2010). Using the methods described above, multiple plausible dose-response models for exposure to *Coccidioides spp.* could be generated. Any of these models could be used as part of a risk analysis for exposure to *Coccidioides spp.* However, it is considered a best practice to use data gathered by exposing subjects to the pathogen by a similar exposure route as that which is most relevant to the exposure model (Jones and Su, 2015). It is also generally accepted in biological dose-response assessment that models based on animals which are closer biological analogues to humans are more likely to simulate the actual response of a human (Phillips et. al, 2014). As such, our final model selection favored respiratory exposure studies with nonhuman primate subjects.

3. RESULTS

3.1 Exposure parameters. The inhalation rate (B) for an agricultural worker was assumed to be comparable to that of outdoor workers, so a value for general construction workers/laborers was used (USEPA, 2011). The fraction of inhaled arthroconidia deposited in the lungs (f) was determined using a previous study assuming moderate activity and 1 L of tidal air volume in an 8 second cycle period of breathing for the range of particle sizes (2 to 5 microns) which correspond to *Coccidioides* spp. arthroconidia (Heyder et al., 1986). A range of removal efficiencies (E) for N95, surgical, and cotton masks were used from challenge testing studies with respirable particles (Lindsley et al., 2021), which aligned with ranges reported elsewhere (Konda et al., 2020). The Bureau of Labor Statistics reports that many farmers work more than 40 hours per week (BLS, 2022). Exposure time (t) for laborers was assumed to range from 8-12 hours per day, with a 60-h work week upper bound due to potentially high demands during peak harvesting season.

Information was sparse regarding the concentrations of *Coccidioides* spp. arthroconidia in soil (C_{soil}) and especially air (used to derive a ratio of aerosolized arthroconidia per unit mass of soil (A)). Concentrations were reviewed in the literature to inform exposure estimates (**Table 3**). Air concentrations were estimated based on information provided in the published literature and ranged from 0.007-120.7 CFU/m³ (with an estimated 0.005 gc/m³ from molecular measurements) (Chow et al., 2016; Gade et al., 2020). Only one study provided comparisons of arthroconidia in air during dust storms vs. non-storm periods. The highest air concentration was measured before a dust storm rather than during or after the storm, highlighting the uncertainties related to arthroconidia fate and transport from meteorological activity. As a result, there is uncertainty regarding contributions of a particular activity to the airborne arthroconidia load, and therefore considerable uncertainty surrounding the background (b) term in the model. Because hot spots are so difficult to estimate and there was not data available to support a background air contribution estimate for arthroconidia, we chose to focus the risk assessment on potential event-driven contributions of arthroconidia and set the background equal to zero for the purposes of this model. During farming activities, airborne dust was assumed to be composed of soil and was estimated as the respirable dust levels generated per m³ air for planting and harvesting activities (Nieuwenhuijsen et al., 1999) (**Table 2**). It was assumed that soil concentrations of *Coccidioides* spp. remain constant per unit mass as they are aerosolized

within the respirable range (approximately $<5\ \mu\text{m}$) as there were no direct measurements of *Coccidioides* spp. during farming activities.

Five studies reported percentages of positive samples in soil using molecular methods and sample masses used to estimate concentrations ranging from 0.02 to 0.46 gc/g (Baptistas et al., 2012; Barker et al., 2012; Bowers et al., 2019; Chow et al., 2016, 2021). Due to variable copy numbers of genes in the *Coccidioides* spp. genome, depending on the PCR assay used for quantification, copies per genome could vary between 20-146 copies per genome for *Coccidioides* spp. (Johnson et al., 2015) and 57-85.7 copies per genome for *C. posadasii* and *C. immitis* (Chow et al., 2016), which are similar to ranges reported for another fungal organism, *Aspergillus fumigatus* (38-91 copies per genome) (Herrera et al., 2009). There is only one paper (Elconin et al., 1964) in the San Joaquin Valley which used culture-based methods that can be used to approximate a concentration distribution by the most probable number (MPN) approach (Elconin et al., 1964). Estimated concentrations ranged from below detection to 5.67 arthroconidia per g soil (**Table 3**). The culture-based measurements were used for risk assessment for C_{soil} due to uncertainties associated with viability and copy number of molecular measurements. Assuming a detection limit of 1 arthroconidia/10 g soil assayed would yield a theoretical detection limit of 0.1 arthroconidia/g soil. This was used to fit an interval-censored distribution using fitdistrplus in R v.4.2.2. (Delignette-Muller & Dutang, 2015). A gamma distribution best described the data with parameters shape=0.408, rate=0.189, AIC=34.59 (**Supplemental Figure S1**).

Inactivation of arthroconidia populations after soil disturbance but before infection was not considered in the model due to previous work regarding the robustness of arthroconidia to environmental conditions (Kolivras et al., 2001). Arthroconidia population growth during that period was not included in the model as arthroconidia are only known to germinate once they infect a host or return to the soil (Kollath, Miller, et al., 2019). Spatial and temporal variation in the presence of *Coccidioides* spp., as well as contributions from environmental events (e.g., dust storms, monsoons, or earthquakes) were not considered due to uncertainties discussed above. While *Coccidioides* spp. are thought to occur in “hot spots”, these areas are difficult to predict, so the results of this QMRA are conditional on the presence of the arthroconidia in soil at levels determined by our analysis of data supplied by Elconin et al. 1964 (Dobos et al., 2021). The Elconin et al. 1964 data were collected from an endemic area identified by the investigators based on previous work in the San Joaquin Valley (Egeberg & Ely, 1956; Elconin et al., 1957) and could therefore be representative of a “hot spot” rather than an average over a general area. This would be a conservative assessment of risk and assumes that agricultural activities

would be taking place in a potential hot spot during the entire period of exposure; however, we emphasize there is significant uncertainty associated with the concentrations of arthroconidia expected in hot spots versus other areas, and their potential contributions to the total airborne concentration. The background (*b*) was assumed to be negligible for the purposes of this QMRA, with a focus on the excess risk provided by specific agricultural events.

3.2 Development of dose-response models. Of the 1,206 unique papers identified in the literature search, 121 appeared to meet initial inclusion criteria and full texts were obtained based on these abstracts. Generally, the goal of these studies was to provide data about novel (at the time of their publication) methods for vaccination against or therapeutics for treatment of coccidioidomycosis. Data from the untreated control groups of these experimental studies were potentially useful for dose-response modelling. After review of full texts, five contained data that met the inclusion criteria for a model of respiratory dose-response and five others contained data that met the inclusion criteria for exposures other than respiratory (**Table 4** and PRISMA diagram in **Supplemental Figure S2**). Also included in Table 4 were data from studies which did not fully meet the inclusion criteria, but which provided some dose-response information and were useful for contextualization of the data presented by other studies. Of the papers which provided data useful for dose-response modelling, four were found to have acceptable fits to the exponential or beta-Poisson models for the respiratory route of exposure and are described below. Model fits based on nine studies for which the MLE performed was able to converge on parameters are summarized in **Table 5** and displayed graphically in **Figure 1**. Models that did not have significant fits are shown in **Supplemental Figure S3**.

One study attempted to quantify the relationship between exposure to *Coccidioides immitis*, strain Cash and development of severe pulmonary disease (Converse et al., 1962). Doses of *C. immitis* arthroconidia were cultured from a human patient who had experienced nonfatal, disseminated coccidioidomycosis. Once cultured, arthroconidia were aerosolized to expose three groups of five *Macaca mulatta* monkeys to estimated inhaled doses of approximately 10,000, 300, or 50 arthroconidia. Exact doses within each group varied $\pm 15\%$ by monkey. Exposed monkeys were placed in a 4,800 liter chamber into which the aerosolized arthroconidia were introduced. Two additional, unexposed, control monkeys were kept in cages with monkeys from the highest exposure group to determine if secondary transmission occurred. Progress of the disease was tracked via coccidioidin skin and serum tests, body weight loss measurements, and a series of five chest x-rays over the 14-month observational period following exposure. Four of the five monkeys in the 10,000-arthroconidia group died

within 51 days after exposure and three of the five monkeys in the 300-arthroconidia dose group died within 253 days after exposure, with acute primary pulmonary coccidioidomycosis being the determined cause of death in all cases. All five monkeys in the 50-arthroconidia group developed a milder form of pulmonary disease and survived until the end of the observation period. Necropsies were performed on all monkeys who died spontaneously during the observation period and on those who were sacrificed at the end of the observational period. Necropsies confirmed that all 15 exposed monkeys became infected regardless of dose group and developed some degree of pulmonary disease, while the two control monkeys remained entirely free of infection or disease (Converse et al., 1962).

Another study attempted to quantify the effect of ketoconazole on mice who had been infected with *C. immitis*, strain Silveira (Levine & Cobb, 1980). Three independent experiments were run as part of this study, each of which exposed two groups of NAMRU (Naval Medical Research Unit) mice to arthroconidia, after which one group was treated regularly with ketoconazole while the other received only a placebo of water by gavage. Infection was achieved by suspending calculated doses of arthroconidia in 0.9% otherwise sterile saline solutions which were administered intranasally. Mice were between six to eight weeks old at the time of the experiment and weighed between 25-28 grams. Animals were necropsied as they died during the study period or after sacrifice at the end of the study, at which point organ cultures were performed to confirm coccidioidomycosis. Data from each of the three placebo groups were used as independent data points for dose-response modelling. The groups of 29, 40, and 10 mice received an intranasal dose of 42, 47, or 150 arthroconidia, which resulted in the deaths of 9/29, 15/40, and 9/10 of the animals in the respective groups.

The third study from which data was used for dose-response modelling sought to determine the efficacy of a cell wall antigen from *C. immitis* as a vaccine against arthroconidia from *C. immitis*, strain Silveira (Lecara et al., 1983). Multiple experiments were performed as part of this study, one of which exposed groups of male DBA/2J mice (Jackson Laboratories, Bar Harbor, Maine) to arthroconidia by the intranasal route. This experiment included infection of six groups, three of whom received the proposed vaccine and 3 of whom received a placebo. The three placebo groups, which were composed of 25, 30, and 25 mice each were exposed to calculated doses of 50, 500, or 1500 arthroconidia, which resulted in the deaths of 11/25, 21/30, and 23/25 of the animals in the respective groups.

