Am. J. Trop. Med. Hyg., 84(6), 2011, pp. 951–956
doi:10.4269/ajtmh.2011.11-0016

Net Risk: A Risk Assessment of Long-Lasting Insecticide Bed Nets Used for Malaria Management

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Abstract. Despite the demonstrated ability of bed nets that have been factory-impregnated with long-lasting insecticides (LLINs) to protect people from malaria and despite the ambitious plans for their widespread use, the health risks from the LLINs themselves have not been adequately investigated and reported in the peer-reviewed science literature. Here, we use a probabilistic risk assessment approach to estimate the risks to Africans from inhalation, dermal, and oral exposures to the newer LLINs with permethrin, α-cypermethrin, or deltamethrin as the insecticide active ingredient. We estimated exposures to LLINs using 17 age groups to incorporate different body weights and sleeping behaviors. Risk quotients (exposure divided by toxic threshold) at the 50th and 90th percentiles for non-cancer risks were < 1.0 for lifetime adjusted risk and all youth and adult age groups. Risk quotients for infants and toddlers (0–3 years) and child groups from 3 to 10 years were ≥ 1.0 for specific bed nets.

INTRODUCTION

Studies clearly show that using bed nets that have been factory-impregnated with long-lasting insecticides (LLINs) is an effective malaria management tactic. This was shown perhaps most dramatically by Fegan and others,[1] who observed a 44% decrease in malaria mortality of children in Kenya with the use of LLINs. Lengeler and deSavigny[2] said of the Fegan and others[1] study: "With this work, the use of insecticide-treated bed nets is confirmed as a major child-survival intervention." Consequently, LLINs have become a key component of malaria management programs worldwide.[3]

Much attention has been devoted to how best to distribute the LLINs. Teklehaimanot and others[4] argue for full distribution and universal access to LLINs to achieve community-wide protection against malaria. Furthermore, they suggest that, by giving enough bed nets to cover every sleeping space, the reservoir of infection is replaced by the nets' community effect, thereby significantly reducing malaria transmission.[4]

Despite the ability of LLINs to protect people from malaria and despite the ambitious plans for their widespread use, the health risks from the LLINs themselves have not been adequately investigated and reported in the peer-reviewed science literature. A scientifically rigorous, objective, and transparent examination of the health risks associated with LLINs is needed to provide risk–benefit considerations of this promising technology.

A brief review of risk assessments associated with bed nets highlights some important issues and information gaps. There are only two peer-reviewed risk assessments of insecticide-treated bed nets in the literature.[5,6] Both assessments used deterministic values (i.e., single-point inputs) and relied on surrogate data to estimate risks from deltamethrin[5] and permethrin, deltamethrin, λ-cyhalothrin, α-cypermethrin, and cyfluthrin.[6] Barlow and others[5] assessed risks from field-treated bed nets that rely on soaking the nets in an insecticide-treated solution. Macedo and others[6] assessed risks to deployed military forces, not civilian populations with various age groups of men, women, and children. Estimates of inhalation exposure to the insecticides from respiration under the bed nets were based on Bomann,[7] who used only cyfluthrin in an indoor study. Estimates of dermal exposure to the insecticides used removal of insecticide applied to carpeting as a surrogate for how much insecticide might be removed from netting. In addition, the World Health Organization (WHO) Pesticide Evaluation Scheme (WHOPES) has summarized safety assessments for their recommended bed nets,[8–13] but these also are based on deterministic surrogate inputs.

Because the previous risk assessments are deterministic and use uncertain surrogate values, a probabilistic risk assessment is needed to estimate the range of possible risk values and better understand uncertainty and sensitivity of the exposure model. In this paper, we use a probabilistic risk assessment approach to estimate the risks to Africans from exposure to the newer factory-impregnated LLINs such as Olyset Net (Sumitomo Chemical Co., London, United Kingdom), PermaNet 2.0 (Vestergaard Frandsen, Lausanne, Switzerland), DawaPlus 2.0 (Tana Netting, Bangkok, Thailand), Yorkool (Yorkool International Co., Tianjin, P. R. China), DuraNet (Clarke, Roselle, IL), Netprotect (Bestnet Europe, London, United Kingdom), and Interceptor (BASF, Ludwigshafen, Germany), which are fully recommended or have interim recommendations by the WHO for malaria management.

