Current Commentary

Insect Repellants During Pregnancy in the Era of the Zika Virus

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Health care providers must be equipped to provide appropriate advice to reproductive-aged patients for protection against the potentially devastating consequences of prenatal Zika virus exposure. The goal of this commentary is to summarize what is known about the safety and toxicity of N,N-diethyl-meta-toluamide (DEET) as a topical insect repellant and the pyrethroid permethrin for treatment of fabric, endorsed in the fight against Zika virus. Reviews assessing the safety and toxicity of DEET conducted by the U.S. Environmental Protection Agency and the Canadian Pest Management Regulatory Agency conclude that DEET has low acute toxicity and does not appear to pose a significant health concern to humans when used as directed. Some experimental animal and limited epidemiologic data suggest that prenatal pyrethroid exposure may adversely affect learning and behavior, but this level of evidence pales in comparison to the known risks of Zika virus to the fetal brain. The available evidence has led to the strong recommendation by the Centers for Disease Control and Prevention for use of these products by pregnant women as personal protection against mosquito bites in the fight against Zika virus infection. This message has been affirmed by our obstetrics and gynecology professional organizations. Because Zika virus is unlikely to be the last disease requiring vector control, those with environmental health expertise must continue to join with infectious disease specialists to communicate the potential vulnerability of our youngest (fetuses, infants, and young children) to vector-borne disease, both to the disease itself and to the strategies employed to mitigate the spread of such disease.

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Prenatal Zika virus infection has been linked with devastating consequences for the fetus and newborn, including fetal death, neonatal death, microcephaly, central nervous system lesions, uteroplacental insufficiency and growth restriction, and hearing loss.[1] Obstetrician–gynecologists must be knowledgeable about appropriate advice to provide reproductive-aged patients for protection against this devastating disease. The goal of this commentary is to summarize for providers and patients what is known about the safety and toxicity during pregnancy of two specific insect repellants, N,N-diethyl-meta-toluamide (DEET) and permethrin. Based on the available evidence, these U.S. Environmental Protection Agency (EPA)–approved insect repellants have been strongly recommended for use during pregnancy by the Centers for Disease Control and Prevention (CDC) as a key component in the multipronged approach for avoiding mosquito bites in the fight against Zika virus infection,[2] an approach affirmed by our obstetrics and gynecology professional organizations.[3] We refer readers to two Internet-accessible living documents for further details about prenatal Zika virus infection and

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for up-to-date guidelines regarding counseling, screening, and diagnosis of infection during pregnancy.[2,3] Recommendations for use of insect repellants on infants and young children may differ from those for adults and pregnant women, so health care providers and parents should consult the pediatric guidelines for the appropriate use of insect repellants in children.[4]

The biology of the primary mosquito vector transmitting Zika virus, *Aedes aegypti*, has implications for vector control.[5] Importantly, *Aedes aegypti* mosquitoes are quite adaptable to human settings and can bite both indoors and outdoors, with a preference for indoor biting. Biting can occur throughout the day, and, with enough artificial light, biting can even occur at night. In contrast, *Anopheles* mosquitoes, the vectors that transmit malaria, feed from dusk until daybreak. Bednets, which have been a cornerstone of the strategy for prevention of malaria transmission, will not be as useful in the fight against the Zika virus. Personal protection through repellant use combined with other measures to decrease the mosquito population is central to prevention. We turn our attention now to review what is known about DEET and permethrin during pregnancy.

DEET

DEET has been marketed as an insect repellant worldwide since the 1950s and is used by an estimated 50 to 100 million individuals in the United States yearly.[6] DEET previously has been recommended by the CDC for use by pregnant women in the United States for protection against West Nile virus[7] as well as Lyme disease,[8] because DEET also repels ticks. In head-to-head comparisons against other insect repellants available in the United States, DEET products provided the longest protection against mosquito bites, outperforming products containing IR3535 (ethyl butylacetylaminoproprionate), citronella, lemongrass oil, cedar oil, geranium oil, and peppermint oil.[9] Another insecticide alternative to DEET is picaridin, although in at least one investigation it was less effective in providing protection against *Aedes* mosquitoes compared with DEET.[10] DEET is generally considered the most effective insect repellant available on the market, which is why it is specifically named in Zika guidelines as the repellant of choice. Although picaridin appears relatively nontoxic and safe to use,[11] information is less extensive, especially its safety during pregnancy.

