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## Risk assessments for the insect repellents DEET and picaridin

Frank B. Antwi<sup>a,1</sup>, Leslie M. Shama<sup>b,2</sup>, Robert K.D. Peterson<sup>a,\*</sup><sup>a</sup> Department of Land Resources and Environmental Sciences, Montana State University, 334 Leon Johnson Hall, Bozeman, MT 59717-3120, USA<sup>b</sup> Sacramento-Yolo Mosquito and Vector Control District, Elk Grove, CA 95624-1477, USA

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## ABSTRACT

For the use of topical insect repellents, DEET and picaridin, human health risk assessments were conducted for various population subgroups. Acute, subchronic, and chronic dermal exposures were examined. No-observed-effect-levels (NOELs) of 200, 300, and 100 mg/kg body weight (BW) were used as endpoints for DEET for acute, subchronic, and chronic exposures, respectively. For picaridin, a NOEL of 2000 mg/kg BW/day for acute exposure and a NOEL of 200 mg/kg BW/day for subchronic and chronic exposures were used. Daily exposures to several population subgroups were estimated. Risks were characterized using the Margin of Exposure (MOE) method (NOEL divided by the estimated exposure), whereby estimated MOEs were compared to an MOE of 100. Estimates of daily exposures ranged from 2 to 59 mg/kg BW/day for DEET and 2 to 22 mg/kg BW/day for picaridin. Children had the lowest MOEs. However, none of the estimated exposures exceeded NOELs for either repellent. At 40% DEET for acute exposure, children  $\leq 12$  years had MOEs below 100. For subchronic and chronic exposures children at  $\geq 25\%$  DEET and at 15% picaridin had MOEs below 100. Therefore, we found no significant toxicological risks from typical usage of these topical insect repellents.

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## 1. Introduction

DEET (*N,N*-diethyl-*meta*-toluamide or *N,N*-diethyl-3-methylbenzamide) has been recognized widely as a broad spectrum insect repellent since its introduction more than five decades ago. It is efficacious against mosquitoes and other insects of medical and veterinary importance, and is used at least once in a season by approximately 30% of the U.S. population (USEPA, 1998; Veltri et al., 1994).

Picaridin [2-(2-hydroxyethyl)-1-piperidinecarboxylic acid 1-methylpropyl ester] is a new insect repellent for human use (Wahle et al., 1999; WHO, 2000; Scheinfeld, 2004; Carpenter et al., 2005), with initial registration in the U.S. in 2001 (USEPA, 2005). It has been shown to be effective against mosquitoes and a wide range of hematophagous arthropods (Frances et al., 2004; Scheinfeld, 2004; Carpenter et al., 2005).

Topical application of insect repellents to exposed skin, as part of personal protection measures, reduces human contact with vector and nuisance arthropods (Gupta and Rutledge, 1994). Repellents are of primary importance when other methods of protecting humans against arthropod vectors are not possible or

practical (Debboun et al., 2006). Even when comprehensive mosquito control measures are implemented, personal protective measures can influence the infection rates of West Nile virus (WNV) and other arthropod vector-borne pathogens of disease (Gujral et al., 2007). Insect repellents are of benefit to civilians during outdoor activities and for military personnel during combat, peacekeeping, and training (Frances et al., 2003; Debboun et al., 2005). Military personnel deployed to areas where malaria and other vector-borne diseases are prevalent commonly use repellents as part of personal protective measures.

Despite the extensive use and efficacy of DEET and its history of seemingly safe use, there have been a few observations of high exposures leading to potentially unacceptable health risks (Robbins and Cherniack, 1986; Veltri et al., 1994; Qiu et al., 1998). These reports are associated with seizures and encephalopathy in children (Moody, 1989; Osimitz and Grothaus, 1995; Osimitz and Murphy, 1997; Sudakin and Trevathan, 2003) and extensive skin absorption that leads to entrance of large amounts of DEET into systemic circulation (Robbins and Cherniack, 1986). This suggests that exposures with frequent or prolonged topical applications of DEET may result in central nervous system toxicity in some individuals. DEET, picaridin, IR 3535 (3-[-butyl-*N*-acetyl]-amino propionic acid), PMD (*para*-methane-diol), lemon eucalyptus oil, and citronella oil are among the few insect repellents registered for topical applications to humans. The application of DEET and picaridin on the skin may be made at home, outdoors, and by children or untrained individuals who may apply them in a manner

\* Corresponding author. Fax: +1 406 994 3933.

