ADVANCING ENVIRONMENTAL HUMAN HEALTH RISK ASSESSMENT THROUGH BAYESIAN NETWORK ANALYSIS

Joseph W. Zabinski

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Approved by:

Jacqueline MacDonald Gibson

Mark Borsuk

Gregory Characklis

Rebecca Fry

Janice Lee

ABSTRACT

Joseph W. Zabinski: Advancing Environmental Human Health Risk Assessment through Bayesian Network Analysis
(Under the direction of Jacqueline MacDonald Gibson)

Regulatory agencies rely on quantitative risk assessment to design policies, such as environmental quality standards, to protect public health. Although risk assessment forms the foundation of important policy decisions, recent reviews have indicated the need for technical and practical improvements to risk assessment. This dissertation advances the application of Bayesian networks (BNs) in environmental human health risk assessment in response to this need. BNs were developed to support causal inference in artificial intelligence applications but are not currently used by environmental regulatory agencies.

First, a proof-of-concept BN is developed to test BN performance in predicting the effect of maternal exposure to arsenic in drinking water on the risk of newborn lower birthweight for gestational age. The network is the first of its kind to model a dose-response relationship connecting an environmental hazard to a human health outcome. In addition, unlike prevailing regulatory risk assessment approaches, it accounts for inter-individual metabolic differences. The BN is shown to outperform current regulatory risk assessment methods in balancing predictive sensitivity and specificity.

Second, a BN is developed to predict the effect of arsenic exposure in drinking water on the risk of diabetes and prediabetes, while accounting for inter-individual differences in arsenic

metabolism and body mass index. In addition, the BN's utility to risk managers is demonstrated by using the model to predict the population-level health consequences of reduced arsenic exposure (including decreased diabetes prevalence). These predictions demonstrate the importance of considering both cancer and non-cancer outcomes when making policy. BNs' ability to facilitate cost-benefit calculations in regulatory contexts is highlighted.

Finally, improvements to risk assessment utility by using BNs are illustrated through a model developed to quantify risk to wastewater treatment workers of contracting Ebola virus disease from contact with contaminated wastewater during an outbreak. The model is used to identify key factors affecting risk and captures risk under different mitigation strategies.

These results suggest that BNs offer a quantitatively sophisticated, flexible, and transparent method that addresses key challenges in current risk assessment practice in support of policymaking.

In memory of Richard J. Zabinski

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PREFACE

This dissertation is organized in a non-traditional format, including three manuscripts. Chapter 1 provides introduction, background material, and justifications. Chapters 2, 3, and 4 must stand alone as manuscripts to be submitted for publication. As such, they may contain some redundancies with other chapters. Chapter 5 discusses conclusions of the work, implications, and provides suggestions for future research.

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CHAPTER 1: INTRODUCTION

1. Introduction

Quantitative risk assessment plays a central role in U.S. environmental policy decisions intended to protect public health from environmental contaminants. Risk assessment is used to determine costs and benefits of changes in policy and regulation, and weighing these factors determines what regulations are ultimately set. Risk assessment estimates, for example, the number of cases of disease avoided or years of life saved through new policy; these estimates can then be compared with costs to businesses and the economy of complying with the policy. In the United States every major new environmental regulation must undergo a cost-benefit analysis prior to promulgation. Such analysis is required by Executive Order 12291, signed by President Reagan in 1981 and continued by every president since then.[1] The order requires analysis of the proposed regulation's "net benefit to society" and of "alternative approaches that could substantially achieve the same regulatory goal."

For environmental regulations designed to protect human health, calculation of benefits requires quantitative risk assessment to aid in predicting the number of deaths or illnesses that the proposed regulation could prevent.[2] The predicted numbers of avoided deaths and illnesses are then incorporated into a risk management process, in which these predictions are monetized in order to weigh regulatory benefits against implementation costs to industry and others. As a consequence, quantitative risk assessment is one of the most important tools in environmental policymaking.

The vital relevance of risk assessment to risk management in environmental health policy-making is illustrated well in the process by which the EPA introduced a new standard lowering the Maximum Contaminant Level (MCL) for arsenic in drinking water. In 1996, the EPA was tasked by Congress to review and revise this standard from its then-current value of 50 μg/L. EPA based its primary justification for reducing the MCL on cases of bladder and lung cancer avoided calculated in the course of its risk assessment, stating in its proposed rule change that "although arsenic causes numerous health effects, bladder and lung cancer are the only endpoints for which an Agency-approved metric for evaluating arsenic-related risk currently exist."[3] Based on this cancer-focused risk assessment, the EPA initially proposed a revised standard of 5 μg/L.[4] Subsequent tradeoff analysis estimated the benefits at this level at $191.1-$355.6 million, but costs were estimated at $414.8-$471.7 million; thus, costs outweighed benefits.[3] Public comment revealed significant concern as a result, and the EPA ultimately decided on a standard of 10 μg/L to "maximize health risk reduction benefits at a cost that is justified by the benefits."[5] At 10 μg/L, benefits were estimated at $139.6-$197.7 million and costs at $180.4-$205.6 million. Upper and lower bound estimates of the cost-benefit tradeoff were calculated at several different proposed MCLs (3, 5, 10, and 20 μg/L) and at two discount rates (3% and 7%) using Monte Carlo simulation analyses. The 10 μg/L level was the lowest value at which the net benefit was positive for at least a portion of the scenarios simulated (Table 1).

Table 1. Net benefits of each regulatory option ($ millions). (adapted from Arsenic in Drinking Water Rule Economic Analysis[3])

MCL (μg/L)		3	5	10	20
3% Discount Rate					
Net Benefits	lower bound	(484.0)	(223.7)	(40.8)	(0.6)
	upper bound	(206.8)	(59.2)	17.3	8.5
7% Discount Rate					
Net Benefits	lower bound	(578.3)	(280.6)	(66.0)	(10.3)
	upper bound	(301.1)	(116.1)	(7.9)	(1.2)

While risk assessment plays a central role in environmental policymaking, a 2009 U.S. National Research Council report (*Science and Decisions: Advancing Risk Assessment*) highlighted numerous challenges to the current practice of environmental risk assessment.[6] The report states that "risk assessment…is at a crossroads, and its credibility is being challenged," adding that the usefulness of risk assessment to policy-making is also in question: "disconnects between the available scientific data and the information needs of decision-makers hinder the use of risk assessment as a decision-making tool."[6] Nonetheless, the report concluded, "risk assessment remains the most appropriate available method for measuring the relative benefits of the many possible interventions available to improve human health and the environment and that its absence or its inappropriate application will result in seriously flawed decisions." The report recommended steps to improve (1) the technical soundness of risk assessment and (2) the utility of risk assessment to decision-makers.

This dissertation advances the use of a novel technical approach – Bayesian network (BN) modeling – to improve both the technical quality and the utility of risk assessment. Importantly, while BN models have been used in ecological risk and food safety assessment, they have never before been used in assessing human health impacts of exposure to contaminants in environmental media (water, air, or soil). BN methods are not currently used

to support regulatory decision-making at EPA or other environmental regulatory agencies. The dissertation demonstrates for the first time how Bayesian network approaches can improve the technical analysis underlying environmental risk assessments of public health outcomes. In addition, the dissertation demonstrates how Bayesian networks can improve the practical utility of risk assessments to decision-makers focused on decreasing environmental risks to public health in specific contexts. Specifically, the dissertation

- develops the first machine-learned BN models linking environmental exposure and health outcome data,
- demonstrates that these machine-learned BN models are significantly more accurate in predicting observed health outcomes than prevailing methods in risk assessment, and
- illustrates in two separate contexts how BNs could improve the practical utility of environmental risk assessments to decision-makers concerned about human health outcomes.

2. National Research Council recommendations for improving risk assessment

The National Research Council's 2009 report, in which key challenges to risk assessment were identified, built upon an earlier publication by the same organization in which the risk assessment process was given formal structure. This study, *Risk Assessment in the Federal Government: Managing the Process*, has served as the EPA's guideline for risk assessment since its publication in 1983.[7] In it, the environmental risk assessment is broken down into four steps:

1. hazard identification: "the process of determining whether exposure to an agent can cause an increase in the incidence of a health condition [by] characterizing the nature and strength of the evidence of causation"[7]

2. dose-response assessment: “the process of characterizing the relation between the dose of an agent administered or received and the incidence of an adverse health effect in exposed populations and estimating the incidence of the effect as a function of human exposure to the agent”[7]
3. exposure assessment: “the process of measuring or estimating the intensity, frequency, and duration of human exposures to an agent currently present in the environment or of estimating hypothetical exposures that might arise from the release of new chemicals into the environment”[7]
4. risk characterization: “the process of estimating the incidence of a health effect under the various conditions of human exposure described in exposure assessment” [7]

These four steps remain the NRC’s current recommendation for conducting risk assessment.[6]

2.1. Technical improvements

The 2009 NRC report identifies improvements in dose-response assessment models as the chief need for improving the technical analysis that supports risk assessment. As Figure 1 (reproduced from the NRC report) illustrates, the key limitations include

- inconsistency between dose-response assessment methods for cancer and non-cancer outcomes,
- lack of consideration of low-dose effects for non-carget outcomes,
- lack of a quantifiable risk measure for non-carget endpoints and for cancer endpoints for which evidence of a response threshold exists,
- lack of sufficient consideration of inter-human variability, and
- lack of uncertainty characterization.[8,9]

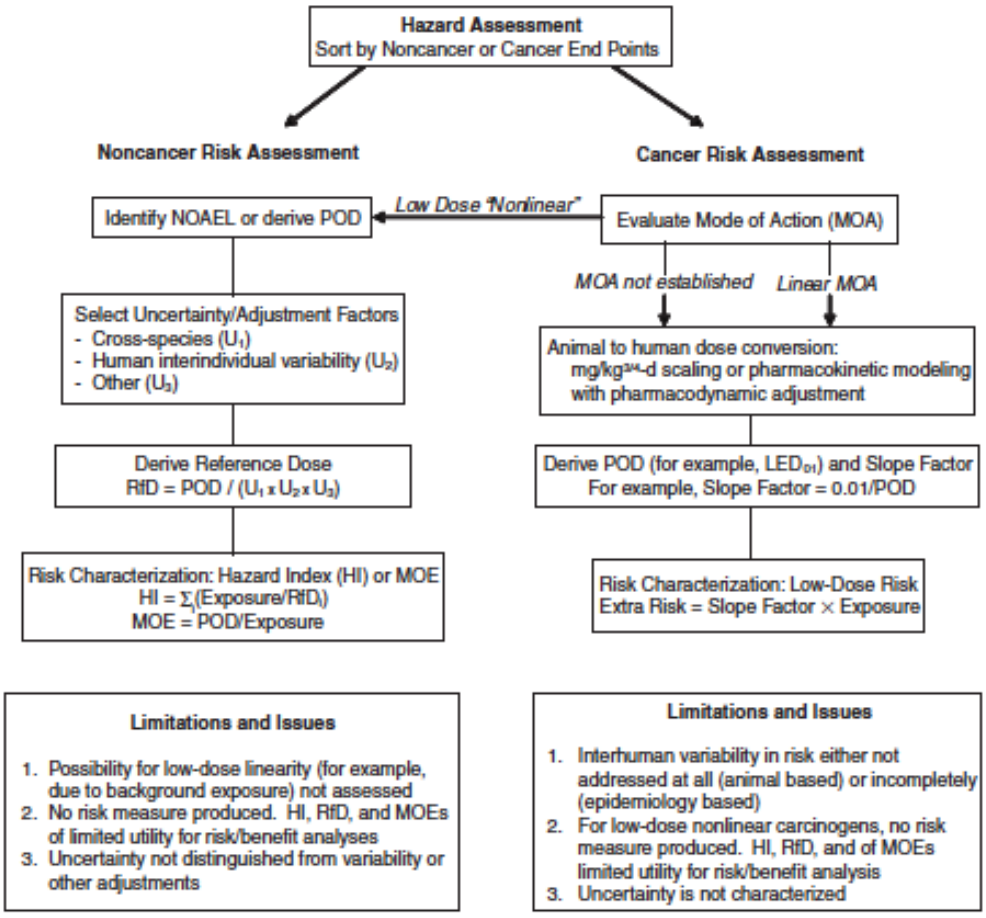


Figure 1. Current approach to non-carget and cancer dose-response assessment. (from *Science and Decisions: Advancing Risk Assessment*[6])

Dose-response assessment for non-cancer outcomes is currently conducted by first examining available human (if available) and animal studies relating the hazardous substance under evaluation to health outcomes. Health endpoints and indicators are chosen by regulators (for example, liver function as measured by sorbitol dehydrogenase levels), and data from a study containing this information are used to compute points of departure (POD) for further calculation. This POD may be either the no/lowest observed adverse effects level (NOAEL or LOAEL), or a benchmark dose (BMD) calculated according to an assumption of functional form to correspond to some predetermined response level (like a 10% increase over baseline risk of

the outcome under consideration).[10] This POD is then divided by factors of 1, 3, or 10 to account for different types of uncertainty: EPA guidance states that "uncertainty factors are applied as needed to account for extrapolation of results in experimental animals to humans, interindividual variability including sensitive subgroups, extrapolation from a LOAEL to a NOAEL, extrapolation of results from subchronic exposures to chronic exposures, and database inadequacies."[10] The resulting value for a chosen health outcome, termed a reference dose (RfD), is used as a limit below which risk of the outcome of concern is presumed absent.

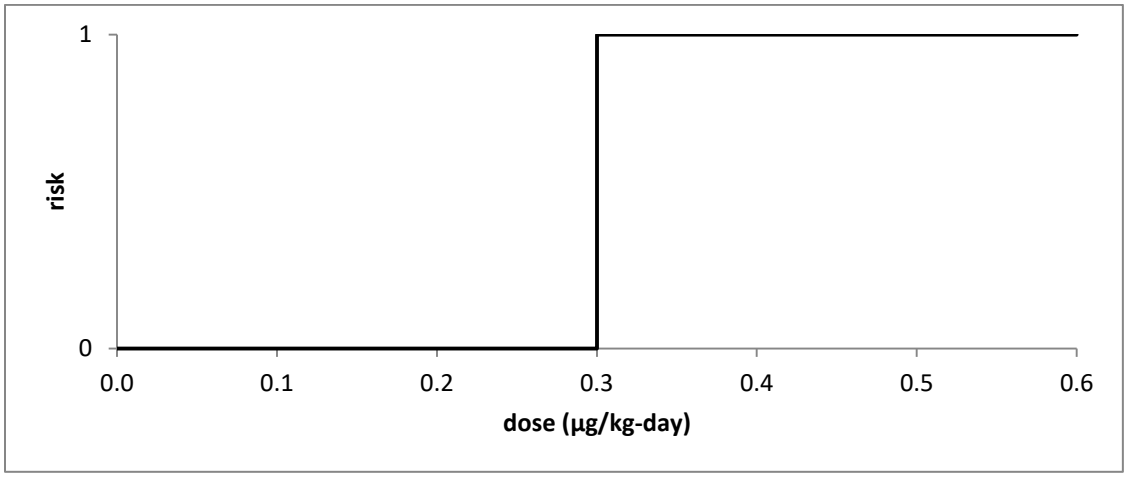


Figure 2. Reference dose approach. The reference dose for inorganic arsenic, 3×10-4 mg/kg-day11 (1991), is shown at the center of the axis. Under this approach, risk is presumed absent below this level and present above it.

In risk assessment, the reference dose is used to express risk of the non-carget outcome through calculation of a hazard quotient (HQ). This value is simply the ratio of exposure dose to the reference dose[11]:

$$HQ = \frac{exposure\ dose}{reference\ dose}$$

(1)

EPA guidelines state that "exposures at or below the reference level (HQ=1) are not likely to be associated with adverse health effects," but cautions that the HQ "should not be interpreted as a probability of adverse effects."[11]

For cancer outcomes, a different procedure is used. When specific mode of action data are available, these data may be taken into account to understand a range of safe doses of the carcinogen (for example, there is evidence that some carcinogenicity arises from effects on cell division only present at higher doses).[12,13] Unless these data lead to a definitive conclusion of no risk at low doses, however, no dose of the carcinogen is presumed safe. In addition, unless conclusive evidence demonstrates otherwise, the relationship between exposure and probability of developing cancer is considered to be linear: "linear extrapolation is used as a default approach, because linear extrapolation generally is considered to be a health-protective approach."[8] As with non-cancer outcomes, data are drawn from animal or, if available, human studies linking exposure to different levels of the carcinogen to outcomes. These data are used to determine a POD at which a response of interest is measured (for example, tumor development). The slope of a line drawn from the POD to the origin is termed the slope factor, and cancer risk is established as the product of the slope factor and exposure level.[8]

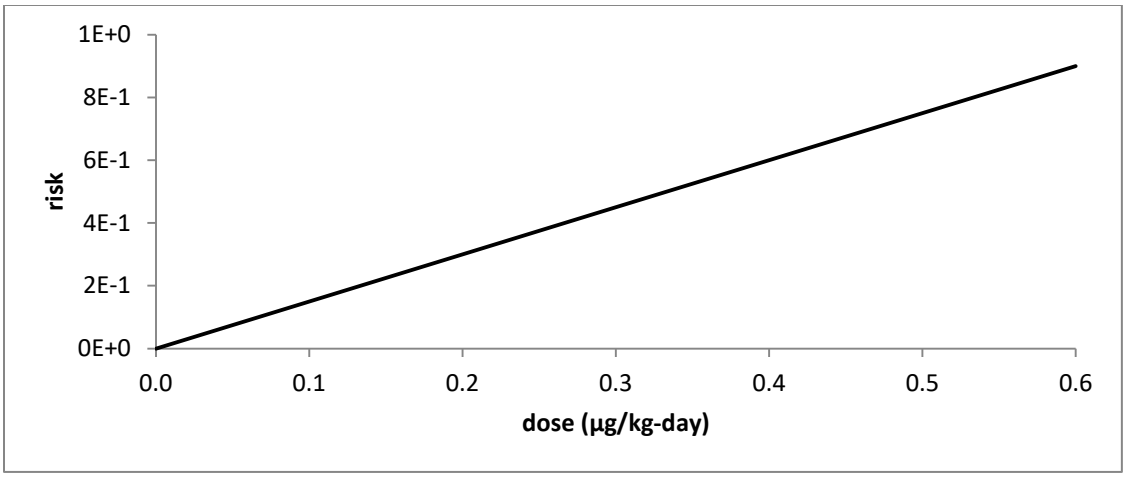


Figure 3. Slope factor approach. The slope of the line is the slope factor for inorganic arsenic, 1.5×10^{-3} per µg/kg-day[14] (1995); risk is the product of this factor with dose.

Note that the functional form of this dose-response model is identical to a simple linear regression model with a single covariate (dose) and regression coefficient (slope factor; the intercept term is zero due to the assumption of no safe dose).

$$risk = slope\ factor * exposure\ dose \quad (2)$$

The divide between cancer and non-cancer outcomes is primarily due to the historical development of the risk assessment process. Cancer risk assessment was first based on the assumption that chemical carcinogenesis was mechanistically similar to radiation carcinogenesis, which was understood to be capable of damaging DNA at all levels of exposure.[15] As such, no dose of a carcinogen has been presumed safe in risk assessment even though subsequent research has shown a far broader range of carcinogenic mechanisms through which risk does not necessarily scale linearly with toxicant exposure.[16] Non-cancer outcome dose-response assessment, in contrast, was developed according to the older toxicological concept of a threshold dose below which harmful effects are not present[17]; subsequent research has shown that this assumption of threshold effect does not always hold

either.[18,19] As such, the continued separation of methods used for dose-response assessment of cancer and non-cancer outcomes does not adequately reflect underlying biological realities, and a unified approach is needed.[20]

As a result of the differences between cancer and non-carget risk assessment approaches, the NRC indicates, "non-cancer effects have been underemphasized, especially in benefit-cost analyses."[6] The lack of attention to non-cancer consequences is due to the inability of the RfD approach to produce a risk measure, for example the change in the number of diabetes cases (or cases of some other observable health outcome) expected due to a change in exposure to a toxin. Instead, the RfD approach produces only a binary indicator of whether the exposure is above or below a level of concern. A quantified estimate of the number of outcomes prevented by a proposed regulation is necessary to include the outcome in cost-benefit analysis. A related limitation of the RfD approach is that it does not allow for assessment of low-dose exposure risks without low-dose exposure data, because it assumes risks are zero below the RfD even if there is biological evidence of potential risks. A similar limitation applies to cancer risks for which EPA has determined a risk threshold exists.

An additional limitation of technical approaches for dose-response assessment described in the NRC report is the lack of characterization of uncertainty and population variability. Points of departure are selected from one study, rather than reflecting the uncertainty evident from differing possible points of departure across studies. In addition, within-study uncertainty is not characterized explicitly, for example by providing confidence intervals around cancer slope factors. Uncertainty in RfDs currently is characterized with uncertainty factors selected through judgment of EPA staff. The NRC recommends the "use of

probabilistic distributions instead of uncertainty factors when possible" in order to capture uncertainty as indicated in available data.[6] Inter-human variability also is not captured by current methods (except through the use of uncertainty factors). Dose-response assessment methods that characterize population variability could add significant value by identifying at-risk subgroups.

2.2. Utility of risk assessment

The NRC report also identified a need for advances in risk assessment beyond those suggested for dose-response assessment. It concluded that the risk assessment process as a whole can benefit from improvements that better align it with the decision-making it is intended to inform. The critical need for improving the utility of risk assessments is a framework that first identifies risk management options, in collaboration with decision-makers and stakeholders, and then organizes the risk assessment to evaluate the effects of each option on health outcomes. The 2009 NRC report identifies this need as fundamental to improving the utility of the risk assessment process, noting that "[the earlier] framework was not oriented to identifying the optimal process for complex decision-making but rather to ensuring the conceptual separation of risk assessment and risk management."[6] This separation has taken root in practice, leading to risk assessment processes that frequently devote time and effort to answering questions of little practical use for risk management while leaving other relevant questions (especially regarding the effects of different policies) unanswered.

To address this issue, the NRC proposed a reorganized framework in which risk analysis is integrated with risk management decision-making. As shown in Figure 4, the proposed framework includes explicit consideration of how risk assessment will inform the effects on risk

of proposed policy options in its first stage (problem formulation and scoping). The process also includes an explicit step involving confirmation of the assessment's utility to decision-making, and suggests that if utility is insufficient, the assessment should be revised. This kind of iterative risk assessment framework requires modeling approaches that are easy for decision-makers to understand and, ideally, that enable them to interactively assess changes in risk in response to changes in key decision variables.

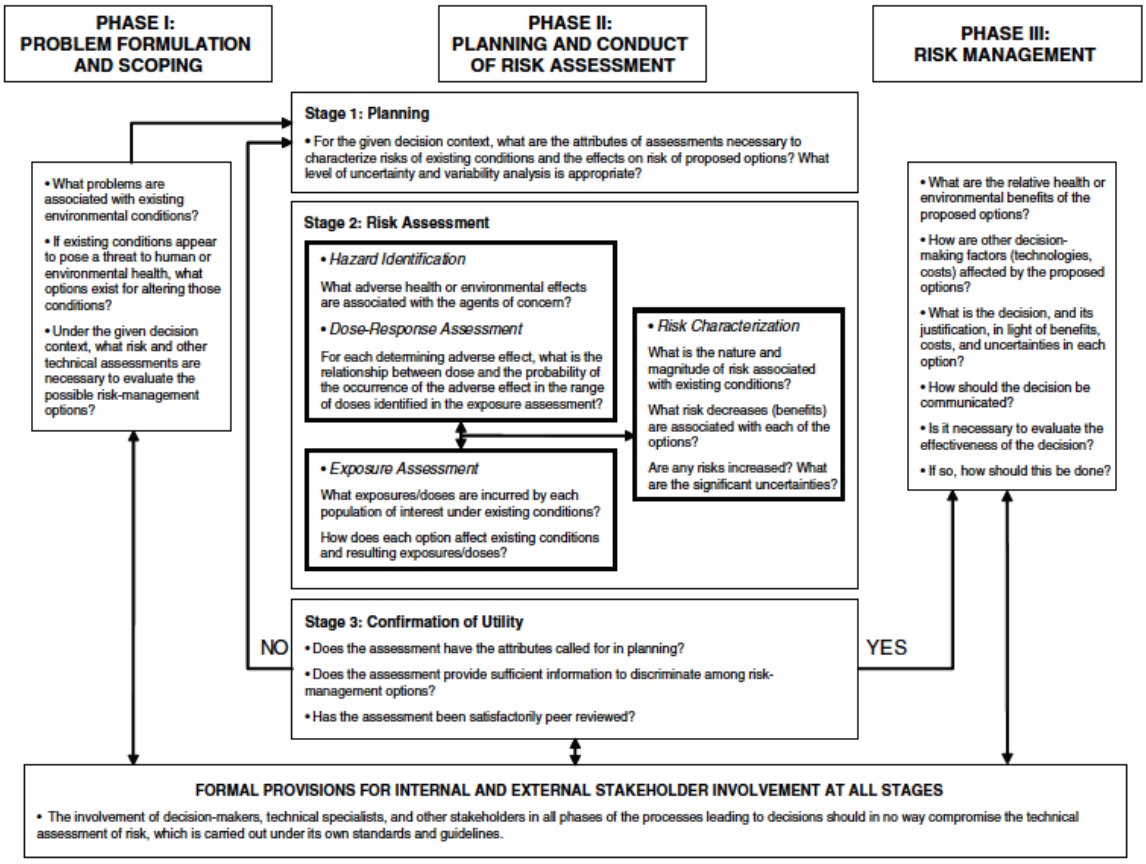


Figure 4. A framework for risk-based decision-making that maximizes the utility of risk assessment. (from *Science and Decisions: Advancing Risk Assessment*[6]).

3. Potential for Bayesian networks to address key risk assessment challenges

Bayesian networks are not currently used in regulatory risk assessment at the EPA. However, they may provide a framework for addressing several of the key risk assessment

challenges identified by the NRC. In particular, BNs may be able to improve dose-response assessment by harmonizing approaches to cancer and non-cancer outcomes and by allowing for reduced dependence on assumptions of functional dose-response form (particularly in low-dose regions). BNs' ability to perform diagnostic inference could also help to identify subpopulations at particular risk, and their inherent use of probabilities to describe variables could shift characterization of uncertainty in dose-response assessment to the use of distributions rather than uncertainty factors, as the NRC suggests. More broadly, Bayesian networks may be able to improve the utility of risk assessment by providing an interactive, visual modeling platform that could make risk assessments useful to decision-makers. Updating based on information could also improve risk assessment utility through scenario analysis, by which different risk management options can be tested for costs and benefits. In order to more fully explore these potential advantages, though, an understanding of Bayesian networks' properties is necessary.

3.1. Overview of Bayesian networks

Bayesian networks were first formulated by Judea Pearl as a way of exploring causal inference in complex systems.[21,22] Formally, they are directed acyclic graphs that represent variables as nodes and connections between variables as arcs (Figure 5). Bayesian networks specify the joint distribution of included variables, and use Bayes' Rule to update conditional probabilities given evidence. Bayesian networks have been used across a diverse range of fields, including software engineering[23], threat evaluation[24], drug efficacy analysis[25], tourism management[26], and environmental modeling[27] among many others. Early applications were constrained by limited computing power, but increases in memory availability as well as Pearl's

solution algorithms and software platforms implementing them have resulted in substantially expanded BN use.[28,29] Even so, the potential for BN applications is still far from fully realized.[30]

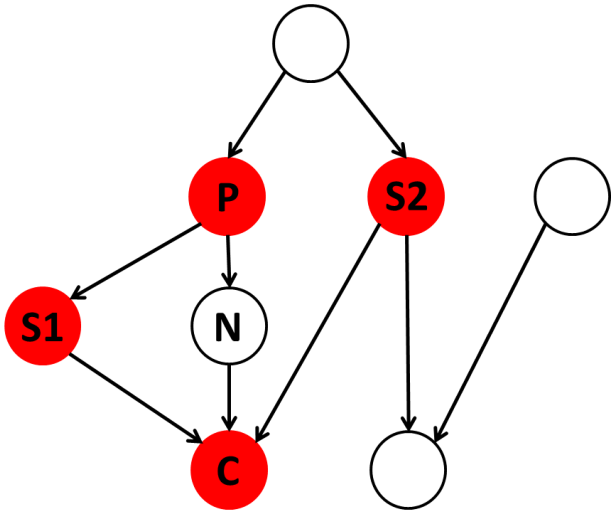


Figure 5. A simple Bayesian network. Node *N* has parent node *P*, child node *C*, and spouse nodes *S1* and *S2*. The unmarked nodes are also part of the network, but node *N* is conditionally independent of them given the states of the red nodes. The set of red nodes (all parents, children, and spouses) is termed node *N*'s Markov blanket, and every node in a Bayesian network is conditionally independent of all other nodes given its Markov blanket.

Each node X_i in a Bayesian network is characterized by a probability distribution $P(X_i)$. Nodes that are not directly connected are conditionally independent of each other if nodes between them are specified: for nodes X_i and X_k not directly connected, with intermediate node X_j, $P(X_i|X_j,X_k) = P(X_i|X_j)$ and $P(X_k|X_j,X_i) = P(X_k|X_j)$ In addition, node X_i is conditionally independent of all other nodes given its parents Pa_i (other nodes directly connected to X_i by arcs terminating in X_i): denoting all non-parents of X_i as Np_i, $P(X_i|Pa_i,Np_i) = P(X_i|Pa_i)$. This property is termed the local, or parental, Markov condition.[31] Using it and the chain rule of probability calculus, the joint distribution of an entire Bayesian network with n nodes can be expressed as[32]

$$P(X_1, \ldots, X_n) = \prod_{i=1}^{n} P(X_i|Pa_i)$$

(3)

This factorization of the joint distribution into a discrete, limited number of conditional distributions allows the network to be solved analytically. Finally, Bayes' Rule is key to the propagation of information in Bayesian networks. If X_p is a single parent node of X_i, Bayes' Rule gives an expression of the probability of X_p conditional on information on X_i:

$$P(X_p|X_i) = \frac{P(X_i|X_p)P(X_p)}{P(X_i)}$$

(4)

This relationship allows information added to a Bayesian network to influence the probability of its parents, in addition to its children – and through them, the rest of the network.

3.2. Improving technical soundness of risk assessment

Bayesian networks have a number of properties that could enable them to respond to the technical needs identified by the NRC for improvements in dose-response methodology. Because of their probabilistic structure, they do not require assumptions of functional form (like those underpinning current dose-response methods) to link variables. In addition, Bayesian networks have well-demonstrated advantages in performing classification: assigning a group of specifications across a variable set **X** to a class of variable Y. More simply, classification algorithms seek to predict an outcome of interest from available data. This is precisely the aim of dose-response assessment, potentially making BNs' advantages in performing classification relevant to dose-response applications.