The fourth study was designed to assess the role of reactive oxygen intermediates in the formation of protective immunity to coccidioidomycosis in mice (Margolis et al., 2011). This study exposed 2 control groups of 8 female C57Bl/6J mice to 150 or 250 arthroconidia of the

R.S. strain of *C. immitis* intranasally to initiate pulmonary infection. After 30 days, this exposure had resulted in the deaths of 5/8 mice from the 150-dose group and 8/8 mice from the 250-dose group.

Data from the remaining studies in Table 4 which met the some of the inclusion criteria were rejected from the final dose-response models because they did not have enough independent dose groups to allow for sufficient degrees of freedom in the model, did not have an intermediate response, did not individually pass the Cochran–Armitage test of trend, or their models did not converge due to numerical constraints. Across the studies, it was generally confirmed that any dose of *Coccidioides* spp. is capable of initiating infection, but that larger doses usually correspond to more serious illness and a higher likelihood of death. As such, rather than describing the relationship between exposure to an inhaled dose of *Coccidioides* spp. and infection, the first five dose-response models in **Table 5** describe the relationship between an inhaled dose by an individual with no prior immunity and the development of severe Valley Fever illness.

Model fit statistics for non-respiratory data from the five studies in Table 4 which met the inclusion criteria for dose-response modelling are also presented in Table 5. While data from these studies and the resultant dose-response models generated from them are not directly relevant to the respiratory exposure scenarios presented by this study, they may be useful for future researchers attempting to model exposure by other routes. They also serve to demonstrate the general virulence of exposure to *Coccidioides* spp. arthroconidia in various contexts.

Based on the analysis of dose-response datasets, the Beta-Poisson model from Converse et al. (1962) was chosen due to the use of a similar non-human primate host organism (monkeys), an inhalation exposure route that approximated the case study pathway chosen, and an endpoint of death that could be used to represent a human disease outcome. The Beta-Poisson model was the preferred model compared to the Exponential model based on the statistical fit to the experimental data.

3.3 Risk of infection. A QMRA model was conducted across 8 scenarios (**Table 1 and Figure 2**). Parameters from dose-response model no. 1 were used, as data from that model was sourced from (Converse et al., 1962) which exposed monkeys (a closer biological analogue to humans than the mice used by the other studies) by a direct inhalation pathway (while the others used arthroconidia suspended in saline solution and injected intranasally to simulate aerosol exposure). Median daily workday risks ranged from 2.53×10^{-7} (scenario 4) to 1.33×10^{-3}

(scenario 5). Median risks from planting by hand (mean across scenarios 1-4: 1.25×10^{-5}) were lower than harvesting risks (mean across scenario 5-8: 6.33×10^{-4}) by a factor of approximately 50. The greatest risks were for scenarios with no mask (scenarios 1 and 5), with risk reductions depending on the mask type used. N95 masks provided up to 99% reductions in risk. A sensitivity analysis using bivariate Spearman rank correlations indicated that the arthroconidia concentration in soil (C_{soil}) and the aerosolization factors for planting (A_p) or harvesting (A_h) were the most influential variables in each model (**Figure 3**). Other influential factors included the air inhalation rate. It is noted that within-scenario variability was greater than between-scenario variability (**Figure 2**), indicating that only varying the scenarios for aerosolization of arthroconidia (A_p or A_h) and use of personal protective equipment (E) in alignment with management-associated factors may not reflect greater sources of variability and/or uncertainty introduced by the quantification of arthroconidia in environmental media, aerosolization rates, etc..

3.4 Outbreaks of Valley fever for use in risk model calibration. To provide comparison for the risk of infection output by our model, we searched for epidemiological data related to specific events which were demonstrated to cause outbreaks of coccidioidomycosis. Nineteen studies which reported outbreaks of coccidioidomycosis following a specific exposure event or general activity which may have led to exposure are summarized in **Supplemental Table S1**, ordered by increasing population size of potentially exposed individuals. The events described by these studies ranged from small groups of individuals disturbing soil in a single incident, to large-scale population level events such as an earthquake. When attack rates were not directly presented by the studies, a simple attack rate was calculated by dividing the number of infected (confirmed by serological or skin testing) by the total number of those potentially exposed. Generally, exposure events which were experienced by small groups of individuals demonstrated higher attack rates, with some events having caused 100% of those exposed to develop the disease. However, there is considerable uncertainty introduced due to the potential for exposed individuals to have been missed during epidemiological studies and therefore not considered within the denominator of attack rates. For example, large-scale exposure events, such as construction projects employing thousands, resulted in lower reported attack rates. However, smaller-scale exposure events (e.g., a group of college students involved in a biology field trip (Davis et al., 1942)) might have a better-characterized denominator of exposed individuals compared with a larger group of workers assessed for exposure (Wilken, Marquez, et al., 2015)). Determining the actual proportion of exposed individuals from the reported

numbers of those who were potentially exposed is not possible from the epidemiologic data presented by many of the larger studies. All the studies presented in **Supplemental Table S1** either describe environmental sampling to confirm the presence of *Coccidioides* spp. at or near the exposure site, or state that the exposure event took place in a location where the fungus is known to be endemic. However, none of the studies provided quantification of their environmental samples or presented a calculated or measured dose of arthroconidia received by those exposed. Most studies on small populations included survey or skin testing data which indicated that those infected were experiencing first-time infection.

3.5 Review of environmental factors affecting Valley Fever cases. Studies regarding meteorological factors (**Supplemental Table S2**) have attempted to determine which conditions are optimal for infection, and developed models to predict incidence on the basis of several meteorological factors. *Coccidioides* spp. flourish in environments with warm air temperatures and dry soil. Populations living in regions that experience frequent changes in their weather may also be more susceptible to Valley Fever. Several meteorological factors have been used to serve as predictors for Valley Fever incidence, such as dust storm frequency and antecedent precipitation. Mathematical models have been developed to calculate estimated incidence of Valley Fever based on measurements of such meteorological factors. Additionally, several studies have analyzed changing trends in Valley Fever spread in relation to climate change (Gorris et al., 2018, 2019; Tong et al., 2017). Multiple areas in the Southwestern United States are experiencing increases in Valley Fever cases, such as Maricopa and Pima counties in Arizona due to changes in climate change, susceptible population movement, revised reporting and testing practices, and land use changes (McCotter et al., 2019). Temperature increases of 0.7°F per decade (1991-2020) have been observed, along with precipitation decreases of 0.92 inches per decade (1991-2020) (AZ State climate Office, 2023).

4. DISCUSSION

4.1 Developing a risk framework and compendium of data for the Valley Fever risk assessment community. The modelling presented by this study provides a framework for evaluating the risk of environmental exposure to *Coccidioides* spp. in eight specific scenarios related to farming activities. Activities with greater dust exposures (e.g., mechanical harvesting compared to planting) were drivers of inhalation risks, indicating the potential to reduce risk by using PPE. These scenarios were chosen based on their applicability to occupational settings in

regions most affected by coccidioidomycosis. Eight new dose-response models were developed as part of this work, which can be used to simulate various risk scenarios for Valley Fever. All significant model fits presented here are acceptable for use in QMRA depending on context. Factors such as host relevance (e.g., primates are often used as a proxy for human exposures; however in some cases other test organisms may be more relevant based on the mechanism of action, target organ, and progression of pathogenesis), health endpoint considered, and exposure route (e.g., a QMRA for inhalation exposure might focus on intranasal or inhalation exposures or use a conversion factor based in observed data if extrapolating across routes (Hamilton et al., 2017)) should be considered in their use. Future analysts should judge the component factors of the individual dose-response models when choosing the model most appropriate for a particular scenario. When data from one study fits both models (Exponential and Beta-Poisson), the preferred statistically fitting model between the two fitted options should be chosen.

4.2 Implications of Valley Fever risk models. To implement effective risk management and communication practices for Valley Fever, awareness of safety measures related to agriculture can be improved. For example, (Sipan et al., 2022) observed that 73% (n=119) of migrant farmers residing in seasonal housing centers in Kern County, California had previous awareness of Valley Fever. While many participants were aware of the benefits of respirator protection, almost half (46%) of participants believed that Valley Fever is contagious (person-to-person transmission) and one-quarter (28%) that it can also be contracted through contaminated food or water. Additionally, almost all participants (91%) believed that the disease can be contracted by pesticide exposure. This population (74%) expressed concern regarding Valley Fever due to lack of insurance or inability to miss work (80%). However, there are challenges associated with communicating health risks of climate-sensitive diseases, such as Valley Fever, to diverse communities and decision-makers (M. Matlock et al., 2019), and total avoidance is likely not feasible. Prevention messages for farmers may include the use of respirators, such as N95, N99, or N100, when their work activities include soil disturbance. Skin tests which indicate an established immune response can be used to determine prior infection and likely immunity (Wack et al., 2015). Since our dose-response models indicate that a higher first-time dose is more likely to lead to severe disease, individuals who do not have a positive skin test should be especially careful when performing any work which disturbs soil in an area where the disease is endemic. Soil wetting practices before farming activities can prevent dust

and arthroconidia aerosolization. However, regions where Valley Fever is endemic are also prone to drought and such activities could conflict with water conservation practices.

4.3. Model limitations. Few studies are available which provide measurements of arthroconidia in soil or air, and only one study reviewed provided a comparison of detections in air and soil (Chow et al., 2016). One study on airborne concentrations did not indicate that concentrations increased after dust storm events (Gade et al., 2020). As such, dust is an imperfect surrogate for arthroconidia. Arthroconidia concentrations may be underestimated due to detection limitations and arthroconidia released during sampling events (i.e., it was generally assumed that arthroconidia were from the grain portion of the soil, but it is more likely that arthroconidia occupy many of the pore spaces in soil which are released into the air when collection disturbs the soil). Largescale meteorological patterns may affect the arthroconidia ecologic niche or cause dispersion over a larger land area compared to localized disturbance events such as farming, with complex relationships between land use, population movement, climate change, events such as dust storms or soil disturbances, and Valley Fever cases (Comrie, 2021; Pearson et al., 2019; Tobin et al., 2022). Additionally, as ambient concentrations of arthroconidia in air were taken in an area with a high frequency of dust storms (“haboobs”) (Gade et al., 2020), the magnitude of wind effects may increase by several orders of magnitude as these events release new arthroconidia from deeper soil layers (including from animal burrows which have been shown to correlate highly with Valley Fever incidence) (Kollath, Teixeira, et al., 2019). Arthroconidia, due to their small size and aerodynamically favorable shape, may remain in the air and travel far distances even months after the last dust storm event.