DEET's purported mechanism of action is a disturbance in the receptors of the mosquito antennae that allow it to locate humans.[12] There are more than 200 DEET products available on the market in concentrations as high as 100%.[13] DEET's effectiveness increases with rising concentration of the chemical but plateaus at a concentration around 50%, rendering products with higher concentrations of DEET unlikely or uncertain to offer additional benefit.[14] Dermal absorption studies using nonpregnant adult volunteers have documented absorption in the range of 5–15%.[15] Theoretically, absorption may be higher among pregnant women given increased dermal blood flow, but this has not been studied. Exposure also could occur by inhalation if the product is aerosolized during application or ingestion from food contaminated by hands covered with DEET. After absorption in humans, DEET is metabolized by the kidney and undergoes fairly rapid excretion within about 24 hours.[13]

The safety and toxicity of DEET was reviewed extensively by the EPA in 1998[16] and reaffirmed in 2014.[13] The Canadian Pest Management Regulatory Agency also performed a thorough review of DEET in 2002.[17] These reviews have consistently concluded that DEET has low acute toxicity and does not appear to pose a significant health concern to humans when used as directed. Most adverse effects described are local skin reactions. A few scattered reports of adverse neurologic effects with extremely high exposures, including seizures and encephalopathy, have been noted but appear rare and secondary to intentional poisoning by ingestion or extraordinarily excessive repeated dermal applications. DEET is not considered genotoxic or carcinogenic by the EPA.[13] Animal data do not suggest a particular vulnerability to the chemical among the young, in contrast to many other chemicals that do display age-dependent differential toxicity. The Canadian Pest Management Regulatory Agency no longer registers products containing more than 30% DEET based on their evaluation of the margins of exposure (the ratio of the estimated dose to the no observable adverse level in animal studies).[17] The EPA has not been as strict with product registrations.

There is an isolated case report describing a child born with craniofacial malformations (hypertelorism, poorly developed philtrum, broad nasal bridge) who was subsequently diagnosed with developmental delay.[18] During the pregnancy, his mother was working in Africa and used chloroquine for malaria chemoprophylaxis and applied DEET daily. In addition, there is a case–control study reporting an adjusted odds ratio for hypospadias of 1.81 (95% confidence interval 1.06–3.11) from exposure to unspecified insect repellants during pregnancy.[19] Exposure was assessed by maternal recall, often several years after

the incident pregnancy. These very limited reports with considerable limitations are insufficient to establish significant concern about the teratogenicity of DEET. Based on more extensive available animal data, the EPA has concluded that DEET is neither a reproductive nor a developmental toxicant.[13,16] Similarly, sources such as REPROTOX[20] and the Teratogen Information Source[21] conclude that there is no demonstrated increased risk of congenital anomalies after exposure to DEET from data currently available.

Second- and third-trimester DEET use has been studied in one randomized controlled trial conducted among 897 pregnant women in an area with endemic malaria along the Thai-Myanmar border.[22] Women were randomized to apply thanaka, a locally sourced topical cosmetic paste, alone or in combination with 1.7 g of DEET at night. Unfortunately, it is challenging to compare this dose with standard concentrations in products available in the United States. Skin warming as reported by the mothers was more frequent among women in the DEET group; other side effects assessed did not differ by group. No significant differences were noted between the two groups in birth weight, newborn anthropometrics, a newborn neurologic examination, or developmental milestones in the first year of life. Exposure to DEET was measured among a subset of patients. None had detectable DEET, suggesting that the women were able to metabolize the repellant without accumulation despite daily administration. Cord blood was also collected from 50 newborns in the DEET group. In four (8%) of these cord blood samples, DEET was detectable, demonstrating that placental transfer occurs. All four children with measurable cord blood DEET had normal physical and neurologic examinations at birth and through the first year of life.