MATERIALS AND METHODS

Insecticides, body weights, and sleep times. The insecticides used to factory-impregnate bed nets currently being used include permethrin (Olyset Net),[10,14] deltamethrin (PermaNet 2.0, Netprotect, Yorkool, and DawaPlus 2.0),[10,11,15,16] and α-cypermethin (Interceptor and DuraNet).[12,15] The target dose of each insecticide is the amount of insecticide applied to the bed nets, and in the case of Olyset Net, it is the average application concentration that is measurable on the net's surface.[14] We assumed that all nets were between 14 and 15 m^2.[5,7,12,14,15,17,18] (Table 1). To be conservative, we assumed that the insecticide applied to the LLINs did not degrade over time because of repeated washing or other factors. The insecticides in LLINs degrade over time, but the degradation can be highly variable.[11]

Exposures to LLINs were estimated using several different age groups to incorporate different body weights and sleeping behaviors. These age groups were separated by gender and

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Table 1
Long-lasting insecticide-impregnated bed nets used in the risk assessment

Bed net brand name	Insecticide active ingredient	Application rate (mg/m^2)
Olyset Net	permethrin	30*
Netprotect	deltamethrin	63
PermaNet 2.0; Yorkool	deltamethrin	55
DawaPlus 2.0; DuraNet	deltamethrin/α-cypermethrin	80/261
Interceptor	α-cypermethrin	200

*Average concentration of permethrin on the bed net's surface.

included 17 groups between the ages of 0 and 70 years. We estimated exposure and risk for both males and females, but in this paper, we are only presenting data for females; because of their lighter body weight, they are more sensitive receptors than males.

Body weights for African children were obtained for girls ages 3.5–10.4 years ($N = 651$) from rural South Africa and were extrapolated for all bed net users within defined age groups.[19] Body weights were obtained for women between the ages of 15 and 64 years ($N = 544$) from South Africa.[20] Body weights for girls ages 11 to 14 years were obtained from Portier and others.[21] Because there were no weight data for African girls in that age group, we used data from Portier and others,[21] who estimated the age-specific body weight distributions for US residents using data collected by the National Health and Nutrition Examination Survey in four surveys over the past 24 years. Body-weight distributions for infant and toddler girls (ages 0 to 3 years) were log-normal and also were obtained from Portier and others[21] (Table 2). Body-weight distributions for all of the above groups were log-normal (Table 2).

Sleep durations (the amount of time the person was exposed to the net per 24-hour day) were assumed to range between 6 and 12 hours. Infants and toddlers, defined as individuals between the ages of 0 and 3 years, were assumed to sleep an average of 11 hours, with a uniformly distributed range between 10 and 12 hours. Children in the age groups between 3 and 10 years were assumed to sleep an average of 10 hours distributed uniformly between 8 and 12 hours. Individuals in the age groups greater than 10 years were assumed to sleep an average 8 hours a day distributed uniformly between 6 and 10 hours (Table 3).

Table 2
Female body weights for age groups used in the exposure assessment

Group	Mean (SD) in kg	Ref.
Infants and toddlers (0–3 years)	9.1 (1.24)	21
Children (3.5–10.4 years)		19
3.5	12.5 (2.30)	
4.5	14.6 (2.90)	
5.6	16.1 (2.00)	
6.5	17.6 (2.70)	
7.5	19.1 (2.90)	
8.4	20.2 (3.30)	
9.4	22.0 (3.30)	
10.4	21.8 (5.10)	
Youth (11–14 years)	36.16 (7.12)	21
Adults (15–64 years)		20
15–24	62.2 (12.10)	
25–34	69.1 (15.60)	
35–44	77.8 (18.10)	
45–54	78.6 (13.80)	
55–70	77.3 (12.30)	