Most classifiers can be categorized as either generative or discriminative.[33] Generative classifiers use data to estimate P(**X**,Y) – the joint distribution of all variables – and use Bayes' rule to calculate P(Y|**X**), the probability of some outcome of interest given available information. In contrast, discriminative classifiers assume a certain structure of the relationship between **X** and Y and estimate parameters to determine P(Y|**X**) directly. Logistic regression is an extremely popular discriminative classifier. For binary classification, it assumes a functional relationship of the form

$$P(Y = 1|\boldsymbol{X}) = \frac{\exp(\beta_0 + \sum_i \beta_i X_i)}{1 + \exp(\beta_0 + \sum_i \beta_i X_i)} \quad (5)$$

and uses maximum likelihood to estimate the regression coefficient vector **β** (as the equation has no closed-form solution). This expression can be transformed to express the familiar log-likelihood:

$$\ln\left(\frac{P(Y = 1|\boldsymbol{X})}{P(Y = 0|\boldsymbol{X})}\right) = \beta_0 + \sum_i \beta_i X_i \quad (6)$$

The logistic regression maintains an important assumption: that the log odds (logit) can be accurately represented as a linear combination of explanatory factors.[34] This representation can be used to account for interactions among variables (including higher-order self interactions), but in practice, it can be difficult to select which interactions to include because of the great number of potentially relevant interactions in even a moderately complex system and limits on data in assessing these factors' unique contributions. Choosing which interactions

to study is usually done through expert judgment or a stepwise approach, either of which can introduce bias.[34]

Unlike logistic regression models, Bayesian networks belong to the group of generative classifiers because they reconstruct the joint distribution P(**X**,Y) from which data are generated.[33] When used exclusively for prediction, the structure of a Bayesian network matters a great deal. Naïve Bayes is the simplest algorithm used to generate BNs from data.[35] It is 'supervised', in the sense that the modeler chooses the target variable to be predicted, and it makes a very strong assumption about the network's structure: that the non-target variables are conditionally independent given the target variable. The algorithm first learns P(**X**|Y) (the probability distribution of each non-target variable given different states of the target variable) as well as P(Y) (the marginal distribution of the target variable), and finally uses Bayes' Rule to estimate P(Y|**X**). Classification of a case is performed by calculating the probability of each state of the target variable using observed data on non-target variables, and then choosing a state of the target variable as the case's class according some decision rule. For example, available data about a person (age, gender, education level, etc.) could be used to estimate the probabilities that the person did or did not smoke; the person would be classified as a smoker if and only if his estimated probability of smoking was greater than his probability of not smoking.

The assumption of conditional independence has the benefit of significantly reducing the complexity of estimating P(**X**|Y) and P(Y). Perhaps surprisingly, it frequently performs well in classification tasks even though the underlying assumption is unrealistic.[36] For cases in which conditional independence is unlikely, other learning algorithms that relax the strict assumption are available. The first of these is the tree augmented naïve Bayes (TAN). It allows relationships

between non-target variables, but imposes a spanning tree structure on them: each non-target node must be connected to some other non-target node, and can have at most one non-target node parent.[35,37] Further relaxations like the augmented naïve Bayes (BAN) remove the requirement of tree structure and permit learning across a broader set of available relationships at the expense of greater computing intensity.[38] This learning can be accomplished by algorithms that test all possible relationships between non-target variables for independence (constraint-based algorithms), or that search different available network structures to find one that maximizes the likelihood of available data (score-based algorithms). In practice, the former tend to be more efficient (especially when the number of variables is large) while the latter tend to be more accurate.[39] The two approaches can also be hybridized; further details are available in Bielza and Larrañaga (2014).[40]

Under certain conditions, Bayesian network classifiers can be shown to be equivalent to logistic regression classifiers. In particular, BNs constructed with the objective of maximizing the likelihood of $P(Y|\mathbf{X})$ map to logistic regressions. Naïve Bayesian networks correspond exactly to 'simple' logistic regression; TAN networks correspond to regression in which interaction terms are incorporated.[41,42] It is important to note that even this expansion is highly nontrivial: to match a TAN network, a logistic regression must include all possible interactions (of all orders). In practice, this is generally not feasible given the amount of data available. Furthermore, more relaxed BNs (like BAN models) cannot be mapped to logistic regression at all, and complex variable transformations may be necessary to approximate a match while satisfying the logistic regression's underlying assumption of linearity in the log likelihood.[35]

These matches have been termed discriminative-generative classifier pairs, and it is instructive to investigate their performance in the same settings. Ng and Jordan provide a foundation for this analysis. They showed that discriminative classifiers' asymptotic variance is bounded above by their paired generative classifier's asymptotic variance: in other words, a discriminative classifier will always perform at least as well as its generative counterpart as data availability approaches completeness relative to the total population being modeled.[43] However, generative classifiers converge to their asymptote more quickly. (Ng and Jordan show that generative classifiers achieve uniform closeness in parameters to their asymptotic values with log(n) samples, rather than n samples for discriminative classifiers).[43] In practice, this means that generative classifiers will generally perform better in environments where data is sparse relative to the total population.

In addition, BNs learned using more advanced algorithms (like TAN or BAN) can have both theoretical and practical advantages over logistic regressions. As noted above, TAN networks can technically be represented through logistic regression with interactions specified. In practice, specifying all possible interactions is not generally feasible. The number of interactions among variables is 2^n-2, excluding self-interactions. Of course, most of these are usually insignificant – but excluding them from a regression formalizes this assumption, while explicitly including them quickly causes identification issues in all but the most data-rich environments.[34]

The insights gained from theory can be examined in practice through parallel applications of discriminative and generative classifiers. We would expect Bayesian network techniques to have performance comparable or superior to regression methods in performing

classification when data is sparse relative to the population being studied, or when relationships among variables with relevance to the classification task are either difficult or impossible to capture in the regression format.

These patterns generally emerge from the literature across a broad range of contexts. Huang et al., for example, used BNs to predict the ideal temperature for a cooling system and compared performance to regression models.[44] Their BN model determined ideal temperature with an order of magnitude greater accuracy than the regression model, and the authors noted that this is specifically due to the nonlinear thermodynamics governing temperature within the system they studied. Van der Gaag et al. demonstrated superior performance by BN model over logistic regression in predicting the success of in-vitro fertilization, noting that the complex relationships they hypothesize connect their predictor data to their outcome of interest cannot be capture by their logistic models.[41] Zuo et al. provided a particularly elegant example of a Bayesian network's elicitation of a known non-monotonic behavior.[45] They used radio-frequency identification (RFID) data from sensors attached to shoppers' carts to monitor movement around a store, and attempted to predict binary purchasing decisions from this information as well as available demographic data. They showed a 'tedium effect': that purchasing likelihood increased with time spent in the store, to a point, but then began to decrease again. Its ability to capture this non-monotonicity allowed their BN model to perform significantly better than a logistic regression model given the same data (ROC AUC 0.90 v. 0.81). In addition, the literature reveals a number of instances in which BNs' classification outperformance is directly attributable to superior ability to handle sparse data. Lee et al. demonstrated such results in a study of 54 patients to predict radiation pneumonitis, a

consequence of radiation therapy.[46] They used bootstrapping to simulate further instances from their small dataset and showed clear improvement by the BN over a regression model in predicting the condition. Ducher et al. reported similar behavior when using data on 149 patients to predict incidence of immunoglobulin A nephropathy: the stability of BNs in small data environments (ultimately due to their faster convergence to asymptotic error) resulted in superior performance relative to regression predictions.[47] Furthermore, this advantage is evident in BNs' ability to recover parsimony from available data. Milns et al. used both BNs and logistic regressions to attempt to learn the structure of complex ecological relationships among different birds and characteristics of their environments.[48] They found that the relationships modeled by the BN were 'realistically sparse', in contrast to the regression approach's inability to discount insignificant relationships while retaining realistic ones.

It is important to consider conditions in which Bayesian networks offer no significant advantages over more familiar regression techniques in performing classification. First, the ability of BNs to capture nonobvious and complex relationships only matters when these are present in the data. Prosperi et al. note that the linear classifiers they used to predict responses to allergens may perform just as well as the nonlinear methods they studied (including BNs) due to the absence of these nonlinear relationships in their data, but also emphasize that their dataset may be insufficient to capture actual relationships (rather than concluding that these relationships do not exist).[49] Similarly, attempting to predict certain outcomes without any data on factors driving the outcomes is usually an exercise in futility regardless of the method chosen. Frizzell et al. encountered this issued in attempting to predict 30-day all-cause hospital readmissions for heart failure patients.[50] Even with a dataset of over 56,000 patients,

containing many different potential explanatory variables (demographics, medical history, medical history, lab test results, etc.), all models they tried performed comparably and poorly (average AUC ROCs of 0.62). They conclude that there is simply too much variability in all-cause hospital readmission to be captured by their explanatory variables. A similar conclusion was reached by Buursma in attempting to predict the outcomes of soccer matches using a number of different kinds of models.[51] Finally, theory predicts that in circumstances where available data is both comprehensive (capturing all predictive variables) and nearly complete ('large' relative to the population being studied), regression methods will predict outcomes with greater accuracy than BN models (as long as no complex relationships are relevant). In practice, such ideal circumstances hardly ever occur.

The literature reviewed allows several general conclusions about using Bayesian network models for classification and prediction. The models rarely underperform regression techniques severely in classification accuracy; their performance is usually equal or superior, though rarely extremely so. However, authors consistently return to a number of other advantages of using Bayesian network models. First, and perhaps most important, is the ability to perform prediction in *incomplete* data environments (for example, diagnosing illness when only a subset of relevant clinical indicators have been observed). This is not the same as predicting in *sparse* environments – when only a small subset of cases is available, but these cases are complete. In this instance, models face the added challenge of cases lacking some relevant data. This kind of prediction is studied less frequently in the literature as models tend to be trained on complete datasets, but is vital when these models are actually used in practice.

Wang et al. cite this capability of BNs as a key reason to prefer them for clinical application after developing models to predict metastasis of lung cancer tumors to the brain.[52]

In addition, the ease of use and transparency of Bayesian networks recur as positive features that favor their use. BNs have an intuitive structure, and provide a clear visual representation of the effects of evidence propagating across the network (Gevaert et al. term them 'white-box' models[53], in contrast to 'black-box' approaches like neural network techniques in which variable interaction is often opaque).

Researchers also cite the ability of Bayesian networks to capture nonlinear behaviors and interactions among variables; this is particularly evident in settings in which researchers are aware of these kinds of complex interactions *a priori*, and they are accurately reproduced by the Bayesian network. BNs' ability to incorporate expert knowledge is also consistently cited as an advantage, especially in concert with insight gained from data. In fact, several studies have demonstrated cases in which the best-performing models are BNs that combine both – and the worst-performing models rely only on expert knowledge. For example, Sesen et al. developed models to guide clinical decisions and predict survival for lung cancer patients.[54] They found that a BN model populated only with experts' prior beliefs on relevant factors performed worse than any other model they tried, while a model combining these beliefs with information learned from data performed best. These advantages are summarized in Table 2, which highlights relevant information on a sample of papers from across disciplines comparing Bayesian networks with other modeling approaches.

Table 2. Literature comparison of Bayesian network models with other approaches.

Paper	Context	Outcome predicted	Other models	Metrics	Results	BN advantages*
Bozkurt & Uyar	983 patients	prostate cancer	logistic	sensitivity,	logistic	cause-effect

(2011)[55]			regression with forward selection	specificity, ROC AUC	better (AUC 0.775 v. 0.750)	modeling; integrating priors and study data
Feng & Timmermans (2016)[56]	1554 trips (53,258 data points)	transportation mode	multinomial logistic regression	sensitivity, Cohen's kappa, hit ratio	BN better (sensitivity: 99.474% v. 94.510%; kappa: 0.993 v. 0.921; all hit ratios ≥0.997 v. as low as 0.758 for logistic)	stable, robust, general; flexible; not a black box
Huang et al. (2016)[44]	8760 hourly demand and temperature readings	ideal cooling system temperature	simple linear and quadratic regression	RMSD	BN better (0.2-0.3°C v. 2.3-3.3°C)	captures nonlinear thermodynamic relationships – mean reversion in regressions
Stokes et al. (2017)[57]	113 beaches (77 predictors)	beach hazard and lifetime risk	multiple linear regression	R^2, RMSE, R_S	logistic better at out-of-sample prediction; otherwise comparable (small data set)	ranking; ease of communication; capturing complex relationships; predictions where some data is missing
Lee et al. (2015)[46]	54 patients (network learned over 200 bootstrapped sets)	radiation pneumonitis	multivariate logistic regression	ROC AUC	BN better (AUC 0.83 v. 0.77)	prediction with incomplete information (better than imputation)
van Koten & Gray (2006)[58]	110 software cases	software maintainability	multiple linear regression (backwards elimination and stepwise selection)	absolute residuals, magnitude of relative error	BN even to better	predictive capability depends on dataset characteristics and learning algorithm
Milns, Beale, & Smith (2010)[48]	*birds and habitats*	*ecological networks*	*lasso regression*	*'sparseness'*	*BN network recovered known relationships*	*advantage over regression in being 'realistically sparse'*
Ducher et al. (2013)[47]	149 patients	IgA nephropathy	stepwise logistic regression	ROC AUC	BN better (AUC 0.83 v. 0.75)	can deal with small sample sizes and missing data; also appropriate for different conditions (clinics etc.); 'continual apprenticeship'
Frizzell et al. (2016)[50]	56,477 patients	heart failure hospital readmissions	backwards stepwise and lasso logistic	C statistic (ROC AUC)	similar (AUC 0.618 v. 0.624 v.	limits on availability of data driving

			regression		0.618)	outcome
van der Gaag et al. (2008)[41]	152 women	in-vitro fertilization success	logistic regression	ROC AUC	BN better (AUC 0.85 v. 0.68)	BN advantage in sparse data environments and small datasets; complex BNs cannot map to regressions
Ezawa & Schuermann (1995)[59]	179,256 debt files	uncollectable debt	linear and quadratic discriminant analysis	sensitivity	BN better (25.91% v. 1.35%)	highly significant outperformance in asymmetric data environment
Gevaert et al. (2006)[53]	856 patients	ectopic pregnancies	multicategorical logistic regression	ROC AUC	BN better (AUC 0.88 v. 0.82)	explicit use of expert priors on structure and parameters; advantage in interpreting network outcome
Lee, Abbott, & Johantgen (2006)[34]	*nursing data*	*nursing relationships*	*logistic regression*	*ability to handle large datasets*	*BN models surpass regression assumptions*	*BNs overcome linearity in logit and additivity; interactions difficult to assess in practice through regression approaches without a priori knowledge*
Sesen et al. (2013)[54]	117,426 patients	lung cancer survival and treatment	logistic regression	ROC AUC	comparable (both AUCs 0.81)	typical BN advantages (complex data modeling); also, BN from expert design performed worst
Buursma (2011)[51]	75 matches	soccer match outcome	linear and logistic regression	sensitivity	comparable	difficult to predict without complete data on inputs driving performance
Sohn et al. (2016)[60]	751 patients	surgical site infection	logistic regression	ROC AUC	BN better (AUC 0.827 v. 0.719)	incorporation of natural language processing key
Wang, Makond, & Wang (2014)[52]	36,043 patients	brain metastasis from lung cancer	logistic regression	accuracy, sensitivity, and specificity	mixed results	BN advantage in nonlinear situations, missing data, and transparency
Prosperi et al. (2014)[49]	461 patients	allergen responses	logistic regression	accuracy, sensitivity, and specificity	comparable	higher-order interactions were not found in available data but cannot be

						ruled out
Zuo, Yada, & Kita (2015)[45]	1155 shopping paths	bread purchasing	logistic regression	ROC AUC	BN better (AUC 0.9023 v. 0.8094)	nonmonotonic tedium effect on stay time – increasing time in store increases purchase likelihood to a point, but not beyond

*the advantages listed summarize the conclusions of the authors of the papers reviewed

In addition to their potential advantages in advancing dose-response assessment methodology, Bayesian networks may also address the need for improvements that make risk assessment more useful for decision-makers. The NRC emphasizes the need to integrate, rather than separate, risk assessment and risk management. BNs offer particular promise in responding to this need because they are easy to interact with, and show the effects of risk mitigation decisions on both the outcome of interest as well as other characteristics of the system modeled. They also permit backwards diagnostic inference – the determination of factors influencing known risk.

In current practice, risk management decisions are often analyzed using Monte Carlo simulation.[61] In these applications, models are used to transform a set of inputs (some of which may be uncertain) to generate a numerical outcome of interest – the probability of risk or failure of a system, for example.[62] Unlike in classification, there is generally no attempt to conduct out-of-sample 'prediction' that can be tested against some known result. Rather, this kind of modeling is concerned with integrating many different factors to characterize an outcome of interest and understand uncertainty associated with it.[63]

An example of this Monte Carlo simulation approach for environmental risk management applications is provided in the EPA's arsenic risk assessment, in which the

reduction in risk of bladder cancer from lower arsenic exposure is estimated.[4] Lifetime cancer risk from inorganic arsenic exposure through drinking water is defined as the product of lifetime average daily dose (LADD) and the cancer slope factor (SF) derived from the dose-response assessment. The LADD, in turn, is the product of the concentration of inorganic arsenic in drinking water [As] with intake rate (I), divided by body weight (BW):

$$lifetime\ cancer\ risk = LADD * SF = \frac{[As] * I}{BW} * SF \quad (7)$$

To calculate estimates of lifetime cancer risk, this equation is solved 2000 times; each iteration draws from distributions characterizing the parameters above. Body weight is assumed normally distributed by age and gender. The cancer slope factor is also assumed to be normally distributed based on early estimates using data on arsenic exposure and cancer outcomes in Taiwan. The concentration of inorganic arsenic in drinking water is captured by a nonparametric probability distribution based on observed data for current health assessment; to estimate concentration under new regulatory policy, existing systems with concentrations above the proposed limit are adjusted to a concentration equal to 80% of the limit. Other systems are left unchanged. These simulations resulting from this repeated process are then used to characterize average risk as well as confidence intervals on it.[4]

Bayesian networks offer an alternative way of generating these kinds of estimates based on probabilistic reasoning, relying on conditional probabilities to connect variables. A pure model built only through specifying these probabilities would rely on the joint distribution to transfer input parameter uncertainty to the output. BN models can also incorporate functional

dependencies and simulate variables based on specified distributions. In this sense, they can absorb some MC simulation characteristics.[32]

Monte Carlo simulation methods are fundamentally unidirectional, and lack an interactive link between inputs and outputs.[64] In practice, this means that when an MC simulation is run, an output is generated; backwards inference – through which causes of a particular output are diagnosed – is not possible. In addition, MC simulations sample from underlying distributions that do not (necessarily) interact.[64] While they can incorporate dependencies among variables in theory, in practice this can be quite challenging to implement. In contrast, Bayesian networks are grounded in underlying interactions. Because they contain a full representation of the joint distribution of all variables, they are not unidirectional and can be used for both forward-looking prediction and backwards-looking diagnostic inference. In addition, they are able to update all parameters (not just 'outputs') based on the addition of new information. Finally, Bayesian networks incorporate interactions among variables explicitly, and changing one parameter can affect others directly and indirectly. This is particularly useful in environmental public health policy settings in which different regulatory options must be examined in incomplete data environments. BNs' ability to diagnose factors affecting downstream risk and propagate the effects of changing one system variable on other elements of the system are key attributes that could improve the utility of risk assessment to decision-makers beyond what is possible through more traditional Monte Carlo simulation approaches. Bayesian networks have two key disadvantages relative to MC simulation methods. First, they are computationally complex due to the need to estimate and update many nodes' probabilities simultaneously. While this is only a challenge relative to available computing

resources, it can be substantial when simulating complex systems with many interacting factors.[62] In addition, Bayesian networks typically require discretization of nodes into a finite and usually relatively small set of states.[64] While discretization can generally be accomplished without distorting results, it can reduce precision by approximating rather than directly specifying underlying distributions. If incorrectly done, discretization can bias results and cause important relationships to be overlooked.[63]

The EPA's analysis in support of changing the drinking water arsenic standard referenced above provides an illustrative case in which traditional use of Monte Carlo simulation was used for risk assessment. To generate scenarios representing avoided cases of lung and bladder cancers, as well as costs associated with complying with different regulatory standards, EPA used a number of MC simulation models. These models drew from distributions representing different variables (daily water consumption, body weight, etc.), and outputs were used to generate point estimates and confidence intervals. Applied in this context, BNs would offer a number of concrete advantages. First, probabilistic relationships among variables could be established, and drawing from one would not necessarily be independent of another. Models could simulate outcomes but also identify parameters to which these outcomes were most sensitive, perhaps illuminating particular populations for whom intervention would be particularly impactful. Finally, different decision options could be added to the model in parts to observe network effects.

A broad range of literature has been developed over the past two decades illustrating some of the advantages of Bayesian networks in decision-making contexts, often in situations in which a Monte Carlo simulation would otherwise be used. Bayesian network literature with

greatest relevance to human health and risk assessment falls into four broad categories: food safety, ecological risk assessment, engineering risk assessment, and medical diagnostics.

Bayesian networks have been used extensively in quantitative microbial risk assessment (QMRA) in food safety since their application to this area was first proposed in 2004.[65] Because the prevailing technique in this domain has been Monte Carlo simulation, the QMRA literature provides a useful region of research in which BN methods and model outcomes are compared to expected performance of MC simulation approaches. Beaudequin et al. provided a recent survey of 15 papers in this vein.[66] A number of key themes emerge from their review. First, BNs are used to simulate the effects of decisions, and to consistently characterize and reduce uncertainty across an entire interactive system rather than in a singly model output. (One particularly elegant demonstration of BNs' ability to absorb data to reduce network parameter uncertainty that is highlighted in the review was performed by Rigaux et al. They built a BN model to capture *Bacillus cereus* in zucchini puree, updated it using observations of actual bacterial concentrations, and found that approximately 25% of nodes updated strongly.[67] This updating would be difficult to impossible to achieve in an interactive way in a more traditional MC simulation model.) Bayesian network models are also used in data-sparse or data-poor environments (for example, where the only experimental evidence comes from small studies). Backwards diagnostic inference and simultaneous updating are also consistently cited as advantages. Finally, the clarity gained through BNs' intuitive visual representation of complex systems and their dependencies is also emphasized. As could be expected, discretization and computing power demands are cited as key disadvantages. The acyclicity of BN models is also mentioned, though this issue can be overcome by using dynamic Bayesian networks (at

significant computational cost) or by specifying nodes to correspond to long-term average behaviors within systems rather than short-term system responses.[68,69] These conclusions are confirmed in other studies.[70]

BNs have also seen significant use to understand complex interactive systems in the fields of ecology and ecological risk assessment. Particularly extensive work has been done in modeling aquatic environments. BNs have been used to assess progress in meeting water quality directives[71], and in exploring tradeoffs in water resource management.[72–75] BNs have also been used to describe the spread of disease[76] and the effects of chemical stress[77] in fish populations, as well as to model the factors driving fish population decline[78] and to inform fish stock management practices.[79,80] Finally, BNs have been used to assess best practices in monitoring and managing invasive species.[81–83] BNs have also seen application in assessing the interaction of human activity with aquatic ecosystems through connecting agricultural phosphorus concentrations to algal blooms[84,85] and examining eutrophication.[86,87] A thorough review of the merits of using BNs in environmental and resource management was conducted by Barton, Borsuk et al. in 2012.[88] Further analysis by Letcher, Borsuk et al. examined BNs as well as several other methods in environmental assessment and management applications. They identified several conditions (including prediction and decision-making under uncertainty) in which BN methods offer significant advantages.[89]

Risk assessment in engineering contexts has also seen application of Bayesian network modeling in the literature. Specific examples include how to assess and manage offshore oil and gas leaks (including how to prevent such accidents[90,91], model risks from tanker collisions[92], characterize the efficiency of oil-cleanup efforts[93], and minimize risks to sensitive

ecosystems[94]). Finally, researchers have also used BNs as the backbone of a proposed new method for assessing the environmental impact of hazardous chemicals[95] and to map out best practices in managing site cleanup.[96–98]

BNs have also been used to inform medical decision-making through diagnostic inference and decision support, being used, for example, to analyze the risk of developing cancer[99] as well as the process of accurately diagnosing it.[100] Many of the studies cited above in the survey of BNs' performance in classification tasks fall into this medical diagnostics category.

In spite of their demonstrated advantages in a number of fields, Bayesian network models have not yet been used in regulatory risk assessments of the benefits of environmental policies for public health. Their characteristics and their potential ability to respond to the need for advances in both dose-response assessment methods and the utility of risk assessment to decision-makers make a clear case for the investigation of BN model performance in these areas. The projects in this dissertation test whether Bayesian network models can help to advance dose-response assessment and the utility of risk assessment in support of environmental public health policy. By examining Bayesian network performance in these contexts, this dissertation offers a novel contribution to the environmental human health risk assessment literature.

4. Aims of this dissertation

In this dissertation, the potential of Bayesian network modeling approaches to respond to the NRC's call for improved dose-response and risk assessment methods is assessed. Ultimately, expanded use of Bayesian networks could shift the environmental risk assessment paradigm by enabling dose-response assessments to reflect nonlinear relationships; by

incorporating the ability to predict differences in responses for subpopulations with different metabolic, genetic, or other characteristics; by integrating data from multiple studies; and by providing diagnostic as well as predictive capability. In this dissertation, the potential usefulness of Bayesian networks in quantifying environmental risks to human health is illustrated through the use of BNs to solve three different risk assessment problems. The dissertation is novel in its quantitative comparison of BN models for dose-response assessment to established approaches. In addition, it adds to the as-yet very limited literature demonstrating the use of BNs in characterizing risks to support regulatory decision-making and improving risk assessment's utility to that process.

This dissertation has three specific objectives:

Objective 1: to develop a proof-of-concept BN capturing a dose-response relationship, and to test its performance in predicting incidence of health outcome against prevailing dose-response methods

Hypothesis 1: A BN model will have stronger predictive capability than a traditional regression model in predicting the risk of lower birthweight for gestational age as a function of arsenic exposure in drinking water and its metabolism.

Objective 2: to confirm the proof-of-concept model's findings, using a different health outcome, larger dataset, and expanded comparisons to existing methods; and to demonstrate how BN use can improve utility of the risk assessment process to risk management through population outcome simulation

Hypothesis 2a: A BN model will more accurately predict incidence of dysglycemia from demographic, arsenic exposure, and arsenic metabolism data than a reference dose model or logistic regression-based model.

Hypothesis 2b: A BN model incorporating a dose-response assessment can provide useful guidance for the development of environmental policy to protect public health through identification of at-risk subgroups and simulation of the effects of changes in population characteristics.

Objective 3: to illustrate the use of a BN model to support regulatory decision-making by developing a BN model to support decisions about the potential future regulation of discharge of hospital waste into municipal sewer systems during infectious disease outbreak conditions

Hypothesis 3: BNs can provide an easy-to-use interactive tool for supporting quantitative analysis of the potential health benefits of alternative regulatory scenarios while also providing diagnostic capability.

The next three chapters of this dissertation present the results of research toward each objective. In Chapter 2, a BN model is developed to predict the risk of lower birthweight for gestational age from available data. Models based on current dose-response assessment methods (reference dose and linear regression) are also developed. Out-of-sample prediction is assessed by measuring sensitivity and specificity. Superior performance is found in the BN model's performance, demonstrating the concept that BNs can capture dose-response relationships and confirming the hypothesis of superior performance over current methods (Hypothesis 1).

The performance of the BN method in dose-response assessment is tested in Chapter 3 through development of a different model with a different health outcome (dysglycemia), with a larger dataset and comparison to a more sophisticated logistic regression-based model in addition to a reference dose model. The superiority of BN performance in out-of-sample prediction is demonstrated through both single-point sensitivity and specificity, and receiver operating characteristic (ROC) curve comparison. The hypothesis of improved performance (Hypothesis 2a) is confirmed.

In addition, the BN model developed in Chapter 3 is used to investigate interactions in subgroups within the cohort, including the effects of arsenic metabolism in different body mass index (BMI) groups (normal, overweight, obese). A novel relationship between the effect of arsenic metabolism and BMI group is demonstrated. The BN is also used to simulate the effects of shifts in population characteristics – specifically, BMI and arsenic exposure through drinking water – on dysglycemia risk in the population, while maintaining the underlying dose-response model. These simulations are translated into public health consequences (cases of disease avoided) to inform policy. These applications of the BN model confirm Hypothesis 2b and show that BNs can be used to improve the utility of the risk assessment process to risk management decision-making in the environmental public health context.

A BN model is developed in Chapter 4 to calculate risk of developing Ebola virus disease in wastewater system workers through occupational exposure to contaminated wastewater. This model quantifies risk, including to different subgroups of workers. The model is used to diagnose key factors to which workers' risk is most sensitive, and simulation of policies through changes in these parameters (for example, the adoption of in-hospital waste disinfection) is

used to demonstrate the potential benefits of different regulatory scenarios at the level of individual workers and hospitals. This analysis confirms Hypothesis 3: that BN models can support regulatory decision-making through both their ability to easily simulate the effects of policy changes (forward inference) and to diagnose key drivers of risk (backwards diagnostics). Finally, Chapter 5 summarizes key findings and provides direction for future research.

5. Novelty and intellectual contributions of this dissertation

The projects within this dissertation constitute the first application of Bayesian networks to achieve the National Research Council's recommended improvements of dose-response assessment of chemicals in the environment. Chapters 2 and 3 demonstrate BN models' performance in dose-response contexts, and show how these models achieve predictive performance equal or superior to current methods while also fulfilling the NRC's criteria for improved dose-response modeling methods (equal applicability to cancer and non-cancer outcomes, consideration of susceptible subgroups, explicit characterization of uncertainty through probability, and ability to integrate dose-response for non-cancer outcomes with cost-benefit calculations).

In addition, this dissertation also constitutes a novel application of Bayesian networks to achieve the NRC's recommendations around improving the utility of risk assessment for decision-makers. Chapter 4 demonstrates the explicit integration of a risk assessment and risk management process through a BN, highlighting how BNs' characteristics (especially updating based on partial information and backwards diagnostic inference) achieve the iterative assessment-management process that the NRC has proposed. Chapter 3 also uses a BN model to simulate the effects of changes in population characteristics on health risk given an

underlying dose-response model, translating these effects into health consequences and informing decision-making around population-level health policy. This is the first time such a Bayesian network model has been used to quantify risk from a toxicant in the environment and link that dose-response assessment to public health decision-making outcomes.

In sum, this dissertation offers a novel demonstration that Bayesian networks can provide a platform for addressing critical limitations of risk assessment in support of U.S. environmental policy decisions designed to protect public health from environmental contaminants. The results obtained confirm BNs' hypothesized advantages in these contexts and provide direction for future research.