The dose-response parameter was demonstrated to be the most influential input to calculated risk according to sensitivity analysis, indicating the importance of this variable for risk assessment. It is recognized here that few datasets that met initial literature review inclusion criteria met the criteria for model fitting. This is typical of QMRA-based dose-response analyses (Breuninger & Weir, 2015; Hamilton et al., 2017) likely due to the fact that most published dosing studies were not designed with QMRA applications in mind and therefore do not have multiple dose groups or report data in quantal format. As noted earlier, most studies reported here were designed with the research goal of analyzing the effect of therapeutics or vaccines. Additional empirical dose-response relationships could be used for model fitting and other authors have taken alternative approaches (Haas, 2015; Nicas & Hubbard, 2002). There is also the potential that the dose-response models proposed here have other limitations for

generalizability related to QMRA criteria which could be applied to other scenarios. Both inhalation and non-inhalation dose-response models are presented for use in varying QMRA contexts. Our dose-response model does not consider specific vulnerabilities to the disease experienced by immunocompromised individuals and those with specific genetic factors which make them more susceptible to infection or severe disease. Also, our models do not consider age, socioeconomic status, coinfection, or other factors which may influence an individual's risk for development of severe coccidioidomycosis after exposure to aerosolized arthroconidia.

Virulence and infectivity of *Coccidioides* spp. is a function of many factors related to the pathogen, its environment, and its host. Species, strain, and life stage of the pathogen likely have an effect on virulence and infectivity, including the presence of specific genes and the proteins they produce (Guevara-Olvera et al., 2000; Mandel et al., 2006). There are at least 17 strains of the pathogen maintained for study at present, with many more having been used for previous study, and even more likely to exist in nature (Kirkland et al., 2022). Environmental conditions dictate which species and strain will be present at a point of exposure, but research on which factors lead to which specific species or strains is limited, aside from general trends in geographic dispersion. The specific susceptibility of some hosts compared to others have been identified, including individuals with known immunosuppressive disorders such as HIV/AIDS, those taking immunosuppressive medications, or with discrete genetic defects, especially those of the interleukin-12/interferon- γ and STAT3 axes (Odio et al., 2017).

Since the human immune response to challenge with this agent is likely different than the response of monkey immune systems, the exact risks experienced by exposed populations are likely different than what we present here. However, it is generally accepted that humans have more competent immune systems than monkeys or small mammals, so the risk estimates presented here should be conservative in that the actual risks for most immunocompetent individuals should be lower than our dose-response parameters imply.

While a dose-response model based on data collected from a human exposure study would yield a more accurate assessment of the risk posed by the disease, such exposure studies were not available. Epidemiological data could be useful for confirmation that the animal exposure studies assessed here serve as an appropriate analogue for the human dose-response relationship. However, to be useful in this context epidemiological studies must present both a received dose of arthroconidia and an attack rate, the first of which is generally challenging to confirm after the fact and the second of which can be difficult to accurately assess for large populations. With improved environmental sampling methods designed for quantification rather than simple confirmation, it may be possible to estimate the dose

associated with a reported attack rate. Similar to other uses of epidemiological data for environmental exposures, this effort would be complicated by a myriad of factors for which data would be difficult to acquire such as duration and magnitude of individual exposure; individual characteristics of the exposed population like immunocompetency or prior infection status; and the effects other potential covariates such as age, sex, socioeconomic status, historical access to healthcare resources, or coinfections. While QMRA theory indicates that a single pathogen is sufficient to cause an infection, the probability of infection is considered a function of dose. In addition to dose, the conditional probability of illness given infection (morbidity ratio) has not been accounted for here but likely is a function of immunogenetics and other factors not fully addressed by models based on animal experiments (Galgiani et al., 2023). Nevertheless, the dose-response models developed are useful for risk assessments of *Coccidioides* spp. exposures in a naïve host. Because dose-response models presented here do not account for immunity from prior exposures or susceptible populations, the current risk estimates may over- or under-estimate risk in those cases, respectively.

4.4 Recommendations for additional Valley Fever risk analysis. This study presents an analysis of the risk for developing severe Valley Fever after exposure to aerosolized *Coccidioides* spp. arthroconidia from eight scenarios related to farming activities. It is not a complete analysis of the risks posed by the fungus in other contexts. The basic risk assessment structure provided here can be applied to more scenarios to develop a better understanding of the risks posed by the disease in other contexts and to more specific populations. Areas where research interest may be most usefully applied to better understand the risks posed by the disease include predicting conditions which lead to growth of the fungus in the environment, and how the interactions of people or wildlife with that environment influence propagation during its saprophytic life stage and eventual release as an aerosol pathogen. This study consolidates risk assessment information about *Coccidioides* spp. arthroconidia. However, insights are needed into where and when individuals are most likely to be exposed (i.e., the location of so-called “hot spots”), which are major factors in the population-level risk of the disease. Additional systematic literature reviews are recommended for variables other than the dose-response parameter(s) to fill in gaps for Valley Fever QMRA. There is significant uncertainty surrounding the drivers of human exposure that are recommended for further investigation.

5. CONCLUSIONS

The proposed framework provides a model to determine the risk of developing coccidiomycosis following exposure to airborne *Coccidioides* spp. arthroconidia which have been locally released from soil by farming activities. The highest predicted risk results from a scenario during which an agricultural worker operates a harvesting machine without a contained cabin or PPE. Since individuals are most susceptible to the disease the first time they are exposed, it is important that individuals in any region where the disease is endemic know their personal history with the disease. Given the tendency for this disease to be misdiagnosed or underreported, localized skin testing to detect prior infection and likely immunity may be a useful method for reducing the burden of disease.

The risk models developed for this study are based on data collected from the available body of relevant published research. Findings of this work would be strengthened by epidemiological data which ties an attack rate to a specific received dose. Future research to better understand the environmental conditions which elicit growth of *Coccidioides* spp. would be valuable for those attempting to predict or prevent outbreaks, especially if they assess the relative abundance of varying species and strains of *Coccidioides*. Experimental studies designed to directly assess the virulence of various types of *Coccidioides* spp. arthroconidia available for study against various types of hosts would be valuable for future dose-response modelling and to validate the models proposed by this study. Ongoing research to develop a vaccine for the disease may provide alternate strategies to reduce its burden.

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FIGURES AND TABLES

Table 1. Exposure scenarios for QMRA model

Scenario No.	Exposure pathway (varying choice of A in the model)		PPE (varying choice of E in the model)			
	Planting by hand	Harvesting with machine (no cab)	No mask	Cotton mask	Surgical mask	N95
1	x		x			
2	x			x		
3	x				x	
4	x					x
5		x	x			
6		x		x		
7		x			x	
8		x				x

Table 2. Monte Carlo parameters

Parameter	Symbol	Unit	Distribution	Parameters	Source
Mask efficiency	E	Unitless fraction	Point Normal (truncated at 0)	No mask: 0% N95: $\mu=99\%$, $\sigma=0.3\%$ Surgical mask: $\mu=59\%$, $\sigma=6.9\%$ Cotton mask: $\mu=51\%$, $\sigma=7.7\%$	(Lindsley et al., 2021)
Fraction of arthroconidia deposited to the lungs	f	Unitless fraction	Uniform	min = 0.39, max = 0.86	(Heyder et al., 1986)
Air inhalation rate	B	m ³ /h	Normal	$\mu = 1.44$, $\sigma = 0.66$; left-truncated at 0	(US Environmental Protection Agency, 2011) Table 6-50 Inhalation rates for outdoor workers (GCW/laborers)
Exposure duration	t	h/day	Uniform	Min=8, Max=12	(BLS, 2022)
Arthroconidia concentration in soil	C_{soil}	# arthroconidia /g	Gamma	Shape = 1, rate = 0.678	(Elconin et al., 1964); this study Table 3/ section 3.1
Planting aerosolization	A_p	mg/m ³	Lognormal	$\mu=\ln(0.15)$, $\sigma=\ln(3.10)$	(Nieuwenhuijsen et al., 1999); This study Table 4 ground preparation (non-enclosed, respirable dust levels mg/m ³)
Harvesting aerosolization	A_h	mg/m ³	Lognormal	$\mu=\ln(7.93)$, $\sigma=\ln(3.13)$	(Nieuwenhuijsen et al., 1999); This study Table 2 machine harvesting (non-enclosed, vegetable commodities, respirable dust levels mg/m ³)
Arthroconidia concentration in ambient background air	b	# arthroconidia /m ³	Point	0	Assumed negligible for the purposes of this model due to uncertainty regarding background levels highlighted in (Gade et al., 2020)
Dose-response parameter	α, N_{50}	Unitless	Point	$\alpha=0.4311$, $N_{50}=573.0$	(Converse et al., 1962); This study section 3.1; Tables 4-5, Figure 1 Beta-Poisson model; inhalation exposure; death in monkeys as surrogate for human illness

1028 **Table 3.** Detections of *Coccidioides* spp. in environmental media (<DL = below detection limit;
1029 NR= not reported; NA= not applicable, MPN= most probable number, CFU= colony forming
1030 unit). Terms for arthroconidia units are reproduced as reported by each reference cited.
1031