To summarize, based on currently available information, DEET appears safe for use topically in pregnancy. It is not considered a developmental or reproductive toxicant, and there is no indication that the young (eg, fetuses) are more vulnerable. We agree with recommendations for its use by pregnant women who must travel to or who live in areas where the Zika virus has been reported. Safe use includes application of products at a concentration of 30% or less, avoiding products combined with sunscreen, applying sunscreen first when required, and not reapplying more frequently than recommended by the specific product being applied. Two relevant patient fact sheets, "Insect Repellants" and "DEET (N,N-ethyl-m-toluamide) and Pregnancy," have been created by the Organization of Teratology Information Specialists and are available online.[23,24]

PERMETHRIN

For avoidance of mosquito bites, the CDC also recommends that pregnant women treat clothing with the repellant permethrin. It should not be applied directly to the skin.[2] Permethrin is the only repellant currently registered to treat fabric in the United States.[25] Permethrin is also applied as both a residential and commercial insecticide for control of mosquito populations within homes, in agricultural fields, and in communities.[26] It can both repel and kill insects. Permethrin is additionally available as a pharmaceutical in the form of topical cream for the treatment of scabies. No increase in the risk of congenital anomalies has been noted from the limited data available on topical use as a treatment of scabies.[27,28] The U.S. Food and Drug Administration classifies permethrin cream as class B during pregnancy.[29] The World Health Organization considers permethrin compatible with breastfeeding.[30]

Permethrin is a pyrethroid, a synthetic compound related to naturally occurring pyrethrins, which are derived from the extract of chrysanthemum flower. Naturally occurring pyrethrins have some insecticidal activity but become unstable with light exposure and may be more likely to cause allergic reactions.[26] As a class, pyrethroids are neurotoxicants and work by inhibiting sodium channels in the nerve cell.[31] Their mechanism of action is negatively correlated with temperature, making them particularly toxic to cold-blooded organisms such as insects and fish.[26] Toxicity to mammals such as humans is considered to be fairly low secondary to our higher body temperature, more abundant detoxifying enzymes, and a lower sensitivity of the mammalian sodium ion channel to inhibition from pyrethroids.[25] Moreover, absorption is poor from the human gastrointestinal tract, and the liver metabolizes it fairly quickly.

For permethrin specifically, absorption after a single application of the cream to the scalp or skin is less than 1%, with near-complete elimination of metabolites by 1 week.[32,33] Studies conducted among military personnel wearing permethrin-treated clothing demonstrate that exposure from chronic daily wear correlates with duration of exposure and is higher than the background exposure among the general population.[34,35] Nonetheless, calculated daily exposures were still lower than exposure from topical pharmaceutical application.[26] Mild side effects from human exposure to pyrethroids as a class (not permethrin specifically) include numbing, tingling, and a burning sensation in the skin. High exposures can lead to acute neurotoxicity with

symptoms of nausea, vomiting, shortness of breath, and seizures.[36] Pyrethroids are also lipophilic and have the potential to accumulate in the brain and fat and be transferred to breast milk.

Unlike DEET, there does appear to be differential toxicity to pyrethroids depending on age, with younger mammals potentially more susceptible to side effects.[36] Given that the nerve cell is the target for pyrethroids, a particular concern is the potential neurotoxicity of pyrethroids to the very young. Experimental animal data suggest that prenatal pyrethroid exposure may adversely affect learning and behavior, but exposures are much higher in such experiments than in typical human exposures and metabolism may be quite different. Extrapolation of these results to the human situation is therefore challenging. The potential for low-level prenatal or infant exposures in humans to disturb neurodevelopment is an emerging area of investigation. One group of researchers found that children in New York City exposed to higher levels of piperonyl butoxide, the typical solvent used with pyrethroid products, scored lower on the Bayley Mental Development Index at 36 months even after adjustment for potential confounders.[37] Piperonyl butoxide was specifically chosen as an exposure biomarker for permethrin because pyrethroids are notoriously difficult to measure in air given their volatility and difficult to measure in plasma given rapid metabolism. The appropriate conclusion as to whether the potential neurotoxicity is related to the permethrin or to its piperonyl butoxide solvent is not clear, and the potential for developmental toxicity after low-level pyrethroid exposure remains uncertain. Furthermore, the applicability of studies such as this to exposures from permethrin-treated fabric rather than residential and commercial pyrethroid pesticide use is unclear.

DISCUSSION

In light of the extensive neurologic harm that can be caused by prenatal Zika virus infection combined with what is known about the safety of DEET and permethrin if used as intended, CDC has made strong recommendations for the use of these repellants during pregnancy for prevention of Zika virus infection. Unfortunately, personal avoidance measures alone, which include application of insect repellants, will not prevent 100% of mosquito bites. Wider issues of vector control for Zika prevention will need to be considered by governments and affected communities –how and when to recommend larvicide or insecticide spraying and which are the most efficacious, safest, and least likely to harm living creatures or accumulate in the environment. To the extent that risks from prenatal and early-life exposure to specific insecticides remain unclear, additional research should be funded by government and nongovernmental organizations.