CHAPTER 2: ADVANCING DOSE-RESPONSE ASSESSMENT METHODS FOR ENVIRONMENTAL REGULATORY IMPACT ANALYSIS: A BAYESIAN BELIEF NETWORK APPROACH APPLIED TO INORGANIC ARSENIC[1]

1. Introduction

Every major new US environmental regulation must undergo cost-benefit analysis to establish whether anticipated public health and environmental gains outweigh regulatory costs.[101] If costs outweigh benefits, the Office of Management and Budget may return the proposed regulation to the Environmental Protection Agency (EPA) for modification or withdrawal.[102,103] In order to predict health benefits, cost-benefit analysts rely on dose-response functions. These functions predict the number of deaths and illnesses in a population exposed to contaminants. If dose-response functions are inaccurate, the resulting benefits estimates could be either too high, leading to inefficient regulations, or too low, leading to regulations insufficient to protect public health.

For most contaminants, dose-response functions used for regulatory impact analyses are based on decades-old data collected in studies of laboratory rodents or, in a few cases, human populations.[104,105] Dose-response functions for carcinogens assume a linear relationship between contaminant exposure and the lifetime probability of cancer. That is, to predict cancer risks, analysts multiply the estimated exposure dose by a constant known as the "cancer slope factor." For all regulations other than those involving ambient air quality, dose-response

[1] This chapter previously appeared as an article in Environmental Science & Technology Letters. The original citation is as follows: Zabinski, J.W. et al. "Advancing Dose–Response Assessment Methods for Environmental Regulatory Impact Analysis: A Bayesian Belief Network Approach Applied to Inorganic Arsenic*," Environ. Sci. Technol. Lett.*, 2016, 3 (5), pp 200–204.

assessments for non-carcinogenic effects are categorical: if the exposure dose is above a threshold known as the reference dose (RfD), then the exposed individual is assumed to be at risk, while exposures below the RfD are assumed to pose zero risk. These prevailing dose-response functions fail to incorporate modern biomedical data that have arisen from new analytical technologies, such as methods for sequencing DNA, analyzing DNA expression, and characterizing metabolic profiles. In addition, the approaches used for cancer and non-cancer health outcomes are inconsistent (the latter assuming a categorical response with a threshold and the former assuming a linear, no-threshold response). Due to these and other concerns, Congress has held hearings on and called for National Research Council reviews of EPA's processes for developing dose-response functions,[106] heightening the urgency of developing alternatives that can incorporate complex biomedical data while employing a consistent process for cancer and non-cancer risks.

We propose that Bayesian belief networks (BBNs) could provide a platform for developing dose-response functions that incorporate modern biomedical data. BBNs emerged from the artificial intelligence field in the 1980s as a means to support causal inference.[22] Although ecologists have long used BBNs in resource management and risk assessment,[107–110] to our knowledge BBNs have not been previously used in human health risk assessment for environmental regulatory applications. We demonstrate the development of a BBN-based dose-response model for analyzing the risk of lower birthweight for gestational age as a function of arsenic exposure via drinking water, metabolic data, and demographic factors. We parameterize and test our model using data from a cohort of 200 mothers and newborns in an

arsenic-endemic region of Mexico. We compare the BBN's predictive capability to that of prevailing dose-response assessment methods.

2. Materials and methods

2.1. Maternal birth cohort

To compare a BBN-based dose-response assessment approach to the prevailing RfD and slope factor approaches, we used maternal health, demographic, environmental exposure, and birth outcome data from the Biomarkers of Exposure to Arsenic (BEAR) prospective pregnancy cohort.[111] This cohort was recruited in 2011-2012 from Gomez Palacio, Mexico, where 400,000 people are exposed to high arsenic levels.[112] Participant recruitment methods are described elsewhere.[111]

For each participant, social workers collected information on age, education, smoking and alcohol consumption behaviors during pregnancy, seafood consumption, and sources of drinking and cooking water. Attending physicians reported infant birthweights and gestational ages at delivery. Maternal urine samples collected at delivery were analyzed for total, inorganic, and methylated arsenic as described in Laine et al. (2015).[113]

2.2. Birth outcome measure

Infants with birthweights below the 10th percentile for gestational age are typically classified as small for gestational age.[114] We calculated the small-for-gestational age cutoff values using a World Health Organization tool.[115] Using this definition, only 14 infants in the cohort were small for gestational age. Due to the small sample size, we developed dose-response models to predict the probability that the birthweight-to-gestational-age (BWGA)

ratio was below the 25th percentile, an outcome that we designate as "lower BWGA." Of the 200 infants, 57 were designated as lower BWGA.

2.3. Reference dose approach

Current US environmental policies define the RfD for assessing non-carget risks as[116]

$$RfD = \frac{NOAEL}{UF_{inter} * UF_{intra} * UF_{other}} \quad (8)$$

where NOAEL is the no observable adverse effects level (the largest dose at which no statistically significant effects are observed) and the *UF*s are uncertainty factors accounting for interspecies extrapolation, intra-species differences, and uncertainty sources. The current arsenic RfD, 0.3 µg arsenic/(kg body weight-day), was derived from 1968 data on hyperpigmentation and keratosis incidence in a Taiwanese population exposed to arsenic in drinking water.[117] Because this RfD does not consider birth outcomes, we computed an RfD for the BEAR cohort using Equation 1. Consistent with the current RfD, we assumed UF_{inter}=UF_{intra}=1 and UF_{other}=3.[14] In addition, we compared the BBN-based approach with the current regulatory RfD. For both analyses, we assumed that pregnant women drink 0.872 liters/day and weigh 75 kg.[118] All women exposed at levels above the RfD were assumed to be at risk of delivering an infant with lower BWGA. Sensitivity and specificity were estimated by comparing the resulting assignment of risk status to the true birth outcome for each participant.

2.4. Slope factor approach

The current arsenic slope factor, 1,500 kg-day/µg, was developed from data collected in 1968 and 1977 on skin cancer prevalence as a function of arsenic exposure in the previously

mentioned arsenic-endemic region of Taiwan. Because this slope factor is not applicable for estimating adverse birth outcomes, we estimated a slope factor for lower BWGA risk using the BEAR cohort. Consistent with the general approach for estimating cancer risk slope factors, we computed a maximum likelihood estimator (using Stata) by regressing BWGA against inorganic arsenic exposure concentration in drinking water along with other covariates (total maternal urinary arsenicals, maternal urinary monomethylated arsenic, age, education, alcohol and seafood consumption during pregnancy, smoking during pregnancy, and infant gender). Covariates were chosen based on a prior BEAR cohort analysis.[111] BWGA and all covariates measured on continuous scales were treated as continuous. We tested sensitivity and specificity using via leave-one-out cross-validation: each cohort member was removed from the data set, a regression model was fitted to the remaining 199 members, the model was used to predict BWGA for the corresponding test subject, and this estimate was converted to an indicator of lower BWGA status and compared against the case's true status.

2.5. BBN approach

A BBN that predicts lower BWGA from the same covariates used in the regression model for the slope factor analysis was constructed using BayesiaLab (Laval, France) software. To the explanatory variables in the regression model, we added urinary inorganic and dimethylated arsenic, which were excluded from the regression model due to multicollinearity. In brief, a BBN is a probabilistic model represented as a directed acyclic graph in which nodes are variables and edges represent causal dependencies.[22,119] A fully parameterized BBN represents the joint probability distributions among the variables. Our team's biomedical experts developed the BBN structure based on known or suspected mechanisms through which

ingested inorganic arsenic is converted to potentially hazardous arsenic metabolites. The BEAR cohort data were then used to parameterize the model. All BBN variables were discretized (Table 3). We calibrated the posterior probability threshold above which lower BWGA status is assigned to maximize sensitivity first and then specificity. Sensitivity and specificity were tested using a leave-one-out cross-validation approach, in which the BBN was fitted to 199 cases and its prediction of lower BWGA status in the remaining case was compared to the case's actual status.

Table 3. Nodes in the Bayesian belief network.

Title	Name	Units	States and Prior Distributions
Maternal Education	*edu*	[categorical]	[college, highschool, none]; [0.205, 0.540, 0.255]
Mother's Age	*age*	years	[[0,22], (22-29], >29]; [0.480, 0.355, 0.165]
Drinking Status	*drink*	[categorical]	[no, yes]; [0.790, 0.210]
Smoking Status	*smoke*	[categorical]	[no, yes]; [0.925, 0.075]
Seafood Consumption	*fish*	[categorical]	[no, yes]; [0.775, 0.225]
Infant Gender	*sex*	[categorical]	[female, male]; [0.480, 0.520]
Arsenic in Tap Water	*dwias*	µg/L	[[0, 19.282], (19.282, 105.591], >105.591]; [0.585, 0.260, 0.055]
Total Arsenic in Urine	*utas*	µg/L	[[0, 31.115], (31.115, 79.291], >79.291]; [0.625, 0.295, 0.080]
Urinary Arsenic as IAs	*ias*	µg/L	[[0, 1.536], (1.536, 4.143], >4.143]]; [0.595, 0.310, 0.095]
Urinary Arsenic as MMAs	*mmas*	µg/L	[[0, 1.869], (1.869, 5.05], >5.05]; [0.650, 0.250, 0.100]
Urinary Arsenic as DMAs	*dmas*	µg/L	[[0, 27.938], (27.938, 70.531], >70.531]; [0.635, 0.290, 0.075]
Birthweight for Gestational Age	*bwga*	g/weeks	[lower, normal, higher]; [0.285, 0.430, 0.285]

3. Results and discussion

3.1. Fitted models

To estimate an RfD relating lower BWGA risk to arsenic exposure, we divided the LOAEL in the BEAR cohort (0.461 µg/liter, the detection limit) by an uncertainty factor of three, resulting in an RfD of 0.00179 µg/kd-day. This estimated RfD is more than two orders of

magnitude less than the current US regulatory RfD of 0.3 µg/kg-day, which is based on skin hyperpigmentation and keratosis.

To estimate a model consistent with the slope factor approach, we used a multivariate linear regression to predict BWGA from the inorganic arsenic concentration in drinking water and other covariates summarized in Table 4. Consistent with prior research on this cohort,[111] the urinary concentration of monomethylated arsenic was highly significant (p=0.003), and the drinking water arsenic concentration was marginally significant (p=0.107) (Table 4).

Table 4. Summary statistics and regression coefficients for variables in regression dose-response model.

Variable	**Counts**	**Mean**	**Range**	**Regression Coefficient**	**Variable p-value**
Birthweight divided by gestational age (g/weeks)	-	85.0	[52.9, 128]	-	-
Mother's age (years)	-	24.0	[18, 41]	0.39*	0.01
Completed high school	149 yes; 51 no	-	-	-2.02	0.321
Completed university	41 yes; 159 no	-	-	1.10	0.567
Occasional or frequent smoker	15 yes; 185 no	-	-	-5.48	0.108
Occasional or frequent consumer of alcohol	42 yes; 158 no	-	-	2.22	0.251
Arsenic in drinking water (µg/L)	-	24.6	[0.33, 235.55]	0.04	0.107
Total arsenic metabolites in urine (µg/L)	-	35.5	[1.89, 488.20]	0.04	0.209
Monomethylated arsenic in urine (µg/L)	-	2.28	[0.07, 25.46]	-1.10**	0.003
Occasional or frequent consumer of seafood	45 yes; 155 no	-	-	-1.39	0.485
Newborn is male	104 yes; 96 no	-	-	4.96**	0.003

Number of observations:	200
F(10, 189):	2.6
p-value:	0.0056
R^2 value:	0.1224

We fit a BBN model to predict lower BWGA status as a function of the same variables used in the regression model plus two additional descriptors of maternal arsenic metabolism (inorganic and dimethylated arsenic concentrations in urine) that could not be included in the regression model due to multicollinearity (Figure 6).

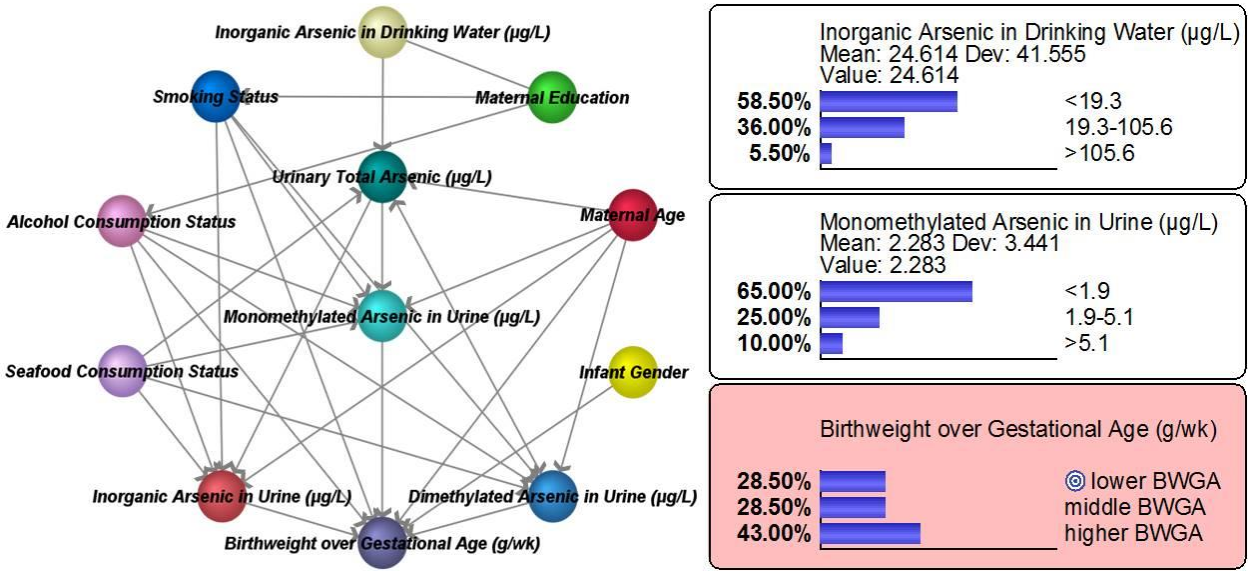


Figure 6. Bayesian belief network model for predicting the risk of lower birthweight for gestational age as a function of maternal arsenic exposure, arsenic metabolism, and behavioral and demographic factors.

The lowest node predicts birthweight divided by gestational age (BWGA) as a function of all of the other variables in the network; the target symbol indicates that the lower BWGA node state is the outcome of interest. The corresponding belief bars show probabilities of lower BWGA (< 25th percentile), middle BWGA (25th–75th percentile), or higher BWGA (>75th percentile) conditional on baseline states of the other nodes. Underlying all nodes are conditional probability tables fitted to the data set used in this study. Updated predictions of BWGA can be obtained by specifying the state of any node or set of nodes, and by performing the necessary probability calculus. While a number of nodes influence BWGA directly, several others' effects are mediated by intermediates. The choice of structure was made to elicit predictive power while also maintaining biological plausibility.

A sensitivity analysis showed mother's age, infant gender, and urinary concentration of monomethylated arsenic have the greatest information value for predicting BWGA status (Figure 7).

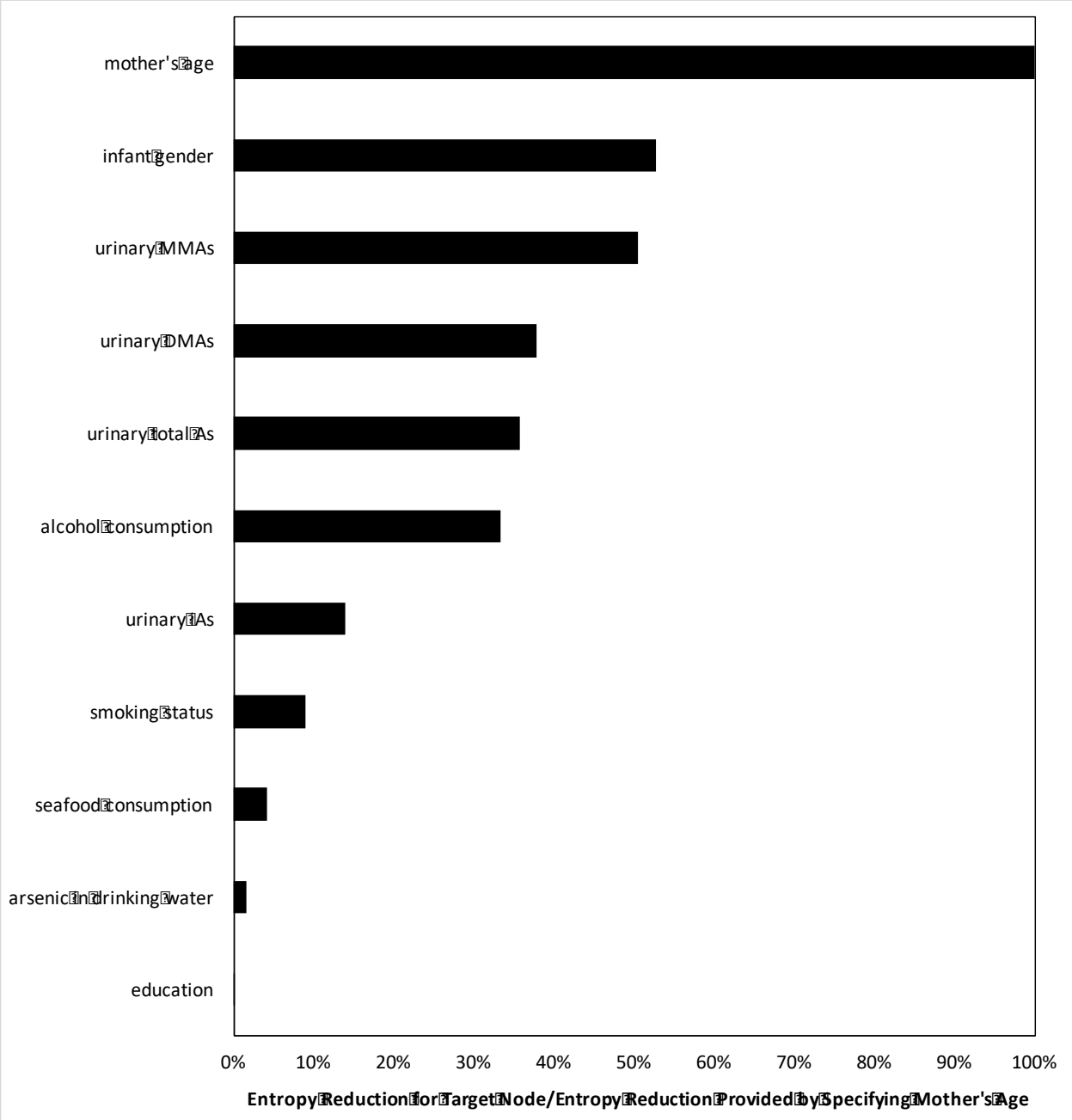


Figure 7. Relative sensitivity of birthweight over gestational age to network nodes calculated using reduction in entropy.

Values above represent the magnitude of entropy reduction relative to the greatest such reduction achieved.

3.2. Model sensitivity and specificity

The RfD derived from the BEAR cohort predicted that every infant was in the lower BWGA category. Sensitivity and specificity were therefore 100% and 0% (Figure 8). In contrast, using EPA's current RfD (28.6 µg/L), sensitivity and specificity were 25%, and 73%, respectively (Figure 8). Therefore, the current RfD misclassified 75% of lower BWGA cases.

The slope factor approach also yielded skewed results. Though the data set contained 57 lower BWGA cases, the regression predicted three such cases (and of these three, only one was an actual case). The corresponding sensitivity and specificity were 2% and 99%, respectively. In contrast to the other methods, the BBN achieved a more even balance between sensitivity (71%) and specificity (30%; Figure 8).

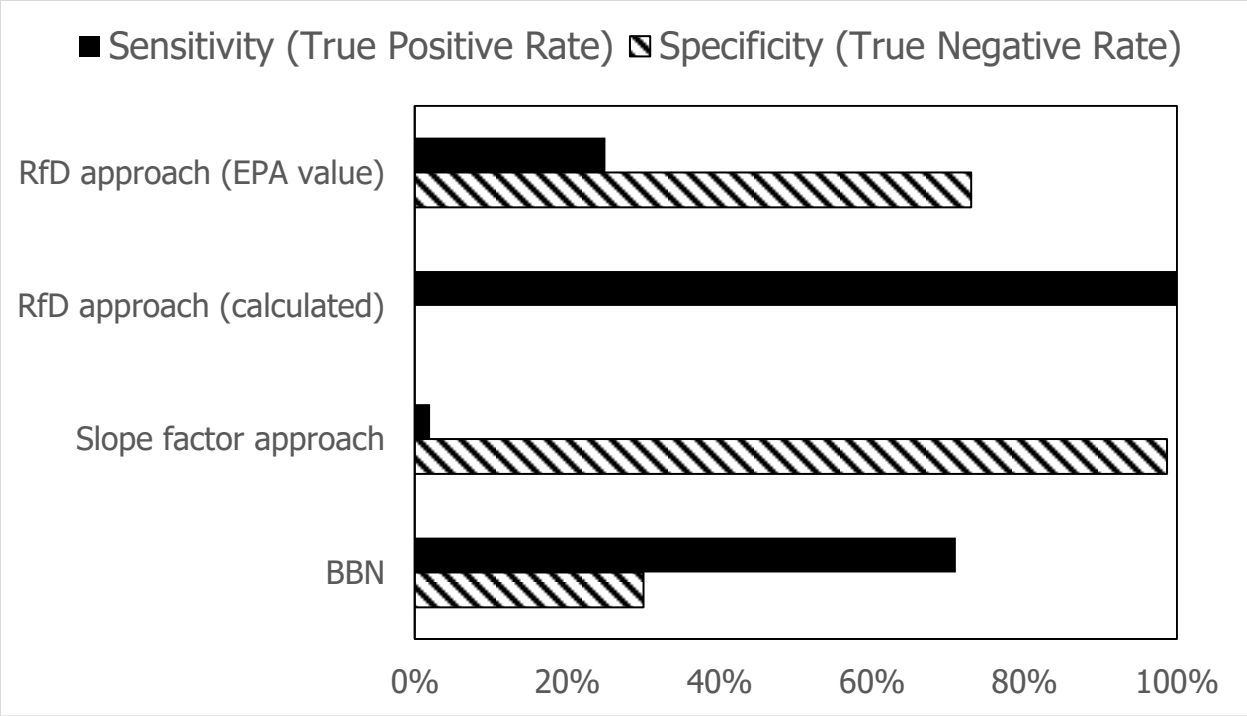


Figure 8. Sensitivity and specificity of alternative dose-response functions for predicting lower birthweight for gestational age. RfD=reference dose; BBN=Bayesian belief network.

As a sensitivity analysis of model performance, cross-validation was repeated with 10% of the data used as a testing set. The BBN model still outperformed the other methods in balancing sensitivity and specificity. The sensitivities of the RfD, regression, and BBN models were 100%, 2%, and 65%, respectively; specificities were 0%, 98%, and 29%.

3.3. Relevance

Accurate risk assessment requires methods that balance the public health costs of false negatives with the potential excess regulatory costs of false positives. As demonstrated, our BBN model outperformed the RfD and slope factor methods in balancing sensitivity and specificity when predicting lower birthweight risk as a function of inorganic arsenic exposure in water. Specifically, the BBN achieved higher sensitivity (71%) than the slope factor approach (2%) and higher specificity (30%) than the RfD approach (0%). Furthermore, unlike the RfD

approach, the BBN also was able to incorporate data on maternal arsenic metabolism, thought to be an important factor in fetal risk.[111] Unlike the slope factor model, the BBN included multiple, correlated measures of maternal metabolism.

We hypothesize that the BBN outperforms the conventional methods for several reasons. The binary RfD approach cannot account for covariates or metabolic factors affecting infant risk. While the regression model includes metabolic indicators and demographic variables, its ability to do so is limited by the requirement of independence among predictors, the assumed linear relationship between BWGA and predictors, and limited ability to detect complex interactions.[120] The regression model's low R^2 (0.122) indicates its limited predictive power. The BBN, in contrast, is distribution-free and can account for linear and nonlinear relationships (or even relationships that may have both linear and nonlinear regions) along with correlations and complex interactions among predictor variables.

Although this work represents the first comparison of BBN-based and prevailing methods for human health dose-response assessment in an environmental context, a number of previous studies have compared BBN performance to that of prevailing predictive methods. For example, multiple studies have explored the capability of BBNs to predict health outcomes under alternative medical treatment regimes.[121–126] Similar to in our study, many of these studies found that BBNs outperformed conventional prognostic methods. As an example, Forsberg et al. (2011) demonstrated that a BBN outperformed conventional approaches in estimating survival in patients with operable skeletal metastases.[126] In addition, other studies of medical outcomes have compared the performance of BBNs to that of regression models and found BBN performance comparable to or better than that of regression approaches. As an

example, Stojadinovic et al. found that a BBN for estimating healthcare outcomes in severely wounded veterans was comparable in predictive capability to a logistic regression model.[123] Despite their comparable performance, the authors recommended use of the BBN over regression because it was able to reveal associations between factors that were not evident in the regression and because its intuitive graphical structure could help clinicians understand causes of alternative health outcomes. In addition to medical applications, applications in ecological risk assessment have demonstrated superior performance of BBNs in comparison to traditional methods. As an example, Walton and Meidinger (2006) found that a BBN method for classifying ecosystem types in mapping applications outperformed the prevailing approach, which was based on expert review of various ecosystem measures.[127] This evidence suggests that BBNs deserve further consideration for dose-response modeling, due to both their intuitive structure and their powerful analytic capabilities.

The major limitation of this study is the small size of the data set. In addition, the newborns in this cohort were generally of healthy weight, perhaps due to the "Mexican paradox," the tendency for Mexican newborns to be at lower risk for underweight birth than expected from demographic data.[128] Nonetheless, our model was more effective than both prevailing methods in classifying cases according to lower BWGA status. Future research with larger cohorts and/or additional variables representing the mechanisms through which arsenic acts on BWGA should improve model performance.

We have demonstrated that a BBN model outperforms prevailing RfD and regression-based slope factor approaches in predicting birthweight outcomes from arsenic exposure and maternal metabolic data. The BBN achieves this superior performance by incorporating

information in a nonlinear, nonparametric structure that offers greater freedom than traditional approaches. In addition, the organization of the BBN is visually intuitive: relationships between variables are mapped clearly, and the structure lends itself to the development of risk assessment tools that may be more user-friendly than those currently available. Unlike the separate RfD and slope factor approaches, the BBN model also offers a unified and consistent way of assessing both cancer and non-cancer risks. Perhaps most importantly, BBNs allow for the incorporation of modern biomedical data into dose-response functions, offering a promising opportunity for advancing dose-response assessment and health environmental regulatory impact analysis.

CHAPTER 3: DOSE-RESPONSE ASSESSMENT AND PREVALENCE SIMULATION OF ARSENIC-MEDIATED DIABETES AND PREDIABETES THROUGH BAYESIAN NETWORK MODELING

1. Introduction

Regulatory risk assessment requires dose-response models that accurately link exposure to toxicants to the probability of adverse health outcomes. In current U.S. practice, different dose-response models are used by regulatory agencies depending on whether the health outcome of interest is a form of cancer or is a non-cancer illness. For non-cancer outcomes, dose-response models are binary: they assume a threshold (called the "reference dose," denoted RfD) above which risk is presumed present and below which it is presumed absent.[129] This approach does not allow for the computation of a quantitative risk measure that can be used in comparing health benefits of programs to reduce toxicant exposure. Rather, it provides only a binary "safe" or "might not be safe" categorization. On the other hand, for cancer outcomes, the risk of cancer is assumed to be a linear function of dose with no safe threshold.[8] The cancer approach assumes that this linear function can be used to estimate the probability of cancer in an exposed population. This probability, in turn, is used to quantify the number of cancer cases that could be prevented by decreasing toxicant exposure. The estimated number of cases avoided is then converted to an economic measure of the health benefits of the proposed preventive program.

In 2009, the National Research Council (NRC) published a report (*Science and Decisions: Advancing Risk Assessment*) reviewing current risk assessment practices and recommending ways in which risk assessment could be improved.[6] As part of this process, the NRC identified

several key needed improvements to dose-response modeling methods. First, and most important, a unified approach to both cancer and non-cancer outcomes is needed. The NRC recommended that this unified approach produce a quantified risk measure that can be used in cost-benefit analysis, pointing out that "the end products of non-cancer . . . . assessments in the current paradigm . . . are inadequate for benefit-cost analyses or for comparative risk analyses." The report concluded, "Separation of cancer and non-cancer outcomes in dose-response analysis is artificial [and] . . . leads to undesirable risk-management outcomes, including inadequate attention to non-cancer end points, especially in benefit-costs analyses." Second, modeling approaches that can capture nonlinear relationships are needed. The NRC noted that the EPA's default approach for capturing nonlinearity is to assume a safe threshold dose, below which risks are negligible. Finally, the NRC recommended, dose-response models should "characterize individuals and subgroups according to whether they have co-exposures to key nonchemical stressors, specific polymorphisms influencing metabolism or DNA repair, pre-existing or endogenous disease processes, high background endogenous or exogenous exposures, and other determinants of increased susceptibility."

We propose that Bayesian network (BN) models can respond to these challenges. Bayesian networks are directed acyclic graphs, representing variables as nodes and relationships among them as arcs. They emerged in the computer science field in the 1980s to elucidate causal inference in complex systems[21] and have been used increasingly to support prediction across a range of fields, from medical diagnostics[46,47,55] to engineering safety assessment.[92,94,130] Because BN models express relationships among variables through conditional probability tables, they do not require assumptions of functional form imposing an

assumed relationship (like linear dependency) between inputs and outputs. In addition, they can simultaneously incorporate multiple different data types, potentially including biological endpoints such as genes expression, protein expression, metabolite level, and other data derived from multiple sources in order to represent variability in individual susceptibility. Indeed, prior evidence from other fields suggests that BNs offer advantages over other methods in prediction and in eliciting causal relationships among variables in complex systems [47,48,66,121,131,132] BNs' ability to represent complex, nonlinear relationships and to incorporate diverse data types, in addition to previous evidence of their predictive accuracy, make them particularly promising tools for conducting dose-response assessment. However, to our knowledge, only a single study by our own research group has assessed BN performance in predicting observable health outcomes from doses and metabolism of environmental contaminants.[133] In that study, we demonstrated the capability of a BN to predict the risk of lower-birthweight for gestational age due to arsenic exposure in drinking water, considering inter-individual metabolic and dietary variability, and showed that the BN outperformed a quasi-linear regression model. The model was constructed from a modest (n=200) data set from an arsenic-endemic region of Gómez Palacio, Mexico.

In this work, we build on our prior research by comparing the performance of a BN model to current dose-response methods in predicting incidence of dysglycemia (defined as the presence of either diabetes or prediabetes) from exposure to arsenic in drinking water, arsenic metabolism (indicated by the proportions of methylated metabolites of inorganic arsenic), and demographic data. The present paper uses a larger data set (n=1050) than our prior research and considers co-morbidity data, along with metabolic differences. Our work also builds on

prior research establishing an association between incidence of dysglycemia and exposure to and metabolism of inorganic arsenic.[134] We compare the performance of the BN model in predicting dysglycemia to the prevailing reference dose approach and to a quasi-linear no-threshold approach consistent with current EPA methods for assessing cancer risks. We use the network to gain new insights about potential mechanisms affecting dysglycemia risks from arsenic exposure. In addition, we assess the potential effects of a BN approach on regulatory decision-making by comparing health benefits (bladder cancer cases avoided) estimated by the current approach to those estimated using a BN approach (diabetes cases avoided).