Species	Location	Environmental matrix	No. positive samples/ total samples	Sample volume or mass	Method (culture or PCR)	Calculated concentration ^a	Units	Reference
<i>C. immitis</i>	Kern County, CA	Soil	NR	NR	Culture	NA	NA	(Stewart & Meyer, 1932)
<i>C. immitis</i>	Panoche Valley, San Bonito County, CA	Soil	NR	NR	NR	NA	NA	(Davis et al., 1942)
<i>C. immitis</i>	AZ	Soil	NR	NR	Guinea pig infectivity assay	NA	NA	(Emmons, 1942)
<i>C. immitis</i>	San Joaquin Valley, CA	Soil (including animal burrows)	35/500 (120 collected after wet season)	1g (with two subsequent dilutions 1:100 and 1:500)	Culture	7.25-36.3 (assuming 1:100 or 1:500 dilution)	<i>C. immitis</i> / g	(Egeberg & Ely, 1956)
<i>C. immitis</i>	Inyokern, CA	Soil (archaeological site and rodent burrows)	NR	10g (1:10 dilution)	Culture	NA	NA	(Plunkett & Swatek, 1957)
<i>C. immitis</i>	San Diego County, CA	Soil	NR	10g	Culture and mouse infectivity assay	NA	NA	(Walch et al., 1961)
<i>C. immitis</i>	Woodville, CA	Soil	4/37	0.1, 5, or 10g	Culture and mouse infectivity assay	NA	NA	(Levine & Winn, 1964)
<i>C. immitis</i>	NR	Soil	NR	20g	Culture and mouse infectivity assay	NA	NA	(Omieczynski & Swatek, 1967)
<i>C. immitis</i>	Various counties, CA	Soil (Spring and Winter)	22/22	10g (with 1:80 dilution)w	Culture	NA	<i>C. immitis</i> / g	(Orr, 1968)
<i>Coccidioides</i> spp.	San Joaquin Valley, CA	Soil	NR/>5000	10g (with two subsequent ten-fold dilutions; i.e., 0.1g)	Culture	0.27-5.67 in monthly samples ^b	arthroconidia / g	(Elconin et al., 1964)
<i>C. immitis</i>	San Diego and Kern County, CA	Soil	7/7 5/35	20g (1:10 suspension)	Culture Mouse infectivity assay	1-70 (reported by authors)	Colonies/ mL	(Swatek & Omieczynski, 1970)
<i>C. immitis</i>	San Diego, Kern, Butte, Madera, and Merced Counties, CA	Soil	32/395	10g	Culture	0.008	NA	(Lacy & Swatek, 1974)
<i>C. neoformans</i> <i>C. immitis</i>	Cordoba, Argentina	Soil	3/65 2/80	10-20g (dilution plated unknown)	Culture	NA	NA	(Rubinstein et al., 1989)
<i>C. immitis</i>	Tecate, WA	Soil	NR	NR	Mouse infectivity assay	NA	NA	(Cairns et al., 2000)
<i>C. immitis</i>	San Joaquin Valley, CA	Soil (Spring)	3/535 (1997) 140 (1995) 45 (1994)	NR	Culture, PCR, microsatellite typing	NA	NA	(Greene et al., 2000)

<i>C. immitis</i>	CA, AZ, TX, Mexico	Soil	NR/2	NR	Culture, PCR	NA	NA	(Fisher et al., 2001)
<i>C. posadasii</i>	Teresina, Brazil	Soil	24/24 6/24	NR 1g	PCR Mice infectivity assay	NA	NA	(de Macêdo et al., 2011)
<i>Coccidoides</i> spp.	Tucson, AZ	Soil	11/124 0/124	5g	qPCR (ITS, C1A, and ITS C2) Culture	0.02 <DL	gc/ g NA	(Barker et al., 2012)
<i>Coccidoides</i> spp.	Valle de las Palmas, Ensenada, and San Jose de la Zorra, Mexico	Soil including from animal burrows, large mammal dens, and heteromyid latrines	PCR: 71/100 nested PCR 43/100 diagnostic PCR 32/43 sequencing confirmed from PCR+ samples	20g	Nested PCR, diagnostic PCR, and amplicon sequencing	0.02 (sequencing confirmed)	gc/ g	(Baptista-rosas et al., 2012)
<i>C. immitis</i>	Kern County, CA	Soil	24/285 (2008) 7/261 (2009)	30g (0.25g extracted)	Multiplex PCR	0.35 0.11	gc/g	(Lauer et al., 2012)
<i>C. immitis</i>	Kern County, CA	Soil	17/23 sites	NR	Multiplex PCR	NA	NA	(Lauer et al., 2014)
<i>C. immitis</i> , <i>C. posadasii</i>	Dinosaur National Monument, UT	Soil	1/2 (<i>C. immitis</i>), 1/2 (<i>C. posadasii</i>)	5g	PCR, ITS region sequencing	0.14	gc/g	(Johnson et al., 2014)
<i>C. immitis</i>	Benton County, WA	Soil	6/22	NR	PCR, sequences	NA	NA	(Marsden-Haug et al., 2014)
<i>C. immitis</i>	WA	Soil	6/22 (2010) 16/25 (2014)	NR	PCR (CocciDX), whole genome sequencing	NA	NA	(Litvintseva et al., 2015)
<i>C. immitis</i> , <i>C. posadasii</i>	AZ	Soil	66 soil-derived isolates	NR	PCR, microsatellite typing	NA	NA	(Teixeira & Barker, 2016)
<i>C. immitis</i>	Antelope Valley, CA	Soil	17/42	~25g	PCR	0.02	gc/ g	(Colson et al., 2017)
<i>C. posadasii</i>	Venezuela	Soil	15/15	0.25g (PCR), 5g (mouse assay)	qPCR, mouse infectivity assay, sequences of ITS region	NA	NA	(Alvarado et al., 2018)
<i>Coccidoides</i> spp.	Tucson, Phoenix, and Flagstaff, AZ	Soil	4/73	1g	qPCR (CocciDX and CocciENV assay)	0.06	gc/ g	(Bowers et al., 2019)
<i>Coccidoides</i> spp.	Tucson, Tombix, Florence, and Flagstaff AZ	Soil	105/456	NR	qPCR (CocciDX and CocciENV assay)	NA	NA	(Kollath, Teixeira, et al., 2019)
<i>C. immitis</i>	Washington	Soil	70/278	0.75g (soil mass used for DNA extraction; 5 g total)	qPCR, whole genome sequencing (ITS1, CocciDX)	0.039	gc/ g	(Chow et al., 2021)
<i>Coccidoides</i> spp.	Tucson, AZ	Soil	0/NR	5g	qPCR	NA	NA	(Kollath et al., 2023)

<i>Coccidioides</i> spp.	Florence/Tucson, AZ	Soil and air (dust) collected 2-3 months after seasonal rains	Soil: 10/34 Air: 3/25	0.75g (soil mass used for DNA extraction); five air filtration methods used ^c	qPCR, ddPCR (CocciDx Q assay; extended amplicon region)	Air: 0.005 ^c Soil: 0.46	gc/ m ³ gc/g	(Chow et al., 2016)
Total arthronconidia	Phoenix, AZ	Air	Before dust storm: 18/21 During/ after dust storm: 4/21	Air sampler with 100 Lpm flow rate over 24 h period	Culture qPCR (ST nested, CocciEN V)	Ranges in detected samples ^d : Before storm 0.007-120.7 During storm 0.715-13.2 After storm 0.035-4.16	CFU/ m ³	(Gade et al., 2020)
Total fungal community	San Joaquin Valley, CA	Soil (burrow cores) and air (November 2017)	4/238 soil samples-Hwy33 (rodent burrows); 0/499 soil core samples-KARE; 0/265 air samples 1,002	0.25g (soil); 13 passive air samplers	Metabarcoding of internal transcribed spacer (ITS) 2 variable region of fungal rDNA	NA	NA	(Wagner et al., 2022)

^aCalculated using MPN formula, where the estimated sample mean of n samples with p positive samples and V sample volume is $-\frac{1}{V} \ln \left(\frac{n-p}{n} \right)$. Percent positive samples must be $0 < x < 100$ to use this method; "NA" reported otherwise. MPN calculated only for direct environmental culture samples.

^bAt least 36 samples collected monthly for 8 years. Percentage positive estimates from Figure 2 in original reference (25, 43.3, 33.3, 0, 2.7, 0, and 19.4% positives from April 1955- May 1962) used to compute concentration using MPN formula assuming 36 samples total for each monthly sampling event from Figure 2 in original reference.

^cAir concentrations calculated using MPN formula with 3/25 air samples. Volume of air sampled computed from difference in time between start and end time. Flow rate reported used to compute volume of air sampled for each case. The average of high flow sample volumes (29.3 m³) used for computing concentration (0.17gc)/(29.3m³ air) = 0.006 gc/m³ air

^dConcentrations obtained from Gade et al. 2020 supplemental Information Table 3. For example, maximum reported concentration of 17,378 CFU/filter 1 day before a dust storm. Assuming 24 h (1440 min) of total sampling operation equates to 144,000 L air filtered. Concentration in CFU/m³ computed using (17,378 CFU/filter)*(filter/144,000L)*(1000L/m³).

1046 **Table 4.** Dose-response data for *Coccidioides* spp., separated into two date-ordered groups by
1047 route of exposure (respiratory vs non-respiratory)

Host	Dose (# arthroconidia)	Exposure route	Challeng e species	Maxim um follow- up time	Health endpoint	No. positive response (positive/tot al)	Reference
Monkey (<i>Macaca mulatta</i>)	56, 336, 11,296	Inhalation	<i>C. immitis</i> , strain cash	59 weeks	Death	0/5, 3/5, 4/5	*(Converse et al., 1962)
Monkey (unspecified)	7500	Inhalation	<i>C. immitis</i> , strain cash	4 months	Death	8/9	(Converse et al., 1965)
Mice (NAMRU)	52	Intranasal	<i>C. immitis</i> , strain silveira	30 days	Death	5/5, 5/5, 8/10	(Levine et al., 1975)
Mice (Swiss- Webster)	2000	Intratrachea l	<i>C. immitis</i> , strain silveira	30 days	Death	10/11	(Lawrence & Hoeprich, 1976)
Mice (NAMRU)	42, 47, 150	Intranasal	<i>C. immitis</i> , strain silveira	160 days, 84 days, 28 days	Death	9/29, 15/40, 9/10	*(Levine & Cobb, 1980)
Mice (DBA/2J)	50, 500, 1500	Intranasal	<i>C. immitis</i> , strain silveira	35 days, 40 days, 35 days	Death	11/25, 21/30, 23/25	*(Lecara et al., 1983)
Mice (swiss-webster albino)	100	intratrachea l	<i>C. immitis</i> , strain silveira	23 days	Death	8/10	(Hoeprich & Merry, 1987)
Mice (BALB/c)	10	Intranasal	<i>C. immitis</i> , unspecifi ed	22	Death	22/22	(Cox, 1988)
Mice (C57BL/6)	80	Intranasal	<i>C. posadasii</i> , strain C735	14 days	Infection (regular serological measuremen ts)	8/8	(Xue et al., 2005)
Monkey (<i>Macaca fasciculari</i>)	2500	Intratrachea l	<i>C. posadasii</i> , strain Silveira	13 weeks	Radiographic imagery of spherules formed in lungs	4/4	(Johnson et al., 2007)
Mice (C3H/OuJ)	20, 47, 93	Intranasal	<i>C. posadasii</i> , strain silveira	35 days	Death	1/10,4/10,10/ 10	*(Awasthi, 2010)
Mice (C57Bl/6J)	150, 250	Intranasal	<i>C. immitis</i> , strain R.S.	30 days	Death	5/8, 8/8	*(Margolis et al., 2011)

