A quantitative approach for integrating multiple lines of evidence for the evaluation of environmental health risks

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Decision analysis often considers multiple lines of evidence during the decision making process. Researchers and government agencies have advocated for quantitative weight-of-evidence approaches in which multiple lines of evidence can be considered when estimating risk. Therefore, we utilized Bayesian Markov Chain Monte Carlo to integrate several human-health risk assessments, biomonitoring, and epidemiology studies that have been conducted for two common insecticides (malathion and permethrin) used for adult mosquito management to generate an overall estimate of risk quotient (RQ). The utility of the Bayesian inference for risk management is that the estimated risk represents a probability distribution from which the probability of exceeding a threshold can be estimated. The mean RQs after all studies were incorporated were 0.4386 with a variance of 0.0163 for malathion and 0.3281with a variance of 0.0083 for permethrin. After taking into account all of the evidence available on the risks of ULV insecticides, the probability that malathion or permethrin would exceed a level of concern was less than 0.0001. Bayesian estimates can substantially improve decisions by allowing decision makers to estimate the probability that a risk will exceed a level of concern by considering seemingly disparate lines of evidence.

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Introduction

Modeling and decision theory are being used increasingly for comparative and uncertainty analysis in risk management (Ascough *et al.* 2008). Researchers have advocated for a quantitative weight-of-evidence approach for estimating environmental risks from stressors such as contaminated sites and pesticides so that decision makers can comprehensively consider all evidence (Dale et al. 2008; Weed 2005). The U.S. National Research Council (NRC) found that the U.S. Environmental Protection Agency (USEPA) needs to develop methods to address and communicate uncertainty and variability in all phases of the risk assessment process (NRC 2009). The NRC stated that "Uncertainty forces decision makers to judge how probable it is that risks will be overestimated or underestimated for every member of the exposed population…" (NRC 1994). In particular, the NRC reports found that depending on the risk-management options, a quantitative treatment of uncertainty and variability is needed to discriminate between management options to make informed decisions (NRC 1994; NRC 1996; NRC 2009).

When making decisions regarding risk, there are often multiple lines of evidence that need to be considered. Information often is generated and gathered from different sources, so risk analysts and managers are confronted with the issue of combining data from these sources to improve the decision-making process. However, the ability of people to make precise and significant statements about risks diminishes with increasing amounts of information and complexity (Zadeh 1965). The incorporation of multiple lines of evidence into a weight-of-evidence framework allows risk assessors and managers to generate a single estimate of the risk (Dale *et al.* 2008). Currently, the most common way to incorporate dissimilar lines of evidence is by determining the weight-of-evidence estimate through qualitative risk assessments or through listing evidence (Chapman et al. 2002; Hull & Swanson 2006; Linkov et al. 2009; Menzie et al. 1996; Sanchez-Bayo et al. 2002; Suter II & Cormier 2011; USEPA 2005a; Weed 2005), which can have fundamental mathematical limitations compared to quantitative estimates (Cox Jr. *et al.*

2005). These methods are important contributions to the decision making process, but they do not provide a comprehensive and structured approach for integrating multiple lines of evidence from different study types (Linkov *et al.* 2009).

Rather than testing for a specific relationship (e.g., the probability of obtaining values as extreme or more extreme than the values observed in the study), decision makers may ultimately be interested in making inferential conclusions about environmental health risks (Assmuth & Hilden 2008; Ellison 1996; Hill 1996). Bayesian inference can address inferential conclusions by providing a framework, based on probability calculus, by quantifying the uncertainty in parameter estimates and determining the probability that an explicit endpoint is exceeded given a set of data (Ellison 1996; Hill 1996). Bayesian inference is a way of updating prior knowledge given new information becoming available to generate a posterior estimate of the parameters of interest (i.e., risk) (Ellison 1996).

Currently there are few quantitative frameworks that integrate data into a framework that can be utilized by risk managers (Assmuth & Hilden 2008). A quantitative framework for integrating and interpreting multiple lines of seemingly disparate evidence into an overall risk estimate is critically needed for complex risk assessments (Dale *et al.* 2008).