2. Methods

Analysis proceeded in several steps (Figure 9). First, several models were developed using data from a study cohort to predict incidence of dysglycemia. These models were trained on a subset of the data and their predictive performance was tested on the remaining subset. Then, the BN was used to simulate the effects on dysglycemia risk and prevalence of changes in arsenic exposure through drinking water. The results of these simulations were assessed to quantify benefits to public health. Finally, the Bayesian network dose-response model was used to investigate sub-populations (based on gender, age, and body mass index category) for novel interactions among variables not previously discovered in the data. Simulations within these subpopulations were conducted to further explore these interactions.

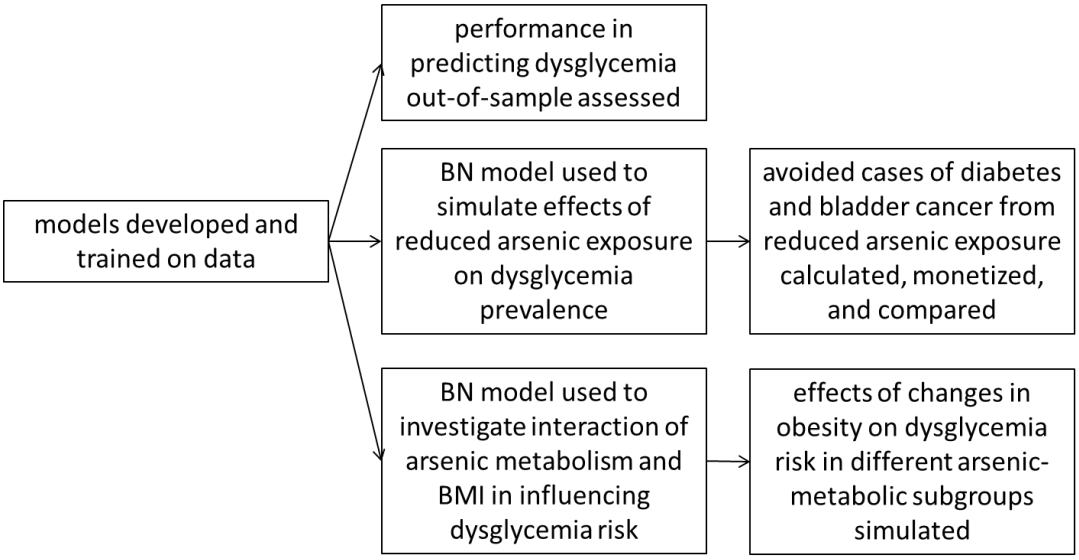


Figure 9. Conceptual model of analytical steps.

2.1. Cohort

Dose-response models predicting dysglycemia and related health indicators as a function of arsenic exposure in drinking water were fitted to data from a previously established cohort of 1050 adults from an arsenic-endemic region of Chihuahua, Mexico.[134–136] Participants were recruited between 2008 and 2012, and demographic information (gender, age, smoking, alcohol consumption, etc.) was collected during home visits.[134] Samples of subjects' drinking water were gathered and analyzed for inorganic arsenic concentrations. In addition, samples of subjects' urine were analyzed to quantify levels of arsenic metabolites (inorganic, monomethylated, and dimethylated arsenic) present. Taken together, these values constitute an individual's arsenic metabolism profile. Details on data collection, drinking water analysis, and urinary analysis are available in Mendez et al (2016).[134]

2.2. Outcomes of interest

Prior work on this dataset showed associations between certain cardiometabolic function indicators and subjects' arsenic metabolism profiles. In particular, higher levels of

dimethylated arsenic and lower levels of monomethylated arsenic corresponded to increased risk of dysglycemia (diabetes or prediabetes).[134] Dysglycemia was chosen as the outcome of interest for this dose-response assessment. Following the definitions in Mendez et al., subjects were classified as diabetic if fasting plasma glucose exceeded 126 mg/dL or 2-hour plasma glucose exceeded 200 mg/dL, or if diabetes diagnosis or use of diabetes medication was reported by the subject. Subjects were classified as prediabetic if fasting plasma glucose exceeded 110 mg/dL or 2-hour plasma glucose exceeded 140 mg/dL. All diabetic and prediabetic subjects were classified as dysglycemic, and all others were classified as normoglycemic.

2.3. Testing-training methodology and performance metric

All models were trained using randomly selected subsets comprising 75% of the available dataset (the 'training set'). Out-of-sample prediction of dysglycemic status was then conducted on the remaining 25% of the dataset (the 'testing set'). For each model, this process was repeated ten times, and performance was averaged. Model performance in predicting dysglycemia was quantified through sensitivity (true positive rate) and specificity (true negative rate).

2.4. Reference dose method

In current regulatory practice, the EPA calculates a reference dose (RfD) when performing dose-response analysis with a non-cancer health outcome.[10] To determine the RfD, a point of departure (POD) is first determined using available data; the POD can be the lowest observed adverse effect level (LOAEL) – the lowest level of toxicant at which the health change under assessment is detected. The POD is then divided by uncertainty factors to account for

uncertainty to arrive at the RfD.[10] In this form of dose-response model, risk is assumed absent at exposures below the RfD, and present at exposures above it.

To calculate a reference dose, a point of departure was first determined from the training set. The LOAEL of arsenic in drinking water at which dysglycemia was observed was at the limit of detection (0.005 μg/L) in nine of ten training sets studied, and was 0.01 μg/L in the tenth. These LOAEL values were averaged to generate a POD of 0.006 μg/L. Divided by an uncertainty factor of 3 (the factor used in the current EPA arsenic reference dose calculation to account for uncertainty in reproductive toxicity) yielded a reference dose of 0.002 μg/L.

The EPA has developed an alternate method of determining a POD for RfD calculations in an attempt to incorporate more information into the RfD. This alternate POD is a benchmark dose (BMD), and is calculated by fitting a model of assumed functional form (linear, exponential, etc.) to available data. The fitted model is then used to determine the dose that will generate a given response (for example, a 10% increase in the level of a particular biological indicator).[10] In developing the RfD model, derivation of a BMD to use as a point of departure was also attempted, consistent with preferred EPA risk assessment practice. However, the dataset was unsuitable for this kind of analysis due primarily to the absence of dose groups.[137] Attempts to cluster subjects into dose ranges based on arsenic exposure through drinking water did not yield meaningful or consistent benchmark doses.

2.5. Regression method

Multiple logistic regression was used to predict presence or absence of dysglycemia in subjects from exposure to inorganic arsenic in drinking water and arsenic metabolism; this approach is conceptually consistent with EPA's current approach for cancer dose-response

assessment, in which a linear relationship between dose and probability of developing cancer is assumed.[8] Arsenic metabolism was characterized by dimethylated arsenic as percent of total arsenic metabolites in urine (PCTDMA), as well as the ratio of urinary dimethylated arsenic to urinary monomethylated arsenic (DMA:MMA ratio). Regressions initially controlled for the other factors used in Mendez et al. (age, gender, education, ethnicity, smoking, alcohol consumption, body mass index (BMI), drinking water source (well, plant, other), and seafood consumption. Following Mendez et al., arsenic concentration in drinking water as well as DMA:MMA ratio were log-transformed to improve normality. Due to collinearity, PCTDMA and DMA:MMA ratio could not be included in the regression model simultaneously. Because DMA:MMA ratio captures information on both dimethylated and monomethylated arsenic, the model using it as the marker of arsenic metabolism was used for subsequent analysis. Backward-selection was used to determine a subset of variables to use for predictive modeling based on lowest AIC and BIC scores (inclusion threshold $p<0.1$). The variables selected were age, BMI, elementary, ≥highschool, water_source_plant, ln(DMA:MMA ratio), and ln(water arsenic) (μg/L). Forward-selection using the same inclusion threshold was conducted as a sensitivity test, and yielded the same subset of variables.

2.6. Bayesian network model

A Bayesian network model was constructed using BayesiaLab (Version 6, Laval, France). A node indicating dysglycemia (presence or absence) was used as the target for analysis. All explanatory variables used in the regression model were used in the BN model. Nodes corresponding to naturally categorical variables (gender, smoking, alcohol consumption, etc.) were discretized into states corresponding to these categories. Continuous nodes were initially

discretized into seven states each using BayesiaLab's multivariate LogLoss-GenOpt algorithm, which assigns state boundaries to minimize the difference between the envelope of the discretized states and the shape of the underlying distribution. Analysis was repeated using re-discretization of continuous variables into six, then nine, states but did not lead to substantial improvements in predictive performance.

The model's structure and joint probability tables were then learned from the training set using an augmented naïve Bayes algorithm. This is a modified version of the well-known naïve Bayes algorithm, in which the conditional probability of each state of each non-target variable is first learned from training data given a state of the target variable under an assumption of conditional independence among non-target variables. Then, Bayes' Rule is used to compute the posterior probabilities of states of the target variable given values of the non-target variables.[138] In this project, the algorithm used augmented the basic naïve Bayes procedure by relaxing the assumption of conditional independence among non-target variables to allow for the discovery of dependencies among these variables. This algorithm is itself a relaxation of the tree-augmented naïve Bayes algorithm, which also allows for discovery of relationships among non-target variables under the assumption of tree structure (in which each node, except one without parents, has exactly one parent).[37] Removing the requirement of tree structure adds computational complexity because of the need to search over the variable space for dependencies, but results in better predictive power on testing sets.

Once learned, sensitivity and specificity of predictions were computed. To assess the relative influence of different factors on probability of dysglycemia, mutual information between dysglycemia and the non-target variables was determined. This metric is used

frequently in Bayesian network analysis and quantifies the reduction in uncertainty of the target variable (*Y*) gained through knowledge about the non-target variable (*X*):

$$mutual\ information\ (X,Y)$$
$$= \sum_{x,y} p(X,Y) log\left[\frac{p(X,Y)}{p(X)p(Y)}\right] = \sum_{x} p(X) \sum_{y} p(Y|X)\ log\left[\frac{p(Y|X)}{p(Y)}\right] \quad (9)$$

Interested readers can find more information on this metric from Nicholson and Jitnah.[139]

2.7. ROC curve analysis

To compare the predictive capability of the logistic regression and BN models, receiver-operating characteristic (ROC) curves were used. ROC curves offer a graphical representation of the tradeoff between sensitivity and specificity in models and are useful for evaluating model performance over a range of discrimination thresholds, rather than at a single point.[140] The curves are generated by plotting sensitivity against 1-specificity. Model performance can be assessed by computing the area under the ROC curve (AUC); a naïve model would have an AUC of 0.5, and models that gain more than one incremental unit of sensitivity for each unit of specificity lost generate curves with AUC values >0.5. To examine the performance of the regression and BN models, ROC curves were generated for each. (As the reference dose approach outputs a binary prediction for dysglycemia, rather than a probability, a ROC curve cannot be generated for it.)

2.8. Effects on dysglycemia risk of changing population characteristics

To provide additional insights about interactions among arsenic exposure and other factors affecting dysglycemia risk, the Bayesian network model was used to study scenarios in which population characteristic changes were simulated. Holding the percentage of the

population with overweight BMI (25 kg/m^2 – kg/m^2) constant, the percentages of the population with obese BMI (>30 kg/m^2) and normal BMI ($\leq$ 25 kg/m) were adjusted by ten percent from their baseline levels to simulate the effect of individuals moving from one category to the other. Prevalence of dysglycemia was observed under these simulated scenarios. This analysis was then repeated after restricting the population to individuals with DMA:MMA ratio values in the lowest and highest quartiles.

Finally, the BN model was used to simulate the effects on predicted dysglycemia prevalence in the Mexican population of changes in exposure to inorganic arsenic through drinking water. Age distribution and gender ratio were first adjusted to correspond to the population (the study group was significantly more female, and slightly older, than the Mexican population). The distributions of these nodes, as well as other non-target nodes not causally affected by changes in arsenic exposure, were then fixed. The thresholds between states in the arsenic in drinking water node were changed to 10 μg/L, 25 μg/L , 50 μg/L, 100 μg/L, 150 μg/L, and 200 μg/L, and predicted dysglycemia prevalence in the simulated population was then observed. Next, people in the highest category of arsenic exposure (>200 μg/L) were distributed among the remaining states to simulate the effect of eliminating cases of exposure above 200 μg/L. The corresponding predicted dysglycemia prevalence was observed. This procedure was repeated, successively eliminating all cases above 100 μg/L, above 50 μg/L, above 25 μg/L (the current Mexican national guideline value[141]) and finally above 10 μg/L (the current U.S. standard and World Health Organization recommendation[141]). At each stage, predicted dysglycemia prevalence was observed. Details on the characteristics of the simulated Mexican population are available in the Supporting Information file.

2.9. Calculation of bladder cancer and diabetes cases avoided

The National Water Commission of Mexico estimated that approximately 1.3 million people live in area with high levels of arsenic in drinking water in the states of Durango, Chihuahua, and Coahuila.[142] The BN model was used to estimate changes in bladder cancer and diabetes prevalence in this population to demonstrate BN utility in translating dose-response relationships to changes in public health through policy.

Predicted dysglycemia prevalence under the scenario in which all exposure was below the current Mexican standard was used to estimate the number of cases of diabetes avoided, assuming that half of avoided dysglycemia cases were diabetes (the ratio in the study group). Because regulatory policy on arsenic in drinking water has focused on bladder cancer cases avoided, estimates of reduction in bladder cancer prevalence under the same scenario were also determined using EPA methodology.[4] See the Supporting Information file for calculation details.

2.10. Monetized health benefits calculation

Monetized benefits of reductions in bladder cancer and diabetes incidence were calculated using the same process employed by EPA to estimate these benefits in proposing a standard for arsenic in drinking water. In its proposed reduction of the arsenic standard, EPA valued each premature death due to bladder cancer at $6.06 million; each nonfatal case was valued at $178,405 based on cost-of-care data (1999 dollars).[4] To calculate monetized benefits of avoided cases of diabetes, the same value of premature death was used. Dall et al. estimated an annual cost of $9677 for treatment of diabetes; discounting 15 years of treatment (based roughly on average life expectancy from diagnosis) at a rate of 3% provides a present value of

$118,989 (2007 dollars).[143,144] These values were adjusted to 2017 dollars using an annual inflation rate of 2% (Table 5).

Table 5. Values of nonfatal cases for bladder cancer and diabetes.

	Bladder cancer		Diabetes	
	1999 dollars	2017 dollars	2007 dollars	2017 dollars
Value of nonfatal case	$178,405	$254,806	$118,989	$145,047

EPA estimated a 20-year mortality rate of bladder cancer at 26%. A similar value for diabetes is difficult to determine due to the interaction of diabetes with other health conditions in causing death, but for this calculation, 11% was used based on available literature.[145,146] Combining these estimates yielded present values from avoided cases of bladder cancer and diabetes in the population studied.

2.11. Interactions between arsenic exposure and other diabetes risk factors

In order to examine interactions among arsenic exposure and other factors affecting diabetes risk, the BN model was also used to examine the association between arsenic metabolism and multiple dysglycemia-associated health outcomes (dysglycemia, fasting plasma glucose and 2-hour plasma glucose) within population subgroups. The association was studied in subgroups generated by specifying gender, age category, and BMI category. For each parameter, the model was first restricted to consider only subjects within a certain subgroup (for example, only females). Null hypotheses of statistical independence between the dysglycemia-associated target variable and arsenic metabolism variables (PCTDMA and DMA:MMA ratio) were then tested using G-tests.[147] Analysis was repeated using re-discretizations of continuous variables into six, then nine, states to ensure results were not due only to discretization choices.

3. Results

3.1. Fitted models

To compare the performance of a Bayesian network dose-response model to prevailing reference dose and regression approaches for predicting health risks of exposure to arsenic in drinking water, models based on all three approaches were fitted to arsenic exposure and health outcome data from a cohort of 1,050 adults in an arsenic-endemic region of Chihuahua, Mexico.

For the reference dose approach, a reference dose (RfD) 0.002 μg/L was calculated using a point of departure of 0.006 μg/L (the lowest exposure level at which dysglycemia was present in the data) and an uncertainty factor of 3. This uncertainty factor is used in the current EPA assessment to account for a lack of information on arsenic's potential reproductive toxicity as well as individual susceptibility. While determined in a consistent manner, the RfD is substantially lower than the current EPA drinking water standard (10 μg/L).

In the regression approach, logistic regression models were used to predict dysglycemia from data on arsenic exposure in drinking water, arsenic metabolism, and control variables. Variables for inclusion were selected using backward-selection. The model indicated a marginally significant positive association between arsenic exposure through drinking water and dysglycemia (p=0.065), and predicted a 6% increase in the odds of dysglycemia for every natural log-unit increase in arsenic concentration in water (Table 6). The model also confirmed that arsenic metabolism, indicated by proportions of the methylated arsenical. is significantly associated with dysglycemia (p=0.004), with a 92% increase in dysglycemia odds for every natural log-unit increase in DMA:MMA ratio. Increases in dimethylated arsenic, and decreases

in monomethylated arsenic, as portions of total urinary arsenic both increase DMA:MMA ratio and result in greater risk of dysglycemia.

Table 6. Logistic regression output.[2]

Variable	Odds ratio (e^{β})	95% confidence interval
age (years)**	1.04	[1.03, 1.05]
bmi (kg/m^2)**	1.09	[1.06, 1.12]
*elementary**	0.70	[0.50, 0.98]
≥highschool	0.44	[0.18, 1.08]
*water_source_plant**	1.57	[1.10, 2.24]
*ln_DMA:MMA RATIO***	1.92	[1.30, 2.82]
ln_water arsenic (μg/L)	1.06	[1.00, 1.13]

***p<0.01 *p<0.05*

The Bayesian network model was learned using dysglycemic status as the target variable and the demographic and behavioral variables used in the logistic regressions (Figure 10). Unlike the logistic regression, the BN model was able to incorporate both of the arsenic metabolism indicators, even though they are collinear. In addition, concentrations of arsenic metabolites in urine and metabolite ratios were not log-transformed as BNs do not require assumptions of distributional form. A G-test of the null hypothesis of independence of dysglycemic status and arsenic level in water could not be rejected (p = 0.24). However, a null hypothesis of independence of dysglycemic status and arsenic metabolic indicators was rejected after G-tests (p = 0.000 for DMA:MMA ratio). The augmented naïve Bayes algorithm also elucidated a number of secondary relationships among different non-target variables, indicated by the solid arcs in Figure 10. Consistent with the results of the regression model, the factors with greatest effect on dysglycemic status were age, BMI, education and arsenic metabolism as measured by mutual information.

[2] *elementary* and *≥highschool* refer to education level relative to a baseline of illiteracy. *water_source_plant* distinguishes subjects who obtain drinking water from a plant from other sources. Finally, *ln_DMA:MMA RATIO* is the natural log of the ratio of a subject's urinary dimethylated arsenic to their urinary monomethylated arsenic.

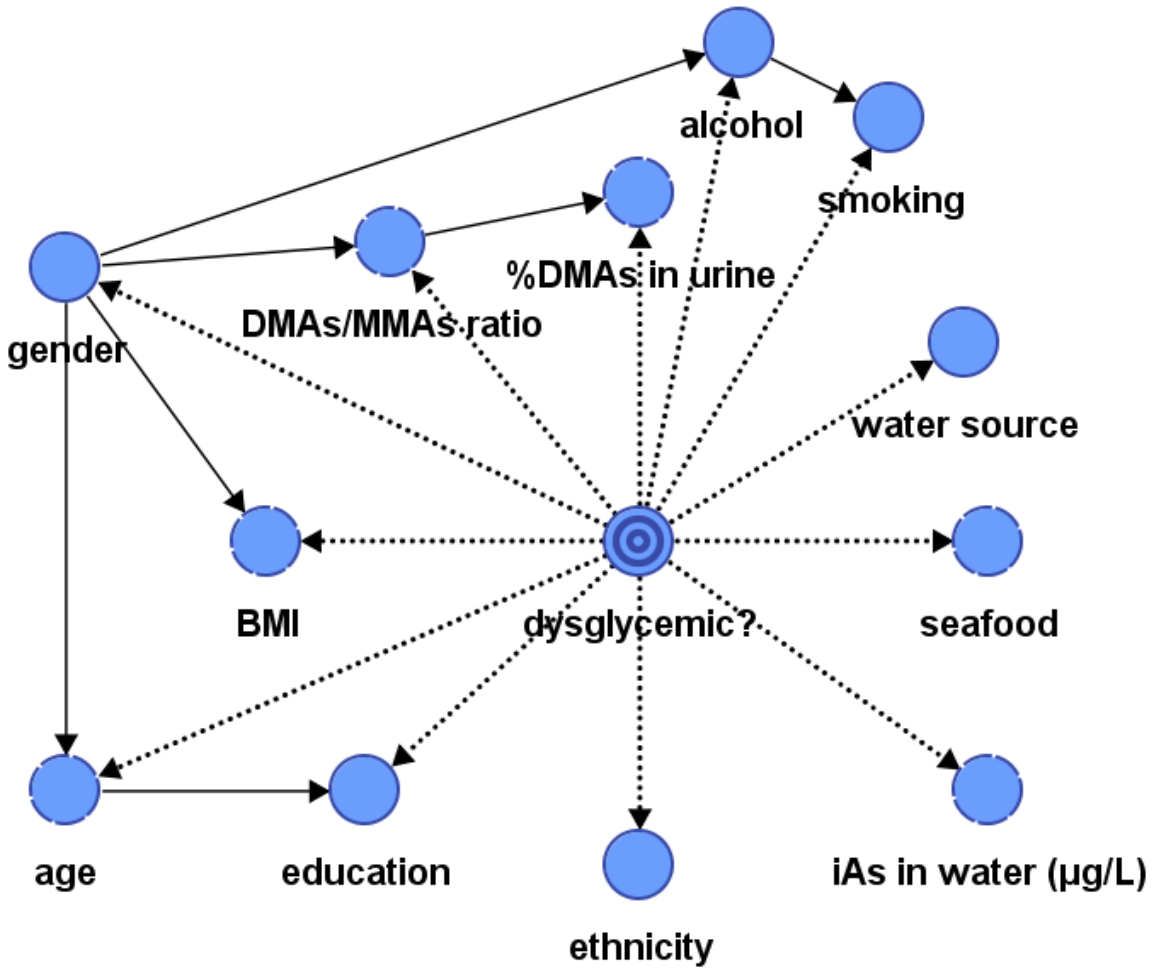


Figure 10. Bayesian network model learned from data using the naïve Bayes algorithm. The dotted arcs indicate the first step of the algorithm in which connections are made between the target node (*dysglycemic?*) and other nodes. The solid arcs represent additional relationships among non-target nodes learned by the algorithm. Note in particular the association between gender and many of the other variables.

3.2. Model performance

Sensitivity (true positive rate) and specificity (true negative rate) were calculated for each set of predictions to quantify model performance (Figure 11). Because the reference dose model yielded a reference dose below the limit of detection for arsenic in drinking water, the model predicted that all subjects would be dysglycemic. As such, sensitivity was 100% and specificity was 0%. Using the EPA's current drinking water standard of 10 µg/L, sensitivity was 85% and specificity was 18%.

For the regression approach, sum of sensitivity and specificity were assessed; the maximum sum was found at a point with sensitivity of 73% and specificity of 63%. The Bayesian network model's performance was comparable to that of the regression approach. At this level of specificity (63%), the BN achieved sensitivity of 75%.

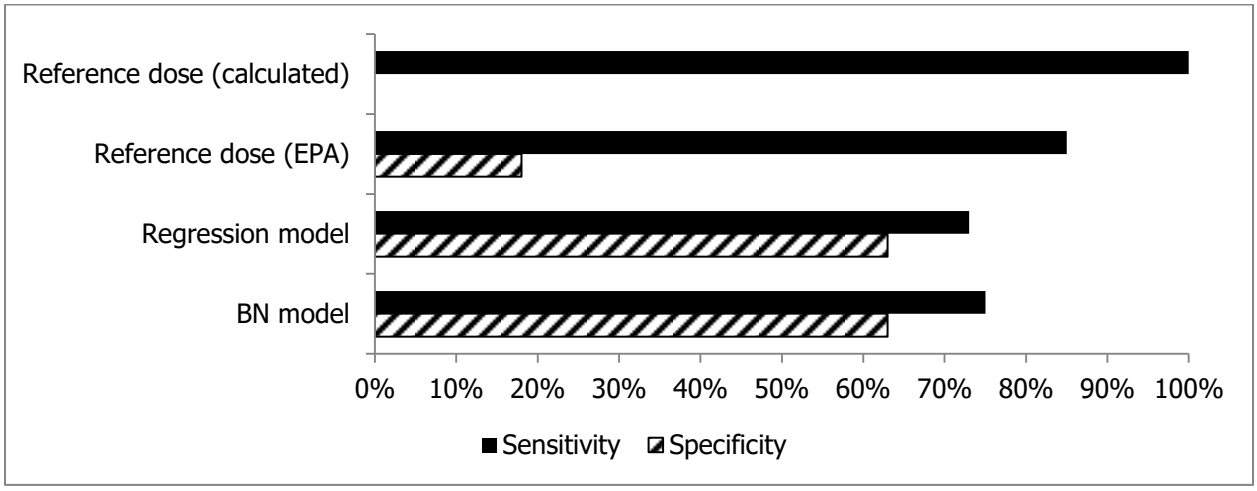


Figure 11. Sensitivity and specificity profiles for models in predicting dysglycemia from available data. Both reference doses yield high sensitivity, but low specificity. The regression and Bayesian networks perform much better in balancing sensitivity and specificity.

To further compare predictive capability of the BN and logistic regression models, receiver operating characteristic (ROC) curves were plotted and the areas under the curves (AUCs) were calculated (Figure 12). AUCs for the regression and BN models were 0.74 and 0.76 respectively.

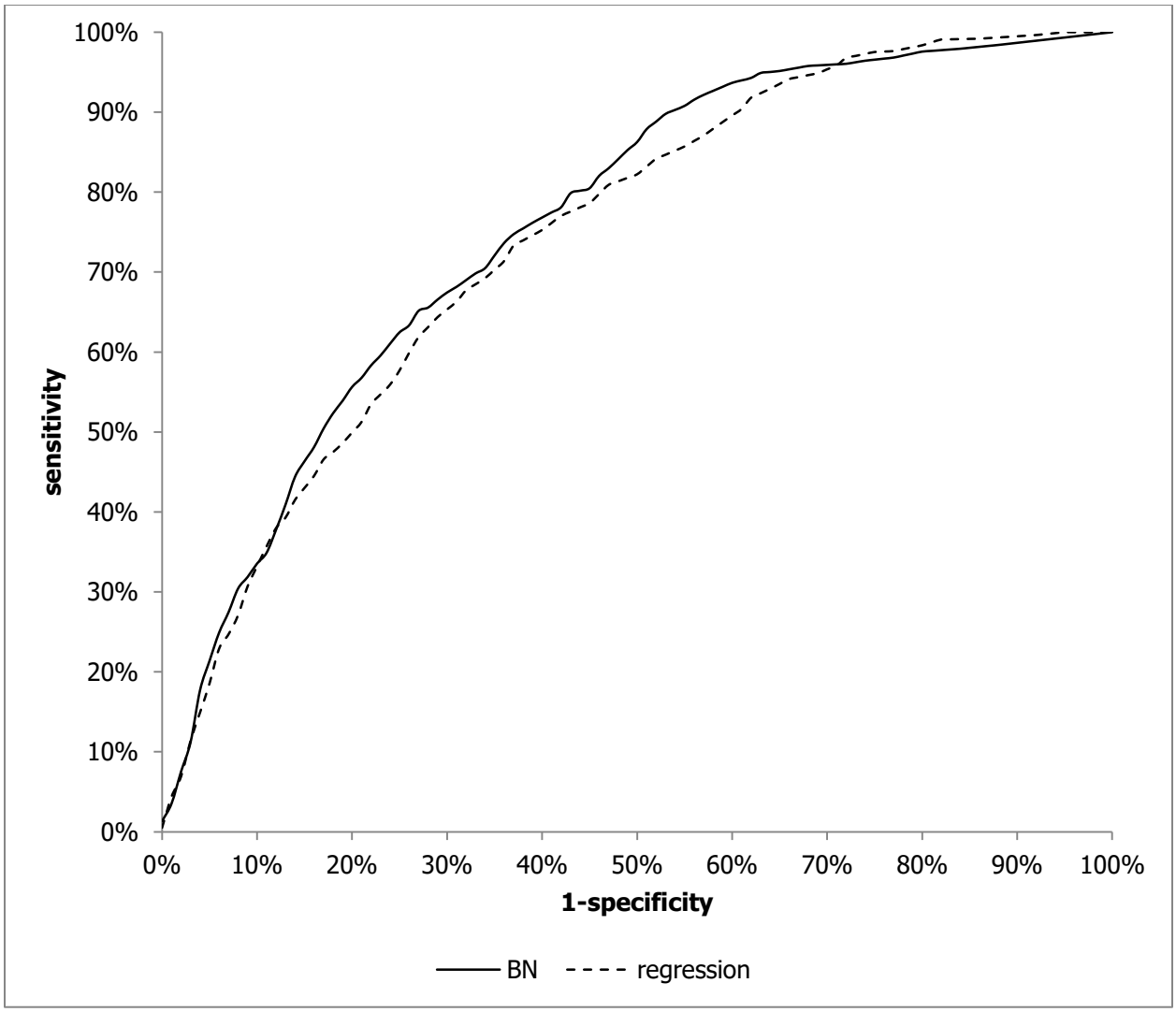


Figure 12. Receiver-operating characteristic (ROC) curves for the regression and Bayesian network models. These curves show incremental gains in sensitivity as the model's threshold of detection is lowered, and its specificity is reduced. The area under the curve for the BN model is 0.76, with 0.74 for the regression model.

3.3. Simulations of changes in dysglycemia prevalence

The Bayesian network model developed to capture a dose-response relationship was also used to simulate the effects of changing arsenic exposure on predicted risk of dysglycemia. After adjusting gender and age distributions to better reflect the Mexican population as a whole, predicted dysglycemia prevalence in the population was 26.7%. Moving all exposure below 25

µg/L (the current Mexican standard) reduced dysglycemia prevalence to 24.0%. Intermediate scenarios showed monotonic reductions in dysglycemia rates (Figure 13).