Mice (Swiss-Webster)	504, 550	Intranasal	<i>C. pasadasii</i> , strain silveira	7 days, 21 days	Infection (fungal burden in lungs)	6/6, 20/20	(Shubitz et al., 2014)
Mice (HLA-DR)	50, 70	Intranasal	<i>C. posadasii</i> , strain C735	50 days	Death	10/10, 10/10	(Hurtgen et al., 2016)
-	-	-	-	-	-	-	-
10-week-old mice (NAMRU)	10, 100, 1,000, 10,000	intraperitoneal	<i>C. immitis</i> ; strain silveira	90 days	Death	17/25, 24/25, 25/25, 25/25	*(Friedman et. al., 1955)
Male mice (white)	10, 100, 1000	intraperitoneal	<i>C. immitis</i> ; strain silveira	60 days	Death	10/10, 10/10, 10/10	(Pappagianis et. al., 1956)
	10,000, 50,000, 100,000		<i>C. immitis</i> ; strain 46			0/10, 5/10, 10/10	
Monkey (<i>Macaca mulatta</i>)	10, 100	Subcutaneous in the medial surface of the right forearm	<i>C. immitis</i> ; strains: Silveira, Cash, M-11, D-76, CW1	10 months	Presence of draining lesion	4/20, 3/15	(Converse, et. al., 1964)
					Presence of enlarged lymph node	2/20, 7/15	
Male mice (NAMRU)	4,600	intraperitoneal	<i>C. immitis</i> ; strain silveira	40 days	Death	9/10	*(Collins & Pappagianis, 1976)
Female mice (NAMRU)	120, 2,300					16/30, 28/30	
Female mice (DBA/2)	400	Intraperitoneal	<i>C. immitis</i> ; strain silveira	40 days	Death	28/30	(Beaman et. al., 1977)
Mice (BALB/cAnN)	5,000, 50,000	Intraperitoneal	<i>C. immitis</i> , strain R.S.	28 days	Death	10/10, 10/10	(Kirkland & Fierer, 1983)
Female mice (BALB/c)	850	Intraperitoneal	<i>C. immitis</i> , strain R.S.	12 days	Log ₁₀ CFU in omentum, lungs, spleen	7, 5.79, 5.09	(Fierer et. al., 1990)
Female mice (BALB/c x DBA/2)F1	1000					6.22, 4.40, 2.78	
Female mice (CD-1)	180, 200	Intravenous	<i>C. immitis</i> ; strain silveira	49 days	Death	7/10, 10/10	*(Clemons & Stevens, 1991)
Female mice (CD-1)	220, 220, 220, 220	Intravenous	<i>C. immitis</i> ; strain silveira	49 days	Death	10/10, 9/10, 10/10, 9/10	(Lutz et. al, 1997)
Immunosuppressed Male rabbits (New Zealand White)	4,000, 20,000, 150,000 1,000,000	Intracerebral	<i>C. immitis</i> ; strain silveira	47 days	Mean brain tissue fungal culture (log ₁₀ cfu/g)	2.9, 2.93, 4.4, 4.5	(Williams et. al., 1998)
Hamsters (<i>Mesocricetus auratus</i>)	10, 50, 100, 150, 200, 300	Intracardial	<i>C. immitis</i> ; strain AC1	57 days	Death	10/10, 10/10, 10/10, 10/10, 10/10, 10/10	(Finquelievich et. al., 2000)
Female mice (CD-1)	382	Intravenous	<i>C. immitis</i> ; strain silveira	49 days	Death	10/10	(Clemons & Stevens, 2000)

Mice (BALB/c)	2,500	Intraperitoneal	<i>C. immitis</i> ; strain silveira	40 days	Death	10/10	(Jiang et. al., 2002)
Female mice (BALB/c)	51 ± 13	Intraperitoneal	<i>C. immitis</i> , strain R.S.	14 days	Log ₁₀ CFU in lungs, spleen	6.5, 6.55	(Peng et. al., 2002)
Male mice (ICR, outbred)	200	Intravenous	<i>C. spp.</i> , strain 98–1037	50 days	Death	10/10 9/10	Gonzalez et. al, 2004)
Female mice (C57BL/6)	200	Intraperitoneal	<i>C. immitis</i> , strain R.S.	50 days	Death	9/10	(Fierer et. al., 2006)
Female mice (CD4+)						10/10	
Male rabbits (New Zealand White)	50,000	Direct cisternal puncture	<i>C. posadasii</i> , strain silveira	26 days	Death	8/9	(Clemons et.al., 2009)
Male mice (CD-1)	127, 275	Intravenous	<i>C. posadasii</i> , strain silveira	28 days	Death	4/9, 9/10	*(Clemons et. al. 2015)
Female mice (CD-1)	310	Intravenous	<i>C. posadasii</i> , strain silveira	49 days	Death	10/10	(Kovanda et. al., 2021)
Female mice (CD-1)	82	Intracerebral	<i>C. posadasii</i> , strain silveira	45 days	Death	8/9	(Sass et. al., 2021)
*Dose-response model fits for these studies are available in Table 5							

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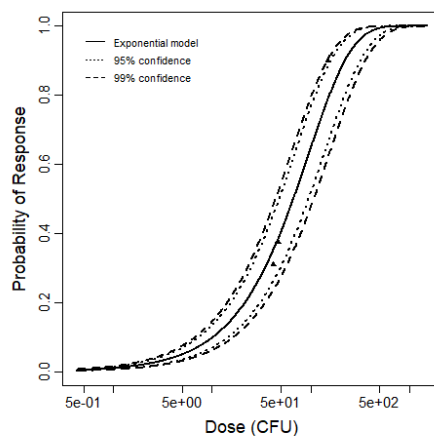
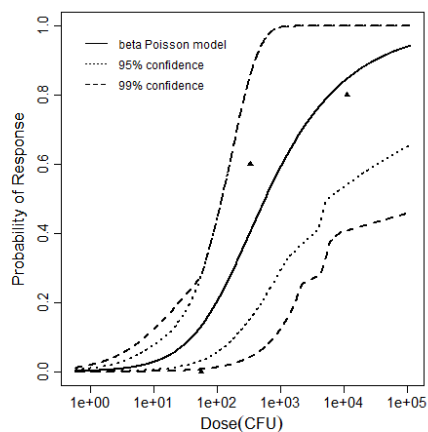
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1051 **Table 5.** Dose-response model fitting results (NA= not applicable)*

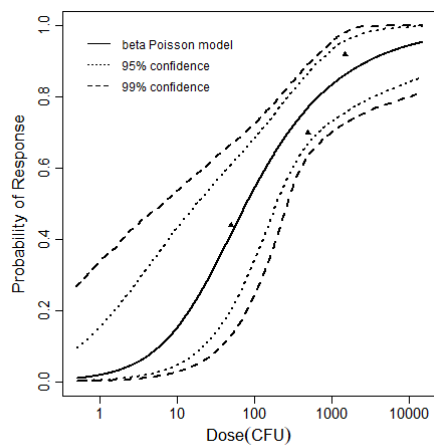
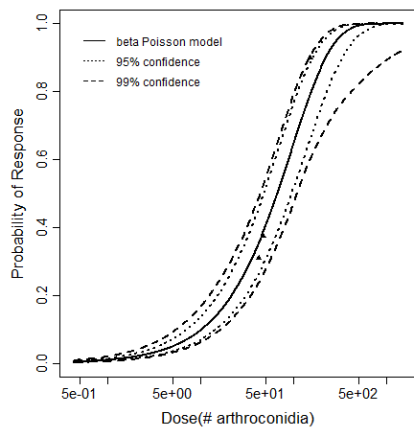
Model No.	Data Ref.	Dose groups	Model Evaluated	Parameter Values	Minimized Deviance	D.O.F. (#dose groups-#parameters)	χ^2_{crit}	Acceptable Fit	p_{fit}	Preferred model ?
1	(Converse et al., 1962)	3	1.1 exponential	$k = 2.795 \times 10^{-4}$	9.948	2	5.992	No	0.0069	Beta-Poisson
			1.2 beta-Poisson	$\alpha = 0.4311$ $N_{50} = 573.0$	2.275	1	3.842	Yes	0.1315	
2	(Levine & Cobb, 1980)	3	2.1 exponential	$k = 1.041 \times 10^{-2}$	1.133	2	5.992	Yes	0.5675	Exponential
			2.2 beta-Poisson	$\alpha = 1866$ $N_{50} = 66.59$	1.134	1	3.842	Yes	0.2869	
3	(Lecara et al., 1983)	3	3.1 exponential	$k = 2.678 \times 10^{-3}$	18.33	2	5.992	No	<0.001	Beta-Poisson
			3.2 beta-Poisson	$\alpha = 0.4814$ $N_{50} = 78.83$	1.662	1	3.842	Yes	0.1973	
4	(Awasthi, 2010)	3	4.1 exponential	$k = 1.661 \times 10^{-2}$	7.614	2	5.992	No	0.0222	Exponential
			4.2 beta-Poisson	$\alpha = 8135$ $N_{50} = 41.73$	7.615	1	3.842	No	0.0058	
5	(Margolis et al., 2011)	2	5.1 exponential	$k = 4.423 \times 10^{-2}$	0.3348	1	3.842	Yes	0.5629	Exponential
			5.2 beta-Poisson	N/A	N/A	0	N/A	N/A	N/A	
6	(Friedman et. al., 1955)	4	6.1 exponential	$k = 6.728 \times 10^{-2}$	8.811	3	7.815	No	0.0319	Beta-Poisson
			6.2 beta-Poisson	$\alpha = 1.212$ $N_{50} = 5.031$	0.1475	2	5.992	Yes	0.9289	
			7.2 beta-Poisson	$\alpha = 629.5$ $N_{50} = 4.416$	24.761	1	3.842	No	<0.001	
7	(Collins & Pappagianis, 1976)	2	8.1 exponential	$k = 3.245 \times 10^{-4}$	1.670	1	3.842	Yes	0.1963	Exponential
			8.2 beta-Poisson	N/A	N/A	0	N/A	N/A	N/A	
8	(Clemons & Stevens, 1991)	2	9.1 exponential	$k = 1.108 \times 10^{-2}$	4.016	1	3.842	No	0.0451	N/A
			9.2 beta-Poisson	N/A	N/A	0	N/A	N/A	N/A	
9	(Clemons et. al. 2015)	2	10.1 exponential	$k = 6.436 \times 10^{-3}$	0.8694	1	3.842	Yes	0.3511	Exponential
			10.2 beta-Poisson	N/A	N/A	0	N/A	N/A	N/A	

