Exposure to N,N-Diethyl-Meta-Toluamide Insect Repellent and Human Health Markers: Population Based Estimates from the National Health and Nutrition Examination Survey

Zuhair M. Haleem,¹ Sandhya Yadav,¹ Minor L. Cushion,¹ Rebecca J. Tanner,¹ Peter J. Carek,² and Arch G. Mainous III^{1,2*}

¹Department of Health Services Research, Management, and Policy, University of Florida, Gainesville, Florida; ²Department of Community Health and Family Medicine, University of Florida, Gainesville, Florida

Abstract. N,N-diethyl-meta-toluamide (DEET) is one of the most commonly used insect repellants in the United States, yet the existing literature regarding DEET's potential deleterious impact on humans is mixed and is based mostly on case reports. The primary aim of this study was to address this lack of population-based evidence of the effects of DEET exposure on human health in the United States. Our primary outcome measures were biomarkers related to systemic inflammation (high sensitivity C-reactive protein), immune function (lymphocyte), liver function (aspartate aminotransferase, alanine aminotransferase, and γ -glutamyl transferase), and kidney function (estimated glomerular filtration rate). We analyzed data from the population-based National Health and Nutrition Examination Survey, 2015–2016, and identified 1,205 patients (age 20+ years) who had DEET metabolite levels recorded at or above detection limits. A Pearson correlation was used to assess the relationship between DEET metabolite, and each biomarker found there was no significant correlation. Thus, there is no evidence that DEET exposure has any impact on the biomarkers identified.

The chemical N,N-diethyl-meta-toluamide (DEET), commonly referred to as “DEET,” is used as the active ingredient in many insect-repellent products.^{1,2} N,N-diethyl-meta-toluamide was developed for the U.S. Army in 1946 to protect soldiers stationed in insect-infested areas and was registered for commercial use in the United States in 1957. Since then, it has become one of the most widely used types of insect repellents in the country.² N,N-diethyl-meta-toluamide is commonly used to prevent bites from arthropods such as mosquitoes, ticks, and fleas. The mechanism of DEET repellency is still unclear, although many believe that smell, ingestion, and contact all have prominent roles in preventing insect bites.^{3–5}

Multiple studies have confirmed that products containing DEET are some of the most efficacious insect repellents on the market.^{6,7} N,N-diethyl-meta-toluamide-containing products come in many forms, including liquid sprays, lotions, and sticks, intended for direct application to the skin.⁸ Products registered for human use can contain between 4% and 100% DEET, although the most common concentration is 30–40%.⁹ It has been estimated that 30% of the U.S. population uses one or more DEET-containing products every year.¹⁰

In 2014, the Environmental Protection Agency completed an interim review of DEET to reassess if it met the safety standards. They were unable to identify sufficient evidence of any risks of concern to human health, nontarget species, or the environment.² However, evidence regarding DEET's potential danger to humans is mixed, with some case reports finding evidence of toxicity.^{11–14} These were cases in which subjects exposed to DEET were using insect repellent in line with the recommended use, as the FDA has warned that the improper use of DEET insect repellent (ingestion, over application, or spraying in enclosed areas) has been known to cause vomiting and nausea.² One randomized trial on the safety of DEET exposure in pregnancy found no evidence of

adverse health impacts related to the survival, growth, or development of the fetuses.¹⁵ On the other hand, another study found that DEET may have an impact on hepatic function by altering the induction of certain genes that affect the body's ability to metabolize certain drugs.¹⁶ A major gap in the existing literature is that there is little population-based information on DEET exposure and human health.

The primary aim of this study was to address this lack of population-based evidence of the effects of DEET exposure on human health in the United States.