Risk assessments, biomonitoring, and epidemiology studies quantitatively estimate the likelihood that exposures to chemicals of interest exceed a threshold of observable effect or increased exposure over background levels in a population (McKone *et al.* 2009). Epidemiological and biomonitoring data can play an important role in hazard identification and can also be considered in the risk characterization phase of the risk assessment process (Samet *et al.* 1998). Therefore, the three seemingly disparate study methods are deriving an estimate of risk given exposure to the chemical of interest. Bayesian inference provides a quantitative framework for integrating these multiple lines of evidence into an overall estimate. Similar approaches have been used for different applications in risk assessment, toxicology, and environmental modeling,

but they have not been utilized to update the risk estimates for anthropogenic chemical stressors as new information becomes available (Bernillon & Bois 2000; Brand & Small 1995; Devine & Qualters 2008; Schenker et al. 2009; Taylor et al. 1993).

There are many advantages of using Bayesian techniques for weighing evidence, including full allowance for all parameter uncertainty in the model, the ability to include other pertinent information that would otherwise be excluded, and the ability to extend the models to accommodate more complex models (Hill 1996; Sutton & Abrams 2001). Studies utilizing Bayesian approaches have considered separate studies with the same study type to estimate an overall value for the parameter of interest (Smith et al. 2002; Wheeler & Bailer 2009). Therefore, to address the need for a quantitative approach for environmental health, we utilized Bayesian Markov chain Monte Carlo to provide a logical and consistent method for estimating the risk of chemicals when multiple studies are available. To demonstrate how Bayesian statistics can be used for decisions regarding environmental and public health risks, we chose insecticides used for adult mosquito management as our case study.

Case Study

To effectively manage infection rates, morbidity, and mortality due to mosquito-borne pathogens, there must be a reduction in contact between infected mosquitoes and humans and animals (Marfin & Gubler 2001). One of the more effective ways of managing high densities of adult mosquitoes that vector human and animal pathogens is ultra-low-volume (ULV) aerosol applications of insecticides. Since West Nile virus (WNV) was introduced into the U.S., more areas of the country have been experiencing large-scale insecticide applications. Consequently, there has been greater public attention on human-health and environmental risks associated with ULV insecticide applications (Peterson et al. 2006; Reisen & Brault 2007; Roche 2002; Thier 2001).

A decade after the initial response to WNV, several quantitative human-health and ecological risk assessments have been conducted to estimate the magnitude of risks associated with the insecticides (Davis 2007; Davis et al. 2007; Gosselin et al. 2008; Macedo et al. 2007; NYCDOH 2005; Peterson et al. 2006; Schleier III 2008; Schleier III et al. 2009a; Schleier III et al. 2008a; Schleier III et al. 2009b; Schleier III et al. 2008b; Suffolk County 2006; USEPA 2005b; USEPA 2005c; USEPA 2005d; USEPA 2006a; USEPA 2006b; USEPA 2006c; Valcke et al. 2008). Also, there have been epidemiology and biomonitoring studies measuring the health effects after potential exposure to mosquito adulticides (Currier et al. 2005; Duprey et al. 2008; Karpati et al. 2004; Kutz & Strassman 1977; O'Sullivan et al. 2005). Most studies suggest negligible public health risks from exposure to adulticides; however, no study has quantitatively combined the results from risk assessment, epidemiology, and biomonitoring studies, and there seemingly disparate data metrics, to obtain an overall estimate of the risk.

Data and Methods

In environmental and human health risk assessments of pesticides, risk quotients (RQ) are often used to quantitatively express risk (Peterson 2006). Risk quotients are calculated by dividing the potential exposure (PE) by its respective toxic endpoint value. Estimated RQs are compared to a RQ level of concern (LOC) or other threshold which is set by the USEPA or another regulatory agency to determine if regulatory action is needed. The RQ LOC used in our assessment was 1.0. An RQ >1.0 means that the estimated exposure is greater than the relevant toxicological endpoint. If an RQ breaches a regulatory LOC (RQ $\geq$ 1) at a lower tier, then risk managers decide to restrict the product use, progress to higher tier risk assessments, or use field-verified models (USEPA 2006d).