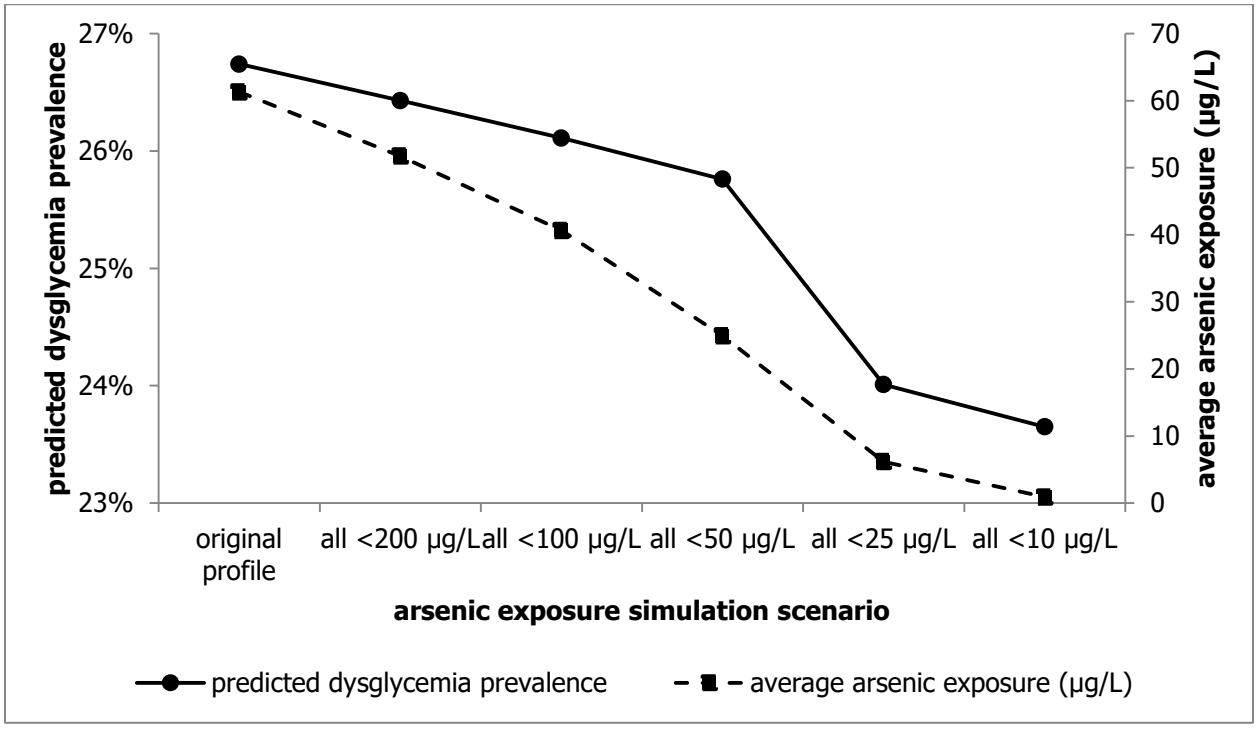


Figure 13. Effects of reducing arsenic exposure on dysglycemia prevalence in the simulated Mexican population in arsenic-endemic regions. At the left, predicted prevalence and average exposure in the population are shown. Each successive data point corresponds to reducing exposure to below the levels specified (200, 100, 50, 25, and 10 µg/L).

Using the same adjustments to gender and age distributions, these changes in dysglycemia prevalence in response to reduced arsenic exposure were compared to similar changes in response to simulated reductions in obesity in the population. Reducing obesity by 5% had roughly the same effect on dysglycemia prevalence (decrease by 0.8%) as the effect of shifting the population to arsenic exposure below 50 µg/L (decrease in dysglycemia prevalence by 1.0%). More substantial shifts resulted in greater reductions in prevalence: reducing obesity by 10% decreased dysglycemia prevalence by 1.6%, while shifting the population below the current Mexican arsenic drinking water standard of 25 µg/L decreased prevalence by 2.7%.

Implementing both of these changes yielded a drop in dysglycemia prevalence of 4.2% (Figure 14).

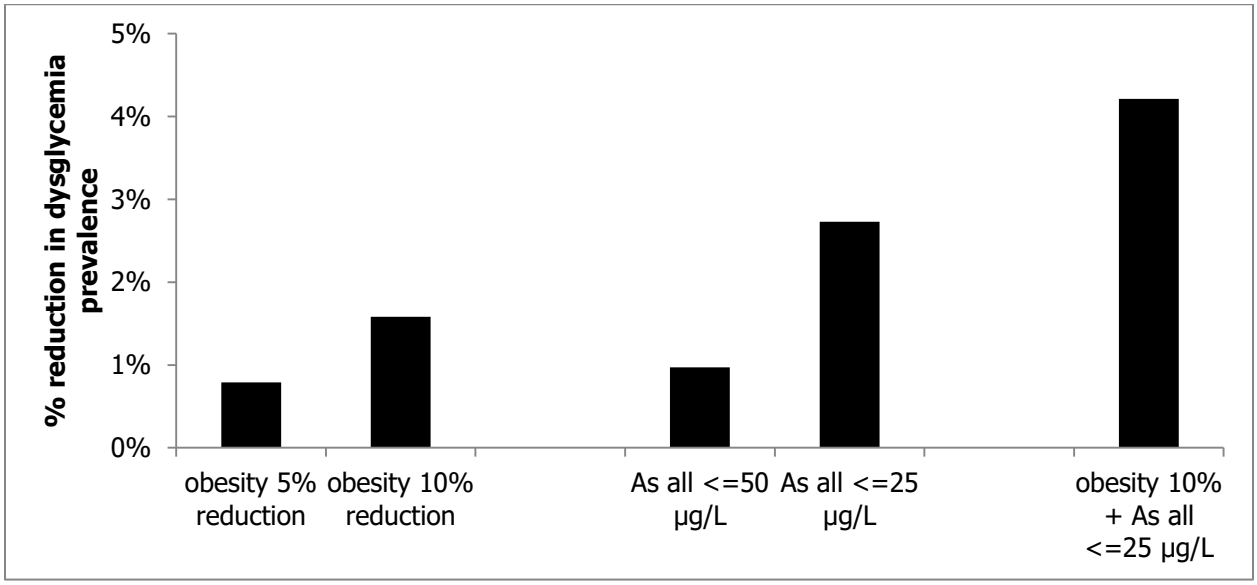


Figure 14. Reductions in dysglycemia prevalence from simulated changes in population obesity characteristics and arsenic exposure. Predicted prevalence changes from reducing obesity by 5% (10%) are roughly equal to predicted changes from reducing arsenic exposure below 50 µg/L (25 µg/L).

3.4. Avoided cases of diabetes and bladder cancer

The scenario in which exposure across the population was reduced below the current Mexican standard was used to estimate the number of cases of diabetes and bladder cancer avoided in a population of approximately 1.3 million Mexicans living an arsenic-endemic region of the country.[142] Reducing arsenic exposure in this population to below the current standard of 25 µg/L resulted in slightly more than 18,000 cases of diabetes avoided. Roughly 1460 cases of bladder cancer were also calculated to be avoided through this exposure change. This is an order of magnitude less than the 18,000 cases of diabetes avoided, and highlights the need to consider multiple health outcomes in setting regulatory policy.

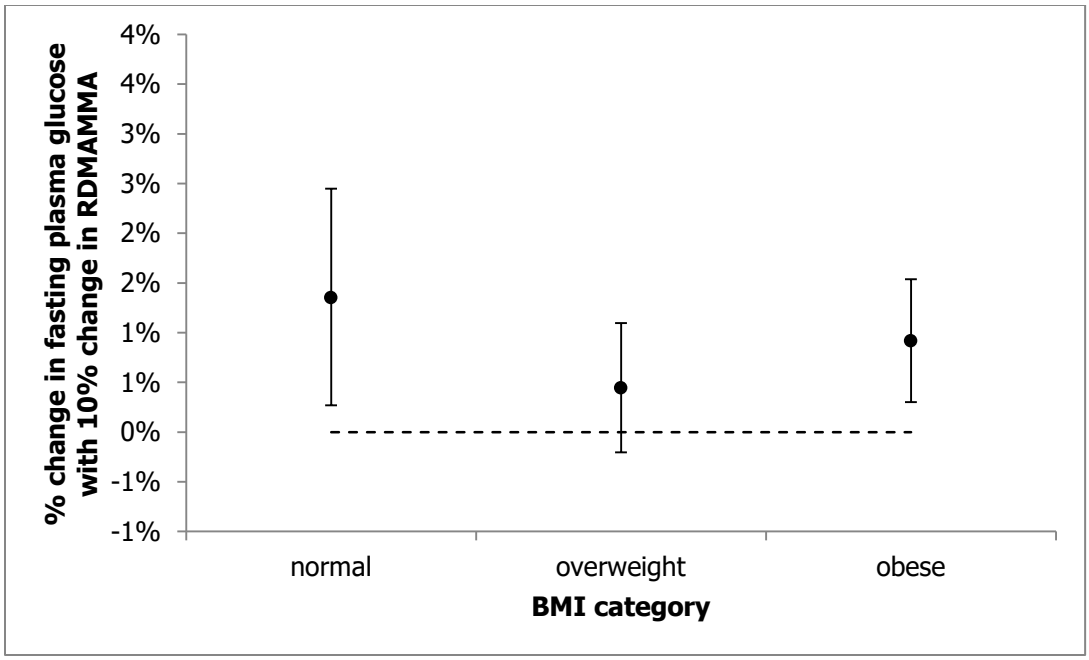
Monetizing these avoided cases using EPA methods showed a present value from the exposure change of $3.6 billion from bladder cancer avoided, and $19.5 billion from diabetes

avoided. While these estimates were calculated using a Mexican population and U.S. economic data, they further illustrate the importance of considering both cancer and non-cancer health outcomes in assessing the effects of public health policy.

3.5. BMI subgroups

G-tests performed using the entire dataset indicated statistically significant associations between dysglycemia-associated indicators (fasting plasma glucose and 2-hour plasma glucose), and measures of arsenic metabolism (percent of urinary arsenic metabolites as dimethylated arsenic (PCTDMA) and ratio of dimethylated arsenic to monomethylated arsenic in urine (DMA:MMA ratio)); associations with level of arsenic in drinking water were marginally significant.

Analysis was also conducted after restricting the model to BMI groups (normal, overweight, and obese). The association between arsenic metabolism indicators and dysglycemia-associated indicators was stronger for the normal and obese BMI groups than for overweight subjects (Figure 15).



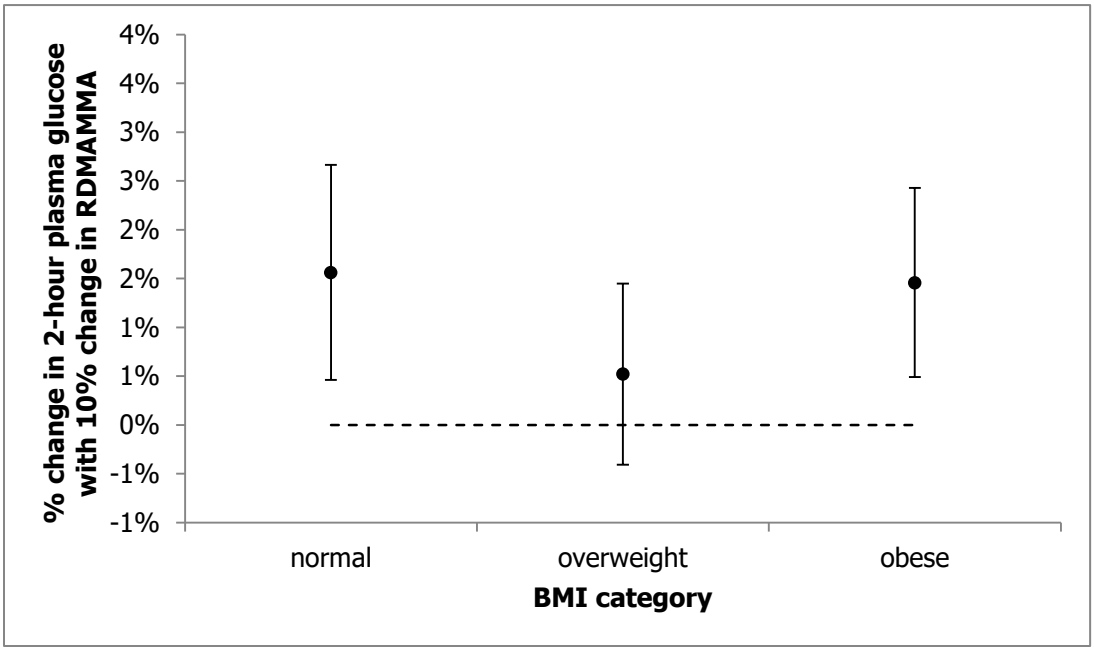


Figure 15. Responses of 2-hour plasma glucose and fasting plasma glucose to 10% change in DMA:MMA ratio, by BMI group. The overall pattern is consistent with the positive relationship between increased DMA:MMA ratio and increased levels of dysglycemia-associated indicators. However, the relationship is not significant in the overweight BMI group for either indicator.

These results suggest that the association between arsenic metabolism and dysglycemia may be weaker in overweight individuals (those with BMIs between 25 and 30) relative to both

normal-BMI and obese subjects. While the data available does not allow a full explanation of this pattern, the possibility of a non-monotonic sensitivity to arsenic metabolism across a range of BMIs warrants further study.

3.6. Simulated changes in health among different arsenic metabolic groups

The conditional probability tables generated within the Bayesian network model allow for exploration of how shifts in population characteristics can correspond to population-level health outcomes.

Discretizing DMA:MMA ratio into four quartiles was used to examine how other population characteristics vary among different arsenic metabolism groups. The predicted fraction of the population in each BMI category changed with DMA:MMA quartile; subjects with lower DMA:MMA ratios had lower BMIs. However, the fraction of the population in the overweight category remained relatively constant. Changes in the normal and obese categories were much more substantial (Figure 16). This insight informed subsequent simulations in which the percentage of the population in each BMI category was varied: the portions of the population in the normal and obese groups were varied, while the portion in the overweight group was held constant.

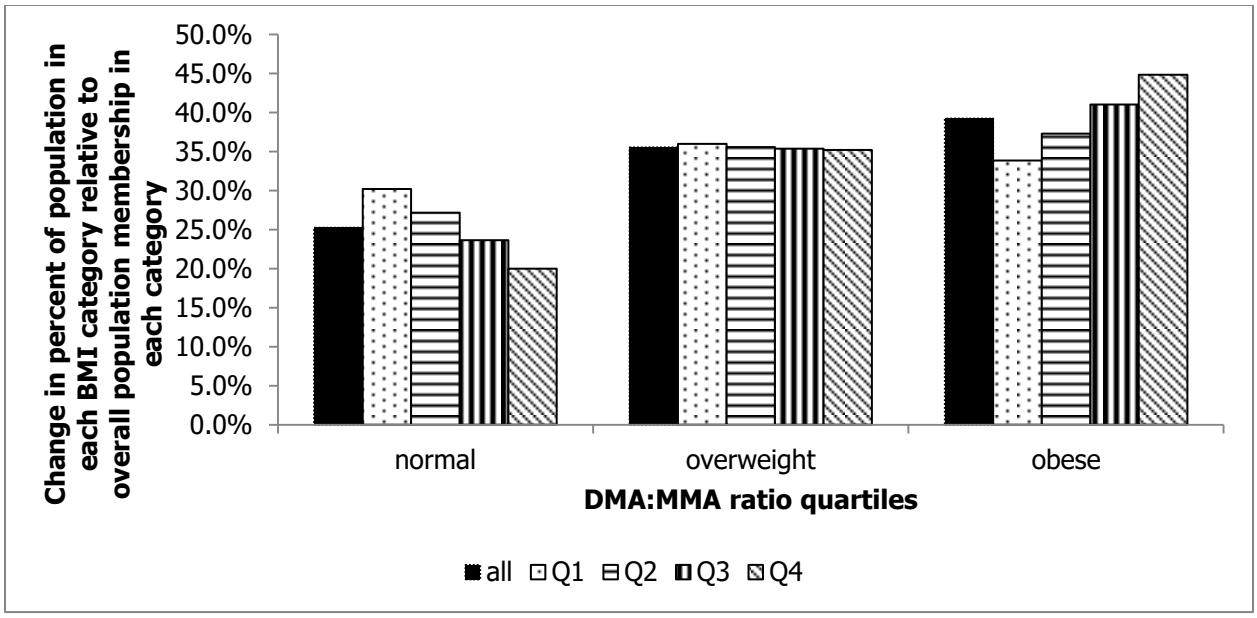


Figure 16. Changes in predicted percent of the population in each BMI category by quartiles of ratio of urinary dimethylated to monomethylated arsenic (DMA:MMA ratio). In the cohort as a whole, 25.2% of people are normal BMI, 35.5% are overweight, and 39.2% are obese. These percentages vary as DMA:MMA quartile is varied. Membership in the overweight category remains relatively constant, while membership in the obese and normal categories varies more substantially.

Given this understanding of BMI category differences by metabolism quartile, the effect of changing BMI categories in the population on dysglycemia risk was simulated. Overall, prevalence of dysglycemia in the population was 32.0%; BMI distribution was 25.2% normal, 35.5% overweight, and 39.2% obese. Holding the overweight percentage constant, as well as other variables in the model, increasing the normal percentage by 10%, and decreasing the obese percentage by 10% led to a 1.8% decrease in predicted population dysglycemia prevalence. Similarly, increasing the obese percentage by 10% and decreasing the normal percentage by 10% increased population dysglycemia risk by 1.8% (Figure 17).

Applying the same BMI category shifts after restricting to the first quartile of DMA:MMA ratio, the magnitude of change in dysglycemia prevalence changed: increasing the normal BMI group percentage by 10% decreased dysglycemia by 1.5%. In the fourth quartile of DMA:MMA

ratio, the effect was more pronounced (increasing normal BMI by 10% decreased dysglycemia by 2.0%). While these effects are small, they demonstrate how a BN model's conditional probability distributions can be used to study simulated shifts in both populations and specific subgroups.

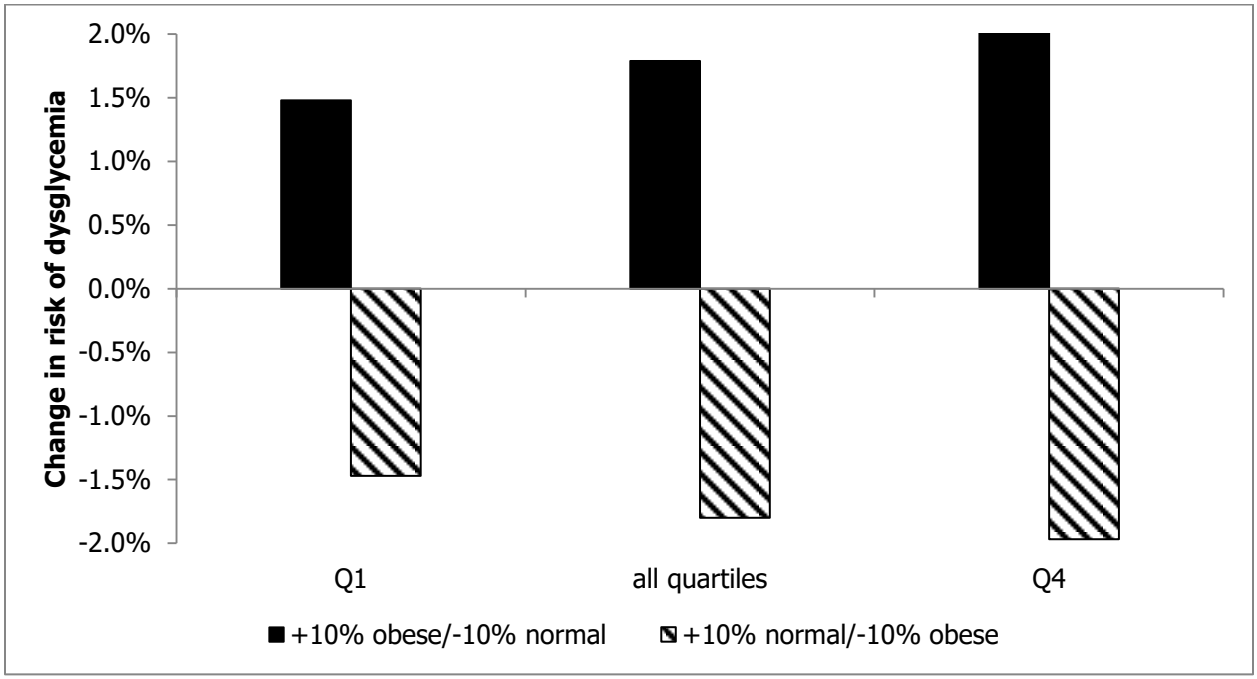


Figure 17. Simulated changes in risk of dysglycemia from shifts in BMI group, by arsenic metabolism profile quartile. In the entire population, increasing the obese fraction by 10% increases dysglycemia risk by 1.8%; decreasing by 10% decreases risk by 1.8%. The simulated effect is stronger in individuals with problematic arsenic metabolism (fourth quartile ratio of dimethylated to monomethylated arsenic in urine – DMA:MMA), and weaker in the first quartile.

4. Discussion

The primary goal of this research was to test the performance of a Bayesian network (BN) model in dose-response assessment in comparison to current methods (reference dose and slope-factor approaches). Specifically, the models were used to predict incidence of dysglycemia out-of-sample from demographic data as well as information on subjects' exposure to and metabolism of inorganic arsenic. The BN model outperformed the reference dose model's sensitivity and specificity of 100% and 0% (resulting from severe over-prediction). The

BN model's performance was comparable to that of a logistic regression model, which achieved optimized sensitivity and specificity of 73% and 63%; at that level of specificity, the BN model achieved sensitivity of 75%. Further analysis using receiver operating characteristic curves showed that the BN model successfully balanced sensitivity and specificity.

Adjusting the BN model to more closely reflect the Mexican population as a whole was used to predict the effect of reducing arsenic exposure on dysglycemia prevalence in arsenic-endemic regions. Estimated prevalence was 26.7% under current arsenic exposure conditions. Reductions in overall exposure corresponded to reduced dysglycemia prevalence, and achieving the current Mexican standard of 25 μg/L for the population resulted in a decrease in predicted dysglycemia prevalence to 24.0%. In a population of roughly 1.3 million people in three arsenic-endemic Mexican states, this reduction in prevalence translated to roughly 18,000 cases of diabetes avoided. Because current arsenic regulation is based on avoided cases of bladder cancer, an estimate of bladder cancer cases avoided was also calculated using EPA methods and yielded 1460 cases avoided. Monetizing the benefits of these avoided cases resulted in $3.6 billion for bladder cancer and $19.5 billion for diabetes. This disparity is substantial, and highlights the need to consider non-cancer outcomes like diabetes in developing regulation and policy to protect health from environmental contaminants. The BN model's ability to generate prevalence estimates for both cancer and non-cancer outcomes suggests its utility to dose-response and risk assessment in support of these policy decisions.

In addition, exploration of the dataset using the BN model yielded novel insight into the relationship between arsenic metabolism and dysglycemia-associated outcomes. While a clear relationship between efficient metabolism and increased risk of dysglycemia across the dataset

was confirmed, subgroup analysis showed that the strength of this effect was much weaker in overweight individuals than in normal-BMI or obese subjects. This pattern was not previously observed and could suggest a moderating effect of body mass in overweight individuals not present in those with normal or obese BMIs. The potential health-protectiveness of being overweight is a highly debated concept in the medical literature[148], and the evidence from this analysis adds to the need for further research to explore these counterintuitive results. Using this insight, the BN model was also used to predict the consequences of shifts in the BMI distribution of the study cohort on risk of dysglycemia given arsenic metabolism information. The simulations showed that, consistent with other findings, the consequences of shifts in BMI across the cohort are enhanced in individuals with arsenic metabolism profiles associated with dysglycemia.

Bayesian network models have been used in a number of health risk assessment contexts, including quantitative microbial risk assessment.[70,131,149] However, their use in dose-response assessment is significantly sparser. Hack et al. used a BN network approach to test different biomarkers for associations with anemia, leukopenia, and acute myeloid leukemia based on data drawn from literature.[150] Their work does not predict incidence of these health outcomes in a population, though, and does not quantitatively compare a BN model's predictive performance to current dose-response methods. To our knowledge, the only other study using a Bayesian network in human health risk assessment to model dose-response for environmental regulatory applications is our own prior work (Zabinski et al., 2016[133]). In that study, incidence of lower birthweight for gestational age in newborns was predicted from demographic information as well as maternal arsenic exposure and metabolism. Our work

builds on that study by demonstrating superior BN model relative to prevailing dose-response methods using a different health outcome (dysglycemia), a significantly larger cohort, and more robust comparisons to regression models.

Other methods have been also used to address challenges to current dose-response methodology, including improving the biological plausibility of models and incorporating different kinds of data. Substantial effort has been devoted to improving the calculation of benchmark doses to use as points of departure in determining reference doses rather than no observed adverse effects levels (NOAELs).[151,152] However, these methods typically rely on studies (often on animals) with dose groups; human cohort information, like the data used in our work, is not amenable to a benchmark dose calculation.[137] Most importantly, efforts to modify the calculation of reference doses still do not provide a risk metric that can be used to support regulatory cost-benefit analysis. In contrast, using a Bayesian network approach allows for direct cost-benefit comparisons among different scenarios considering both cancer and non-cancer health outcomes.

Other studies have focused on assessing the relative performance of different assumptions of functional form (logistic, Weibull, etc.)[153], or on nesting these models within one another to improve performance.[151] Unlike these approaches, this Bayesian network model dispenses with the need for functional form assumptions in favor of a different kind of representation of relationships between variables through conditional probabilities. There has been some interest in using BN models to incorporate different kinds of toxicological and metabolic data into a single analytic framework. For example, Gat-Viks et al. proposed a modeling framework based in part on Bayesian networks to synthesize several different kinds

of information, including high-throughput assay data, into a comprehensive biological model of metabolism and toxicity; they demonstrate this approach to model yeast cells' response to hyperosmotic stress.[154] However, they do not use this proposed model to devise a dose-response relationship or to predict health outcomes.

This study has a number of important limitations. First, Bayesian networks are always sensitive to choices of discretization within nodes. While our results were robust to changes in discretization, selecting appropriate discretization levels in a BN model always requires tradeoffs between precision and statistical reliability. In addition, our conclusions are limited to the context of a largely ethnically homogeneous population (Mexicans of mixed Amerindian-Caucasian descent). As such, the generalizability of our findings to populations in other arsenic-endemic regions of the world could be limited. Finally, while the size of our dataset was adequate for analysis (including the use of testing and training sets), BN models benefit from larger cohorts to better establish conditional probability distributions. Repeating the analysis on a larger dataset or meta-dataset would allow for confirmation of results.

In addition, our study cohort differs from the Mexican population in a number of ways. The cohort itself was substantially more female and more obese than the Mexican population. The cohort is also restricted to adults ages 18 and over; even with this restriction, it remains slightly older than the Mexican adult population. Finally, the study cohort is exposed to inorganic arsenic at a much higher level than the Mexican population. The simulation of changes in dysglycemia prevalence after adjusting the model to better reflect population characteristics does not change the underlying distribution of arsenic exposure learned from the dataset, and is thus more reflective of the population in arsenic-endemic regions. While

comprehensive information on dysglycemia prevalence and arsenic exposure across Mexico is not yet readily available[142,155], further Bayesian network analysis on fuller datasets could better translate the effects of changes in exposure into health outcomes for the country as a whole.

There is a rich body of literature studying the relationships among body mass index, arsenic metabolism, and cardiometabolic health (including dysglycemia).[156,157] Interactions among these factors are not yet fully understood, and eliciting these underlying mechanisms – including causal relationships – is certainly beyond the scope of our work in this project. In addition to these factors, recent literature has explored others (including gender, genetic polymorphisms, age, pregnancy, and environmental stressors) on differential arsenic metabolism.[158,159] Emerging evidence suggests that the gut microbiome plays a key and complex role in mediating the interactions between metabolism, obesity, and cardiometabolic health outcomes.[160,161] Indeed, the association of higher BMI, greater risk of dysglycemia, and higher DMA:MMA ratio we observed in our cohort using the BN model is supported by similar conclusions from some earlier, more targeted studies of these interactions. For example, Gomez-Rubio et al. demonstrated a significant association between higher BMI and higher DMA:MMA ratio in a cohort of adult women exposed to arsenic through drinking water[162]; Nizam et al. found significantly higher DMA levels in arsenic-exposed subjects with diabetes than in those without.[163] Other studies, however, have questioned these associations: for example, Chen et al. found no relationship between arsenic exposure and diabetes prevalence in a large cohort of roughly 11,000 people from Bangladesh.[164] These relationships clearly merit further study, and while our model was not designed to map them exhaustively or to elucidate

causality among factors, Bayesian networks could be used to do so if more comprehensive data encompassing relevant factors in cohort were available.

Even with these limitations, understanding how changes in different factors influence dysglycemia prevalence is vital to guiding effective public health interventions to reduce prediabetes and diabetes rates. Diabetes is a currently major public health challenge in Mexico, with both higher prevalence and lower rates of effective management than most other countries[165,166]; a recent estimate attributed nearly 14% of deaths in Mexico to diabetes as the primary cause.[155] While determining prevalence is hampered by poor data availability, most recent studies estimate the rate of diabetes in Mexico at around 15%.[167] Given the significance of diabetes in Mexico, we believe that our models' simulation of changes in dysglycemia prevalence from reduced arsenic exposure can have implications for public health – particularly in arsenic-endemic regions.

Taken together, our results support increased use of Bayesian network models in dose-response assessment and population simulation contexts. From a methodological perspective, the BN approach performed significantly better than the reference dose method and comparable to the regression approach. In addition, the potential for subgroup analysis in Bayesian networks can lead to non-obvious results like the interactions of arsenic metabolism and BMI category discovered in this analysis. While these interactions may be accessible using other tools, BNs excel in rapidly and transparently examining them. Similarly, population shift simulation using Bayesian networks takes advantage of the conditional probabilities within the models to allow exploration of nuanced, interacting scenarios. For these reasons, Bayesian

networks should play a greater role in dose-response contexts and human health risk assessment.