We analyzed data from the population-based National Health and Nutrition Examination Survey, 2015–2016. The NHANES is a multistage probability sample of the civilian, noninstitutionalized U.S. population. The survey examines a nationally representative sample of about 5,000 persons each who are located in counties across the country, 15 of which are selected randomly each year. The NHANES includes physical examinations, laboratory tests, and interviews with participating individuals. This study uses data that were not specifically collected for the study, and no member of the study team has access to subject identifiers linked to the specimens or data. Accordingly, this study is not considered human subject research according to the 2018 Revision of the Common Rule.¹⁷

Our initial unweighted sample included 1,266 participants. One-third of the total NHANES sample had the DEET metabolite assessed. From this group, we examined the presence of the DEET metabolite 3-(ethylcarbamoyl) benzoic acid among individuals who did not have a diagnosis or history of kidney disease, liver disease, and cardiovascular disease/events. Participants younger than 20 years were excluded from our sample because this group did not have the information on the diagnosis or history of kidney disease, liver disease, and cardiovascular disease/events (chronic heart disease, heart attack, or stroke), to ensure that any evidence of a relationship was not due to previous disease. Our final weighted sample was representative of 170,921,067 Americans.

To assess DEET exposure, we used the urinary concentration of 3-(ethylcarbamoyl) benzoic acid (ng/mL) (DEET metabolite) rather than self-reported use of and exposure to

* Address correspondence to Arch G. Mainous III, Department of Health Services Research, Management and Policy, University of Florida Health Sciences Center, P. O. Box 100195, Gainesville, FL 32610. E-mail: arch.mainous@ufl.edu

TABLE 1

Demographic characteristics of the study population aged 20 years and older ($N = 1,205$, weighted $N = 170,921,068$)

	Weighted %	
Gender		
Male		47.9
Race/ethnicity		
Non-Hispanic white		63.8
Non-Hispanic black		11.8
Hispanic		16.4
Other		8.0
Age at screening (years)	Mean	Standard error
	45.1	1.0
Health markers		
DEET metabolite (ng/mL)	100.1	28.7
High-sensitivity C-reactive protein (mg/L)	3.5	0.3
Lymphocyte %	30.7	0.3
Neutrophil %	57.5	0.3
Aspartate aminotransferase (IU/L)	25.4	0.4
Alanine aminotransferase (IU/L)	25.3	0.6
γ -Glutamyl transferase (U/L)	25.1	0.8
Estimated glomerular filtration rate (mL/min)	100.0	1.3

DEET. This measure of DEET exposure was chosen because there is evidence that urinary metabolites of DEET are more sensitive biomarkers of exposure and can decrease exposure misclassification using other methods.¹⁰

High-sensitivity C-reactive protein (HS-CRP) has been shown to be an extremely sensitive objective indicator of systemic inflammation.¹⁸ It is widely used for the evaluation of stress, trauma, infection, and toxic exposures. The detection limit for HS-CRP in the sample was 0.11 mg/L.

Whole blood samples were analyzed using standardized procedures at the Medical Examination Centers used for the collection of NHANES data. Laboratory procedures are provided in detail in the NHANES laboratory manual.¹⁹ Lymphocyte percent and segmented neutrophils percent were both assessed to examine whether there were any impacts on immune function.

Past literature suggested that DEET exposure may affect hepatocyte functioning.¹⁶ The NHANES contained assays of several liver function tests including aspartate aminotransferase (AST) (measured in IU/L), alanine aminotransferase (ALT) (measured in IU/L), and γ -glutamyl transferase (GGT) (measured in U/L). These enzymes were used as indicators of liver function.

Because of the kidney's role in filtering blood and toxins from the body, kidney function was assessed. The estimated glomerular filtration rate is a commonly used measure of kidney function. The estimated glomerular filtration rate was calculated using the CKD-EPI creatinine equation defined in Levey.²⁰

Analysis was conducted in SUDAAN. This allows us to account for the complex survey design of the NHANES and for

stratum-level and primary sampling unit differences by using appropriate weights. By using these weights and sampling design variables, we were able to make reliable population estimates for the noninstitutionalized adult population of the United States. The distribution of the DEET metabolite and each health-related biomarker was assessed. All but three of the biomarkers/DEET metabolites were not normally distributed. The three biomarkers which were normally distributed were lymphocyte percent, neutrophils percent, and eGFR. Descriptive characteristics of the sample were assessed. A Pearson correlation was used to estimate the relationship between the DEET metabolite and each biomarker. Missing data were handled using list-wise deletion. This resulted in Pearson correlations being estimated on 1,205 cases for the full sample (aged 20+ years).

