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Safety and Efficacy of DEET and Permethrin in the Prevention of Arthropod Attack

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Many preventable diseases affecting troop strength are directly attributed to disease-carrying insects. The first line of defense against arthropod vectors is the use of personal protective measures. The concurrent application of DEET (*N,N*-diethyl-*m*-toluamide) repellent on the skin and permethrin [(3-phenoxy-phenyl)methyl(±)*cis,trans*-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-carboxylate] insecticide on the battle dress uniform, while the uniform is worn properly, is a personal protective strategy officially known as the DOD Insect Repellent System. It is important for troop commanders and field leaders to enforce the use of personal protective measures to prevent insect-borne infectious diseases and to ensure troop and soldier readiness. DEET is a safe and effective repellent. Permethrin is a synthetic pyrethroid insecticide and repellent. Used in conjunction with proper clothing and other personal protective equipment, these repellents provide the best known protection available and are critical in minimizing the occupational health threat of arthropod-borne diseases to troops in the field.

Introduction

Historically, in past military conflicts, combat power has been reduced more by disease and nonbattle injuries (DNBI) than by direct combat casualties.[1] DNBI result in increased outpatient visits, hospitalizations, medical disabilities, and deaths, all of which tax the medical components of the services and directly affect troop capabilities and readiness. Many diseases affecting the troop strength of deployed units are directly attributed to disease-carrying insects. Not only do these arthropod vectors transmit disease, but their bites can be painfully distracting and can lead to devastating secondary infections, dermatitis, or allergic reactions.[2] Fortunately, vector-borne infectious diseases are preventable and can be controlled with the proper use of insecticides, repellents, and the physical separation of humans from the insect vectors. In this article, the safety and efficacy of the insect repellent and insecticide used for personal protection by the U.S. military, known as the DOD Insect Repellent System, will be reviewed. Troop commanders and field leaders, armed with the knowledge of safe and effective preventive measures, can effectively enforce the use of the DOD Insect Repellent System to prevent insect-borne infectious diseases and to ensure soldier readiness.

The DOD Insect Repellent System

The percentage of hospitalizations caused by disease has greatly overshadowed that of both battle and other nonbattle injuries. In past major conflicts, the disease hospitalization rates of 85, 61, and 69% for World War II, the Korean conflict, and the Vietnam War, respectively, exceed the battle injury rates of 4, 23, and 17% during the same conflicts.[1] The trend continued in a recent armed conflict in southwest Asia, in which the rate of hospitalization from disease was 72% compared with a 4% rate for battle injuries and a 24% rate for other nonbattle injuries. Conflicts of the future involving military personnel will probably continue in this trend because technological advances leading to "stand-off" weaponry generally portend an increased ratio of DNBI to battle casualties. Also, the deployment of U.S. troops to various trouble spots around the world exposes soldiers to infectious agents not routinely present in their homeland.

Diseases transmitted by insects remain a viable threat to our deployed soldiers. Although some diseases are preventable through the use of vaccines and/or prophylactic drugs, these options are limited. Vaccines are available for only a few diseases, and none are effective for malaria, dengue fever, and leishmaniasis (among others). Drugs, both prophylactic and therapeutic, are available for only a few diseases, and drug-resistant strains of organisms are a growing problem. Widespread pesticide use is limited by the tactical situation and may not be feasible. To demonstrate the capability of insect vectors to transmit disease, Table I lists some major arthropod pests of military importance and the primary diseases they transmit.[2-4]

Fortunately, there exists a safe strategy in the fight against vector-borne disease. Although appropriate screening and mosquito netting are effective as a preventive treatment in occupied areas, the first line of defense against arthropod vectors is personal protection, consisting of the use of repellents and insecticides. Historical and anecdotal information suggests that these measures have been used improperly or have been underused. Field and unit commanders, sensitized by reports of adverse effects in the lay press, may not fully monitor or enforce the use of the protectants. These perceived adverse effects include the ability of the protectants to cause illness, cancer, and/or death. Misinformation, resulting in decreased protectant use, can lead to increased exposure to disease agents and to the belief that the protectants not only do not work but may be more harmful than beneficial.