CHAPTER 4: A BAYESIAN BELIEF NETWORK MODEL ASSESSING THE RISK TO WASTEWATER WORKERS OF CONTRACTING EBOLA VIRUS DISEASE DURING AN OUTBREAK[3]

1. Introduction

1.1. Background and motivation

Ebola virus is a highly infectious pathogen with the potential to spread through direct contact with bodily fluids.[168] The 2014 outbreak of Ebola virus disease (EVD) provided renewed incentive to study and quantify the risk of EVD to different populations. Though the outbreak was concentrated in West Africa[169], cases emerged worldwide as infected individuals traveled from the outbreak's epicenter to other countries. Several cases occurred in the United States, and a combination of a lack of Ebola-specific protocols and public concern with the possibility of infection led to broad variation in procedures for handling patients and their liquid waste.[170] Policies to address the risk of disease transmission via wastewater contaminated with liquid patient waste require that this risk be well-characterized, but to date such characterizations remain sparse. Though the Centers for Disease Control and Prevention (CDC) regulates disposal of hospitals' liquid waste, questions have surfaced over whether the CDC's policies are sufficient to appropriately manage EVD risk.[171]

The CDC has determined that liquid waste from Ebola patients could be flushed directly into municipal wastewater systems, without disinfection, based on guidance from the World Health Organization. This policy differs from the CDC's guidelines for handling other kinds of

[3] This chapter previously appeared as an article in Risk Analysis. The original citation is as follows: Zabinski, J.W., Pieper, K.J., MacDonald Gibson, J. "A Bayesian Belief Network Model Assessing the Risk to Wastewater Workers of Contracting Ebola Virus Disease During an Outbreak," *Risk Anal.*, 2017, doi:10.1111/risa.12827. (electronic publication ahead of print)

EVD patient waste (linens, food service items, cloths, etc.), for which autoclaving or incineration is recommended.[172] Furthermore, the U.S. Army Institute of Public Health and several states developed protocols that contradict the CDC's guidelines by requiring disinfection before flushing.[173] This inconsistency across guidelines created confusion among municipal wastewater system managers and public health officials about whether wastewater workers could be at risk if untreated EVD patient liquid waste were flushed into municipal sewers. Beyond the risk of infection, wastewater system employees' potential reaction to the perceived risk was also concerning.[174] If workers were sufficiently worried about occupational exposure to Ebola to stay home from work, wastewater systems could face operational difficulties due to labor shortages.

To address concerns about the magnitude of risks wastewater workers might face under a future epidemic of Ebola or similarly virulent pathogen and to inform future decisions about hospital management of patient liquid wastes prior to flushing into the sewer, we developed a model to quantify risk to wastewater workers under different exposure and hospital waste treatment scenarios. The model, which is based on principles of quantitative microbial risk assessment (QMRA), uses a Bayesian belief network (BBN) to integrate characteristics of Ebola virus, infected patients, hospitals, and wastewater systems to generate numerical risk estimates and associated uncertainties.

1.2. Relevant literature

Multiple prior studies have sought to determine whether wastewater workers are at increased risk of infectious diseases due to occupational exposure to pathogens. Most of this work, however, has been epidemiological, relying on surveys, clinical data, and biomedical tests

to examine the connections among symptoms, work tasks, and incidence of infectious illnesses. Literature with greatest relevance to the risk of EVD to wastewater workers focuses on other viruses' capacity for transmission through wastewater, in particular different varieties of hepatitis virus. A literature survey by Keeffe provides a useful summary of studies on hepatitis A virus (HAV) risks to wastewater workers in different locations (Ohio, Texas, the United Kingdom, Germany, and Canada).[175] All the studies assessed these workers' occupational hazard for HAV by measuring anti-HAV seroprevalence. Associations between work tasks and anti-HAV seroprevalence were found to be significant overall, but other factors (including age and national origin) were also significant; as such, a definitive risk from wastewater exposure alone could not be established. Other research has focused on hepatitis E virus. For example, Jeggli et al. used prospective cohort studies to examine risk to wastewater workers of increased incidence of infection from hepatitis E or *Helicobacter pylori*.[176,177] They concluded that such increased risk was not present. This was the case even though other work has demonstrated a higher prevalence of HEV in both sewage and treated wastewater relative to other enteric pathogens.[178] Van Hooste et al. also examined incidence of *Helicobacter pylori* in wastewater workers and found no significant association between disease occurrence and occupational exposure.[179] Overall, these studies demonstrate the continued lack of consensus about the existence and magnitude of risks of transmissible disease for workers with occupational exposure to wastewater.

To our knowledge, only one other study has evaluated the risk to wastewater treatment workers of contracting EVD through occupational exposure to contaminated wastewater. Bibby et al. have recently developed a QMRA model to assess wastewater workers' risk of developing

the disease through inhalation exposure, published as a report by the Water Environment Research Foundation (WERF).[180] The model uses Monte Carlo simulation and focuses on risk through inhalation for workers closest to the hospital in which the EVD patient is being treated under scenarios in which workers do or do not use personal protective equipment (PPE; in this case, a properly-fitted, NIOSH-approved N-95 respirator). The model does not consider in-hospital disinfection as a risk mitigation strategy.

To our knowledge, ours is the first model to quantify Ebola risks to wastewater workers under alternative protocols for handling liquid wastes from Ebola patients prior to flushing the wastes into the sewer. This information can guide the development of appropriate protocols to protect wastewater workers and help improve clarity of decisions about handling waste in future epidemics, not only of Ebola but also involving other infectious pathogens.

2. Methods

2.1. BBN introduction

The QMRA to investigate the risk of Ebola transmission through wastewater was encoded as a BBN. BBNs are directed acyclic graphs that represent the joint probability distribution of a set of variables and outcomes of interest.[181] Variables are represented as nodes, with inter-nodal relationships shown as arcs. A major advantage of BBNs, in comparison to the Monte Carlo methods typically used in QMRAs, is the potential for diagnostic inference analysis of how the state of outcome variables influences the prior probabilities of predictive factors.[63] For example, if a wastewater worker were to become infected with Ebola, this finding could be entered in the model, and the BBN would automatically update probability distributions in all other nodes to enable understanding of factors that may have contributed to

virus transmission. Sensitivity analysis (in the absence of direct observations) within the model can also identify parameters that most affect risk, and this information can be used to target and optimize system interventions to reduce risk. BBNs have been used in multiple previous studies of health and environmental risk. For example, BBNs have mapped the spread of West Nile virus, combining human epidemiologic data with information on changes in environmental conditions to pinpoint indicators of change in disease vector populations and the disease patterns that result.[182] BBNs have also combined data on pathogen behavior with supply chain structures to model risk of *Staphylococcus aureus* in milk sold as 'pasteurized'.[183] A full review of BBN studies in the context environmental risk assessment can be found elsewhere.[27]

2.2. Model overview

Wastewater workers' risk of EVD depends on their exposure to wastewater containing active Ebola virus, and quantifying this risk therefore depends on assessing active viral concentrations at different locations in the wastewater system where workers could be exposed under alternative scenarios that consider patient, hospital, and sewer system characteristics. Active viral particles enter the wastewater system when EVD patient diarrhea ('EVD waste') is flushed down the toilet in the patient's room (Figure 18A). This EVD waste mixes with other hospital wastewater before discharging into a sewer main (Figure 18B), and travels through the system before reaching primary and secondary (Figure 18C) and tertiary (Figure 18D) treatment.

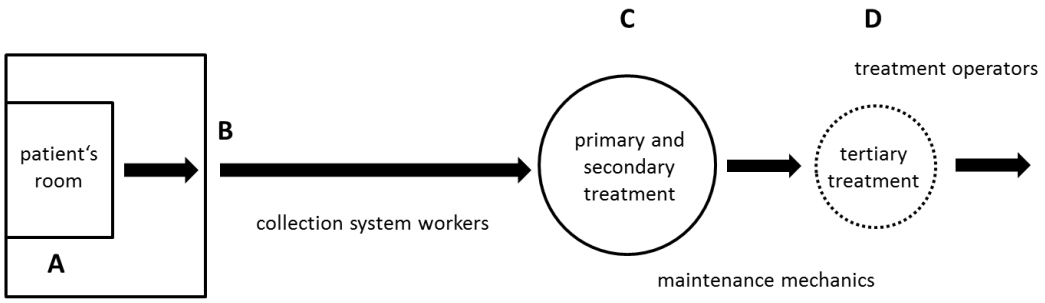


Figure 18. Conceptual model of wastewater flow. Water flows from the patient's room (A) to the hospital-wastewater system interface (B) and finally through the wastewater system, including primary and secondary treatment at the treatment plant (C) as well as tertiary treatment (D) when present. The model considers exposure points from when hospital waste enters the system (B) through tertiary treatment (D). Three categories of workers are examined: collection system workers, maintenance mechanics, and treatment plant operators. Workers in the latter two categories can be exposed to wastewater both prior to and after tertiary treatment.

Workers could be exposed at any location between the hospital discharge pipe and the treatment plant effluent pipe. The BBN is structured to reflect the movement and survival of Ebola virus along this potential exposure pathway. Combined with an estimate of the worker's occupational exposure to wastewater, an exposure dose of active viral particles is then calculated. Finally, a dose-response model is used to quantify the probability of developing EVD based on this exposure dose. Figure 19 shows the full network structure, with the central column of nodes representing this conceptual modeling framework.

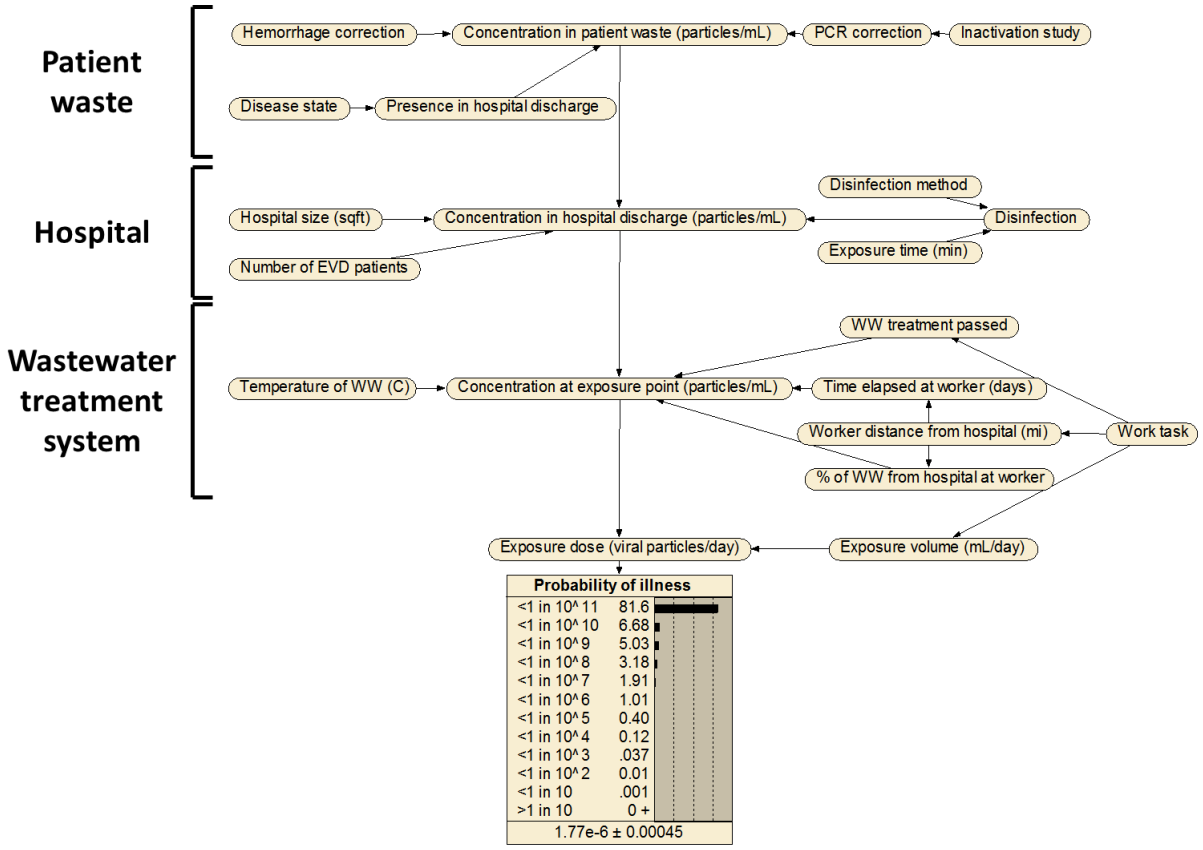


Figure 19. Influence diagram for estimating risk of Ebola virus disease for wastewater workers exposed to hospital discharges under future outbreak scenarios. The central column represents changes in Ebola virus concentration as patient waste travels through hospital pipes and the sewer system to points at which wastewater system workers could be exposed. The final node shows the probability of illness, which can be updated by specifying values of other nodes in the network.

Table 7 defines all the variables, their possible states and prior probabilities, and the information sources used to characterize them. Additional information on uncertainty arising from characterization of variables and on model construction (including node state discretization, conditional probability estimation, and causality assumptions) is available in the Supporting Information file. The BBN was constructed using Netica (Norsys Software Corp., Vancouver, Canada).

Table 7. BBN model nodes, with descriptions and sources.

Title	Name	Units	Equation or States	Description	Sources
Disease state	*state*	-	{severe, nonsevere}	phase of illness with	184185186187

				diarrheal discharge ≥1L/day, or not	
Initial viral concentration	*presence (PR)*	particles/mL	$viral\ concentration = e^X, where\ X = \begin{cases} U\sim[0, ln(3)]\ if\ state = nonsevere \\ U\sim[ln(3), ln(7)]\ if\ state = severe \end{cases}$	calculation of uncorrected viral concentration in diarrhea from patient	n/a
Hemorrhage correction	*hemorrhage (HC)*	-	{study 1, study 2, study 3, study 4, study 5, study 6, study 7}	probability of patient experiencing gastrointestinal hemorrhaging	[185] [188] [189] [190] [191] [192] [169]
Concentration in patient waste	*conwaste (CW)*	particles/mL	$concentration\ in\ patient\ waste = initial\ \ concentration * hemorrhage\ correction * PCR\ correction$	calculation of viral concentration in patient waste	n/a
Disinfection method[1]	*disinfection (DI)*	-	{bleach, quats, peracetic acid, none}	type of disinfectant used in hospital	n/a
Exposure time[1]	*exposure*	minutes	{two min, fifteen min, thirty min}	duration of exposure to disinfectant used in hospital	n/a
Attenuation	*attenuation*	-	{none, low bleach, med bleach, high bleach, low quats, med quats, high quats, low peracetic, med peracetic, high peracetic}	viral attenuation from hospital disinfection	(Sassi et al., 2016)[2]
Temperature of WW	*tempeffect (TE)*	^oC	{<15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, >29}	expected temperature of wastewater in system	[193] [194]
Number of patients	*number (NU)*	number of patients	{1, 2, 3, 4, 5, 6, 7}	number of EVD patients in the hospital	n/a
Work group	*group*	-	{collection system worker, maintenance mechanic, WW treatment operator}	wastewater worker type	[195]
WW treatment passed	*treatment (TT)*	-	{pretertiary, tertiary}	whether worker is exposed before or after tertiary wastewater treatment	[195]
Worker distance from hospital	*distance*	miles	{up to 1, up to 2, up to 3, up to 4, up to 5, greater than 5}	worker's distance from hospital (in pipe-miles)	[195]
Time elapsed at worker	*time*	days	{less than half, up to 1, up to 2, greater than 2}	time taken by wastewater to flow from	[195]

				hospital to worker	
Concentration in hospital discharge	*condischarge (CD)*	particles/mL	$concentration\ in\ hospital\ discharge = concentration\ in\ patient\ waste * disinfection\ effect * dilution\ factor * number\ of\ \ patients$	intermediate calculation of viral concentration in wastewater	n/a
Hospital size	*hospital (HS)*	square feet	{up to 500k, 500k to 1000k, greater than 1000k}	size and internal dilution of hospital	[196]
% of WW from hospital at worker	*percent (PC)*	-	{less than 5%, 5%-50%, 50%-95%, greater than 95%}	fraction of total wastewater at worker originating in hospital	[195]
Concentration at exposure point	*conexpose (CX)*	particles/mL	$concentration\ at\ exposure\ point = concentration\ in\ hospital\ discharge * system\ dilution\ factor * temperature\ effect^{time} * tertiary\ treatment\ effect$	final calculation of viral concentration in wastewater	n/a
Exposure volume	*exposevol (EV)*	mL/day	{zero, daily inhalation, 10-second ingestion, 1-min ingestion}	estimate of daily wastewater volume ingested or inhaled by worker	[197] [198]
Inactivation study	*study*	-	{study 1, study 2, study 3}	viral presence to infectious virus correction	[199] [200] [201]
PCR correction	*correct (CO)*	-	$correction\ factor = e^{Y}, where\ Y = \begin{cases} ln(0.0398)\ if\ study = study\ 1 \\ U\sim[ln(0.001), ln(0.1)]\ if\ study = study \\ U\sim[ln(0.0079), ln(0.1)] if\ study = study \end{cases}$	calculation of viral presence to infection virus correction	n/a
Exposure dose	*dose (DO)*	particles/day	$exposure\ dose = concentration\ at\ exposure\ point * exposure\ volume$	calculation of dose of infectious viral particles to worker	n/a
Probability of illness	*sick*	-	*dose-response model*	calculation of probability of developing EVD	(Haas, Rose, Mitchell, and Rycroft, 2016)[2]

[1]choice nodes leave specification of state to the user, with prior assumption of equal probability for each state

[2]unpublished – manuscript in preparation

2.3. Viral concentration in EVD waste

2.3.1. Initial viral concentration

An EVD patient's diarrhea may contain active viral particles if the patient is experiencing internal hemorrhaging. For such patients, the volume of diarrhea and concentration of viral particles increase as the illness becomes more severe.[184–187] In the model, the patient's disease state was divided into two phases : 'severe' if daily diarrhea discharge exceeds 1 L and 'nonsevere' otherwise. The 'severe' phase was assigned a prior probability of 33% based on literature estimates of the fraction of an EVD patient's hospital stay during which daily diarrhea discharge exceeds 1 L.[184–187] This information was encoded in the node **Disease state**.

Viral concentration during the severe phase ranges from approximately 10^3 to 10^7 particles/mL, and up to approximately 10^3 particles/mL during the nonsevere phase. Concentration was modeled as

$$initial\ viral\ concentration = e^X, where\ X = \begin{cases} U \sim [0, ln(3)]\ if\ state = nonsevere \\ U \sim [ln(3), ln(7)]\ if\ state = severe \end{cases} \quad (10)$$

Uniform distributions were used because supporting studies only provide ranges for viral concentration in patient waste. These distributions achieve equal representation by order of magnitude across the concentration ranges considered.

2.3.2. Correction for internal hemorrhaging

Not all patients experience the gastrointestinal hemorrhaging that transmits viable Ebola virus to the patient's liquid waste. Therefore, the estimate of viral concentration in diarrhea was modified to account for the probability of patients experiencing hemorrhaging

using information from clinical studies of EVD patients. [169,185,188–192] For each study, the proportion of EVD patients recorded as experiencing gastrointestinal hemorrhaging or relevant related symptoms (i.e., melena, hematochezia, or hematuria) was extracted. Inverse population weighting was used to assign a weight to each such study (results are in the node **Hemorrhage correction**), where for study *m*,

$$weight_m = \frac{number\ of\ EVD\ patients\ studied\ in\ m}{\sum_{m \in M} number\ of\ EVD\ patients\ studied\ in\ m}$$

(11)

2.3.3. Correction for use of PCR methods

Quantifications of viral concentration rely on polymerase chain reaction (PCR) methods. However, there is considerable uncertainty about the fraction of viral particles detected through PCR that are viable.[202] Unfortunately, prior studies of Ebola virus have not estimated this fraction. Therefore, the model incorporated results from three studies comparing poliovirus concentrations detected by PCR and infectious concentrations assessed through cell culturing (node **PCR correction**). These results take the form of log-reduction in the estimate of active virus concentration. One study, for example, estimates a 2-log difference between virus concentration detected and actual infectious concentration. Such log-reduction or log-inactivation factors are used throughout the model where appropriate given underlying literature.

These factors were combined in the node **Viral concentration in EVD waste** (*conwaste, CW*) to produce an estimate of active virus concentration in EVD waste, corrected for the probability of hemorrhaging and for PCR method inaccuracies, in units of active viral particles/mL:

$$viral\ concentration\ in\ EVD\ waste$$
$$= initial\ estimate * hemorrhage\ correction * PCR\ correction$$

(12)

2.4. Viral concentration in hospital discharge

2.4.1. In-hospital waste disinfection

Disinfectants applied by hospital staff to the EVD waste, before flushing, may have a substantial impact on active Ebola virus concentration. Based on unpublished data collected by Sassi et al. (in preparation, 2016), concentration reductions from exposure to three disinfectants (bleach, quaternary ammonium cations [quats], and peracetic acid) over three distinct time intervals (2, 15, and 30 minutes) were incorporated (**Disinfection** node).

2.4.2. In-hospital dilution

Using data from a U.S. Energy Information Administration survey[196], large U.S. hospitals were divided into three categories based on area footprint (limiting consideration to large hospitals as these are the only U.S. facilities approved to treat EVD patients).[203] For each hospital size, the daily wastewater volume produced by a single bed was divided by the wastewater volume generated by the hospital to account for dilution before EVD waste exits the hospital. The resulting dilution factors are captured in the **Hospital size** node.

2.4.3. Number of EVD patients

The model assumes a single EVD patient by default, but the node **Number of EVD patients** allows for up to seven patients to be considered simultaneously. Combining this factor with the effects of in-hospital disinfection and dilution yields the **Viral concentration in hospital discharge** in active viral particles/mL:

$$concentration\ in\ hospital\ discharge = concentration\ in\ EVD\ waste * disinfection\ effect * dilution\ factor * number\ of\ EVD\ patients \quad (13)$$

2.5. Viral concentration at point of exposure

A number of transformative processes affect virus-bearing wastewater and reduce active viral concentration by the time a worker is exposed, with the degree of reduction depending on wastewater temperature, size of the sewer system, and worker location, the latter of which is influenced by work task. To characterize concentrations at potential exposure points, the model uses information from the City of Raleigh's responses to the American Water Works Association's (AWWA) 2014 Utility Benchmarking Survey [195] and conversations with Raleigh wastewater treatment management staff about how to interpret those responses. Raleigh's network is representative of a wastewater collection and treatment system for a mid-sized city, with approximately 2,300 miles of sewer pipe, average flow of 65.2 million gallons per day, service population of 521,000, and staff of 224 people.

2.5.1. Worker group

In the AWWA benchmarking survey as completed by Raleigh, workers were classified into three groups: collection system worker, maintenance mechanic, and wastewater treatment operator. Collection system workers are at highest risk for wastewater exposure, as they are responsible for conducting maintenance and repairs in the sewer lines and pump stations. Maintenance mechanics work in wastewater treatment plants, where exposure risks

are lower than for collection system workers. Wastewater treatment operators are largely confined to control rooms within the plants and consequently have low exposure risk.

2.5.2. Distance from hospital

The worker's spatial distance from the hospital was quantified as the distance between the worker and the hospital discharge point. In the model, probabilities are assigned to values across a range of distances (from less than 1 mile to greater than 5 miles) for each of the three work groups (**Worker distance from hospital** node).

2.5.3. Time elapsed before wastewater reaches worker

A worker's distance from the hospital was multiplied by a constant wastewater velocity of 1.07 m/s (3.50 ft/s) to compute the time elapsed between EVD waste discharge and worker exposure (**Time elapsed at worker** node).[204] At this flow rate, EVD waste is expected to reach most workers within the distance range considered (up to 6 miles) in less than a day.

2.5.4. Temperature-moderated viral attenuation

Ebola virus survives poorly outside the human body, and its die-off rate is greater at higher temperatures. To account for these effects, the results of a study of enveloped virus inactivation in human sewage[193] were used to estimate the percentage inactivation of Ebola virus per unit time as a function of temperature. Raleigh atmospheric data[194] were used to develop a wastewater temperature distribution; the inactivation fractions for different temperatures are specified in the **Temperature of wastewater** node.

2.5.5. In-system wastewater dilution

Dilution occurring between the hospital and the exposure point is captured in the node **% of WW from hospital at worker** node, which contains four states specifying different levels of dilution as estimated from the Raleigh AWWA benchmarking survey.

2.5.6. Tertiary wastewater treatment

Though not present in all systems, the model assumes zero active Ebola virus concentration in wastewater that has undergone tertiary treatment (encoded in the node **Tertiary treatment**). In combination with the preceding factors, this variable yields **Viral concentration at exposure point** in active viral particles/mL:

$$concentration\ at\ exposure\ point = concentration\ in\ hospital\ discharge * system\ dilution\ factor * temperature\ effect^{time} * tertiary\ treatment\ effect \quad (14)$$

2.6. Exposure dose

The node **Concentration at exposure point** updates the concentration of active viral particles in hospital discharge to account for die-off, dilution, and tertiary treatment if present (see equation in Table 7): to estimate exposure dose, the model then multiplies this concentration by assumed exposure volumes for different hypothetical scenarios. The model can estimate doses for inhalation of aerosolized wastewater or direct ingestion of droplets. As data on inhalation for wastewater workers are sparse, a study of aerosolized water inhalation during showering was used to estimate inhalation exposure volumes.[198] Data from the experiment conducted at highest temperature and highest water velocity were used, resulting

in the greatest volume of water inhaled, to be conservative relative to available literature on wastewater aerosolization.[205] In addition, the inhaled volume value from the 10-minute experiment was multiplied by 24 to determine the amount of water expected to be inhaled over a 4-hour exposure. This value— 0.00012 mL – was then used as an estimate of a daily dose of inhaled wastewater and encoded in the node **Exposure volume** for the inhalation scenario.

To estimate a volume of wastewater swallowed via direct ingestion, the EPA Exposure Factors Handbook was used.[197] During a one-hour episode of swimming, a person ingests 23 mL of water. This value was adjusted to determine 10-second and 1-minute 'ingestion episodes', with volumes of 0.383 mL and 0.064 mL respectively. Assuming an average droplet size of 0.05 mL[206], these scenarios are equivalent to swallowing approximately 8 drops and 1 drop of water respectively. Probability distributions across the three exposure volumes in addition to no exposure were specified for each of the three worker groups, although the ideally a model user would specify the exposure scenario in estimating risks.

Incorporating the volumes based on routes of exposure, a dose of infectious viral particles to the wastewater worker over the course of a day is determined. This value is expressed in the node **Exposure dose**.

2.7. Dose-response and probability of illness

To estimate the probability of developing EVD, the exposure dose was used in an exponential dose-response model developed by Haas, Rose, Mitchell, and Rycroft (in preparation, 2016) based on data from prior primate studies. (The Haas et al. model estimates a median infectious dose (dose at which 50% of exposed patients develop the disease) of approximately 9 viral particles.) This prediction is captured in the network's final node,

Probability of illness. The probability of illness is discretized into ten states, each giving a risk range indicating the probability of developing EVD under the assumptions specified throughout the rest of the network. Due to the possible combinations of discrete node states specified in the model, the minimum nonzero probability of illness the model can reliably assess is 10^{-12}; for smaller values, risk is categorized as below the model's limit of detection (LOD).

2.8. Model compilation

Once the model's structure was established, distributions based on data added, and relationships between nodes defined, conditional probabilities were estimated by simulating 100,000 joint instances of the model. In each instance, values for nodes with marginal probabilities encoded were drawn according to these distributions. Values for nodes incorporating random variables were drawn from these distributions. Then, the equations linking nodes were used to generate remaining values. The process produced 100,000 unique cases of the model in which each node had a set value. This simulated set of cases was then used to determine conditional probabilities through frequency analysis. For a detailed example of this process, see the Supporting Information file.

2.9. Scenario analysis

To explore risk under different conditions, multiple scenarios were examined. First, a 'worst-case' scenario was simulated to define an upper bound of EVD risk by setting all parameters that could vary for a particular exposure episode to maximize risk: severe disease state, no hospital disinfection, low temperature, minimal dilution from both hospital and network, no tertiary treatment, exposure close to the hospital, and exposure volume equivalent

to ingestion of approximately 8 drops of wastewater (a 1-minute swimming episode). For simplicity, the number of patients was left at its default setting of 1.

Building on this worst-case scenario, each of the parameters specified was independently varied to simulate different risk scenarios while holding the remainder of the base case settings constant. For each scenario, mean and median single-day risk were recorded. Mean risk was also estimated over an exposure period:

$$mean\ risk_{week} = 1 - (1 - mean\ risk_{day})^7 \quad (15)$$

2.10. Sensitivity analysis

Global sensitivity analysis without any state specification was not carried out because interpretation of results across all scenarios simultaneously is not informative for risk mitigation. Instead, sensitivity analysis was restricted to scenarios. The sensitivity of the model's risk estimates to the key predictor variables was tested under the 1-minute ingestion exposure scenario. Under this setting, the effects of different nodes on the probability of illness were examined by using the BBN software's 'sensitivity to findings' procedure, which varies one node at a time and measures the effect on the outcome node while holding the rest of the network constant. This procedure quantifies the reduction in the outcome node's entropy—the degree of uncertainty about the outcome node's true state. The entropy of node *X* is initially calculated as[207]

$$H(X) = \sum_{x \in X} p_x log_2(p_x)$$

(16)

where *x* indicates the set of states of *X* and p_x indicates the prior probability of state *x*. The change in this entropy given findings at node *S* is then calculated as

$$\Delta H = H(X) - H(X|S)$$

(17)

Sensitivity of risk to several model parameters was also examined under more specific scenarios to investigate sensitivity analysis robustness and variability.

3. Results

3.1. Risks from scenario analysis

A BBN model was developed to assess risk of developing EVD for wastewater system workers during an Ebola outbreak, to test the effects on risk of pretreating EVD waste prior to flushing into the sewer, and to examine which other parameters had greatest influence on risk. There was substantial variation in predicted risk based on the characteristics of the EVD patient(s), the hospitals treating the patient(s), the wastewater system, and specific worker groups. Under the worst-case scenario in which risk is maximized (severe disease state, lowest wastewater temperature, no tertiary treatment, smallest hospital size, and minimum system dilution, distance to worker, and time elapsed), the model estimates a median EVD risk of 5.8×10^{-4} (90% confidence interval: 8.8×10^{-7}–9.5×10^{-2}; mean 3.2×10^{-2}) (Table 8). However, this risk decreases substantially as these worst-case assumptions are removed (Table 8, changed variables highlighted in grey). Scenarios in the table are arranged in decreasing order of impact

on risk: each successive variable has less of an impact on changing risk relative to the worst-case scenario.

Table 8. Estimated risk of Ebola virus disease to wastewater workers under a worst-case and alternative scenarios.