Inhalation. Inhalation exposure was estimated using the equation

$$PE_i = (AC \times RR \times T \times (T/24) \times CF)/BW,$$

where PE_i is potential exposure (mg/kg body weight per day), AC is air concentration of the insecticide (μg/m^3) under the boundaries of the net, RR is respiratory rate (m^3/hour), T is the sleep time under the net (hour), $T/24$ is the correction factor for the proportion of day exposed, CF is the conversion factor from micrograms to milligrams, and BW is body weight (kg). The air concentrations of the insecticide were assumed to be uniformly distributed, with a minimum of 0.02 μg/m^3 and a maximum of 0.06 μg/m^3. This value is based on Bomann,[7] who used cyfluthrin in an indoor study. To our knowledge, no other air concentration data for bed nets have been published. The respiratory rates were assumed to be log-normally distributed resting breathing rates and were obtained for different age groups from the US Environmental Protection Agency's (USEPA) Exposure Factors Handbooks[22,23] (Table 3). Assumptions about sleep times spent under the net per 24-hour period and body weight are explained above.

Dermal. Dermal exposure was estimated using the equation

$$PE_d = (TD \times SA \times TC \times AbR)/BW,$$

where PE_d is potential exposure (mg/kg BW per day), TD is the target dose of the specific insecticide impregnated into the bed net (mg/m^2) (Table 1), SA is the surface area of the person's body in contact with the net, TC is the transfer coefficient of the amount of insecticide transferred to the skin while the person is in contact with the net, AbR is the dermal absorption rate, and BW is body weight (kg). Body surface areas were estimated based on the equation

$$SA = (4 \times BW + 7)/(BW + 90),$$

where SA is surface area (m^2) and BW is body weight (kg).[22,24] The percentage of unclothed body surface area in contact with the net each night was selected from a uniform distribution ranging from 10% to 60%. The transfer coefficient rate was assumed to be 0.49% for permethrin[25] and was assumed to follow a triangular distribution for the other insecticides[5,17] (Table 3). Dermal absorption rates were deterministic values for each insecticide: α-cypermethrin (2.5%), deltamethrin (6.7%), and permethrin (15%).

Oral. Estimates of the oral route of exposure were divided into two categories: hand to mouth contact (hand touching of net and then hand to mouth behavior) and direct mouth contact with the net (sucking on the net). These exposures were estimated for children between the ages 0 and 10 years. The equation used to estimate exposures of children sucking on the net was

$$PE_s = (NA \times TD \times WTC \times SEF)/BW,$$

where PE_s is potential exposure (mg/kg BW per day), NA is the net area sucked on per night (0.15% of 15 m^2 or 225 cm^2), TD is the target dose of the specific insecticide impregnated into the bed net (mg/m^2) (Table 1), WTC is the wet-transfer coefficient, SEF is the saliva extraction factor, and BW is body weight (kg). The wet-transfer coefficient is the percentage of target dose that is transferred from the net to the child. Barlow and others[5] estimated this percentage at 20%, and we used this fixed value in our assessment. The saliva extraction factor is the amount

TABLE 3
Values and distributions for probabilistic input variables used in the exposure assessment

Input variable	Group	Value	Units	Distribution	Ref.
Sleep duration	Infants and toddlers (0–3 years)	10–12	hour	Uniform	
Sleep duration	Children (3.5–10.4 years)	8–10	hour		
Sleep duration	Youth (11–14 years)	6–10	hour		
Sleep duration	Adults (15–70 years)	6–10	hour		
Respiration rate	Infants and toddlers (0–3 years)	0.17 (0.02)	m^3/hour	Lognormal	22, 23
Respiration rate	Children (3.5–10.4 years)	0.24 (0.02)	m^3/hour		
Respiration rate	Youth (11–18 years)	0.35 (0.04)	m^3/hour		
Respiration rate	Adults (19–30 years)	0.33 (0.03)	m^3/hour		
Respiration rate	Adults (31–60 years)	0.32 (0.03)	m^3/hour		
Respiration rate	Adults (61+ years)	0.30 (0.03)	m^3/hour		
Air concentration of insecticide under the bed net	All	0.02–0.06	μg/m^3	Uniform	7
Body surface area in contact with bed net	All	10–60	%	Uniform	
Transfer coefficient from dry net to skin	All	0.49–2.5 (0.49 most likely)	%	Triangular	5, 17
Saliva extraction factor	All	25–75 (50 most likely)	%	Triangular	26
Surface area of child's hand	Infants and toddlers (0–3 years); child (3.5–10 years)	0.003–0.004; 0.008–0.01	m^2	Uniform	16

of insecticide available for extraction by the saliva of the child. We assumed a triangular distribution for this value, with a most likely value of 50% and range of 25% to 75%.[26]