We chose two pesticides for our case study, malathion (O,O-dimethyl dithiophosphate of diethyl mercaptosuccinate) and permethrin ([3-phenoxyphenyl]methyl 3-[2,2-dichloroethenyl]-2,2-dimethylcyclopropane carboxylate), because biomonitoring, epidemiology, and risk

assessments have been performed with respect to ULV applications for adult mosquito management (Table 1). We chose adult human males for our case study because it is the only common group assessed by all studies. To ensure that we possessed all publically available studies, a literature review was performed and all relevant studies were pulled from government reports and academic journals from 1900 to 2014 using the Google and Thomas Reuters Web of Science™ search engines. All studies that we found that contained mosquito ULV risk assessments, biomonitoring, or epidemiological measurements for permethrin or malathion were included in this assessment.

The estimated RQs for each study are summarized in Table 1 for each chemical. The same toxicological endpoints were used for all of the risk assessments, which are based on the U.S. EPA's ingestion reference dose for mammals (Macedo et al. 2007; Peterson et al. 2006; Schleier III 2008; Schleier III et al. 2009a; Schleier III et al. 2009b; Valcke et al. 2008), and in the case of probabilistic risk assessments we used the 95th percentile RQ for conservatism.

The literature search found two epidemiological studies and one biomonitoring study for permethrin and malathion. Karpati et al. (2004) analyzed hospital admissions for asthma in New York, NY three days before and after ground based ULV applications of permethrin (n = 510 before spraying and 501 after spraying) and found no increase in admissions for asthma. Currier et al. (2005) analyzed urine samples for metabolites of permethrin in 125 persons in the treated area and 67 persons from two control areas after ground-based ULV applications in Mississippi and found no increase in urinary metabolites. The persons selected in the study were geographically random and were verified by mapping the GPS location of the ground-based applications. O'Sullivan et al. (2005) analyzed hospital admissions for asthma in New York, NY after ground-based ULV applications of malathion in September of 1999 and compared those to September 1997 and 1998 which no malathion treatments occurred (n = 1318 patients presented with a diagnosis of asthma exacerbation). They found no statistical difference between the 1999

asthma admissions and the asthma admission in 1997 and 1998. To incorporate the epidemiology and biomonitoring studies, we assumed that if the researchers did not observe an effect or increase in urinary metabolites of the pesticide, the RQ was assumed to be 0.99 (Table 1). We assumed a RQ of 0.99 to be conservative because of a lack of knowledge on the value, which must be below 1.0 if no effect is observed.

Bayesian inference treats statistical parameters as random variables, and uses a likelihood function to express the plausibility of obtaining different values of the parameter when the data have been observed (Ellison 1996). To define a RQ for adult males we used Bayes' theorem:

$$p(\theta|y) = p(y|\theta)p(\theta) \quad (1)$$

where p is the probability mass, θ is the value of a random variable selected from the prior distribution, y is the evidence being considered, $p(\theta)$ is the prior probability, $p(y|\theta)$ is the likelihood function for the evidence (Congdon 2006; Gelman et al. 2004). We assumed a normal distribution for the likelihood function and used log-transformed risk quotients from table 1. The central limit theorem of classical statistics and the Bayesian analog justify the normal density as an approximation for the posterior distribution of many summary statistics, even when they are derived from non-normal data (Congdon 2006). To estimate the posterior density,

$$p(y|\theta) = 1 \div \sqrt{2\pi\sigma} \exp - 1 \div 2\sigma^2 (y - \theta)^2 \quad (2)$$

where y is a single scalar observation from the RQ's in table 1 from a normal distribution parameterized by a mean of θ and a variance of σ^2 (Gelman *et al.* 2004).