E-mail addresses: [frank.antwi@montana.edu](mailto:frank.antwi@montana.edu) (F.B. Antwi), [lmshama@hotmail.com](mailto:lmshama@hotmail.com) (L.M. Shama), [bpeterson@montana.edu](mailto:bpeterson@montana.edu) (R.K.D. Peterson).<sup>1</sup> Fax: +1 406 994 3933.<sup>2</sup> Fax: +1 916 685 5464.

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inconsistent with label statements. Although there is a restriction on how much active ingredient can be used in the products, there is no restriction on purchasing products containing these active ingredients. These special situations point to the need for human health risk assessments for population subgroups.

Although there have been some toxicity studies and safety reviews for DEET (Robbins and Cherniack, 1986; Osimitz and Grot-haus, 1995; Qiu et al., 1997, 1998; Fradin, 1998; Goodyer and Behrens, 1998; USEPA, 1998; Young and Evans, 1998; McGready et al., 2001; Health Canada, 2002; Koren et al., 2003; Sudakin and Trevathan, 2003; Blanset et al., 2007) and picaridin (Wahle et al., 1999; WHO, 2000), quantitative dermal risk assessments are lacking in the scientific literature. Peterson et al. (2006), Davis et al. (2007), Macedo et al. (2007), and Schleier et al. (2008) have estimated human health and environmental risks from other mosquito management and personal protective tactics. Therefore, in this study, we assessed the risk of DEET and picaridin to human health.

## 2. Materials and methods

### 2.1. Problem formulation

We focused our assessments on human health risks from the application of DEET and picaridin. These active ingredients are present in the largest number of personal protective products currently registered by the United States Environmental Protection Agency (USEPA) in the US for prevention of vector-borne diseases. IR 3535, PMD, lemon eucalyptus oil, and citronella oil insect repellents were not included as part of our risk assessments, primarily because of the lack of robust toxicity data. Our quantitative risk assessment examined acute, subchronic, and chronic dermal exposures. Acute exposures were defined as single-day exposures within 24 h of repellent application. Subchronic exposures were defined as exposure per day for <180 days. Chronic exposures were defined as exposure per day for >180 days.

### 2.2. Effect assessment and toxic endpoints

To determine toxic endpoints, we conducted a MEDLINE search with the keywords DEET, picaridin, and insect repellents. Articles published in English language journals between 1968 and 2007 were identified and reviewed. The World Wide Web, World Health Organization (WHO), U.S. Armed Forces Pest Management Board (AFPMB), ISI Web of Knowledge, U.S. Centers for Disease Control (CDC), U.S. Environmental Protection Agency (USEPA), U.S. Food and Drug Administration, and Health Canada databases were searched for toxicology and other pertinent information. References of relevant articles also augmented the database search.

### 2.3. DEET

Relevant toxicological endpoints and critical no-observed-adverse-effect-levels NOAELs for DEET from existing animal studies have been defined and discussed in depth elsewhere (USEPA, 1998; Tice and Brevard, 1999; Imperial College, 2002). Because of this, we will only present an overview of toxicological effects for our risk assessments.

#### 2.3.1. Acute toxicity

McCain et al. (1997) reported an oral LD<sub>50</sub> of 3664 mg/kg body weight (BW) in the rat. Mount et al. (1991) examined acute dermal toxicity in dogs with dosages of 356, 1426, 1782, and 7128 mg/kg BW. Dogs receiving the highest dosage of 7128 mg/kg BW were affected mildly with signs of hypersalivation, restlessness, uncoordination, and depression. However, all dogs recovered after 19 h. Dogs that received as much as 1782 mg/kg BW showed no clinical signs of toxicity. In a range-finding toxicity test, Carpenter et al. (1974) reported a dermal LD<sub>50</sub> of 3180 mg/kg BW for rabbits. Dermal application of DEET caused no sensitization reactions in guinea pigs and slight to no irritation in rabbits at 75% and 100% DEET (Harvey, 1987). Macko and Bergman (1979) did not observe significant differences in organ-to-body-weight ratios in rats after inhalation (750 mg/m<sup>3</sup>) exposures to saturated vapor. In an acute neurotoxicity screening study, rats with a single dose of DEET by gavage at 0, 50, 200, and 500 mg/kg were observed for 14 days (USEPA, 1998). One hour after dosing, rats showed signs of piloerection, increased vocalization, a decrease in horizontal and vertical activity, and an increase in the response time to heat, and all recovered 24 h after dosing. Decrease in vertical activity was observed during the first 15 minutes at 200 mg/kg. The USEPA concluded that this effect was isolated, transient, and its toxicological significance was not certain. Hence the no-observed-effect-level NOEL for this study was set at 200 mg/kg, and the lowest-effect-level (LEL) set at 500 mg/kg.