The equation used to estimate exposure to children from hand to mouth contact with the bed net was

$$PE_{hm} = (TD \times TC \times SA_h \times DR)/BW,$$

where PE_{hm} is the potential exposure (mg/kg BW per day), TD is the target dose of the specific insecticide impregnated into the bed net (mg/m^2) (Table 1), TC is the transfer coefficient, SA_h is the surface area of the child's hand touching the net each night (30% of the total surface area of the hand; it was assumed to be distributed uniformly between 0.003 and 0.004 m^2 for infants and 0.008 and 0.01 m^2 for children 3 to 10 years of age),[8] and DR is the dislodgeable residue of the insecticide assumed to be dislodged from the hand, transferred to the mouth, and swallowed. We assumed this value was fixed at 10%.[8]

Potential exposures from inhalation, dermal, and oral routes were summed to estimate potential total systemic exposures (also known as total body burden). We assumed that individuals in each age group slept under the LLINs each night for extended periods of time, and therefore, all exposures were considered chronic. We summed total potential exposures for each age group as well as lifetime adjusted daily dose (LADD) by partitioning exposure per age group into proportions of total lifespan and then summing the proportions into a 70-year lifespan.

Risk characterization. Total exposures were compared to chronic, non-cancer endpoints in a risk quotient (RQ) as a ratio of exposure to toxic threshold:

$$RQ = Exposure/Toxic\ threshold.$$

Because exposures from all routes were added and standardized by body weight, we used the acceptable daily intake (ADI) for each insecticide as the toxic threshold. The ADI is the total daily systemic exposure to the insecticide and is based on the no observed adverse effect level (NOAEL) with added safety factors. The oral ADI values that we used were 0.05 mg/kg per day for permethrin,[27] 0.01 mg/kg per day for deltamethrin,[28] and 0.02 mg/kg per day for α-cypermethrin.[29] All ADIs are approximately 1% of the respective NOAELs. We also used the cancer oral slope quotient (Q*) for permethrin, the only carcinogen among the insecticides evaluated in this assessment,[30] to estimate the population cancer risk. Total potential exposures (PE) were estimated according to exposure route and then used to calculate cancer risk:

$$Population\ cancer\ risk\ rate = PE \times Q^*.$$

The Q^* value for permethrin is 9.567×10^{-3} mg/kg per day^{-1}, a value that, when multiplied by the potential exposure, gives an estimate of numbers of cancer cases above a background level. Assumptions for exposure duration were 365 days of exposure over an entire lifetime of 70 years for all cancer and non-cancer risk estimates. Lifetime adjusted cancer risk was estimated by partitioning exposure per age group into proportions of total lifespan (LADD) and then summing the proportions into a 70-year lifespan.

Probabilistic analysis. We used Monte Carlo simulation (Crystal Ball 7.3; Decisioneering, Denver, CO) to evaluate the RQ and input variables used to calculate the RQ. Probabilities of occurrence of RQ values were determined by sampling from the statistical distribution of each input variable used to calculate the RQs. Each of the input variables was sampled so that each input variable's distribution shape was reproduced. Then, the variability for each input was propagated into the output of the model so that the model output reflected the probability of values that could occur.

Analyses were performed using 20,000 iterations to calculate percentile values and other statistics for our estimates of risk. Sensitivity analysis was performed to examine which of the input variables contributed the most variability to the output variability of the model.