Disease state	Disinfection method	Disinfection exposure time (min)	Temperature (°C)	Distance from hospital (mi)	Tertiary treatment	Hospital size (ft^2; in-hospital dilution)	% of WW coming from hospital	Exposure method	Median (Mean) 1-Day Risk	Median (Mean) 7-Day Risk
severe	none	-	≤15°C	≤1	no	≤500k	>95%	1min ingest	5.8×10^{-4} (3.2×10^{-2})	4.1×10^{-3} (2.0×10^{-1})
severe	none	-	>29°C	≤1	no	≤500k	>95%	1min ingest	4.4×10^{-4} (2.8×10^{-2})	3.1×10^{-3} (1.8×10^{-1})
severe	none	-	≤15°C	≤1	no	>1000k	>95%	1min ingest	1.2×10^{-4} (1.6×10^{-2})	8.4×10^{-4} (1.1×10^{-1})
severe	none	-	≤15°C	≤1	no	≤500k	>95%	10s ingest	7.0×10^{-5} (4.3×10^{-3})	4.9×10^{-4} (3.0×10^{-2})
severe	bleach	15 min	≤15°C	≤1	no	≤500k	>95%	1min ingest	3.4×10^{-5} (2.7×10^{-3})	2.4×10^{-4} (1.9×10^{-2})
severe	none	-	≤15°C	≤1	no	≤500k	<5%	1min ingest	2.9×10^{-5} (2.6×10^{-3})	2.0×10^{-4} (1.8×10^{-2})
severe	quats	15 min	≤15°C	≤1	no	≤500k	>95%	1min ingest	5.9×10^{-6} (3.8×10^{-4})	4.1×10^{-5} (2.7×10^{-3})
severe	peracetic acid	15 min	≤15°C	≤1	no	≤500k	>95%	1min ingest	3.8×10^{-7} (2.9×10^{-5})	2.7×10^{-6} (2.0×10^{-4})
severe	none	-	≤15°C	≤1	no	≤500k	>95%	inhalation	8.9×10^{-8} (1.2×10^{-5})	6.2×10^{-7} (8.4×10^{-5})
non-severe	none	-	≤15°C	≤1	no	≤500k	>95%	1min ingest	1.5×10^{-7} (6.7×10^{-6})	1.0×10^{-6} (4.7×10^{-5})

Without prior information about worker or system characteristics (that is, without specifying any node states in the model), the model estimates that wastewater workers' daily median risk of developing EVD from contact with wastewater of hospital origin 6.1×10^{-12} (90% CI: 1.0×10^{-12}–5.4×10^{-9}; mean 1.8×10^{-6}). Median risk when specifying inhalation exposure, but leaving all other nodes unspecified, is 6.7×10^{-12} (90% CI: 1.0×10^{-12}–9.1×10^{-9}; mean 1.2×10^{-7}); specifying 10-second immersion (1-drop ingestion) instead, median risk is higher, at 6.7×10^{-10} (90% CI: 6.3×10^{-12}–7.5×10^{-6}; mean 5.1×10^{-5}). Specifying 1-minute immersion (8-drop ingestion) and leaving all other nodes unspecified yields a median risk of 6.1×10^{-9} (90% CI: 5.5×10^{-11}–7.0×10^{-5}; mean 4.2×10^{-4}). These results indicate that risk is higher under direct ingestion scenarios. Risk also differs across the three worker subgroups included in the model. Without specifying any prior node states other than worker group, the model estimates that collection

system workers are at greatest risk given their assessed potential for wastewater ingestion while working in sewer mains and pump stations, with median risk of 7.1×10^{-12} (90% CI: 1.0×10^{-12}–3.7×10^{-8}; mean 3.2×10^{-6}) . Maintenance mechanics' median risk is 5.5×10^{-12} (90% CI: 1.0×10^{-12}–4.9×10^{-10}; mean 2.3×10^{-7}) due to their small but nonzero probability of wastewater ingestion as well as their potential exposure to wastewater that has not undergone tertiary treatment while working in the wastewater treatment plant. Treatment operators' risk is below the model's limit of detection of $1X10^{-12}$, as most of their work tasks do not result in exposure to wastewater. In general, these results suggest that risk is greatest for workers with exposure to higher volumes of wastewater through ingestion at points closer to hospitals treating EVD patients.

3.2. Effects of in-hospital disinfectant use

The three potential disinfectants that hospitals could apply to waste before flushing into the sewer system and that are included in this model have different effects on mean daily risk of developing EVD based on contact time (Figure 20). Peracetic acid is the most effective, with median risk reduced to 5.8×10^{-12} (90% CI: 1.0×10^{-12}–6.9×10^{-10}; mean 4.3×10^{-8}) after two minutes of contact and to 5.5×10^{-12} (90% CI: 1.0×10^{-12}–8.2×10^{-11}; mean 3.6×10^{-9}) after 15 minutes of contact for a scenario in which all variables other than those related to disinfection are unspecified. Quaternary ammonium cations (quats) were nearly as effective as peracetic acid after two minutes (median: 5.9×10^{-12}, 90% CI: 1.0×10^{-12}–8.9×10^{-10}; mean 6.5×10^{-8}), but longer exposure times did not produce substantial reduction in active viral concentration. Use of bleach yielded slower inactivation than quats during the first two-minute interval (median: 6.7×10^{-12}, 90% CI: 1.0×10^{-12}–3.8×10^{-8}; mean 2.7×10^{-6}), but resulted in a greater degree of

reduction in active viral concentration after 30 minutes than quats (median/mean risks 5.6×10^{-12}/6.9×10^{-9} for bleach, versus 5.8×10^{-12}/$4.5\times10^{-8}$for quats). These results suggest that peracetic acid is preferable to quats and bleach in mitigating downstream EVD risk, as its rapid and effective reduction in viral activity propagates through the network.

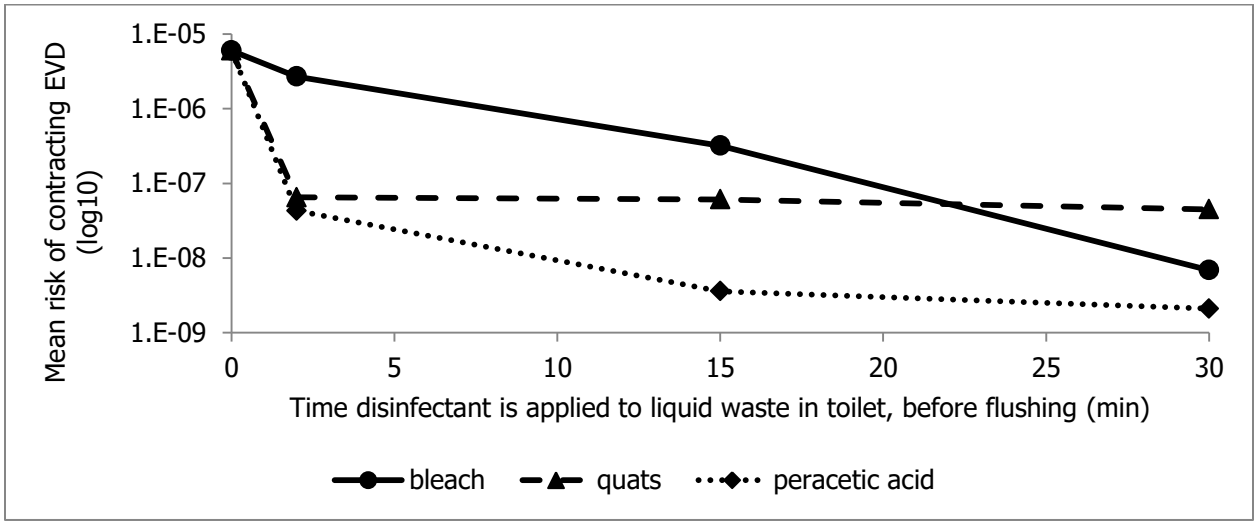


Figure 20. Effects of in-hospital disinfection on the risk to wastewater workers of contracting Ebola virus disease.

3.3. Variation in risk across distance from hospital

Examining risk at increasing distance from the hospital shows a predictable but nonconstant decrease in risk with distance. While the dilution effects illustrated here are specific to Raleigh's wastewater system structure, wastewater dilution in any system will produce a similar effect. The decrease is steepest over the first mile due to the rapid decrease in viral concentration that occurs as wastewater is diluted (Figure 21). A second region of steeper decrease in risk is also present for workers at distances farthest from the hospital due to the model's assumption that workers beyond five miles from the hospital are substantially more likely to be exposed to wastewater that has undergone tertiary treatment (where provided).

Figure 21. Effects of worker distance from hospital on the risk to wastewater workers of contracting Ebola virus disease.

3.4. Changes in risk with increasing number of EVD patients

Varying the number of EVD patients undergoing treatment in the hospital yields an interesting nonlinear response in downstream risk to wastewater treatment workers (Figure 22). Without specifying any nodes, and using the model's default assumption of one EVD patient in the hospital, mean daily risk is 1.8×10^{-6}. The mean risk approximately doubles to $3.8\times10^{-6}$with two patients and triples to 6.2×10^{-6} with three. However, specifying ten patients yields a mean risk of 1.6×10^{-5}, roughly eight times the risk from one patient. Examining this trend at higher numbers of patients generates a concave plot, with risk increasing at a decreasing rate with each successive addition of patients. Mean risk with 100 patients, for example, is 9.4×10^{-5}—approximately 52 times the risk from a single patient. As the distribution of active viral concentration for each patient is skewed (with high likelihood of low concentration), the effect of combining many such distributions is to reduce the simultaneous probability of higher concentrations, leading to a mean risk value lower than that obtained by simply multiplying single-patient risk by number of patients. It is important to note that during

the 2014-2015 Ebola outbreak, no more than two EVD patients were treated simultaneously in any single U.S. hospital.[208] Even so, the behavior of the model with greater numbers of patients offers potential insight into risk under severely worse epidemic conditions, or when dealing with other pathogens where greater numbers of patients could undergo simultaneous treatment.

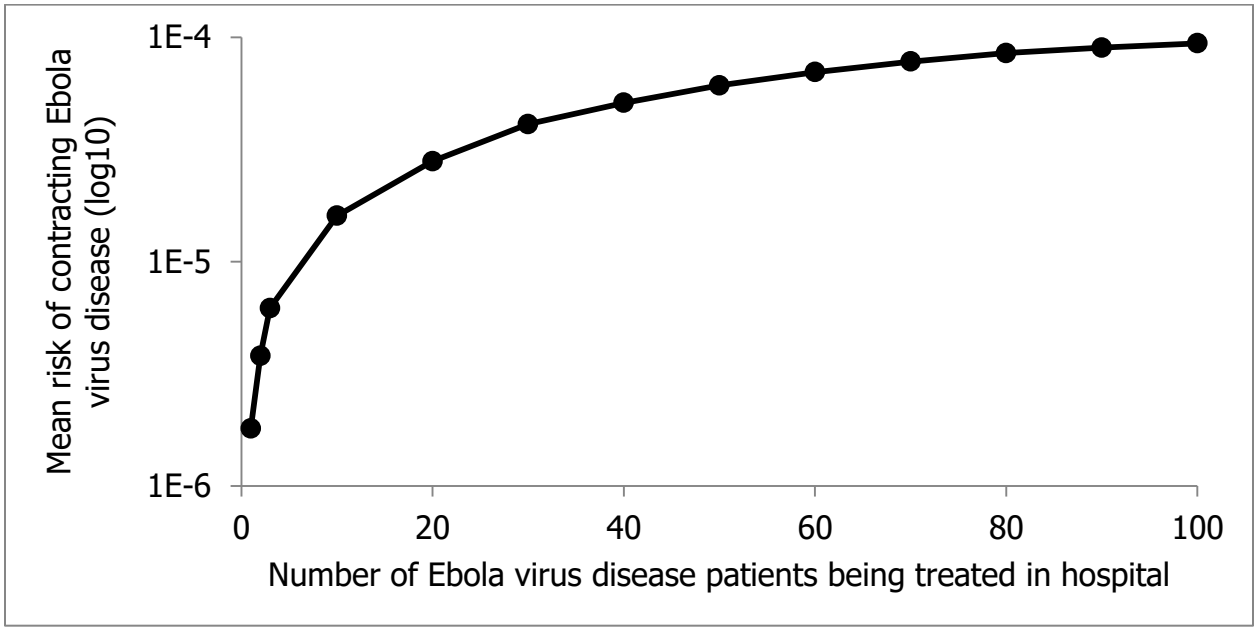


Figure 22. Effects of number of Ebola virus disease patients being treated in hospital on the risk to wastewater workers of contracting Ebola virus disease.

3.5. Sensitivity analysis

Sensitivity analysis was conducted to determine the effects of each parameter on the probability of developing EVD, while holding all other parameters constant under the assumption of 1-minute ingestion exposure (Figure 23). The analysis revealed that the worker's risk of developing EVD is most sensitive to the patient's disease state (i.e., the phase of illness in which daily diarrhea discharge exceeds 1 L heightens risk). Disinfectant used at the hospital ranks second, with dilution from the wastewater system ranking third and worker's distance from the hospital (a partial proxy for system dilution) ranking fourth. In-hospital dilution does

not seem substantial in the sensitivity analysis output, but this is somewhat misleading. In-hospital dilution is very important in reducing risk, but all three hospital sizes have similar dilution values (6.2×10^{-5}, 2.8×10^{-5}, and 1.6×10^{-5} in order of ascending hospital size), as EVD waste makes up a small fraction of the hospital wastewater regardless of the hospital's size.

Finally, time in the system and wastewater temperature have closely related impacts on risk. Ebola virus degrades more rapidly at higher temperatures, and as such, time elapsed has greater effect on risk when temperature is higher. Even so, the assessed sensitivity of risk to time elapsed at the highest temperature evaluated (29^{o}C), as measured by entropy reduction, is only 1.8%; at the lowest temperature assessed (15^{o}C), sensitivity is 0.03%. This relative insensitivity of risk to time elapsed is due to the rapid speed with which wastewater moves through the system. Under an assumption of a constant velocity of 1.07 m/s (3.5 ft/s, or 2.4 mi/hr), the model assigns very low likelihood to worker exposure occurring more than a few hours after EVD waste leaves the hospital.

Specifying time elapsed, however, shows a more substantial effect of variation in temperature at greater time. At the shortest amount of time elapsed in the model (less than half a day), risk sensitivity to variation in temperature is only 0.9%. When the greatest amount of time elapsed (three days) is specified, though, sensitivity to temperature is 10.5%. Variation in temperature can significantly impact a worker's risk of contracting EVD, but only if sufficient time passes before exposure occurs. The model considers such scenarios unlikely given wastewater velocity.

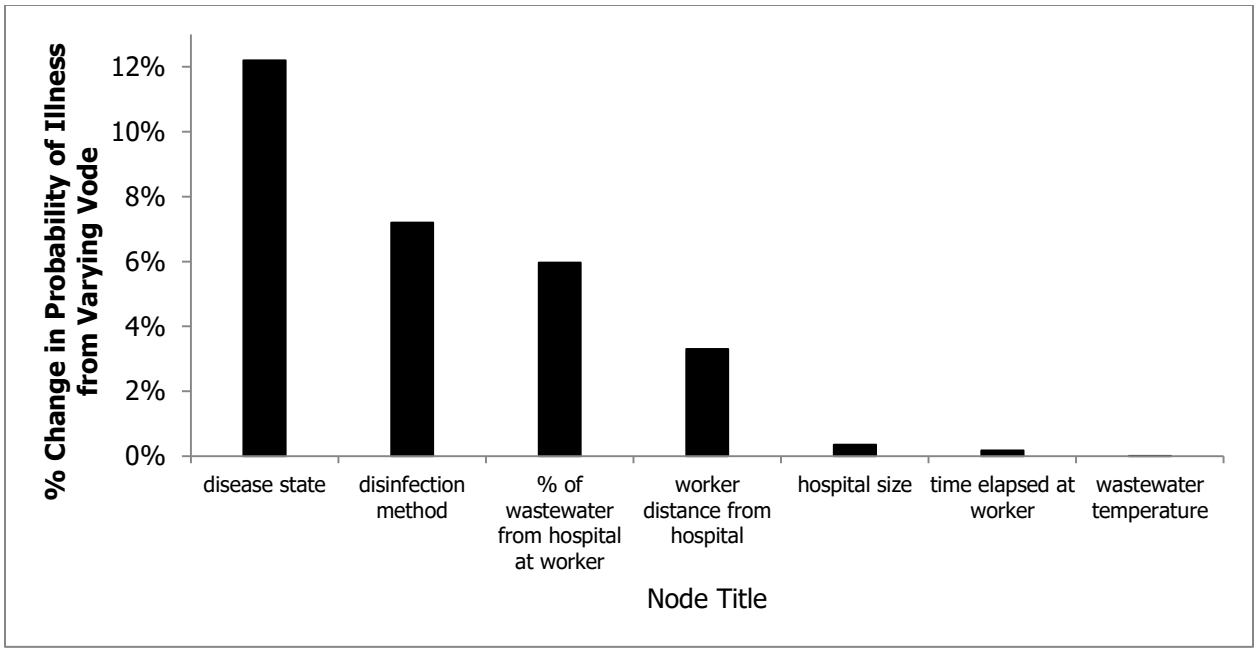


Figure 23. Results of sensitivity analysis, showing the sensitivity (entropy reduction) of risk of developing EVD after 1-min ingestion exposure to different model parameters.

While additional variability in sensitivity is possible with further scenario specification, other parameters' influence on risk remained relatively constant when evaluated under other scenarios. The factors to which risk is most sensitive warrant greatest attention in future research, as best modeling practices specify focus on reducing uncertainty in variables with greatest influence on the outcome of interest.[209]

3.6. Diagnostic inference

To illustrate the utility of BBN models in conducting diagnostic inference, the **Probability of illness** node was set to its highest value, and a most probable explanation analysis was run on the rest of the model. This test sets unspecified nodes in the model to the state(s) most consistent with the evidence entered. As expected, the analysis immediately identified key elements of the worst-case exposure scenario (wastewater ingestion, patient in the severe disease state, absence of in-hospital waste disinfection, etc.).

In a diagnostic application this backward inference procedure could be useful in identifying sets of conditions that could lead to a given outcome. For example, setting both the **Probability of illness** node to its highest state and the **Exposure volume** node to the inhalation exposure state shifted probability mass in the **Number of patients** node completely off the single-patient state. This indicated that even with all states available in all other nodes in the network, the model could not reconcile the highest risk of developing EVD with the inhalation exposure scenario without increasing the number of EVD patients in the hospital. In addition to its potential as a diagnostic tool, this procedure offered useful confirmation of the sensitivity analysis: it identified node states most consistent with high-risk outcomes that the sensitivity analysis identified as key drivers of risk.

4. Discussion

During the recent Ebola epidemic, workers in U.S. wastewater treatment facilities connected to hospitals treating Ebola patients expressed concerns about risks to their health due to hospital practices of flushing liquid waste from Ebola patients into the sewer system without prior disinfection. A BBN model was developed to assess risk of developing EVD for wastewater system workers, to test the effects of pretreatment in-hospital of EVD waste on this risk, and to examine which other parameters had greatest influence on risk. Without specification of any states within the model, mean risk was 5.6×10^{-7}. The 'worst-case' scenario assessed by the model, equivalent to the ingestion of approximately 8 drops of untreated water directly outside the hospital during a patient's severe illness phase, yielded mean daily risk of 8.9×10^{-3}. Through sensitivity analysis, the model determined that the most important factors in reducing risk are dilution and use of disinfectant on EVD waste before flushing. Of the

disinfectants incorporated in the model, peracetic acid was most effective in reducing risk. The substantial reduction in EVD risk for wastewater workers resulting from disinfectant use suggests that it may be advisable to mandate such in-hospital disinfection prior to flushing during future epidemics.

To our knowledge, the only other study assessing wastewater workers' risk of developing EVD through occupational exposure was recently developed by Bibby et al. and published as a report by the Water Environment Research Foundation (WERF).[180] The Monte Carlo model focuses on inhalation exposure for workers closest to the hospital and evaluates scenarios in which personal protective equipment is or is not used. The report concludes that in the worst-case scenario considered—with no personal protective equipment use and a one-to-one correspondence between Ebola concentration measured via PCR and infectious viruses—the median risk is approximately 1.7×10^{-6}. The authors stress that though no acceptable risk of EVD has yet been defined, this risk warrants concern.

While ultimately addressing a similar question, our study differs in a number of ways from Bibby et al.'s report. First, we consider ingestion risk in addition to inhalation exposure. We also account for wastewater system parameters (including temperature and dilution outside the hospital) that allow our model to assess risk for workers other than those adjacent to the hospital. The WERF report includes a thorough literature review to address inactivation of Ebola virus by various agents, but the effects of using disinfectant on EVD waste before flushing are not included in the Bibby et al. model. Our current model does not include a correction for use of PPE. Most important, though, are the differences between the WERF report's Monte Carlo simulation and our BBN approach. The BBN model can adapt to findings at

different nodes to generate risk profiles under different conditions, automatically updating all nodes based on entry of findings. In spite of these differences, under settings closest to those used by Bibby et al., the BBN model estimates mean risk from inhalation exposure for collection system workers close to the hospital as 2.5×10^{-5} (90% confidence interval: 3.7×10^{-9}–8.2×10^{-5}). This value is greater than the Bibby model's mean risk of 1.5×10^{-6}, but of the same order of magnitude as its third quartile risk (2.2×10^{-5}).

The BBN model has a number of limitations. First, the model relies on Raleigh's wastewater system parameters to estimate dilution, travel times, and temperature. The model is restricted to calculation of risk greater than or equal to its limit of detection (1×10^{-10}), which was set based on the model's assessment of risk under low viral concentrations and was required due to the need for state discretization in BBNs. The dose-response function used in the model was developed based on primate studies; consequently, this function may not be wholly accurate in predicting the human response to Ebola virus exposure, but no alternatives are available, and the same function was used by Bibby et al. The methods used to estimate exposure doses are also a limitation and could be improved with rigorous assessment of occupational exposure volumes in the specific context of wastewater workers. In addition, although the BBN model corrects for the potential for PCR to overestimate infectious viral particle concentrations, the correction is not specific to Ebola due to lack of data. Estimating viral concentration in EVD waste also proved challenging due to uncertainties about the presence of blood in waste. Finally, the time- and temperature-dependent degradation parameters for *Ebola virus* used in the model were extrapolated from published data but lack specific experimental confirmation.

More generally, the choice of a BBN rather than a Monte Carlo approach is not without tradeoffs. MC models more transparently incorporate functional dependencies. They are also able to efficiently use continuous variables without the need for discretization into states.[210] While BBNs are able to use continuous variables in theory, in practice the computational requirements for calculating joint and conditional probabilities using continuous distributions are currently prohibitive in most cases other than those involving Gaussian distributions.[63] The disadvantages of a BBN approach can be mitigated to an extent by careful choice of discretizations. Sensitivity of the model to these discretization choices can also be measured to characterize model stability and reliability. In addition, simulation of uncertain parameters can be incorporated into models. In this way, the functional dependencies that inform MC models can be replicated in BBNs. BBNs also provide several advantages over Monte Carlo approaches. First among these is their diagnostic capability, allowing for the tracing of observed outcomes (like cases of disease) to most probable root causes. Smid et al. provide an explicit demonstration of these advantages over MC techniques in the context of modeling pathogen contamination in the food supply chain.[63] In their model, microbial concentration in food is measured after passing through several steps of the supply chain. Knowledge of microbial growth factors during each of these steps allows for diagnosis of which state was responsible for contamination given final microbial concentration. A similar model could be used in an outbreak in which wastewater workers had potential exposure to a pathogen through occupational contact with wastewater as well as through their communities. By specifying known information about an infected worker, for example, the model could aid in pinpointing the actual exposure pathway.

In addition, BBNs' ability to absorb observed data and update all parameters accordingly could be useful in outbreak situations. Patients could be surveyed for relevant information (work tasks, recent location, contact with other patients, etc.), and this information could be added to the BBN. The model would then update remaining parameters (disease characteristics, effectiveness of protective measures, etc.) in relation to the data observed. For example, the model could include a node characterizing the effectiveness of occupational hazard prevention procedures in mitigating pathogen exposure. Added information from patients on their work tasks would update this hazard prevention node and could reveal weaknesses in these prevention procedures for certain groups of workers. The updated BBN could then be used to predict and respond to future outbreaks.

Combining epidemiologic studies with information on pathogen behavior and wastewater system characteristics allows for assessments of the risk of diseases spreading through these systems. BBNs provide a flexible and analytically powerful framework for modeling the interactions of pathogens and wastewater systems, and the model developed provides evidence that under certain scenarios, workers could be exposed to pathogens from wastewater originating in hospitals. Further investigation of this potential for exposure is warranted, including better specification of wastewater system parameters and workers' exposure to wastewater through different routes. Incorporating this information into BBN models would clarify understanding of the need for interventions to decrease risk of infection through occupational exposure to wastewater.

CHAPTER 5: CONCLUDING REMARKS

1. Key Findings

This dissertation advances the use of Bayesian network (BN) modeling to improve environmental health risk assessment in support of policy-making. The National Research Council recently identified key needs for improvement to the risk assessment process[6], and Bayesian networks are shown to respond to several of these needs in practice. Bayesian networks are used to model dose-response relationships between environmental toxicants and health outcomes, and to simulate the effects of changes in toxicant exposure on incidence of these outcomes. A BN is also used to determine risk of infection during a microbial outbreak, identify key factors affecting risk, and simulate the effects of risk mitigation decisions. Together, these projects demonstrate the advantages of using BNs in environmental human health risk assessment.

Chapter 2 describes the use of a Bayesian network model to address the need for improvements to dose-response assessment. It is the first application of a machine-learned Bayesian network to human health dose-response assessment. The model developed is shown to perform significantly better in predicting birthweight for gestational age from available data than either of the two methods (reference dose and slope factor approach) currently used by the EPA for dose-response assessment. The BN also performs much better in balancing sensitivity and specificity in prediction.

In Chapter 3, the performance of a Bayesian network model learned from data relative to other dose-response techniques is demonstrated. The research builds on the proof-of-concept BN approach to dose-response demonstrated in Chapter 2. The BN's ability to perform out-of-sample prediction of dysglycemia (diabetes and prediabetes) while balancing sensitivity and specificity is demonstrated. The BN performs comparably to the logistic regression model in prediction. In addition, the BN dose-response model is used to investigate other relationships between variables in the study cohort. The overall effect of arsenic metabolism on dysglycemia risk is confirmed, but this effect is shown to be weaker in overweight individuals than those with normal or obese BMIs. The model is also used to simulate how changes in the Mexican population could affect dysglycemia risk. The effects of both changes in overall obesity rates and in arsenic exposure levels through drinking water are simulated. A reduction of population exposure to arsenic below 50 μg/L (twice the current Mexican regulatory standard) yields roughly the same decrease in dysglycemia prevalence is predicted from a 5% reduction in obesity. This finding emphasizes the importance of considering arsenic exposure mitigation, as reduced dysglycemia risk could be comparable to gains from more familiar reduction in BMI. These reductions in risk are translated into cases of diabetes avoided for a subpopulation in an arsenic-endemic region of three Mexican states. Finally, these avoided cases are compared to the predicted number of avoided cases of bladder cancer (the health outcome by which regulation has been made in the U.S.[4]) from the same change in arsenic exposure. The results show a reduction of roughly ten times as many cases of diabetes as bladder cancer. Because US agencies currently consider only cancer risk in setting permissible arsenic levels in drinking

water, this finding illuminates substantial benefits to health from reduced toxicant exposure that may be overlooked in the regulatory process.

Chapter 4 provides additional support for the use of Bayesian networks to inform environmental health decision-making. The BN model developed is used to quantify risk to wastewater treatment workers of developing Ebola virus disease (EVD) through occupational contact with contaminated water during an outbreak. The need for this model arose during the 2014 EVD outbreak, and was built in response to a request from the wastewater treatment industry for quantifications of EVD risk and how different risk management options could affect that risk. There was also a need to evaluate the effectiveness of existing policies in protecting workers, and the BN model was developed to respond to these needs for policy analysis and development. The model shows EVD risk to be low (10^{-12}-10^{-9}) in general, but higher by several orders of magnitude (10^{-6}-10^{-4}) under a simulated worst-case scenario involving ingestion of concentrated, untreated wastewater. In addition, the model uses backwards diagnostic inference to identify parameters with greatest effect on risk (wastewater dilution and in-hospital waste disinfection). This capability informs the development of policies to protect wastewater treatment workers; based on model simulations, 15-minute disinfection with peracetic acid prior to flushing reduces risk to workers in the worst-case scenario by several orders of magnitude.

2. Policy Implications

The work in this dissertation demonstrates the ability of BN modeling to respond to the need for specific improvements in the risk assessment process in support of public health decision-making. These projects have direct relevance to several actionable areas of policy.

2.1. Dose-response assessment improvements

The results of this dissertation confirm that Bayesian networks can perform as well as, or better than, current dose-response assessment methods without the need for assumptions of functional form or restriction to data from animal studies in which dose-response relationships are tested explicitly. For this reason, Bayesian networks should be more widely used to conduct dose-response assessment. BNs have a number of characteristics in theory that make them attractive modeling tools. These include probabilistic rather than function-based characterizations of systems, ability to propagate changes to variables to other variables in the network, and the possibility of using backwards diagnostic inference rooted in Bayesian updating to identify key factors affecting outcomes. The advantages identified in theory, and confirmed in practice, make BNs a valuable tool for dose-response analysis; the abilities to capture interacting relationships without assumptions of functional form and to specify risk for particular subgroups are especially relevant. In addition, BNs' flexibility easily allows for the integration of both cancer and non-cancer risk into dose-response and risk assessment frameworks. For this reason, BNs should be used to develop dose-response models for both cancer and non-cancer health outcomes in response to the need identified by the National Research Council for these kinds of dose-response assessments. Given that regulatory analysis currently places disproportionate weight on cancer outcomes[6], unified assessments using BNs can better inform policy-making.

2.2. Unifying dose-response models and simulation of policy effects

As demonstrated in Chapter 3, Bayesian networks permit closer integration of dose-response models with simulation of the effects of changes in exposure to environmental

hazards. This ability can allow policy-makers to rely on a single model to capture both dose-response relationships and population-level health characteristics rather than segregating these models. The addition of cost-benefit analysis to the Bayesian network structure can further integrate risk management and risk assessment, consistent with the goal of an iterative process proposed by the National Research Council.[6] BNs' ability to simulate and quantify effects of policy decisions on incidence of non-cancer health outcomes is particularly relevant given the current lack of attention to these outcomes in setting policy.

2.3. Disease management improvements

The work in this dissertation also suggests more specific use of Bayesian networks in managing response to environmental health risk during crises like outbreaks of infectious disease. While intended to assess risk of Ebola virus disease, the model developed in Chapter 4 could be adapted to reflect the particular characteristics of other pathogens; the underlying parameters of hospitals and wastewater systems remain the same. This suggests the value of using Bayesian networks to capture complex environmental health systems, and then specifying those models to particular pathogens in response to particular outbreaks. The absence of this sort of underlying model we encountered in performing the work in Chapter 4 suggests a need for these kinds of generalized, modular structures. This need has been recognized in the risk management community: for example, the World Health Organization has called for the development of mathematical models that can be used to quickly and effectively map disease risk and spread in order to response to outbreaks.[211] Bayesian networks' demonstrated flexibility and adaptability enforce the advantage they could provide in these contexts.

3. Limitations

The research in this dissertation is limited in a number of ways. First, any analysis of single datasets is bound by the limits of those datasets; error, bias, and simple sampling variability all reduce confidence in any statistical conclusions drawn. While the data used in this dissertation provide insight, results could be confirmed with the use of additional datasets (targeting other health outcomes, and with other relationships driving outcomes). It is important to note that this limitation applies more to the specific implications to policy with respect to arsenic-influenced health outcomes and infectious disease management, rather than the broader ability of BNs to be applied in risk assessment for risk management in public health. Demonstration of this ability in this dissertation is in agreement with a substantial body of theoretical and applied literature reviewed in Chapter 1.