#### 2.3.2. Subchronic toxicity

Dermal application of DEET to micropigs<sup>®</sup> for 13 weeks at dosage levels of 0, 100, 300, or 1,000 mg/kg BW/day did not produce any systemic toxicity (USEPA, 1998). Hence, the NOEL was determined to be 1000 mg/kg BW/day (USEPA, 1998). At the skin application site, treated animals had an increase in desquamation and dry skin (USEPA, 1998). In the rat study using the same dosage levels as in the micropig study, USEPA set the lowest-observed-effect-level (LOEL) at 1000 mg/kg BW/day and the NOEL at 300 mg/kg BW/day based on a decrease in body-weight gain and an increase in liver weight (USEPA, 1998).

Abou-Donia et al. (2001) observed that clinical conditions of rats treated with daily dermal applications of 4, 40, and 400 mg/kg BW DEET in ethanol were not different from the controls. There were also no differences observed in the weight of treated animals when compared to the controls (Abdel-Rahman et al., 2001; Abou-Donia et al., 2001). However, Abou-Donia et al. (2001) suggested that exposures to DEET at 40 and 400 mg/kg BW for 60 days decreased blood-brain barrier permeability in certain brain regions, which may have important physiological or pharmacological consequences. Abdel-Rahman et al. (2001) showed histopathological evidence that subchronic dermal exposure to DEET (40 mg/kg BW/day), leading to significant neuronal cell death and cysto-skeletal abnormalities in surviving neurons, could compromise function of the brain. However, severe signs of central nervous system toxicity due to DEET were apparent only at high dosages (Abdel-Rahman et al., 2001). No exposure-related differences were observed in female and male body weights between control and exposed groups of animals during a subchronic aerosol study. The 13-week exposure to 250, 750, or 1500 mg/m<sup>3</sup> of DEET resulted in no significant changes in oxygen consumption (Macko and Bergman, 1979). Macko and Bergman (1979), therefore, concluded that inhalation at ≤750 mg/m<sup>3</sup> presents little acute inhalation hazard to humans, and concentrations above this level may cause transitory eye and respiratory irritation.

#### 2.3.3. Chronic toxicity

Even though the principal route of DEET exposure in humans is dermal, very little or no toxicity can be produced in laboratory animals by the dermal route of administration (Schoenig et al., 1999). These authors therefore used the oral route of administration to satisfy the criterion of evaluating chronic toxicity at a maximum tolerance dose. Moreover, the data developed by oral route of administration can be extrapolated easily to potential dermal exposure and are amenable to human risk assessments (Schoenig et al., 1999). The oral route of administration avoids the problems associated with repeated dermal administration of undiluted DEET and skin irritation that might be produced.

In a 2-year feeding study using rat, mouse, and dog, depressed body weights and food consumption and slight increases in serum cholesterol were observed in female rats at the high-dose level (400 mg/kg BW/day) (Schoenig et al., 1999). The NOEL was determined to be 100 mg/kg BW/day (Schoenig et al., 1999). The only treatment-related effect in the mouse feeding study was a slight decrease in body weight and food consumption at the highest dose level (1000 mg/kg BW/day) in both males and females. Therefore, the NOEL in this study was 500 mg/kg BW/day (Schoenig et al., 1999). The chronic toxicity study in dogs revealed an increased incidence of emesis and ptialism, decreases in body weight and food consumption, and changes in several clinical pathology parameters at 400 mg/kg BW/day. The NOEL was 100 mg/kg BW/day (Schoenig et al., 1999).

#### 2.3.4. Endpoint selection

For acute and subchronic exposures, we used a NOEL of 200 and 300 mg/kg BW/day (USEPA, 1998) as endpoints, based on the rat acute neurotoxicity and sub-chronic dermal toxicity, respectively (Table 1). For rabbits, the chemical has negligible dermal and limited ocular irritation (WHO, 2000; USEPA, 2005). Picaridin showed no skin sensitization or phototoxicity (WHO, 2000; USEPA, 2005). In an acute dermal toxicity test, no sign of behavioral or pathological anatomical neuro-toxicity was observed at 2000 mg/kg BW (WHO, 2000; USEPA, 2005).