We have no knowledge of the prior distribution, so we assumed an uninformative or diffuse prior which we defined as a normal distribution with a μ_0 of 1 and a τ^2_0 of 1. We chose an uninformative prior because the effect of the prior and data on the updated beliefs depends on the precision of the density of $p(\theta)$ (Congdon 2008). We used Markov Chain Monte Carlo simulation (MCMC) utilizing the Metropolis-Hasting algorithm to obtain the posterior distribution for

156 equation 2 using Matlab® R2010b (MathWorks, Natick, MA, USA). We sampled the purposed
157 posterior distributions using equation 2 by iterating 100,000 purposed values for the posterior
158 distribution and discarded the first 1,000 samples for burn in.

159 **Results and Discussion**

160 The mean posterior RQs after all studies were incorporated were 0.4386 with a variance
161 of 0.0163 for malathion and 0.3281with a variance of 0.0083 for permethrin (Figures 1 and 2).
162 The mean posterior RQs for all studies excluding the epidemiological and biomonitoring studies
163 slightly decreased the mean to 0.4119 with a variance of 0.0158 for malathion and a mean of
164 0.302 with a variance of 0.0081 for permethrin (Figures 1 and 2). Using the posterior mean and
165 variance from the normal distribution, the probability that exposure to malathion or permethrin
166 after ULV applications would exceed a level of concern was less than 0.0001, regardless of
167 whether all of the studies were incorporated or the epidemiological and biomonitoring studies
168 were held out (Figures 1 and 2).

169 The risk assessments used different data and exposure scenarios to estimate the RQ. The
170 utility of the Bayesian inference for risk management is that the estimated RQ represents a
171 probability distribution from which we can obtain a probability of exceeding a threshold (Figures
172 1 and 2). The probability of exceeding a threshold is most likely more intuitive for risk managers
173 and the public to understand than an estimate of the 95th percentile of exposure or risk, which is
174 typically reported in probabilistic risk assessments (Hill 1996). In fact, risk can be defined as the
175 probability and severity of adverse effects (Aven & Renn 2009), which Bayesian statistics
176 directly addresses. The majority of weight-of-evidence studies do not quantify both a risk
177 estimate and variability or uncertainty around that estimate, but Bayesian MCMC methods
178 quantify both (Linkov *et al.* 2009).

179 The USEPA provides guidance on how to perform risk assessments that address
180 variability and uncertainty (NRC 2009; USEPA 1989; USEPA 2004), but they do not provide a

simple method for integrating multiple lines of evidence. Our case study directly addresses the need for a standard approach by which multiple lines of evidence can be interpreted in a framework that ecologists, risk assessors and managers, and NRC have highlighted (Dale et al. 2008; Linkov et al. 2009; NRC 1994; NRC 1996; NRC 2009). Our method also could be utilized by the Network Reference Laboratories for Monitoring of Emerging Environmental Pollutants in the European Union for integrating risk assessments and biomonitoring to prioritize pollutants (Tilghman *et al.* 2009).

The USEPA and other regulatory agencies potentially could benefit from using a value-of-information approach that takes advantage of Bayesian inference to determine if generating new data will significantly improve the risk estimate, similar to approaches used for toxicological studies (NRC 2009; Taylor et al. 1993). Our analysis showed that the addition of epidemiological and biomonitoring studies using conservative estimates did not drastically change the estimate of risk. Biomonitoring assessments could provide a refined RQ estimate if the amount of chemical the person is exposed to is calculated. Bayesian inference can also incorporate expert knowledge of a system which can be used as prior information that is updated by data (Gargoum 2001; Morris 1977).

In ecotoxicology and other disciplines, there are multiple estimates of values like the lethal concentration that kills 50% of a population (LC50) (Wheeler & Bailer 2009). This technique could be used to estimate an overall LC50 for use in risk assessments or setting total maximum daily load limits. Stauffer (2008) showed that in natural resource management there are often multiple estimations for a population of interest. Therefore, Bayesian MCMC methods can be used to estimate the probability of the population being above or below a given threshold.