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1053 *Model parameters from MLE did not converge for Pappagianis et al. (1956)
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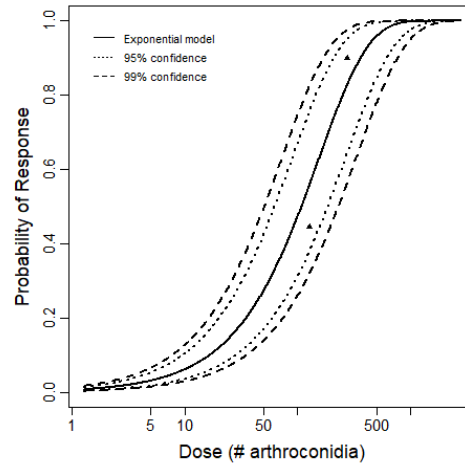
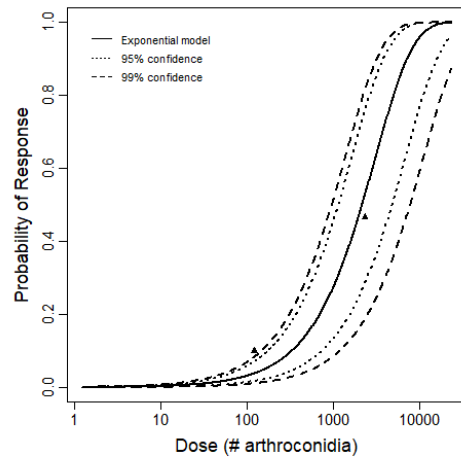
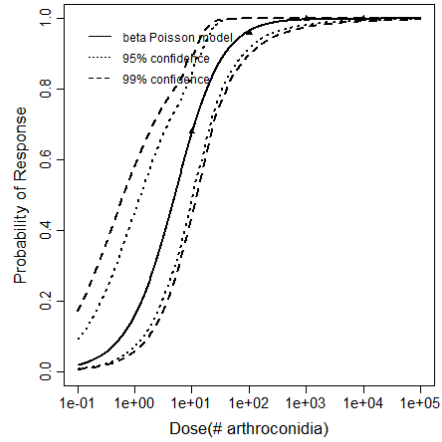
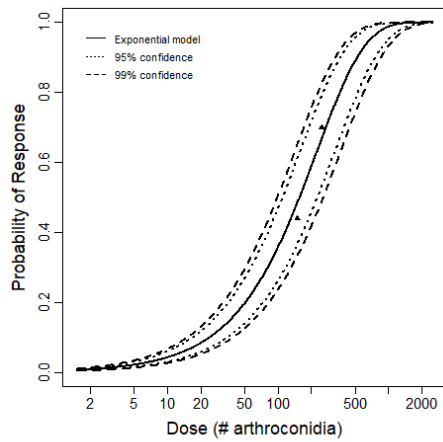
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(b)



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(d)



(e)

(f)

(g)

(h)

Figure 1. Best fit respiratory dose-response model fits for (a) Converse et al. (1962) Beta-Poisson model; (b) Levine and Cobb (1980) Exponential model; (c) Levine and Cobb (1980) Beta-Poisson; (d) Lecara et al. (1983) Beta-Poisson model (e) (Margolis et. al. (2011) Exponential model and non-respiratory dose-response model fits for (f) Friedman et. al. (1955) Beta-Poisson; (g) Collins & Pappagianis (1976) Exponential Model; (h) Clemons et. al. (2015) Exponential model

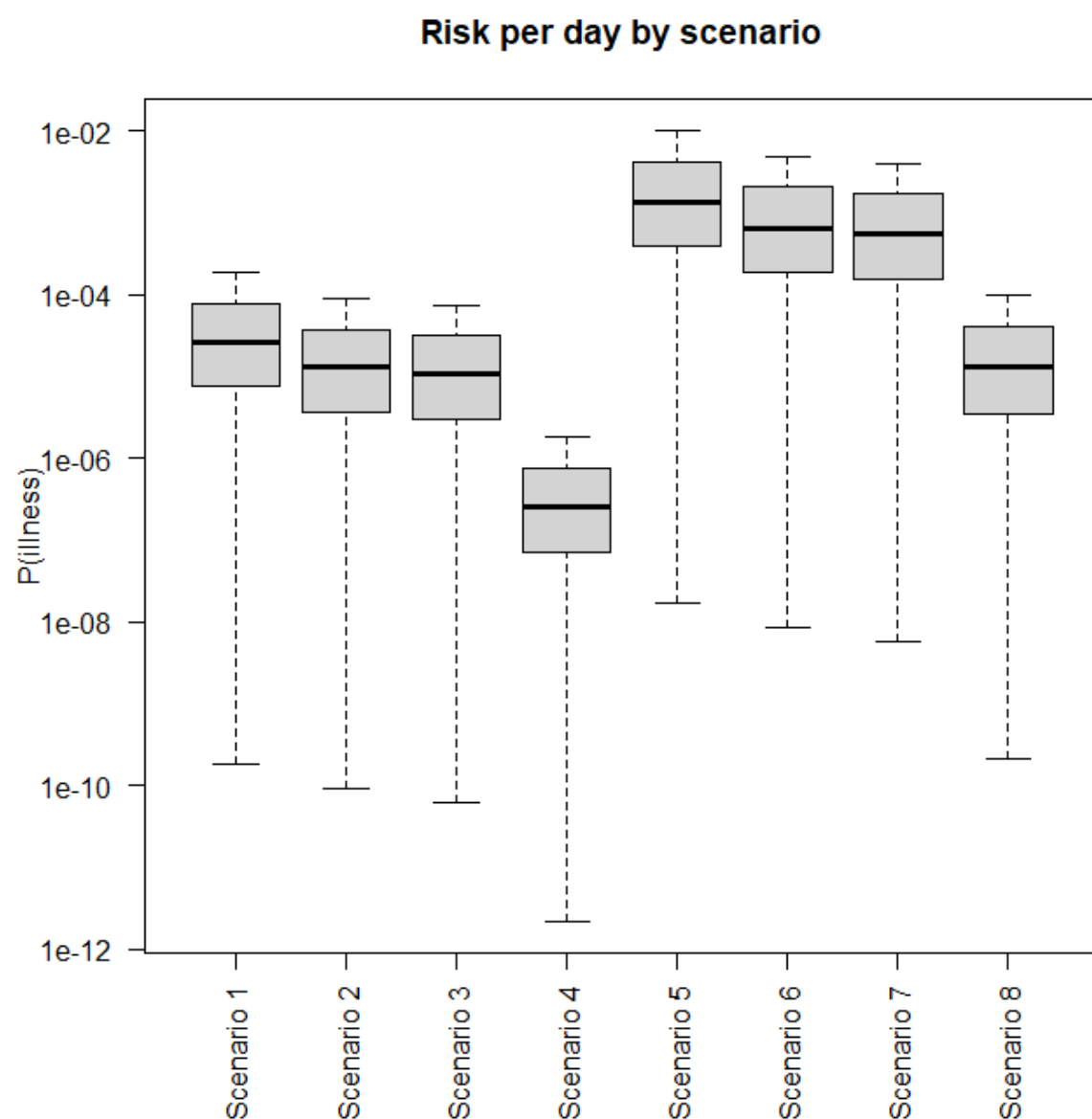


Figure 2. Risk of infection comparison across scenarios

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Parameter	Symbol	Risk per exposure by scenario (Table 1)							
		1	2	3	4	5	6	7	8
Mask efficiency	E		-0.007	-0.007	-0.18		-0.006	-0.006	-0.178
Fraction of arthroconidia deposited to the lungs	f	0.13	0.13	0.13	0.12	0.14	0.14	0.14	0.14
Air inhalation rate	B	0.29	0.29	0.30	0.29	0.29	0.28	0.29	0.28
Exposure duration	t	0.06	0.06	0.06	0.06	0.06	0.05	0.06	0.06
Arthroconidia concentration in soil	C_{soil}	0.64	0.63	0.63	0.62	0.64	0.64	0.64	0.63
Planting aerosolization by hand	A_p	0.62	0.62	0.62	0.61				
Harvesting aerosolization with machine	A_h					0.63	0.63	0.63	0.62

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Figure 3. Sensitivity analysis Spearman rank bivariate correlation heatmap showing influence of each Monte Carlo input variable on the output (risk per exposure). Correlations shown are high (absolute value >0.5 in red), moderate (absolute value 0.2-0.5 in yellow), or low (absolute value <0.2 in blue). Dark grey cells are not applicable to that scenario.