The conclusions in Chapter 2 are primarily limited by the size of the available dataset. While the 200-member cohort was sufficient to demonstrate the advantages of using a Bayesian network in performing dose-response assessment over current methods, the model's predictive abilities are still limited. In addition, low birthweight is a complex health outcome that depends on many factors.[212] The dose-response assessment conducted could be improved with additional data incorporating more of these factors.

While the dataset used in Chapter 3 is roughly five times larger than that used in Chapter 2, the complexity of the underlying relationships demands that the chapter's conclusions be considered carefully. As has been discussed in the literature at length, diabetes is a complex disease with a complex set of mitigating and exacerbating factors, some of which remain poorly understood.[213] In addition, the public health predictions derived using the model

are limited by the extent to which it could be adjusted to reflect the broader Mexican population. The decision to focus on approximately 1.3 million people living in an arsenic-endemic region of Mexico was a compromise between focusing on a much smaller population (the study cohort) for which data was readily available, and generalizing to a much larger population (Mexico as a whole) across which the factors considered in the model are impossible to quantify with confidence based on current data availability. In addition, a major limitation of this work is its focus on people of mixed Amerindian-Caucasian descent. Existing literature provides some evidence of variation in arsenic metabolism among people from different ethnic groups (including those of indigenous American ancestry) [214,215] as well as in susceptibility to diabetes.[216,217] While the methods could be applied to data from these other groups, caution must be used in generalizing insights from this research effort to them.

Similarly, the greatest limitation of Chapter 4 arises from the data and assumptions used to characterize several model parameters. Wastewater system variables (distances, wastewater temperature, etc.) were based on data from Raleigh, NC, and extrapolation to other systems with substantially different characteristics should be done with caution. In addition, it was difficult to characterize the probability of internal hemorrhaging (necessary for a patient's waste to contribute a significant viral load to wastewater) due to limited and substantially variant data in the literature. Finally, the model does not correct for the use of personal protective equipment (PPE) by wastewater treatment workers. Literature across a range of fields has shown poor compliance with PPE policies[218–221], which could lessen these policies' impact on risk in practice. However, the potential of PPE to mitigate risk if used properly still merits further attention.

These limitations, though important to consider, do not detract from the major conclusions of this dissertation that BNs are able to address key technical and practical needs in risk assessment. The advantages BNs provide have been shown to apply even given the limitations on data outlined above. Indeed, the specific research conclusions of the projects could be generalized more fully given additional data (on additional wastewater systems, for example, or on other ethnic groups' responses to inorganic arsenic). BNs' demonstrated performance with limited data in responding to needs for improvement to the risk assessment process supports expanded use of BN modeling in risk assessment more generally, including in environments where more data is available.

4. Future Research

The results of this dissertation suggest direction for a number of future research projects. Most prominently, the application of Bayesian network models to risk assessment to support environmental health policy-making should be expanded and tested in practice.

4.1. Regulatory risk assessment of hazardous chemicals based on animal data

One specific project meriting exploration is a comprehensive risk assessment of a toxicant currently regulated by the EPA based exclusively on animal data (like carbon tetrachloride, for example), using a Bayesian network rather than or in addition to current methods. Such an assessment would illustrate the advantages of a BN approach in direct comparison to process currently used. The development of a BN to perform this assessment would start with a review of EPA documentation to determine literature and studies used in the development of the current regulation. This literature review could be augmented by a search for more recent data relative to the assessment. Then, a BN could be developed using the data

from the studies reviewed connecting exposure with health outcomes. In current practice, models are usually based on a single health indicator as the outcome using data from a single study. The BN could incorporate multiple indicators using data from multiple studies to provide a more comprehensive reflection of underlying data.

For example, the current assessment for carbon tetrachloride is based on measurements of serum sorbitol dehydrogenase as an indicator of liver injury; the data used to develop the reference dose comes from a study conducted on rats by Bruckner et al.[222] The assessment, however, reviews a number of other studies as well as additional indictors of injury (including alkaline phosphatase and ornithine carbamoyltransferase). Information on kidney damage is also discussed, though not used in the assessment. A BN model could easily incorporate these different sources of information, with weighting based on the sizes of the studies themselves or on expert knowledge. The BN would contain the current assessment, but its flexibility would allow for the incorporation of additional information that would more comprehensively link exposure data and health outcomes. In addition, the model could test for agreement among studies and different indicators of the same health outcome. This information would be helpful in characterizing uncertainty and informing regulatory policy. Current practice uses uncertainty factors to address deficiencies in underlying data (due to both quality and quantity). A BN could incorporate these factors if desired, but could also assess the reliability of available study data more rigorously by comparing sample sizes, variance within datasets, and agreement across different studies. Once developed, the conclusions of a BN model of this kind could be compared directly to the conclusions underpinning current regulation.

4.2. Using modern toxicity data in risk assessment

Research has established a relationship between epigenetics and a broad range of health outcomes. While the work in this dissertation does not address epigenetics, Bayesian network models are capable of incorporating this information along with other factors to predict incidence of disease or to identify groups at risk. Indeed, the incorporation of epigenetic information into the risk assessment process has been proposed due to the significant information added to understanding risk of disease outcomes[223]; Bayesian networks offer a tool to accomplish exactly this integration. Similarly, methodological challenges around the incorporation of *in silico* toxicity data and information from high-throughput assays into the risk assessment process remain.[224] Bayesian networks' flexibility invites an attempt to use these data along with more traditional dose-response data, in which lab animals' physiological and biochemical responses to calibrated toxicant doses are measured, to better assess relationships among factors driving health outcomes and improve models' predictive performance. Developing methods to integrate these data into dose-response models is a crucial step in expanding the use of BNs in dose-response and risk assessments to take better advantage of their capabilities.

In practice, a Bayesian network incorporating these different types of data could begin with an assessment of links within an epigenetic dataset; the model generated would provide a statistical description of different patterns and epigenetic associations. Recent developments in algorithms to recover these kinds of associations have demonstrated BNs' ability to accomplish the task accurately relative to other methods while also reflecting uncertainty in the relationships discovered.[225] A separate BN could be used to capture relationships between

toxicant exposure and biochemical response from high-throughput assays, using machine learning algorithms similar to those employed in this dissertation.[226,227] Available metabolic data – like that used in Chs. 2 and 3 – could also be linked to health outcomes of interest in a third BN. Once constructed, these BNs could be joined. With no overlapping information (for example, no health outcome data in the epigenetic dataset or epigenetic data in the metabolism dataset), this joining could first be accomplished under guidance from experts (by, for example, building links between particular epigenetic and demographic profiles). Similarly, joining animal or *in silico* data could be accomplished using expert expertise. These expert-defined relationships could be tested more rigorously in the presence of overlapping data between different kinds of datasets. Once compiled, this kind of BN would link available data to allow for the estimation of health outcomes. Furthermore, the BNs' backwards diagnostic inference capability would allow for nodes and states associated with high risk to be identified, potentially informing policy or screening efforts. In addition, BNs offer an ability to characterize uncertainty in this kind of assessment through measures like entropy reduction (used in Ch. 4). These metrics reflect how well different nodes agree or disagree with one another, and can also be used to quantify how much information knowledge of one variable or set of variables brings to outcomes of interest. This information can provide a crucial check on whether data within the model agree, and can also help to prioritize the collection and exploration of additional data with greatest power in reducing model uncertainty.

4.3. Incorporating BN models into regulatory practice

The next step in exploiting BNs' advantages in risk assessment applications is their explicit use by regulatory risk assessors contemplating policy changes. To achieve this

application, future research could involve collaborative work with EPA assessors in which BN models are developed in real time to model changes in regulation under consideration (including these changes' effects). This collaboration would demonstrate the advantages of BNs in policy development to those actually responsible for setting regulations.

To accomplish this collaboration, future researchers should first interview risk assessors to understand changes contemplated and the motivation for updating current regulation; perhaps new data have become available about the toxicant, or evidence about additional health impacts requires consideration. Based on this understanding, researchers would then develop traditional and BN models to respond to risk managers' needs using available data (for example, developing a BN to capture relationships from data on neurodevelopment and inorganic arsenic exposure). The models could be augmented to incorporate features like cost-benefit analysis if desired. Once completed, these models would then be presented to the risk managers for evaluation based on clarity, ease of use, flexibility, content, and confidence in outcomes (including the models' predictive capacity as well as ability to provide insight into biological interactions). Risk managers' input would be solicited through a survey assessing these factors, and their suggestions for changes and expansions to the models to improve utility would also be gathered. Based on this feedback, improvements would be made to the models, which would then be presented to the risk managers again and graded on improvements and flexibility. Again, a survey could be used to capture this feedback in a more structured way.

This study of responses to and perceptions of BNs is crucial to their further application. The data gathered from surveys and collaboration with risk managers could be used to isolate

and illustrate key advantages of BNs (or traditional models) from these managers' perspective, and to guide the development of a formalized protocol for conducting environmental human health risk assessment using BNs as the analytical method of choice. This protocol, developed in collaboration with those whose work depends on risk assessment's outputs, would provide a roadmap for expanded BN use in the risk assessment and risk management processes.

4.4. Software and algorithm needs

The ability of computing resources to handle complex Bayesian networks has grown substantially in recent years. Available software packages (like Netica and BayesiaLab, the applications used in this dissertation) are flexible and relatively straightforward to use. In addition, there exist packages in the open source statistical computing language R that allow BN construction, though using them requires a certain degree of expertise in statistical programming. Together, these tools provide a foundation for the development of BNs for use in human health risk assessment.

However, a key step in the application of BNs to this field in a sustainable, systematic way will be the development of integrated software tools designed to absorb relevant data (outlined above, including demographic, clinical, metabolic, epigenetic, and high-throughput assay data), and provide probabilities of risk as outputs. The ability to conduct cost-benefit analysis will also be a necessary addition to make this tool useful to risk managers and policymakers. EPA's benchmark dose software (BMDS) provides a useful example of this kind of software solution. BMDS incorporates the modeling tools (various kinds of regressions) within an interface designed to accept data from dose-response studies. It allows the user to specify different parameters relevant to dose-response assessment, and outputs functions and

benchmark doses that can be used in the risk assessment process. A BN tool developed specifically for human health risk assessment would similarly include BN 'machinery' (updating, structure learning algorithms, etc.) within a framework designed to accept relevant data and to output health and cost information important to the assessment. Such a software tool would retain the theoretical advantages of BNs while making their use straightforward for risk assessors, managers, and policymakers.

Finally, future research must continue to improve the understanding of BNs and the ability of computational techniques to exploit their advantages to the fullest. Bayesian networks' major computational limitation remains their inability to capture continuous distributions in nodes, necessitating discretization. This limitation is not absolute, as there exist packages that characterize mixtures of Gaussians or exponentials.[228] However, recent literature suggests that the inability of (free) software packages to allow mixing of discrete and continuous data, as well as Bayesian inference, is a particular limitation in combining genomic, clinical, and demographic data in bioinformatics applications.[154] While some solutions to these issues are emerging in the literature[154], the development of BNs that can handle complex biological data with fewer restrictions will increase their usefulness.

There also remain open theoretical questions around methods of efficiently learning Bayesian network structure. In practice, these concerns are not very relevant when data can be processed by available algorithms in a tractable amount of time. In biological situations with many data points, however, improvements to the efficiency and accuracy of algorithms are necessary. Recent research has made progress in the development of exact algorithms for network structure learning. Unlike approximate learning methods, these algorithms guarantee

globally optimal structure according to a particular objective function (an NP-hard problem). While they remain computationally intensive, implementation of algorithms based on integer programming using cutting planes has shown promise; these algorithms would provide substantial value in eliciting structures in biological systems, and merit further research.[229] Finally, the possibilities of the just-emerging field of quantum machine learning to improve Bayesian network performance are truly exciting. While quantum computers are not yet a reality, there already exist theoretical generalization of BNs within the field of quantum information theory (called generalized Bayesian networks).[230] Early work on these systems has shown promise in vastly expanding BNs' ability to elicit causality[231], which could be of tremendous value in better understanding of the relationships within biological systems. Research in this vein should continue so that the theory and algorithms are ready for use when these machines become viable in practice.

5. Conclusions

This dissertation expands the use of Bayesian networks in environmental risk assessment applications to support the development of policies protecting human health. The ability of Bayesian networks to capture dose-response relationships and improve upon current methods is illustrated in Chapter 2; the utility of using BN models in these contexts is demonstrated through simulations of policy effects and resultant population-level health changes in Chapter 3. The assessment of risk to human health from environmental chemical contaminants is complemented by the use of BNs to quantify risk from a microbial source in Chapter 4. The utility of this approach to decision-makers is further demonstrated through

identification of factors driving risk and simulation of the consequences of different risk management decisions.

Crucially, this dissertation establishes a solid justification for applying Bayesian networks in environmental human health risk assessment in response to needs for improvement to the process identified by the National Research Council. BNs' ability to respond to these needs suggests that their use in risk assessment should be further investigated in research, and expanded in practice.

APPENDIX A: SENSITIVITY ANALYSIS METHODOLOGY (CH. 2)

Sensitivity analysis was conducted using Netica software (available from Norsys Software Corp., Vancouver, BC, Canada) according to the following procedure. First, the entropy of the target node *X* (designated *H(X)*) is calculated. This value gives an indication of the sample's homogeneity. The formula used is:

$$H(X) = \sum_{x \in X} p_x log_2(p_x)$$

(18)

where *X* indicates the set of states of *X* and p_x indicates the proportion of cases in state $x \in X$. In this study, for example, *X* = {*lower BWGA*, *middle BWGA, higher BWGA*}, and $p_{lower\ BWGA}$ = 57/200 = 0.285. Choosing a node *S* to test for sensitivity, entropy is then calculated again for the target node *X* given the specification of the test node to each of its possible states. The entropy reduction for each test node is calculated as:

$$\Delta H = H(X) - H(X|S)$$

(19)

A node with high entropy indicates high uncertainty across the states. Correspondingly, a reduction in the entropy of the target node through the specification of another node indicates that information about the latter allows for better specification of the states of the former.

APPENDIX B: POPULATION SHIFT ANALYSIS (CH. 3)

Population shift characteristics

To simulate the Mexican adult population, the gender, age, and BMI group distributions learned from the study group were adjusted. Existing probability relationships within the network propagated these shifts to other variables (smoking, alcohol consumption, etc.).

Table 9. Study group and Mexican population characteristics.

Node	States	Study group	Mexican population
gender[232]	male	36.6%	48.8%
	female	63.4%	51.2%
BMI group[233]	normal	22.6%	35.6%
	overweight	33.0%	36.3%
	obese	38.6%	28.2%
age[232]	<=24	9.5%	18.6%
	<=29	8.9%	11.5%
	<=34	9.8%	11.0%
	<=39	11.2%	10.7%
	<=44	8.8%	10.3%
	<=49	11.3%	8.5%
	<=54	10.3%	7.6%
	<=59	9.0%	6.1%
	<=64	7.4%	4.8%
	<=69	5.1%	3.7%
	<=74	5.0%	2.8%
	>74	3.6%	4.3%

Avoided cases of bladder cancer

In its risk assessment for bladder cancer from exposure to inorganic arsenic through drinking water, the EPA uses two estimates (lower and upper bounds) of lifetime cancer risk slope factor per person per 1 μg/L arsenic assuming average water consumption of 2 L/day: 1.46×10^{-5} and 2.47×10^{-5}.[4] These factors were used to derive lower and upper bounds on numbers of bladder cancer cases under current arsenic exposure conditions for approximately

1.3 million people living in three arsenic-endemic Mexican states.[142] After simulation under which exposure of this population was reduced to below the current Mexican regulatory limit of 25 µg/L, lower and upper bounds on numbers of bladder cancer cases were again estimated. The differences between pre- and post-simulation numbers of cases provide lower and upper bound estimates of cases avoided (1087 and 1839). Details of intermediate calculations are shown in the table below.

Table 10. Calculations of estimated bladder cancer prevalence under current arsenic exposure conditions, and if arsenic exposure were reduced to below the current regulatory limit.

				current				adjusted			
As exposure state (µg/L)	mean As concentration (µg/L)	lower bound lifetime risk per person	upper bound lifetime risk per person	population in each As exposure state, from study data (%)	population in each As exposure state	cases of bladder cancer (lower bound)	cases of bladder cancer (upper bound)	population in each As exposure state (%)	population in each As exposure state	cases of bladder cancer (lower bound)	cases of bladder cancer (upper bound)
<=10	1	1.3E-05	2.2E-05	17%	224,595	3	5	68%	913,949	12	20
<=25	18	2.6E-04	4.3E-04	8%	104,738	27	45	32%	426,152	109	185
<=50	41	6.0E-04	1.0E-03	29%	391,629	234	396	0%	-	0	0
<=100	69	1.0E-03	1.7E-03	30%	395,455	401	679	0%	-	0	0
<=150	119	1.7E-03	2.9E-03	9%	118,764	206	349	0%	-	0	0
<=200	174	2.6E-03	4.3E-03	3%	37,159	95	160	0%	-	0	0
>200	244	3.6E-03	6.0E-03	5%	67,761	242	410	0%	-	0	0
totals					1,340,101	1,208	2,044		1,340,101	121	205

APPENDIX C: MODEL CONSTRUCTION AND NODE PARAMETERS (CH. 4)

Estimation of conditional probabilities

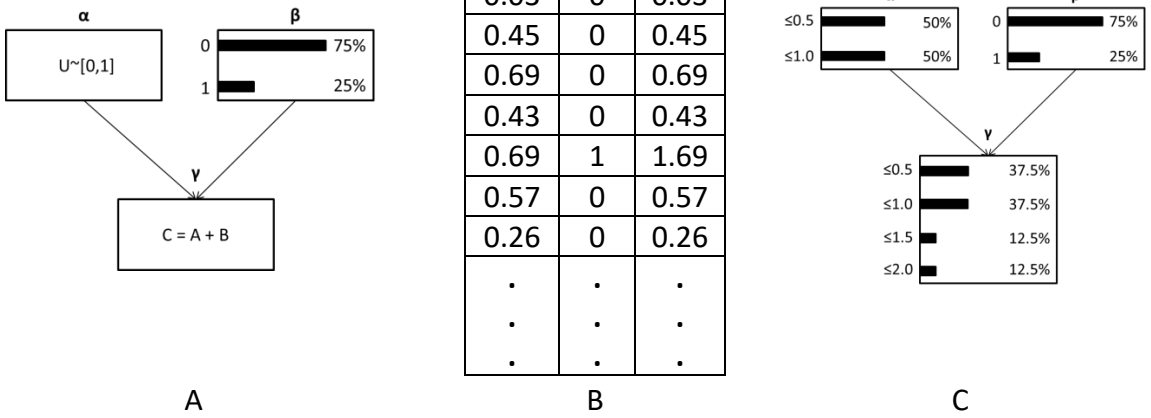
Once the model's structure was established, all equation-based relationships between nodes were added. For example, the value of Concentration in patient waste is the product of Presence in hospital discharge, Hemorrhage correction, and PCR correction. Marginal probabilities were also added to the model where these were known based on underlying literature and data. For example, marginal probabilities of the states of the node Temperature correspond to the frequencies with which these temperatures were observed in the dataset cited.

Simulation was then used to generate 100,000 instances of the model. In each instance, values of nodes without functional dependencies were drawn from their marginal distributions. These values were then used to determine values of nodes functionally dependent on other nodes. The simulated dataset was then used to determine conditional probabilities throughout the network by frequency analysis.

An example of this process is shown in Figure 24. In the simplified network, there are two parent nodes (α and β) and a child node, γ. The value of α is drawn at random from a uniform distribution with range [0,1] and is ultimately discretized into two states of equal width. β has two states, with a pre-defined marginal probability of state 0 of 75% and probability of state 1 of 25%. The value of node C is simply the sum of the values of α and β. Its range is [0,2], and it is discretized into four states using the same increment (0.5) as node α.

The simulation process is represented in Figure 24. For each instance of the model, a row with values of all three nodes is generated. The resulting table is then analyzed to determine

conditional probabilities for all states of γ and all combinations of α and β. The resulting conditional probability table is shown in Table 11.



α	β	γ
0.37	1	1.37
0.03	0	0.03
0.45	0	0.45
0.69	0	0.69
0.43	0	0.43
0.69	1	1.69
0.57	0	0.57
0.26	0	0.26
.	.	.
.	.	.
.	.	.

A B C

Figure 24. Example of BBN compilation process. Nodes are first populated (A) with underlying random variables (α), marginal distributions (β), or functional dependencies (γ). Joint instances of the model are then simulated (B), with each simulation producing a set of values for each node in the model. The resulting simulated dataset is then analyzed to determine remaining distributions (C).

Table 11. Posterior conditional distributions.

C	**A**	**B**	P(**C**|**A**,**B**)
≤0.5	≤0.5	0	100%
	≤1.0	0	0%
	≤0.5	1	0%
	≤1.0	1	0%
≤1.0	≤0.5	0	0%
	≤1.0	0	100%
	≤0.5	1	0%
	≤1.0	1	0%
≤1.5	≤0.5	0	0%
	≤1.0	0	0%
	≤0.5	1	100%
	≤1.0	1	0%
≤2.0	≤0.5	0	0%
	≤1.0	0	0%
	≤0.5	1	0%
	≤1.0	1	100%

Causality

Bayesian belief networks can represent causal associations between variables through the direction of the arc connecting different nodes (the arc points in the direction in which causality flows). In models in which causality is uncertain, assertions of causal relationships must be tested. In the BBN constructed in this paper, the causality underlying connections between variables is derived from underlying source literature and consultations with experts. In particular, factors that quantify the effects of different factors (temperature, in-hospital waste disinfection, etc.) on Ebola virus survival in wastewater are included with a presumption that the relationships themselves are causal – that is, that these factors actually do effect the concentration of viable Ebola virus in wastewater. While BBNs can be used to test for causality when uncertainty is present, doing so in this model would not be informative given as accepting the causality of relationships asserted in underlying literature is a necessary assumption to construct the model.

Discretization

BBNs generally require that all nodes be discretized into a finite number of states. Discretizations in this BBN were chosen based on natural categories arising from the concepts being modeled. When deciding how to construct a node, literature was first consulted to determine appropriate bounds on uncertain parameters and a distributional form to populate the range specified. The range was then divided into a discrete number of states.

For example, the node PCR correction relies on three studies of the factor in question (the correction factor relating viral copies detected by polymerase chain reaction techniques to infectious viruses present). One study arrived at a single value for this factor (0.0398). The other

two presented ranges, without further specification: [0.0001, 0.1] for one study, and [0.00079, 0.1] for the other. Estimates of the correction factor based on these studies were drawn from distributions with uniform dispersion across these ranges. PCR correction was then discretized into five states. One was localized to the point estimate 0.0398, and the other four covered the remaining space from the ranges derived from the studies: [0 to 0.001], (0.001 to 0.01], (0.01 to 0.0398), and (0.0398 to 0.1]. Conditional probabilities for each of these states were then determined using the simulation procedure described in 'Estimation of conditional probabilities' above.

Model nodes, states, and marginal probabilities

Table 12. BBN nodes and supporting information.

Title	Units	States	Marginal State Probability	Number Associated with State (disinfection factor, etc.)	Description	Data Source Type	Source Size per Study (n)	Potential Sources of Uncertainty
Disease state	-	severe nonsevere	0.333 0.667	-	phase of illness with diarrheal discharge ≥1L/day, or not	literature	1; 37; 2; 1	limitations in literature on measurements of viral concentration in waste; small sample sizes
Initial viral concentration	particles/mL	up_to_1e1 up_to_1e2 up_to_1e3 up_to_1e4 up_to_1e5 up_to_1e6 up_to_1e7	0.219 0.221 0.222 0.089 0.084 0.083 0.083	-	calculation of uncorrected viral concentration in diarrhea from patient	literature	-	limitations in literature on measurements of viral concentration in waste; small sample sizes
Hemorrhage correction	-	study 1 study 2 study 3 study 4 study 5 study 6 study 7	0.018 0.221 0.318 0.010 0.011 0.021 0.402	0.243 0.040 0.009 0.250 0.435 0.023 0.057	probability of patient experiencing gastrointestinal hemorrhaging	literature + expert opinion	37; 464; 666; 20; 23; 44; 843	weighting method presumes equal quality of data across studies considered
Concentration in patient waste	particles/mL	up_to_1en2 up_to_1en1 up_to_1e0 up_to_1e1 up_to_1e2 up_to_1e3 up_to_1e4 up_to_1e5 up_to_1e6 up_to_1e7	0.267 0.202 0.178 0.118 0.084 0.075 0.056 0.019 0.004 0.000	-	calculation of viral concentration in patient waste	functional	-	-
Disinfection method[1]	-	bleach quats peracetic acid none	0.250 0.250 0.250 0.250	-	type of disinfectant used in hospital	-	-	-
Exposure time[1]	minutes	two min fifteen min thirty min	0.333 0.333 0.333 0.333	-	duration of exposure to disinfectant used in hospital	-	-	-

Attenuation	-	none low bleach med bleach high bleach low quats med quats high quats low peracetic med peracetic high peracetic	0.250 0.083 0.083 0.083 0.083 0.083 0.083 0.083 0.083 0.083	1.000 0.333 0.039 0.001 0.012 0.010 0.006 0.005 4.3×10^{-4} 3.1×10^{-4}	viral attenuation from hospital disinfection	literature	-	low uncertainty expected; underlying study was designed to examine attenuation of an Ebola virus surrogate in a toilet through disinfectant use
Temperature of WW	ºC	<15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 >29	0.28 0.03 0.05 0.05 0.02 0.05 0.05 0.03 0.03 0.05 0.06 0.08 0.11 0.04 0.01 0.06	0.084 0.145 0.206 0.267 0.327 0.388 0.450 0.510 0.571 0.631 0.692 0.753 0.814 0.875 0.935 0.999	expected temperature of wastewater in system	literature + expert opinion		low uncertainty expected; data is taken from temperature measurements
Number of patients	number of patients	1 2 3 10 20 30 40 50 60 70 80 90 100	1.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.00	-	number of EVD patients in the hospital	-	-	-
Work group	-	collection system worker maintenance mechanic WW treatment operator	0.536 0.219 0.245	-	wastewater worker type	survey data + expert opinion	224	worker group categories limited to those used/defined by Raleigh, NC Wastewater Utility
WW treatment passed	-	pretertiary tertiary	0.673 0.327	1 0	whether worker is exposed before or after tertiary wastewater treatment	survey data + expert opinion	-	worker group categories limited to those used/defined by Raleigh, NC Wastewater Utility
Worker distance from hospital	miles	up to 1 up to 2 up to 3 up to 4 up to 5 greater than 5	0.029 0.116 0.145 0.178 0.180 0.352	0.5 1.5 2.5 3.5 4.5 6.0	worker's distance from hospital (in pipe-miles)	survey data + expert opinion	-	distance built on data and knowledge from Raleigh, NC Wastewater Utility
Time elapsed at worker	days	less than half up to 1 up to 2 greater than 2	0.886 0.068 0.027 0.018	0.1 1.0 2.0 3.0	time taken by wastewater to flow from hospital to worker	survey data + expert opinion	-	constant wastewater velocity presumed
Concentration in hospital discharge	particles/mL	up_to_1en6 up_to_1en5 up_to_1en4 up_to_1en3 up_to_1en2 up_to_1en1 up_to_1e0 up_to_1e1 up_to_1e2 up_to_1e3 up_to_1e4 up_to_1e5	0.591 0.132 0.104 0.075 0.050 0.030 0.015 0.004 9.1×10^{-5} 5.2×10^{-6} 4.7×10^{-9} 0	-	intermediate calculation of viral concentration in wastewater	functional	-	-

		up_to_1e6 up_to_1e7	0 0					
Hospital size	square feet	up to 500k 500k to 1000k greater than 1000k	0.491 0.340 0.168	6.2×10^{-5} 2.8×10^{-5} 1.6×10^{-5}	size and internal dilution of hospital	survey data	1494	low uncertainty expected; data taken from targeted hospital survey, and dilution factors similar across categories
% of WW from hospital at worker	-	less than 5% 5%-50% 50%-95% greater than 95%	0.920 0.045 0.026 0.009	0.025 0.225 0.725 0.975	fraction of total wastewater at worker originating in hospital	survey data + expert opinion	1494	reliant on data and knowledge from Raleigh, NC Wastewater Utility
Concentration at exposure point	particles/mL	up_to_1en9 up_to_1en8 up_to_1en7 up_to_1en6 up_to_1en5 up_to_1en4 up_to_1en3 up_to_1en2 up_to_1en1 up_to_1e0 up_to_1e1 up_to_1e2 up_to_1e3 up_to_1e4	0.324 0.160 0.237 0.106 0.066 0.047 0.031 0.018 0.008 0.003 2.7×10^{-4} 2.3×10^{-6} 8.1×10^{-8} 1.3×10^{-9}	-	final calculation of viral concentration in wastewater	functional	-	-
Exposure volume	mL/day	zero daily inhalation 10-second ingestion 1-min ingestion	0.357 0.614 0.028 0.005	0 1.0×10^{-4} 0.0583 0.3500	estimate of daily wastewater volume ingested or inhaled by worker	literature + expert opinion	-	volumes based on studies of inhaled aerosolized water during showering, and water ingestion volumes during swimming
Inactivation study	-	study 1 study 2 study 3	0.333 0.333 0.333	-	viral presence to infectious virus correction	-	-	-
PCR correction	-	0 to 0.001 0.001 to 0.01 0.01 to 0.0398 0.0398 0.0398 to 0.1	0.123 0.273 0.108 0.333 0.162	-	calculation of viral presence to infection virus correction	literature + expert opinion	-	limitations in literature: study of poliovirus rather than Ebola virus, lack of clarity on study quality, several studies provided ranges rather than values
Exposure dose	particles/day	up_to_1en10 up_to_1en9 up_to_1en8 up_to_1en7 up_to_1en6 up_to_1en5 up_to_1en4 up_to_1en3 up_to_1en2 up_to_1en1 up_to_1e0 up_to_1e1 up_to_1e2 up_to_1e3 greater_than_1e3	0.814 0.067 0.051 0.032 0.020 0.010 0.004 0.001 3.8×10^{-4} 1.0×10^{-4} 1.0×10^{-5} 2.3×10^{-7} 5.5×10^{-9} 1.1×10^{-10} 1.3×10^{-11}	-	calculation of dose of infectious viral particles to worker	functional	-	-
Probability of illness	-	<1 in 10^11 <1 in 10^10 <1 in 10^9 <1 in 10^8 <1 in 10^7	0.816 0.067 0.050 0.032 0.019	-	calculation of probability of developing EVD	literature (dose-response model)	-	dose-response model derived from non-human primate

		<1 in 10^6 <1 in 10^5 <1 in 10^4 <1 in 10^3 <1 in 10^2 <1 in 10 >1 in 10	0.010 0.004 0.001 4.0×10^{-4} 1.2×10^{-4} 1.0×10^{-5} 3.6×10^{-9}					studies

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