The use of repellents and insecticides is a practical means of protection against disease-carrying vectors and nuisance arthropods, particularly in conjunction with the proper wearing of clothing. The concurrent use of DEET (*N,N*-diethyl-*m*-toluamide) repellent on the exposed skin and permethrin [(3-phenoxyphenyl)methyl(±)*cis,trans*-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropane-carboxylate] insecticide on the battle dress uniform, while the uniform is worn properly (pant cuffs tucked into the boots, sleeves worn down, undershirt tucked into the pants), is a personal protective strategy officially known as the DOD Insect

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TABLE I

SELECT ARTHROPODS OF MILITARY IMPORTANCE AND THE MAJOR DISEASES THEY TRANSMIT

Common Name	Genus	Diseases
Biting midges	*Culicoides*	Visceral filariasis, oropouche fever
Body lice	*Pediculus*	Epidemic typhus, relapsing fever, trench fever
Black flies	*Simulium*	Onchocerciasis
Chiggers	*Leptothrombidium*	Scrub typhus
Fleas	*Xenopsylla*	Plague, murine typhus
Kissing bugs	*Rhodnius, Triatoma*	Chagas's disease (American trypanosomiasis)
Mosquitoes	*Aedes, Anopheles, Culex*	Malaria, dengue, yellow fever, viral encephalitis, viral fevers, lymphatic filariasis
Sand flies	*Lutzomyia, Phlebotomus*	Leishmaniasis, sand fly fever, bartonellosis
Ticks (hard)	*Ixodes, Dermacentor, Amblyomma, Hyalomma*	Lyme disease, tick-borne encephalitis, Rocky Mountain spotted fever, human ehrlichiosis, babesiosis, Crimean-Congo hemorrhagic fever
Ticks (soft)	*Ornithodoros*	Relapsing fever
Tsetses	*Glossina*	Trypanosomiasis (African sleeping sickness)

Repellent System (Fig. 1). Because there are no vaccines or effective prophylactic drugs available for most arthropod-borne diseases, use of this system is critical as it provides maximum personal protection.[5-10]

Skin and clothing repellents/insecticides are relatively inexpensive and are easily applied by the individual soldier. Other control measures, such as area application of pesticides, are often more expensive and manpower-intensive, can be hazardous and environmentally abusive, and may not be feasible during combat. In the burgeoning spirit of environmental stewardship, current Department of Defense (DOD) environmental policy stresses a concentrated attempt to drastically reduce pesticide dispersal within military programs (50% reduction from the fiscal year 1993 level by the end of fiscal year 2000).[11] As part of this overall effort, use of personal protective techniques will help reduce the need for pesticide applications during contingency operations as well as during routine training activities.

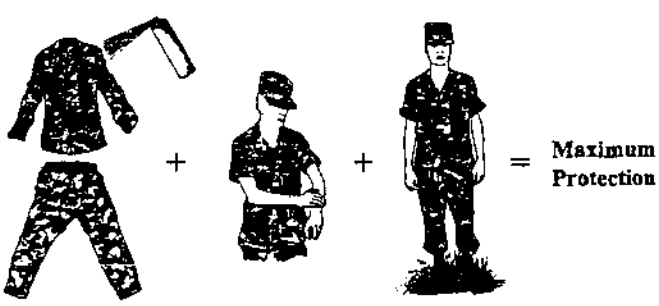

Fig. 1. DOD Insect Repellent System.

DEET

The most effective armament in the military system to prevent insect bites and the transmission of vector-borne infectious diseases is the repellent DEET. Chemically, DEET is an aromatic amide, and it is approved by the U.S. Environmental Protection Agency (EPA) as an insect repellent. Used since 1946 by the Army and since 1957 by the general population, DEET is considered to be the best "all around" insect repellent ever developed and is the most widely used insect repellent in the world.[12] It is estimated that 50 to 100 million people use DEET each year worldwide, with few cases of adverse reaction reported.[13] DEET is an effective repellent against mosquitoes, biting flies, and ticks, as well as other insects. It is the active ingredient in many popular over-the-counter insect repellents. Many formulations using various concentrations of DEET (from 5 to 100%) are available. The current formulation used by the military is a 33% extended-duration lotion. Regardless of the formulation, DEET is poorly absorbed through the skin, with less than 10% of the applied dose absorbed systemically.[14]