1089 **SUPPLEMENTAL INFORMATION**

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1091 **Supplemental Table S1.** Outbreaks and case reports of Valley Fever

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Event	Population	Location of exposure	Year	Month	# potentially exposed	# infected (**confirmed)	# ill (symptoms)	Abnormal radiographs	Visited ER	# hospitalized	Disseminated disease	# dead	Attack rate?	Mask use?	
Outdoor working (not specified)	Working crew	Delano Ranch, near San Joaquin Valley, CA	1932	NR	NR	4	NR	NR	NR	NR	NR	NR	NR	NR	(Stewart & Meyer, 1932)
Digging around rattlesnake hole during biology field trip	College students and faculty	San Benito County, CA	1940	April	9	7	6	7	NR	1	NR	0	*78%	NR	(Davis et al., 1942)
Archaeological camp site	Residents	San Diego County, CA	1950-1957	NR	NR	24	NR	NR	NR	NR	NR	NR	NR	NR	(Walch et al., 1961)
Backyard play	Children	Woodville, CA	1961	September	10	10	9	9	NR	4	NR	0	*100%	NR	(Winn et al., 1963)
Exposure near residence	Children	El Paso, Texas	1965	November	10	10	NR	6	NR	NR	NR	0	*100%	NR	(Roberts & Lisciandro, 1967)
Family outing to excavation area	2 families	Beeville, Texas	1966	December	10	9	8	7	NR	1	1	0	*90%	NR	(Teel et al., 1970)
Ruin excavation	Archaeology students	Butte County, CA	1970	June/July	103	27	61	30	NR	4	6	0	65%	NR	(Werner et al., 1972)
None	Residents	Alta Gracia, Argentina	1989	NR	65	22	NR	NR	NR	NR	NR	NR	NR	NR	(Rubinstein et al., 1989)
Earthquake	Residents	Ventura County, CA	1994	Jan-March	669,016	203	NR	NR	1	55	NR	3	30 per 100,000	NR	(Schneider et al., 1997)

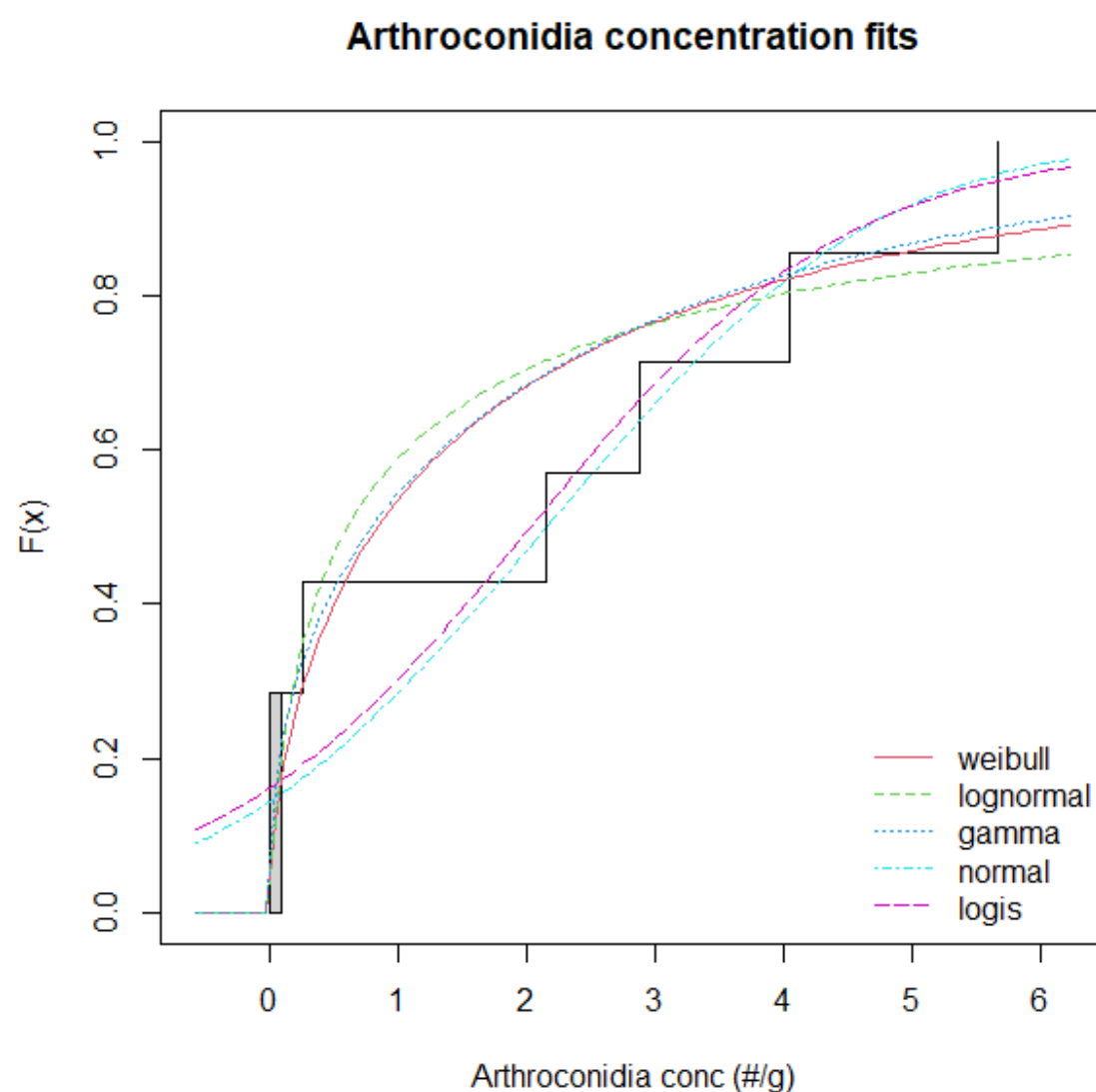
Constructi on in Tecate Mexico	Church group	Tecate Mexico/ Seattle, WA	199 6	July	126	27	20	NR	NR	NR	NR	0	17%- 36%	NR	(Cairns et al., 2000)
Archaeolo gists sifting soil	Archaeolo gists	Northeas tern Utah	200 1	June	10	9	10	10	NR	8	NR	0	91%	No	(Petersen et al., 2004)
Soil excavatio n for pipe installatio n	Constructi on workers	Camp Roberts, CA	200 7	Octobe r	12	8	10	7	NR	1	1	0	83.3%	No	(Cummin gs et al., 2010)
Various outdoor exposures	Residents	Eastern WA	201 0- 201 1	June and August	NR	3	3	1	NR	1	NR	0	NR	NR	(Marsden -Haug et al., 2013)
Outdoor film set	Cast/crew	Ventura, CA	201 2	Januar y	655	5	10	NR	5	2	NR	0	1.50%	NR	(Wilken, Marquez, et al., 2015)
Solar farm constructi on	Constructi on workers	San Louis Obispo County, CA	201 1- 201 4	All year	3576	37	44	NR	17	9	2	0	1.2 per 100	Some	(Wilken, Sonderm eyer, et al., 2015)
Highway constructi on	Constructi on workers	Kern County, CA	200 8	June/ July	10	7	7	NR	NR	NR	NR	NR	*70%	No	(Nicas, 2018a)
Solar farm constructi on	Constructi on workers	Montere y County, CA	201 6- 201 7	All year	2410	9	16	NR	5	1	6	0	17.5/100 ,000	Infrequ ent	(Laws et al., 2018)
Wildland firefighting	Inmate firefighter s	Californi a	201 7	July	112	6	10	NR	NR	2	5	0	9%	No	(Laws et al., 2021)
Wildland firefighting	Inmate firefighter s	Tehacha pi Mountai ns, CA	202 1	June	21	3	7	NR	7	3	2	0	14.30%	No	(Donnelly et al., 2022)
*simple attack rate calculated from reported number of infected divided by total potentially exposed. **Cases were considered confirmed by either skin or serological testing after exposure.															

1094 **Supplemental Table S2.** Meteorological studies for Valley Fever (NS= not specified)
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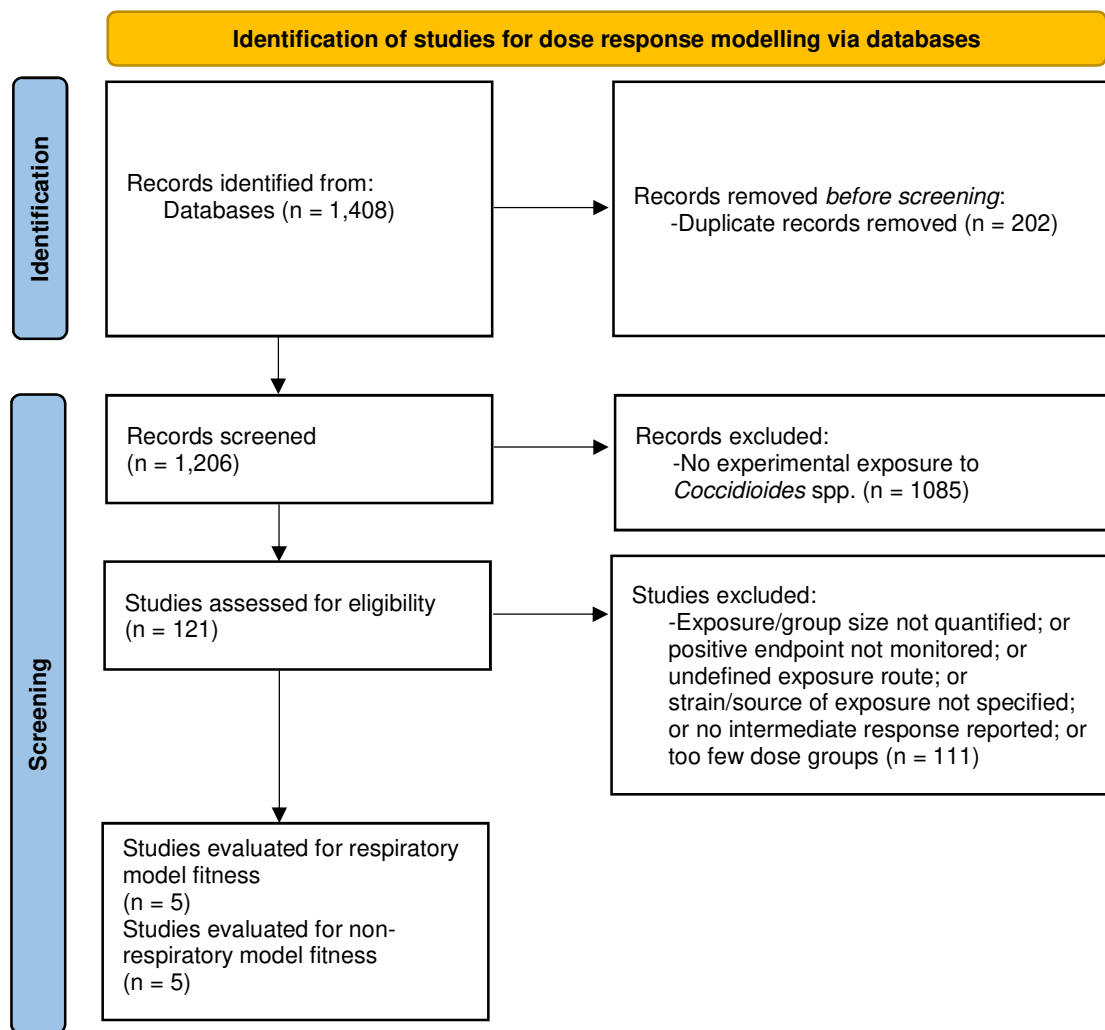
Arthroconidia Species	Geographic region	Modeling approach	Major findings	Environmental factor with positive association	Study limitations	Reference
<i>C. Posadasii</i> and <i>C. Immitis</i>	Phoenix, AZ	Spatial/DREAM model	Creates a model to predict cocci exposure on a basis of haboobs/dust storms	Dust Concentration	Particles larger than 10 µm are not accounted for	(Sprigg et al., 2014)
NS	Arizona (Focuses on Maricopa and Pima County)	Modeled Valley Fever incidence for 9-16 months in advance based on precipitation cycles with regression equations.	Monthly increases in exposure in Maricopa and Pima County since 1995.	Seasonal Precipitation	Restrictions on data availability; only 12 years of case data available which limits statistical confidence.	(Tamerius & Comrie, 2011)
NS	California and Arizona (by county)	Spatial analysis, indices in climate variability	Counties with higher variability indices are more prone to increases in Cocci. incidence	Variability in temperature, precipitation, and drought.	Discrepancies in population sizes.	(Shriber et al., 2017)
NS	The Southwestern United States (Arizona, California, Nevada, New Mexico, and Utah)	Geospatial analysis, linear and nonlinear regression models	Valley fever incidence was greater in areas with warmer air temperatures and drier soils	Air temperature, precipitation, soil moisture, surface dust concentration, normalized difference vegetation index, and cropland area.	Surveillance methods could be implemented to improve disease reporting.	(Gorris et al., 2018)
<i>C. Immitis</i> and <i>C. Posadasii</i>	Maricopa County, AZ and Pima County, AZ	Correlating Incidence rate and dust frequency.	The Southwest has increased in dust frequency which will likely lead to elevated Valley Fever incidence rates in the future	Dust Storm Activity	Time and location restraints affected availability of data.	(Tong et al., 2017)
NS	Kern County, CA	Regression-based analysis	antecedent precipitation is an important predictor of disease	precipitation, temperature, drought severity, PM10, and wind speed	Changes in provider awareness, diagnosis, and/or reporting; inconsistencies in tag times between exposure and diagnosis/reporting ; assumption that disease acquisition occurred in reporting county	(Weaver & Kolivras, 2018)
NS	Kern County, Fresno County, Tulare County, Kings County, San Luis County,	Linear and Poisson regression	Most cases were diagnosed when the environment	Precipitation, temperature, wind speed, evapotranspiration, Palmer	Demographic risk factors are not the same across all counties	(M. N.-R. Matlock, 2019)