There were a total of 1,205 participants who were assessed for the presence of the DEET metabolite and had levels recorded at or above detection limits. The descriptive statistics of the study cohort are shown in Table 1. Results from the Pearson correlation test for the full sample (aged 20+ years) are provided in Table 2. The value of the correlation coefficients of the DEET metabolite with all health-related biomarkers (hS-CRP, lymphocyte %, neutrophil %, AST, ALT, GGT, and eGFR) for the full sample is between -0.02 and 0.02 . The correlations between the DEET metabolite levels and the biomarkers for the subsample of individuals aged 65 years and older are also shown in Table 2. The correlation coefficients for this subsample were slightly larger, ranging from -0.19 to 0.16 . The population-based results yielded in this study suggest essentially no relationship between the level of the DEET metabolite and these health-related biomarkers assessed for this study.

As there is no evidence of a relationship between the level of the DEET metabolite and health-related biomarkers of systemic inflammation (hS-CRP), immune function (lymphocyte), liver function (AST, ALT, and GGT), and kidney function (eGFR), exposure to DEET does not appear to have a deleterious impact on human health. Furthermore, individuals older than 65 years with DEET exposure had little or no impact on these markers, indicating age is not a factor.

General population data were used in this study, and the results reflect normal use of this insect repellent. The information may be limited as individuals who require higher volume of or more frequent applications may not have been assessed. The cross-sectional design of this study allows us to examine the potential prevalence of health effects associated with DEET. Seasonality may be a limiting factor in our assessment of the effects of DEET on human health because individuals are more likely to apply DEET to their skin at higher concentrations during warmer months than in cooler ones, for example.

We controlled for kidney disease, liver disease, and cardiovascular disease/events by excluding individuals with

TABLE 2

Correlation of N,N-diethyl-meta-toluamide with other biomarkers (unweighted sample $N = 1,205$, weighted $N = 170,921,068$ for age 20+ years)

	High-sensitivity C-reactive protein (P-value)	Lymphocyte percentage (P-value)	Neutrophil percentage (P-value)	Aspartate aminotransferase (P-value)	Alanine aminotransferase (P-value)	γ -Glutamyl transferase (P-value)	Estimated glomerular filtration rate (P-value)
DEET metabolite							
Age 20+ years	0.01 (0.50)	-0.02 (0.22)	0.02 (0.28)	-0.01 (0.07)	-0.02 (0.00)	0.00 (0.70)	-0.01 (0.63)
Age 65+ years	-0.03 (0.26)	-0.19 (0.04)	0.16 (0.06)	-0.01 (0.55)	-0.15 (0.05)	-0.02 (0.34)	-0.03 (0.38)

these diagnoses from the study. Similarly, we controlled for age by examining stratified age-groups: those aged 20+ years and those aged 65+ years; it should be noted that individuals aged 65+ years are included in the group aged 20+ years.

N,N-diethyl-meta-toluamide may impact other human functions not tested. Future studies should analyze an expanded set of health-related biomarkers and would be well served to analyze potential associations between DEET and chronic conditions such as chronic obstructive pulmonary disorder, certain types of cancers (e.g., melanoma), nervous system conditions (such as seizures), and heart disease.

N,N-diethyl-meta-toluamide appears to be a safe insect repellent when used in a population setting. Conversely, many Americans remain unsure as to the extent to which DEET is safe to use; they cite the potential effects it may have on their health. To this end, DEET has been pulled from U.S. markets in the past, and in other instances, legislators have unsuccessfully lobbied against the use of DEET in the United States.

This study tests the effects of DEET exposure on human health using population-based data. The results indicate that DEET exposure may not be associated with increased risk for negative health outcomes. The implications suggest that DEET exposure is safe for human use.

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Authors' addresses: Zuhair M. Haleem, Sandhya Yadav, Minor L. Cushion, Rebecca J. Tanner, Arch G. Mainous III, Department of Health Services Research, Management, and Policy, University of Florida, Gainesville, FL, E-mails: zuhair.haleem@ufl.edu, sandhya.yadav@ufl.edu, mcushion@ufl.edu, rtanner@phhp.ufl.edu, and arch.mainous@phhp.ufl.edu. Peter J. Carek, Department of Community Health and Family Medicine, UF Health Family Medicine, University of Florida, Gainesville, FL, E-mail: carek@ufl.edu.

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