Toxicity

DEET is an extremely safe repellent that can be used with confidence. It has been extensively tested for safety in both animals and humans. The risk of serious adverse effects is extremely low.[12] Although numerous animal studies have demonstrated the safety of DEET, adverse effects and poisoning with DEET are possible.[15-17] There have been rare adverse effects in humans (93 incidents between 1966 and 1980), generally confined to local eye or skin irritation, usually in sensitive individuals.[18] Such skin irritant effects range from simple erythema to scarring (bullous dermatitis).[19] Most cases of poisoning are associated with extensive and repeated topical applications or ingestion (e.g., suicide attempts). Symptoms of poisoning are characterized by tremor, restlessness, slurred speech, seizures, impaired cognitive functions, and coma.[20,21]

Extensive laboratory testing using animal models demonstrates the relative safety of DEET. Although it is not considered a selective neurotoxin[12,22] (based on animal studies), in an isolated case of workers with exposures > 4 g/week, some neurotoxic effects were noted.[19] Other cases of adverse systemic effects were also thought to be associated with topical DEET use. Limited to young female children younger than 8 years, these effects included headaches, slurred speech, shaking, convulsions, and, in rare cases, death. However, in three of these deaths, a clear association with DEET exposure remains questionable.[12] Other laboratory tests for embryotoxicity, mutagenicity, and carcinogenicity were all negative.

In 1978, additional toxicity studies were required by the EPA to fill in data gaps for reregistration of DEET. Tested in laboratory animals, DEET was shown to have no reproductive effects (two-generational study), no neurotoxic effects (acute and repeated exposures), and no oncogenic effects (18-month study). Tests were also negative for mutagenic effects and as a dermal toxic hazard.[14] Additionally, studies using both rats and rabbits

show that DEET is not a developmental toxicant. In these studies, there was no evidence of fetal toxicity, no effects on gestational parameters, and no malformations in offspring of adult animals administered DEET.[23]

It is important to note that the metabolism of DEET in humans is very similar to that in the rat and that with the large data base on rodent toxicological studies, predictive extrapolations to humans can be made with confidence.[24] Safety in animals (rats) correlates well with predictive safety in humans.

Efficacy

Various natural and synthetic repellents have been used for centuries to protect individuals from attacking arthropod pests. The discovery of DEET was the single most important event in the evolution of repellents.[13] Since that time, the Armed Forces Pest Management Board's (AFPMB) DOD Repellent Development Program, by combining the efforts of the DOD and the U.S. Department of Agriculture (USDA), has screened thousands of new candidate arthropod repellents in search of alternatives that work at least as well as DEET and that are as safe or safer. After more than 40 years, none has yet been found to be as safe and effective as DEET against as broad a spectrum of crawling and flying pests (see Table II). In a direct comparison of nine commercial repellents using human volunteers, DEET was superior to other repellents against the mosquito *Aedes aegypti*.[25] Other comparisons yielded similar results against a variety of insects.[26-28] In these and similar tests, DEET has virtually eclipsed all other repellents for topical use, and it remains the primary skin repellent in use today.[13]

Repellent formulations containing 50% or less DEET are considered just as effective as those with higher concentrations.[13] The carrier ingredients in a formulation help to determine how long one application will provide protection. In 1990, the U.S. military fielded a state-of-the-art product containing only 33% DEET in a controlled-release polymer base. Although it contains much less active ingredient than the previous military formulation (75%), it provides a much longer protection time. The polymer in the formulation slows the absorption and evaporation of DEET, thereby holding it on the surface of the skin, where it can continue to repel arthropods for an "extended" period of time.[2] Laboratory testing shows that this extended-duration DEET lotion provides 6 hours of at least 95% protection against a variety of mosquito species in a tropical environment, 10 hours in a hot/dry environment, and 12 hours in a forested/wet environment.[29] Because the U.S. military's standard extended-duration formulation slows the depletion of DEET so dramatically, this effect is minimized, necessitating less frequent reapplication of the product.