RESULTS

Exposures to all of the insecticide active ingredients were by far greatest for the oral route in the child age groups (0–10 years). Oral exposure, primarily through sucking directly on the bed net, resulted in > 90% of the total exposure. Depending on the child age group, dermal and inhalation exposure only

TABLE 4
Risk quotient percentiles for selected age groups

Bed net (active ingredient)	Age group: Infants and toddlers (0–3 years) 50%	Infants and toddlers (0–3 years) 90%	Child (3–4 years) 50%	Child (3–4 years) 90%	Child (4–10 years) 50%	Child (4–10 years) 90%
DuraNet (α-cypermethrin)	3.04	4.09	2.80	3.18	1.31–1.96	1.77–2.76
Interceptor (α-cypermethrin)	2.50	3.36	1.87	2.60	1.07–1.87	1.44–2.60
Netprotect (deltamethrin)	1.58	2.13	1.22	1.70	0.72–1.06	0.96–1.49
PermaNet 2.0, Yorkool (deltamethrin)	1.38	1.86	1.07	1.48	< 1	0.84–1.30
DawaPlus 2.0 (deltamethrin)	2.00	2.69	1.55	2.16	0.91–1.34	1.22–1.87
Olyset Net (permethrin)	< 1	< 1	< 1	< 1	< 1	< 1

resulted in 0.9–7% and 0.07% of the total exposure, respectively. For youth > 10 years and adults, dermal and inhalation exposure was 99.7% and 0.3% of total exposure, respectively. As discussed above, we assumed no oral exposure for youth > 10 years or adults.

Risk quotients at the 50th and 90th percentiles for non-cancer risks were < 1.0 (i.e., exposure was less than toxicity threshold) for lifetime adjusted risk and all youth and adult age groups. Risk quotients at the 50th and 90th percentiles for lifetime adjusted risk were 0.33 and 0.42 for DuraNet, 0.27 and 0.34 for Interceptor, 0.19 and 0.25 for Netprotect, 0.24 and 0.45 for DawaPlus, 0.17 and 0.22 for PermaNet and Yorkool, and 0.02 and 0.03 for Olyset Net, respectively. Risk quotients for infants and toddlers (0–3 years) and child groups from 3 to 10 years were ≥ 1.0 for specific bed nets (Table 4). In particular, the LLINs treated with deltamethrin or α-cypermethrin had the largest RQs, but those quotients were generally < 4.0 at the 90th percentile.

Estimates of lifetime adjusted cancer risks to the population were 8.62 and 10.9 additional cancer cases above background levels per 1,000,000 people at the 50th and 90th percentiles of exposure, respectively (Table 5). When exposure to 0–10 year olds was excluded from the analysis (thus removing the large exposure from oral intake), the population cancer risks were 1.26 and 1.99 additional cancer cases above background levels per 1,000,000 people at the 50th and 90th percentiles of exposure, respectively.

Sensitivity analysis of the exposure model for cancer risks revealed that the saliva extraction factor contributed 77% of the variance to the output variance followed by the body surface area in contact with the bed net (14.7%) and infant/toddler weight (5.7%). When saliva extraction factor was fixed at a deterministic value of 50%, uncertainty of the body surface area in contact with the net and infant/toddler weight contributed 67.6% and 23.5% of the variance to the output, respectively. When exposure to 0–10 year olds was excluded from the analysis, 99% of the variance to the output was the result of the uncertainty in the body surface area in contact with the bed net.

Sensitivity analysis of the exposure model for non-cancer risks revealed that, for children < 10 years old, saliva extraction factor and body weight contributed 52–75% and 28–46% of the variance to the output, respectively (Table 6). When saliva extraction factor was fixed at a deterministic value of 50%, infant/toddler weight contributed 99% of the variance to the output. For all other age groups, body surface area in contact with the net and the transfer coefficient from the dry net to the skin contributed 54–99% and 0–44% of the variance to the output, respectively.