### 2.4. Picaridin

#### 2.4.1. Acute toxicity

Picaridin is of low toxicity in rats and mice after oral administration (LD<sub>50</sub>: 4743 mg/kg BW), and in rats after dermal (LD<sub>50</sub>: >5000 mg/kg BW), and inhalation exposure (LD<sub>50</sub>: >4364 mg/kg BW) (WHO, 2000). In rabbits, the chemical has negligible dermal and limited ocular irritation (WHO, 2000; USEPA, 2005). Picaridin showed no skin sensitization or phototoxicity (WHO, 2000; USEPA, 2005). In an acute dermal toxicity test, no sign of behavioral or pathological anatomical neuro-toxicity was observed at 2000 mg/kg BW (WHO, 2000; USEPA, 2005).

#### 2.4.2. Subchronic toxicity

Low toxicity was observed in a 13-week rat dermal study (WHO, 2000). Upon cessation of treatment, local skin changes subsided for all treatment groups including the lowest dosage of 80 mg/kg BW/day. Repeated administration of picaridin showed induction of hepatic cytochrome P450 dependent reactions and an increase in liver weight at the lowest dosage (WHO, 2000). At 200 mg/kg BW/day, no sign of behavioral or pathological anatomical neurotoxicity was observed (WHO, 2000).

**Table 1**

Toxicologic effects and endpoints for DEET

| Type of study                                          | Endpoints (NOEL, LEL) <sup>a</sup>                                                                     | Description of effect (nature, severity)                                                                                                                            |
|--------------------------------------------------------|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Acute toxicity</i>                                  |                                                                                                        |                                                                                                                                                                     |
| Acute neurotoxicity screening study in rats (gavage)   | NOEL = 200 mg/kg BW/day; LEL = 500 mg/kg BW/day                                                        | No gross or microscopic alterations were observed in the central or peripheral nervous system in comparison with controls                                           |
| <i>Subchronic toxicity</i>                             |                                                                                                        |                                                                                                                                                                     |
| 90-day dermal toxicity study in rats                   | NOEL = 300 mg/kg BW/day <sup>b</sup> ; LEL = 1000 mg/kg BW/day <sup>b</sup> ; NOEL = 1000 mg/kg BW/day | Based on decrease in body-weight gain and increase in liver weights <sup>b</sup><br>Based on 13-week study in micropigs; No renal lesions in micropigs <sup>b</sup> |
| <i>Chronic toxicity</i>                                |                                                                                                        |                                                                                                                                                                     |
| Combined chronic and carcinogenicity in rats (2 years) | NOEL = 100 mg/kg BW/day (females and males); LEL = 400 mg/kg BW/day                                    | Based on decreased body weights and food consumption, and increased cholesterol levels in female and male rats <sup>c</sup>                                         |
| Chronic toxicity study in dogs                         | NOEL = 100 mg/kg BW/day; LEL = 400 mg/kg BW/day                                                        | Based on decreases in food consumption and body weights, increase in the incidence of ptialism and a decrease in cholesterol levels                                 |

<sup>a</sup> Endpoint abbreviations: BW, body weight; NOEL, no-observed effect-level; LEL, lowest effect-level.<sup>b</sup> USEPA (1998).<sup>c</sup> Schoenig et al. (1999).

#### 2.4.3. Chronic toxicity

Picaridin was administered at dosages of 0, 50, 100, and 200 mg/kg BW/day in a 2-year dermal toxicity study in rats (Wahle et al., 1999). Body-weight gain, food consumption, clinical observations, and survival were unaffected at all ages for both sexes. Picaridin did not induce ophthalmic toxicity. Laboratory clinical tests, gross lesion incidence, and organ-weight data did not suggest a compound-related effect. Increased incidence of cystic degeneration of the liver was observed at 200 mg/kg BW/day. The authors also noted several possible treatment-related effects which were attributed to methodology and inherent difficulties associated with lifetime bioassay tests via dermal route. Therefore, the changes at the dosage sites associated with picaridin were non-dose responsive, and could be described as adaptive, non-adverse, predictable responses to chronic exposure (Wahle et al., 1999).

#### 2.4.4. Endpoint selection

For acute exposure, we used a NOEL of 2000 mg/kg BW/day (USEPA, 2005) as the endpoint, based on no signs of behavioral or pathological anatomical neurotoxicity (WHO, 2000). For subchronic and chronic exposures, we used a NOEL of 200 mg/kg BW/day as the endpoint (Table 2), based on the lack of adverse and non-skin compound-related effects (Wahle et al., 1999) and no signs of behavioral or pathological anatomical neurotoxicity (WHO, 2000).