Vector control is not unique to our time or place. People living in resource-poor countries have been grappling with this for years because of malaria and other vector-borne health threats. Even when a vaccine becomes available for Zika virus, it is hard to imagine a world free of vector-borne disease. With more than 725,000 human deaths per year, the mosquito remains the world's deadliest animal.[38] In this ever-changing world, obstetrician–gynecologists will continue to field questions from their pregnant patients about vector-borne disease and the use of insect repellants.

REFERENCES

1. Petersen LR, Jamieson DJ, Powers AM, Honein MA. Zika virus. N Engl J Med 2016;374:1552–63.
2. Centers for Disease Control and Prevention. Zika virus: pregnancy. Atlanta (GA): CDC. Available at: http://www.cdc.gov/zika/pregnancy/. Retrieved July 26, 2016.
3. American College of Obstetricians and Gynecologists, Society for Maternal-Fetal Medicine. Practice advisory on Zika virus. Available at: https://www.acog.org/About-ACOG/News-Room/Practice-Advisories/Practice-Advisory-Interim-Guidance-for-Care-of-Obstetric-Patients-During-a-Zika-Virus-Outbreak. Retrieved July 26, 2016.
4. Karwowski MP, Nelson JM, Staples JE, Fischer M, Fleming-Dutra KE, Villanueva J, et al. Zika virus disease: a CDC update for pediatric health care providers. Pediatrics 2016;137:e20160621.
5. Centers for Disease Control and Prevention. Dengue and the Aedes aegypti mosquito. Available at: http://www.cdc.gov/dengue/resources/30Jan2012/aegyptifactsheet.pdf. Retrieved July 26, 2016.
6. Seizures temporally associated with use of DEET insect repellant–New York and Connecticut. MMWR Morb Mortal Wkly Rep 1989;38:678–80.
7. Centers for Disease Control and Prevention. West Nile virus: insect repellant use and safety. Atlanta (GA): CDC. Available at: http://www.cdc.gov/westnile/faq/repellent.html. Retrieved July 26, 2016.
8. Centers for Disease Control and Prevention. Ticks and Lyme disease. Atlanta (GA): CDC. Available at: https://www.cdc.gov/lyme/resources/toolkit/factsheets/10_508_lyme-disease_pregnantwoman_factsheet.pdf. Retrieved July 26, 2016.
9. Fradin MS, Day JF. Comparative efficacy of insect repellants against mosquito bites. N Engl J Med 2002;347:13–8.
10. Lupi E, Hatz C, Schlagenhauf P. The efficacy of repellants against Aedes, Anopholes, Culex and Ixodes spp.–a literature review. Trav Med Infect Dis 2013;11:374–411.
11. United States Environmental Protection Agency. New pesticide fact sheet: picaridin. Washington, DC: EPA. Available at: https://www3.epa.gov/pesticides/chem_search/reg_actions/registration/fs_PC-070705_01-May-05.pdf. Retrieved July 26, 2016.

12. Koren G, Matsui D, Baily B. DEET-based insect repellents: safety implications for children and pregnant and lactating women. CMAJ 2003;169:209–12.

13. United States Environmental Protection Agency. Registration review and proposed interim decisions; notice of availability. Washington, DC: Federal Register. Available at: https://www.federalregister.gov/articles/2014/06/04/2014-12943/registration-review-proposed-and-proposed-interim-decisions-notice-of-availability. Retrieved July 26, 2016.

14. Buescher MD, Rutledge LC, Wirtz RA, Nelson JH. The dose-persistence relationship of DEET against *Aedes aegypti*. Mosq News 1983;43:364–6.

15. Sudakin DL, Trevathan WR. DEET: a review and update of safety and risk in the general population. J Toxicol Clin Toxicol 2003;41:831–9.

16. United States Environmental Protection Agency. Reregistration eligibility decision (RED): DEET. Washington, DC: EPA. 1998. Available at: https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_PC-080301_1-Apr-98.pdf. Retrieved July 26, 2016.

17. Submission Coordination and Documentation Division, Pest Management Regulatory Agency, Canada. Personal insect repellents containing DEET (N, N-diethyl-m-toluamide and related compounds). Re-evaluation Decision Document, RRD2002–01. 2002. Available at: http://publications.gc.ca/site/archivee-archived.html?url=http://publications.gc.ca/collections/Collection/H113-12-2002-1E.pdf. Retrieved July 26, 2016.