Permethrin

Permethrin is a third-generation synthetic pyrethroid that is approved for use as an insecticide by the EPA. It may be found in many household and agricultural insecticidal formulations. Permethrin was first developed by the National Research & Development Corporation (United Kingdom) in the 1970s. Further evaluated by the USDA Medical and Veterinary Entomology Research Laboratory and cooperators in the 1980s as a clothing treatment for use by the military and the public, permethrin was shown to have low mammalian toxicity.

In 1990, the U.S. military adopted permethrin as the standard clothing repellent and fielded three different applications: a 0.5% aerosol in a 6-ounce can; a 40% emulsifiable concentrate in "shake and bake" uniform impregnation kit form (individual dynamic absorption, or IDA, kit); and a 40% emulsifiable concentrate for use in a 2-gallon sprayer. The IDA kit and the 2-gallon sprayer are effective for the life of the uniform. A single can of permethrin aerosol will treat one full battle dress uniform, and the treatment remains effective through five or six launderings. The aerosol and the IDA kit can be used by the individual soldier; the 2-gallon sprayer can be used only by trained personnel, and a respirator is required. A factory uniform impregnation method is planned, to also last the lifetime of the uniform, but has yet to be implemented.

It is recognized that soldiers wearing impregnated uniforms will benefit from the protection offered against vector-borne diseases, both at home and abroad. In the United States, those diseases include Lyme disease, Rocky Mountain spotted fever, and viral encephalitis. Other diseases are listed in Table I.

TABLE II

COMPARATIVE EFFICACY OF DEET AND PERMETHRIN, USED AS SKIN AND CLOTHING REPELLENTS (RESPECTIVELY), SEPARATELY AND IN COMBINATION

Arthropod	References	DEET	Permethrin	Combined System
Biting midges	2,49,50,51,52,53	XXX	XX	XXXX
Black flies	2,54,55,56	XXX	XX	XXXX
Body lice	2,57,58,59	X	XXX	XXXX
Chiggers	2,28,60,61,62,63,64,65	XXX	XX	XXXX
Fleas	2,39,61,66	XXX	XX	XXXX
Kissing bugs	2,61,67,68	X	XX	XX
Mosquitoes	2,4,5,6,7,8,9,10,29,38,39, 46,47,53,54,61,69,70,71,72,73	XXX	XX	XXXX
Sand flies	2,5,53,61,74,75	XXX	XX	XXXX
Ticks (hard)	2,39,44,76,77,78,79,80	XX	XXX	XXXX
Ticks (soft)	2,61,81	XX	XXX	XXXX
Tsetses	2,61,82,83	XXX	XX	XXXX

Where actual field trials have not been conducted using the combined system against a particular type of arthropod, the rating is subjective. XXXX, best available; XXX, highly effective; XX, very effective; X, low to moderately effective.

Toxicity

Much of what is known about the safety and toxicity of permethrin was consolidated by the Subcommittee to Review Permethrin Toxicity from Military Uniforms[30] when it was formed by the Committee on Toxicology at the request of the National Research Council. This extensive review was initiated in response to the Army's concern about potential risks associated with uniform impregnation with permethrin to protect against disease vectors such as mosquitoes, ticks, and other vectors.

The subcommittee extensively examined the exposure assessment, pharmacokinetics, acute and short-term toxicity, skin and eye toxicity, neurotoxicity, liver and other organ toxicity, immunotoxicity, reproductive and developmental toxicity, genotoxicity, and carcinogenicity of permethrin. After reviewing available data and analyzing the risk of adverse health effects to soldiers, the subcommittee concluded that soldiers are unlikely to suffer adverse health effects from exposure to permethrin at suggested exposure levels. The relative safety of permethrin was also detailed in a World Health Organization document reviewing various animal studies and human exposures. Humans exposed to differing amounts of permethrin reported few serious complaints, and physical examinations revealed no abnormal findings.[31]