Bayesian analysis provides a systematic approach for guiding the decision-making process by incorporating new knowledge in the estimate of risk, which directly addresses NRC recommendations (NRC 1994; NRC 2009). However, Bayesian inference does not address the

uncertainties inherent in each risk assessment. For example, there is large uncertainty surrounding the estimate of insecticide air concentrations and deposition on surfaces after ULV applications for adult mosquito management (Schleier III *et al.* 2009a; Schleier III *et al.* 2009b). Models used by the USEPA and other researchers to estimate concentrations are either over- or under-estimating depending on the model (Schleier III & Peterson 2010; Schleier III et al. 2008b). In addition, probabilistic risk assessments demonstrated that the estimated air concentration and deposition of insecticides are contributing the largest amount of variance to the potential exposure (Schleier III *et al.* 2009a; Schleier III *et al.* 2009b). However, the estimate presented here most likely is robust against these uncertainties because the studies used a variety of models, exposure pathways, and monitoring techniques which were not dependent on a standardized assessment protocol.

We recognize that the assumptions about RQ distributions may affect the final results; however, we attempted to reduce the potential biases by making conservative assumptions erring on the side of safety, which is common practice in risk assessment. In addition, probability distributions other than normal can be utilized if enough is known about the underlying distribution of the population, like those used for toxicological studies. Bayesian MCMC also can be utilized with the current data and the incorporation of expert judgments to aid in the determination of risk estimates (Grist *et al.* 2005).

Bayesian analysis techniques have been underutilized with respect to environmental and public health, risk assessment, ecology, and environmental sciences (Clark 2005). Our method is a quantitative approach to statistically derive risk estimates from multiple lines of evidence, which is a relatively simple way of integrating multiple lines of evidence into a framework that can be used by assessors and managers (Assmuth & Hilden 2008; Linkov et al. 2009). In addition to insecticide risk, this approach can be used for other anthropogenic agents such as dioxins and polychlorinated biphenyls, which in many cases have risk assessments, biomonitoring, and

231 epidemiology studies performed for a site. The method presented here can also be utilized for
232 probabilistic ecological risk assessments to derive a distribution for the toxicological endpoints
233 like LC50 or no-effect concentration when multiple values are available for the same species.
234 Future refinements to our Bayesian model would be the development of a method to convert
235 epidemiological study results into a RQ to reduce the uncertainty and conservatism. In addition,
236 biomonitoring studies can quantify the exposure if exposures are above background levels and
237 convert those estimates to RQ.

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Equation 2 as it should appear in the published paper:

$$p(y|\theta) = \frac{1}{\sqrt{2\pi\sigma}} \exp ¿ \frac{-1}{2\sigma^2} ¿ y-\theta ¿^2$$

Table 1(on next page)

Risk quotient estimates for each study

Table 1. Risk quotient estimates for each study

	Malathion	Permethrin
Karpati et al. (2004)[c]	NA[a]	0.99[b]
USEPA (2005c, d)[d]	0.018	0.025
Currier et al. (2005)[e]	NA[a]	0.99[b]
O'Sullivan et al. (2005)[c]	0.99[b]	NA[a]
Peterson et al. (2006)[d]	0.0076	0.0021
Suffolk County (2006)[d]	0.015	0.013
Macedo et al. (2007)[d]	NA[a]	0.023
Valcke et al. (2008)[d]	0.64	NA[a]
Schleier III (2008)[d]	NA[a]	0.00025
Schleier III et al. (2009a)[d]	0.02	NA[a]
Schleier III et al. (2009b)[d]	0.0017	0.000068

[a]Not applicable because the chemical was not assessed

[b]A risk quotient of 0.99 was used because it provides a conservative estimate of the risk for biomonitoring and epidemiology studies and due to a lack of knowledge about the true value, which must be below 1 if no effect is seen.