18. Schaefer C, Peters PW. Intrauterine diethyltoluamide exposure and fetal outcome. Reprod Toxicol 1992;6:175–6.

19. Dugas J, Nieuwenhuijsen MJ, Martinez D, Iszatt N, Nelson P, Elliot P. Use of biocides and insect repellants and risk of hypospadias. Occup Environ Med 2010;67:196–200.

20. Reproductive Toxicology Center. REPROTOX. Available at: https://reprotox.org/. Retrieved July 28, 2016.

21. TERIS: teratogen information system and the on-line version of Shepard's catalog of teratogenic agents. Available at: http://depts.washington.edu/terisdb/. Retrieved July 28, 2016.

22. Mcgready R, Hamilton KA, Simpson JA, Cho T, Luxemburger C, Edwards R, et al. Safety of the insect repellant *N,N*-diethyl-*M*-toluamide (DEET) in pregnancy. Am J Trop Med Hyg 2001;65:285–91.

23. MotherToBaby.Fact sheet: insect repellants. Available at: http://mothertobaby.org/fact-sheets/insect-repellents/. Retrieved July 28, 2016.

24. MotherToBaby.Fact sheet: DEET (N,N-ethyl-m-toluamide) and pregnancy Available at: http://mothertobaby.org/fact-sheets/deet-nn-ethyl-m-toluamide-pregnancy/. Retrieved July 28, 2016.

25. United States Environmental Protection Agency. Reregistration eligibility decision: permethrin. 2007. Available at: https://archive.epa.gov/pesticides/reregistration/web/pdf/permethrin_amended_red.pdf. Retrieved July 26, 2016.

26. United States Environmental Protection Agency. Permethrin facts. EPA 738-F-09-001. Washington, DC: EPA. 2009. Available at: https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/fs_PC-109701_1-Aug-09.pdf. Retrieved July 26, 2016.

27. Kennedy D, Hurst V, Konradsdottir E, Einarson A. Pregnancy outcome following exposure to permethrin and use of teratogen information. Am J Perinatol 2005;22:87–90.

28. Mytton OT, McGready R, Lee SJ, Roberts CH, Ashley EA, Carrara VI, et al. Safety of benzoyl benzoate lotion and permethrin in pregnancy: a retrospective matched cohort study. BJOG 2007;114:582–87.

29. U.S. Food and Drug Administration. Permethrin overview. Silver Spring (MD): FDA. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Retrieved July 28, 2016.

30. Breastfeeding and maternal medication: recommendations for drugs in the eleventh WHO model list of essential drugs. Geneva (Switzerland): WHO. 2002. Available at: http://apps.who.int/iris/bitstream/10665/62435/1/55732.pdf. Retrieved July 28, 2016.

31. Soderlund DM. Molecular mechanisms of pyrethroid insecticide neurotoxicity: recent advances. Arch Toxicol 2012;86:165–81.

32. Tomalik-Scharte D, Lazar A, Meins J, Bastian B, Ihrig M, Wachall B, et al. Dermal absorption of permethrin following topical administration. Eur J Clin Pharmacol 2005;61:399–404.

33. van der Rhee HJ, Farquhar JA, Vermeulen NP. Efficacy and transdermal absorption of permethrin in scabies patients. Acta Derm Venereol 1989;69:170–3.

34. Proctor SP, Maule AL, Heaton KJ, Adam GE. Permethrin exposure from fabric-treated military uniforms under different wear time scenarios. J Expo Sci Environ Epidemiol 2014;24:572–8.

35. Kegel P, Letzel S, Rossbach B. Biomonitoring in wearers of permethrin impregnated battle dress uniforms in Afghanistan and Germany. Occup Environ Med 2014;71:112–7.

36. Shafer TJ, Meyer DA, Crofton KM. Developmental neurotoxicity of pyrethroid insecticides: critical review and future research needs. Environ Health Perspect 2005;113:123–36.

37. Horton MK, Rundle A, Camann DE, Boyd Barr D, Rauh VA, Whyatt RM. Impact of prenatal exposure to piperonyl butoxide and permethrin on 36-month neurodevelopment. Pediatrics 2011;127:e699–706.

38. Statista: The Statistics Portal. The world's deadliest animals. Available at: https://www.statista.com/chart/2203/the-worlds-deadliest-animals/. Retrieved July 26, 2016.