Permethrin is classified by the EPA as a potential carcinogen. Although there may be sufficient evidence of an association between permethrin and cancer in laboratory animals, limited and inadequate human data have been published to support a causal relationship between the compound and cancer. There is no direct information addressing the carcinogenic effects of permethrin in humans. Using animal data, the subcommittee concluded that the carcinogenic risk to soldiers (both field and nonfield) from exposure to permethrin-impregnated fabric is very small (less than 1 in 1 million) and is therefore not a serious carcinogenic risk. Carcinogenicity has also been addressed by the International Agency for Research on Cancer, which ranks permethrin as a group 3 carcinogen not classified as to its carcinogenicity to humans.[32]

Permethrin is not without its toxicity. Animal studies have demonstrated both neurological and skin toxicity at high doses.[33,34] Neurological signs include tremors, salivation, paresthesia, splayed gait, depressed reflexes, and tiptoe gait in animals. These signs may progress in severe cases of poisoning to ataxia, convulsions, and eventually paralysis. At high doses, a reversible axonal injury occurs. These neurological effects have not been substantiated in humans. It is recognized that some people may be hypersensitive to permethrin and may develop skin sensitization, such as transient burning, itching, or stinging sensations. This type of symptom can be easily monitored and the impregnated clothing removed.

In laboratory tests, permethrin does not exhibit teratogenic or mutagenic activity[35] and has no effect on the reproduction of rats.[31] An exhaustive review of available animal testing data by the World Health Organization concludes that there are slight or no irritating effects with eye and skin toxicity tests. The report also indicates no oncogenic potential for permethrin, and studies in mice did not reveal any significant carcinogenic effects.[31] In a chronic 2-year feeding study in rats, no mutagenic, teratogenic, or carcinogenic activity was demonstrated.[36]

Weighing all the evidence on safety, the AFPMB has recommended that the Army proceed with the procurement of permethrin-impregnated battle dress uniforms. At this writing, additional tests are being conducted to further address areas recommended by the report to continue to fill in data gaps regarding the overall safety and toxicity of permethrin.

Efficacy

Permethrin is the most effective clothing impregnant available, exhibiting protection from a wide variety of arthropods (see Table II). Its insecticidal activity lasts several weeks to several months after a single application.[37] Although its primary mode of action is contact toxicity, permethrin also exhibits contact repellency effects. It is odorless, nonirritating, and resistant to washing and wear abrasion (rubbing off).[38,39] Extensive tests have shown that the persistence of permethrin in clothing far exceeds that of any previously known repellent.[13] Permethrin bonds so strongly to fabric that it withstands repeated launderings with detergent and water. After several washings, treated uniforms continue to provide contact repellency, even though they may no longer be toxic to insects.[38]

DEET/Permethrin Combinations

The current recommendation for protection against insects is the concurrent use of DEET repellent on the exposed skin and permethrin insecticide on the clothing. Because it does not evaporate, permethrin does not provide protection to exposed skin adjacent to treated clothing. DEET, on the other hand, is a vapor-active repellent, working well to protect the exposed skin. Because a variety of arthropod pests exhibiting different habits are present in most field situations, both types of treatments are necessary to provide maximum protection. For example, mosquitoes and other biting flies bite exposed skin as well as through lightweight or tightly worn clothing. Black flies, sand flies, biting midges, ticks, chiggers, and fleas will crawl underneath clothing to bite, in addition to biting exposed skin, or they may crawl on top of clothing to locate exposed skin. Application of both skin and clothing repellents is necessary for complete protection.[2]

Toxicity

An unpublished study conducted at the U.S. Army Environmental Hygiene Agency in 1989 to assess the potentiation of concurrent DEET and permethrin exposures revealed unremarkable results. This study was initiated after reports of adverse effects in pets with a formulation that combined DEET and a cyanopyrethroid (fenvalerate) that is similar in structure to permethrin. At the end of the Gulf War, investigators began to look at combinations of compounds that were used by soldiers in an attempt to explore the adverse health effects reported by soldiers on their return that subsequently became known as Persian Gulf War illness. Several compounds were targeted for investigation, including the insect repellents DEET and permethrin and the nerve agent prophylactic drug pyridostigmine bromide. This report will examine only the interactions of DEET and permethrin.