#### 2.5. Exposure assessment

Health Canada (2002) estimated human exposure potential of DEET using survey and usage data. The study involved 540 subjects (men, women, and children) at three locations (Wisconsin, Oregon, and Florida) in the U.S. The difference between the weight of the products for pre- and post-application provided an estimate for the amount of product used per application. Based on all formulation types, the estimated mean amount of product applied was 3.7 g per person per application.

This study also observed that the difference between population groups (men vs women vs children) in the amount of product applied during a single usage was not significantly different (Health Canada, 2002).

Therefore, the amount of active ingredient (DEET or picaridin) deposited on the skin would be:

$$\text{mg active ingredient} = 3700 \text{ mg} \times \% \text{ concentration of active ingredient in product}$$

We estimated dermal exposures for adults and children for one application per day. Dermal exposures were estimated as:

$$\text{Dermal exposure} = \frac{[\text{amount of active ingredient deposited on skin (mg)}]}{[\text{body weight (kg)}]}$$

Daily exposures to several population subgroups were estimated to account for potential age-related differences in exposure. Groups included adult males, females, and children ( $\leq 12$  and 13–17 years of age). Adult males and females were assumed to weigh 78.7 and 67.1 kg, respectively (USEPA, 1998). Children  $\leq 12$  and 13–17 years of age were assumed to weigh 25 and 50.6 kg, respectively (USEPA, 1998).

#### 2.6. Risk characterization

We assessed human health risks in this study by integrating toxicity and exposure. Risks were assessed using the Margin of Exposure (MOE) method. An MOE for each population subgroup was calculated by dividing the appropriate toxic endpoint (i.e. the NOEL) by the daily exposure. We calculated the dermal MOEs using the equation below:

$$\text{MOE} = \frac{[\text{oral NOEL} \times 5 (\text{rat oral-to-dermal conversion factor}) \times 5 (\text{rat-to-human dermal absorption correction factor})]}{[\text{estimated human dermal exposure}]}$$
**Table 2**

Toxicologic effects and endpoints for picaridin

| Type of study                               | Endpoints (NOEL, LEL) <sup>a</sup>                                                  | Description of effect (nature, severity)                                                                                                                                                           |
|---------------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Acute toxicity</i>                       |                                                                                     |                                                                                                                                                                                                    |
| Acute dermal neurotoxicity study            | NOEL = 2000 mg/kg BW/day                                                            | No signs of behavioral or pathological anatomical neurotoxicity was observed <sup>c</sup>                                                                                                          |
| <i>Subchronic toxicity</i>                  |                                                                                     |                                                                                                                                                                                                    |
| Dermal neurotoxicity study                  | NOEL = 200 mg/kg BW/day                                                             | No signs of behavioral or pathological anatomical neurotoxicity was observed <sup>c</sup>                                                                                                          |
| Dermal-rat                                  | NOAEL (systemic) = 200 mg/kg BW/day<br>LOAEL (systemic) = 500 mg/kg BW/day          | Based on diffuse liver hypertrophy, individual necrotic liver cells, hyaline kidney degeneration, increase incidence of foci of tubular regeneration, and chronic kidney inflammation <sup>b</sup> |
| <i>Chronic toxicity</i>                     |                                                                                     |                                                                                                                                                                                                    |
| Dermal chronic toxicity-dog                 | NOAEL (systemic) = 200 mg/kg BW/day<br>NOAEL (dermal irritation) = 200 mg/kg BW/day | No toxicity was observed <sup>b</sup>                                                                                                                                                              |
| Dermal chronic toxicity/carcinogenicity-rat | NOAEL = 200 mg/kg BW/day                                                            | Based on cystic degeneration of the liver with no corroborating liver weight or clinical pathology anomalies <sup>b</sup>                                                                          |

<sup>a</sup> Endpoint abbreviations: BW, body weight; NOEL, no-observed-effect-level; NOAEL, No-observed-adverse-effect-level; LOAEL, lowest-observed-adverse-effect-level; LEL, lowest-effect-level.<sup>b</sup> USEPA, 2005.<sup>c</sup> WHO, 2000.