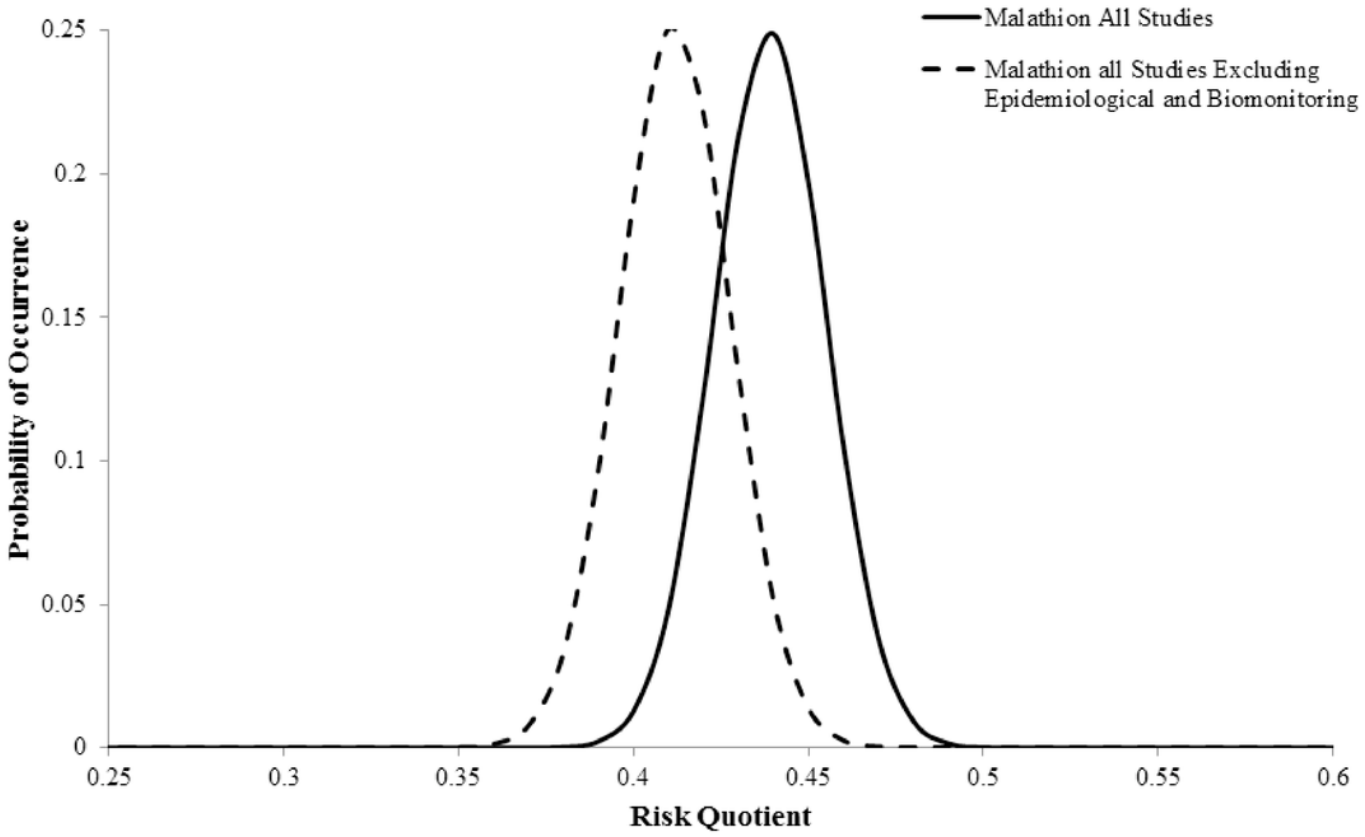
[c] Epidemiological study

[d] Risk assessment

[e] Biomonitoring study

1

Figure 1: Posterior probability distributions for malathion with all available studies and all studies excluding epidemiological and biomonitoring.



2

Figure 2: Posterior probability distributions for permethrin with all available studies and all studies excluding epidemiological and biomonitoring.