TABLE 5
Mean, 50th percentile, and 90th percentile cancer risk estimate for Olyset Net

Age group	Percentile 50%	Percentile 90%	Mean
All ages	8.6×10^{-6}	10.9×10^{-6}	8.7×10^{-6}
Excluding 0–10 years	1.3×10^{-6}	1.9×10^{-6}	1.3×10^{-6}

DISCUSSION

Our risk assessment provides regulatory decision makers with guidance in the event that the RQs or cancer risk estimates exceed regulatory levels of concern. The results reveal that inhalation exposure is negligible compared with dermal and oral exposure, and additional resources expended to better characterize this route of exposure for regulatory reasons would be questionable. The sensitivity analysis reported here identifies three primary input variables that could be refined to meaningfully improve future risk assessments: (1) saliva extraction factor, (2) body surface area in contact with the bed net, and (3) transfer coefficient from the dry bed net to the skin.

To reduce uncertainty associated with our risk estimates, saliva extraction factor would need to be better understood for childhood exposures. Currently, only one study has examined potential saliva extraction by removing insecticides placed onto aluminum foil with sponges wetted with human saliva and similar analogs.[26] Because of the large potential exposure compared with inhalation and dermal exposures, child oral exposure to the bed net through hand to mouth contact and directly sucking on the net needs to be assessed. This would entail studies at night during sleep to determine to what extent infants and children engage in these oral behaviors.

To reduce uncertainty for ages > 10 years, the body surface area in contact with the net and the transfer coefficient from the dry net to the skin would need to be better understood. These input variables currently are highly uncertain. To be

TABLE 6
Sensitivity analysis (percent contribution of the input variable to the output variance) for all insecticides

Input variable	Age group: Infants and toddlers (0–3 years)	Child (3–10 years)	All other age groups (10–70 years)
Saliva extraction factor	72%	52–75%	–
Body weight	28%	24–46%	< 5%
Body surface area in contact with bed net	< 1%	< 1%	54–99%
Dry transfer rate	< 1%	< 1%	0–44%

conservative, we assumed that each night over an entire lifetime, 10–60% of the person's unclothed body would contact the bed net. Provided that the bed net is used properly, the contact should be much less. However, based on the results of our assessment, it would be worthwhile to generate data on contact amount and frequency between skin and the bed net during sleep. This would directly address a large area of uncertainty in the exposure model.

Except for permethrin, which was fixed at 0.49%, we assumed the transfer coefficient from the dry net to the skin was a triangular distribution, with a minimum and most likely value of 0.49% and a high value of 2.5%. We used 0.49% for the most likely value, because the other pyrethroid insecticides are similar to permethrin. However, because there is no publicly available data on transfer coefficients for α-cypermethrin or deltamethrin when factory-impregnated onto fabric, we used the more conservative triangular distribution, with 2.5% as the maximum value. The 2.5% value is from carpet treated with cyfluthrin, another pyrethroid, but the treatment was not from a factory-impregnated process. Instead, it was from a spray used directly on the carpet and then allowed to dry.

Although probabilistic, our analysis used many conservative exposure values, and even at low percentile values, it likely overestimates the risks. For example, we assumed that all children grabbed 15 × 15 cm (225 cm^2) of bed net and sucked on it each night over the first 10 years of their life. If the assumption is refined so that each child from 0 to 3 years does this only every third night, the non-cancer risk would be reduced by 66%. In addition, we assumed that the concentration of insecticide factory-impregnated on the LLIN would not degrade over time through numerous washings or other factors.

Our risk assessment can be used for new LLINs with different insecticide active ingredients or formulations. Although our focus in this paper was the risks presented by the LLINs when used in malaria management in Africa, our risk assessment model also can be used to make risk–benefit decisions for use of LLINs for many insect vector-borne diseases and nuisance situations. Elsewhere, we have conducted and reported the results of risk assessments that address other insect vector management tactics, such as insecticide-impregnated clothing,[6] biological control,[31] repellents,[32] and outdoor space applications of insecticides.[6,33–39] These studies, with the LLIN risk assessment presented here, can provide regulatory authorities and others with information for making improved risk–benefit decisions about personal protective measures and insect management tactics.

Received January 7, 2011. Accepted for publication March 9, 2011.

Acknowledgments: This study was supported by Montana State University and the Montana Agricultural Experiment Station.

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