The oral NOEL was converted to a dermal equivalent NOEL by using pharmacokinetic data from rats. The conversion factor of 5 was derived from measured levels of parent DEET in rat plasma or blood following oral and dermal dosing. Also, studies estimating human dermal absorption of DEET showed an approximately 5-fold difference in dermal absorption in rats (38.5%) and humans (7.5%) (Health Canada, 2002). When using a dermal NOEL as our endpoint, we corrected only for rat-to-human dermal absorption. Margins of exposures less than 100 (i.e., the exposure is greater than 1% of the NOEL) often are considered to exceed a regulatory level of concern (LOC) (Whitford et al., 1999). In this study, we characterized risk by comparing our estimated exposures to NOEL, and estimated MOEs to an MOE LOC of 100.

### 3. Results

#### 3.1. Acute risks

Daily exposure estimates ranged from 2 to 59 mg/kg BW/day for DEET and 2 to 22 mg/kg BW/day for picaridin (Table 3). Potential acute MOEs for DEET ranged from 85 to 2127 (Table 3). For picaridin, acute MOEs ranged from 451 to 4254. The maximum DEET concentrations compatible with an MOE of at least 100 ranged from 33.8 to >100% for children and adults (Table 4). For picaridin, the concentrations ranged from 67.6 to >100% for all population subgroups (Table 4). At a concentration of 40% DEET, children at ≤12 years had an MOE below 100 (Table 3). For picaridin, the MOEs were >100 at 5% and 15% concentrations for all population subgroups (Table 3).

#### 3.2. Subchronic risks

For DEET, subchronic MOEs ranged from 25 to 638. At 25% DEET, children (≤12 and 13–17 years) had MOEs below 100 and at 40% DEET, all population subgroups had MOEs below 100 (Table 3). The maximum DEET concentrations compatible with an MOE of at least 100 ranged from 10.1% to 31.9% for all population subgroups (Table 4).

Picaridin had subchronic MOEs ranging from 45 to 425 (Table 3). At 15% picaridin, children (≤12 and 13–17 years) had MOEs of 45–91 which were below the level of concern. Picaridin required

**Table 4**

Percent concentration of repellents compatible with an MOE of at least 100 for each subgroup and exposure

| Population subgroup | Acute exposure    |           | Subchronic exposure |           | Chronic exposure |           |
|---------------------|-------------------|-----------|---------------------|-----------|------------------|-----------|
|                     | DEET              | Picaridin | DEET                | Picaridin | DEET             | Picaridin |
|                     | Concentration (%) |           |                     |           |                  |           |
| Adult male          | >100              | >100      | 31.9                | 21.3      | 53.2             | 21.3      |
| Adult female        | 90.7              | >100      | 27.2                | 18.1      | 45.3             | 18.1      |
| Child, 13–17        | 68.4              | >100      | 21.5                | 13.7      | 34.2             | 13.7      |
| Child, ≤12          | 33.8              | 67.6      | 10.1                | 6.8       | 16.9             | 6.8       |

a concentration range of 6.8% to 21.3% compatible with an MOE of at least 100 for all subgroups (Table 4).

#### 3.3. Chronic risks

The MOEs for DEET chronic exposure ranged from 42 to 1064 (Table 3). At 25% DEET, children (≤12 years of age), and at 40% DEET, children (≤12 and 13–17 years) had MOEs below 100 (Table 3). For an MOE of 100, DEET concentrations were 45.3 and 53.2% for adult females and males, and 16.9 and 34.2% for children ≤12 years and children 13–17 years, respectively (Table 4).

Picaridin MOEs ranged from 45 to 425. Children (≤12 and 13–17 years) were the only subgroups with MOEs below 100 at 15% picaridin (Table 3). For picaridin, concentrations compatible with an MOE of at least 100 was 21.3% for adult males, 18.1% for adult females, 13.7% for children 13–17 years, and 6.8% for children ≤12 years (Table 4).

### 4. Discussion

None of our estimated exposures equaled or exceeded the NOELs for DEET or picaridin (i.e., MOEs ≤1). However, acute MOEs were below 100 for children (≤12 years) at 40% DEET. For picaridin, all of the population subgroups had margins of exposures