	Obispo County (California)		was drier and more seasonal precipitation indicates higher Valley Fever incidence	Drought Severity Index, and Particulate Matter 2.5 and 10,		
NS	Pima, Pinal and Maricopa County (AZ)	Time-Series model	Moist soil during spring months often led to increased incidence in following months	Soil moisture	Complex relationship between soil moisture and Arthroconidia	(Stacy et al., 2012)
NS	Phoenix, AZ and Bakersfield, CA	Literature review and analysis of Coccidioidomycosis cases in relation to haboobs/ dust storms	No statistical differences in the patterns of coccidioidomycosis cases following dust storms versus non-dust storm conditions	Dust storm activity	Omissions or partial information in dust storm records, lower susceptibility of populations living in core endemic areas, coarse monthly resolution relative to dust storms, case underreporting	(Comrie, 2021)

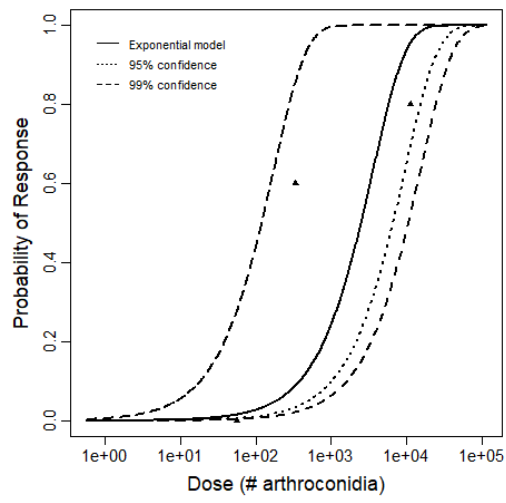
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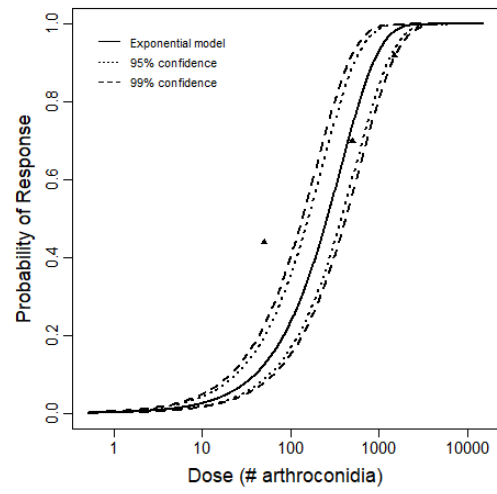
Supplemental Figure S1. Comparison of distribution fits for Elconin (1964) arthroconidia concentrations in soil.



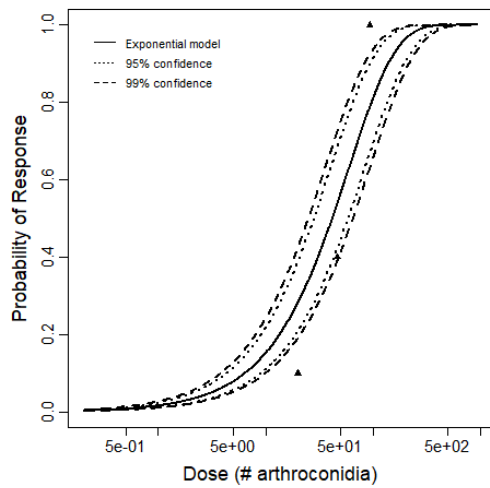
Supplemental Figure S2. PRISMA diagram for dose-response assessment



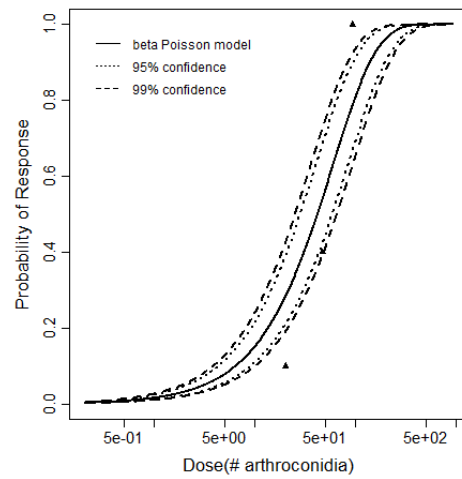
(a)



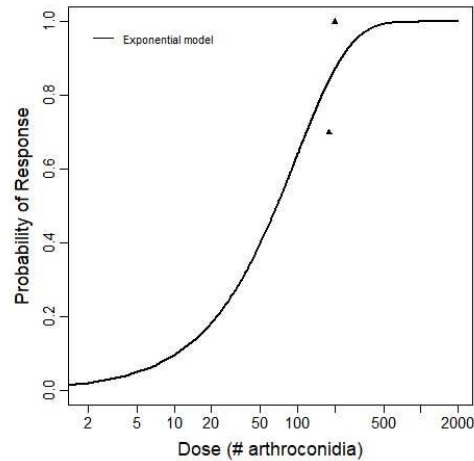
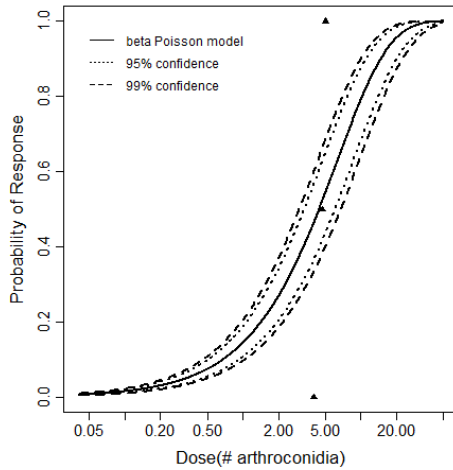
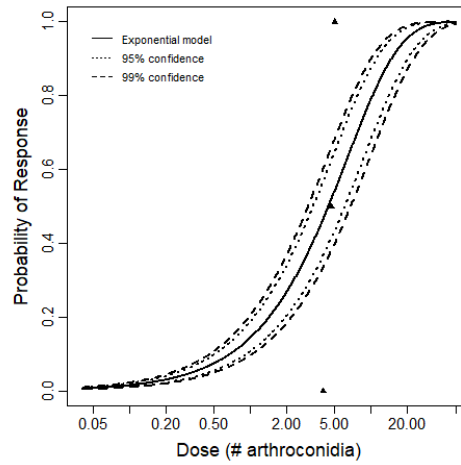
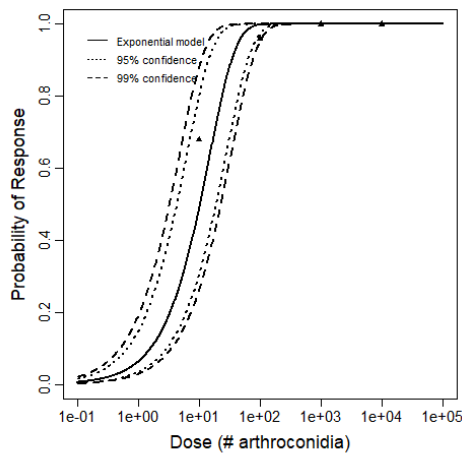
(b)



(c)



(d)



(e)

(f)

(g)

*(h)

Supplemental Figure S3. Poor dose-response-model fits for (a) Converse et al. (1962) Exponential model; (b) Lecara et al. (1983) Exponential model; (c) Awasthi (2010) Exponential model; (d) Awasthi (2010) Beta-Poisson model; (e) Friedman et. al. (1955) Exponential model; (f) Pappagianis et. al. (1956) Exponential Model; (g) Pappagianis et. al. (1956) Beta-Poisson Model; (h) Clemons & Stevens (1991) Exponential model (*parameters for bootstrapping unable to converge for confidence intervals)