**Table 3**  
Margins of exposure for the active ingredients for each population subgroup

| Population subgroup                                      | DEET                  | Picaridin | Acute            |           | Subchronic |           | Chronic |           |
|----------------------------------------------------------|-----------------------|-----------|------------------|-----------|------------|-----------|---------|-----------|
|                                                          |                       |           | DEET             | Picaridin | DEET       | Picaridin | DEET    | Picaridin |
| Adult male<br>Adult female<br>Child, 13–17<br>Child, ≤12 | Concentration         |           |                  |           |            |           |         |           |
|                                                          | 5%                    | 5%        | 5%               | 5%        | 5%         | 5%        | 5%      | 5%        |
|                                                          | Exposure (mg/kg/BW/d) |           | MOE <sup>a</sup> |           |            |           |         |           |
|                                                          | 2                     | 2         | 2127             | 4254      | 638        | 425       | 1064    | 425       |
|                                                          | 3                     | 3         | 1814             | 3627      | 544        | 363       | 907     | 363       |
|                                                          | 4                     | 4         | 1368             | 2735      | 410        | 274       | 684     | 274       |
|                                                          | 7                     | 7         | 676              | 1351      | 203        | 135       | 338     | 135       |
|                                                          | Concentration         |           |                  |           |            |           |         |           |
|                                                          | 25%                   | 15%       | 25%              | 15%       | 25%        | 15%       | 25%     | 15%       |
|                                                          | Exposure (mg/kg/BW/d) |           | MOE              |           |            |           |         |           |
| Adult male                                               | 12                    | 7         | 425              | 1418      | 128        | 142       | 213     | 142       |
| Adult female                                             | 14                    | 8         | 363              | 1209      | 109        | 121       | 181     | 121       |
| Child, 13–17                                             | 18                    | 11        | 274              | 912       | 82         | 91        | 137     | 91        |
| Child, ≤12                                               | 37                    | 22        | 135              | 451       | 41         | 45        | 68      | 45        |
| Adult male<br>Adult female<br>Child, 13–17<br>Child, ≤12 | Concentration         |           |                  |           |            |           |         |           |
|                                                          | 40%                   |           | 40%              |           | 40%        |           | 40%     |           |
|                                                          | Exposure (mg/kg/BW/d) |           | MOE              |           |            |           |         |           |
|                                                          | 19                    |           | 266              |           | 80         |           | 133     |           |
|                                                          | 22                    |           | 227              |           | 68         |           | 113     |           |
|                                                          | 29                    |           | 171              |           | 51         |           | 86      |           |
|                                                          | 59                    |           | 85               |           | 25         |           | 42      |           |

<sup>a</sup> Values in column are margins of exposure per application per day.

greater than 100. For subchronic exposure, MOEs for children ( $\leq 12$  and 13–17 years) were below 100 at  $\geq 25\%$  DEET. At 40% DEET, all population subgroups had MOEs below 100. Picaridin application resulted in MOEs below 100 for children  $\leq 12$  and 13–17 years) at 15% concentration. For chronic exposures, children ( $\leq 12$  and 13–17 years) had MOEs below 100 at 25% and 40% DEET. For picaridin, MOEs were below 100 for children ( $\leq 12$  and 13–17 years) at 15%. The lowest MOE (highest risk) indicated that the exposure was 25- and 45-fold lower than the NOEL for DEET and picaridin, respectively, for children  $\leq 12$  years. Children had the lowest MOEs primarily because DEET is applied to the skin, and hence a higher surface area of skin relative to body weight in children will result in a larger exposure per kg body weight.

Another route of exposure to DEET and picaridin includes ingestion, although it would be much less than dermal exposures. [Blanset et al. \(2007\)](#) estimated that ingestion of DEET in drinking water for specific populations was  $8.2 \times 10^{-5}$  mg/kg BW/day, which was 720-fold less than our maximum dermal exposure estimate. The authors concluded that DEET in drinking water is unlikely to result in significant human health effects in the general population.

The major uncertainties in our risk assessments are associated with dermal exposure of the active ingredients. Data for actual dermal exposures and the variability in the amount of active ingredient absorbed dermally need to be generated to accurately characterize risk. Even though we had access only to information reporting the estimated mean amount of product applied ([Health Canada, 2002](#)), there undoubtedly is variability in the amount of product used within and among subgroups. Future work should be directed towards reducing the uncertainties associated with exposure and absorption of the active ingredients in insect repellent products.

As with any technology, the risks must be considered with concomitant benefits. [Fradin and Day \(2002\)](#) observed that a formulation containing 24% DEET provided bite protection for an average of 5 h. In laboratory studies for mosquito species on forearms, [Frances et al. \(2005\)](#) found that 10% and 80% DEET at a rate of 2.24 and 2.92 mg/cm<sup>2</sup> provided protection of 5 and greater than 8 h, respectively. For picaridin (9% and 19%) optimal protection time was 3–4 h at a rate of 3.23 and 3.39 mg/cm<sup>2</sup> ([Frances et al., 2005](#)). This agrees with [Health Canada \(2002\)](#) that 15% DEET formulations resulted in mean complete protection times of 4.2–7.2 h.

Although we present only estimated exposures and MOEs for the exposure scenario of one application per day, it is possible that people will apply repellents two or three times per day. In these cases, the MOEs, and therefore the risks, are linearly proportional to the increase in exposures (i.e., two applications would double the exposure per day and reduce the MOE by half). We summarize the MOEs for these high-end use scenarios here. MOEs varied from 169 to 532 and 113 to 355 for two and three applications per day, respectively, for acute 10% DEET exposures. For acute exposures at 80% DEET MOEs ranged from 21 to 67 and 14 to 44 for two and three applications, respectively. The MOEs for 9% picaridin ranged from 225 to 709 and 150 to 473 for two and three applications per day, respectively. At 19% picaridin the MOEs ranged from 178 to 560 for two applications, and 119 to 373 for three applications.

For subchronic 10% DEET exposures, MOEs ranged from 3 to 34 and 34 to 107 for two and three applications, respectively. At 80% DEET, MOEs varied from 6 to 20 for two applications, and 4 to 13 for three applications per day. Picaridin at 9% had MOEs of 38 to 118, and 32 to 101 for two and three applications per day, respectively. At 19% picaridin, MOEs ranged from 18 to 56 for two applications per day and 12 to 37 for three applications.

It is commonly understood that insect repellents are important personal protective measures to help prevent disease from vector-borne pathogens (e.g., West Nile virus). However, less

well known are the risks from the arthropod bites. Mosquito and arthropod bite exposure results in a variety of cutaneous reactions and other complications, and may be attributed to antigenic, non-antigenic irritating substances or both ([Feingold et al., 1968](#)). Mosquito salivary secretions contain proteins that are responsible for skin reactions to mosquito bites ([Peng and Simons, 2004a,b](#)). Skin response to mosquito bites consists of an immediate wheal and flare ups, and a delayed indurated papule or nodule ([Peng and Simons, 1997](#)). Other symptoms include “Skeeter Syndrome”, a mosquito bite-induced large local inflammatory reactions accompanied by fever in young children ([Peng and Simons, 2004a,b](#)). The immediate reaction is compatible with that of an IgE-mediated hypersensitivity, is usually pruritic, and consists of erythema and edema. The delayed reaction is consistent with lymphocyte-mediated hypersensitivity, and an IgE-mediated late phase reaction ([Peng and Simons, 1997](#)). It is characterized by erythema and papule and may persist for several days. The skin reactivity sequences occur due to repeated insect bites. This includes a period of induction of hypersensitivity (i.e. no observable skin reactions), delayed skin reaction, immediate skin reactions followed by delayed reactions, immediate reactions only, and no reactivity.

Allergic reactions to mosquito bites are common. Compared to older children, infants and younger children have higher levels of mosquito saliva specific IgE and IgG antibodies, and are at high risk of having allergic reactions to mosquito bites ([Peng et al., 2004](#)). However, there are few epidemiologic data regarding the prevalence of mosquito allergies ([Peng et al., 2004](#)). Antibodies IgE and IgG are associated with mosquito allergy development. [Peng et al. \(2002\)](#) measured antibodies (IgE and IgG), and observed that 18% of 1059 adult blood donors living in an environment with a high summer mosquito population are sensitized to mosquito saliva. [Peng et al. \(2004\)](#) found that levels of IgE peaked in infants aged 6 months to 1 year and earlier for IgG, and levels of both antibodies gradually declined after the age of 5. In individuals aged 16 to 18, mean levels of IgE and IgG antibodies were low and similar to those reported previously in adults ([Peng et al., 2004](#)). Population subgroups with a high level of exposure (i.e., civilian or military personnel outdoor workers), children, immune-deficient persons, and visitors to areas with indigenous mosquitoes to which they have not been exposed to previously are at greater risk for severe reactions to mosquito and arthropod bites.

Our assessment reveals that exposures to DEET and picaridin are unlikely to exceed NOELs. [Health Canada \(2002\)](#) estimated acceptable MOEs greater than 100 for acute risks for products up to 35% DEET for children. For acute risks, we estimated an MOE of 195 for children 13–17 years, and an MOE of 97 for children  $\leq 12$  years for 35% DEET although we have presented analysis only for 5%, 25%, and 40% DEET. [Health Canada \(2002\)](#) estimated subchronic MOEs greater than 100 for products containing 30% DEET or less for adults, and 10% or less DEET for children. Our data show that MOEs greater than 100 for subchronic exposures ranged from less than 10% to 32% DEET and 7% to 21% picaridin for all subgroups.

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