At the USDA Medical and Veterinary Entomology Research Laboratory in Gainesville, Florida, work with German cockroaches revealed questionable synergistic effects with the com-

bination of DEET and permethrin as well as with other compounds.[40] This recently published work reported that DEET was synergistic with some compounds (such as acetylcholinesterase inhibitors) but not with others and suggested that perhaps some mechanism other than acetylcholinesterase inhibition was responsible for this interaction. That mechanism was not identified. Previous interpretation of the cockroach data, provided to the AFPMB, determined that permethrin was not a potent synergist for DEET.[41]

At Duke University, similar research was conducted in chickens.[42] In this study, greater neurotoxicity was described after administration of both DEET and permethrin than was experienced with the individual compounds alone. These results are questionable because the levels of compounds used to elicit the response were extremely high and unrepresentative of the recommended doses of the individual compounds. This study also implied that some individuals with low plasma enzyme (esterase) activity may be predisposed to such neurological deficits.

The Army, in an attempt to characterize unsubstantiated reports of possible synergism with DEET and permethrin, conducted a study to examine the interaction of these compounds in a mammalian model (the rat).[43] Results from this study showed no synergism when DEET and permethrin were administered concurrently by oral dosing. As in the Duke University study, the doses examined were extremely high, far exceeding the recommended application doses.

All of these studies indicated that at very high doses, combinations of the compounds tested may produce adverse health effects. These effects are mostly associated with neurological signs and, in some cases, increased mortality. Lower doses have significantly lesser effects or no adverse effects. Recent and ongoing studies are continuing to investigate the health effects of the repellent and the insecticide at more appropriate (i.e., recommended) doses.

Efficacy

The wearing of permethrin-impregnated clothing in conjunction with the application of DEET to areas not covered by the uniform provides nearly 100% protection against bites from most insect vectors, and thus the exposure to disease agents is greatly reduced. Table II shows the efficacy of DEET and permethrin against medically important arthropods of military significance. The efficacy ratings in this table are subjective, because the studies in the available literature vary so widely in study design (differences in formulation, concentration, species tested, laboratory or field conditions, uniform type, etc.). Ratings are based on one or more of the following criteria: arthropod habits, repellent use pattern (i.e., skin or clothing), persistence, toxicity, and actual results in field tests. In most cases, the efficacy rating for the combined system is intuitive, because field studies have not been performed for the vectors except for mosquitoes and sand flies. References used to develop the ratings for each arthropod are listed.

An example of the rating process follows. Although DEET is actually more effective against chiggers than permethrin, a field study demonstrated that wearing a permethrin-treated uniform resulted in fewer total bites than wearing an untreated uniform plus DEET on the exposed skin. Hence, the higher rating for permethrin alone than for DEET alone. Furthermore, in this same study, the subjects who wore permethrin-treated uniforms but no DEET acquired 80% of their chigger bites in the 2.5-cm-wide band of untreated skin above the boot top. Even with proper blousing, this area of skin is periodically exposed by normal daily movements, such as sitting or stooping, that cause the trouser cuffs to ride up. In the group wearing untreated uniforms plus DEET on the skin above the boot top, less than 10% of the total bites were found on the DEET-treated band of skin. This implies that a combination of DEET on the exposed skin plus permethrin on the uniform would have provided even better protection. Hence the highest rating for the combined system.

Not all arthropod species are equally repelled by a particular repellent. For example, although DEET is highly repellent to most mosquito and several other biting fly species, some species of ticks and anopheline mosquitoes are only partially repelled.[44–47] No repellent has yet been discovered that is 100% protective against every species of arthropod. Therefore, the DOD continues to screen and test new candidate repellents. The current standard military-issue DEET and permethrin repellents provide the best known protection available, with excellent results. Used in conjunction with proper clothing and other personal protective equipment, especially bed nets at night when many mosquito species bite and the least area of skin is generally covered by clothing, these repellents are critical in minimizing the occupational health threat of arthropod-borne diseases to troops in the field.

In a recent publication by the Institute of Medicine concerning health consequences of the Persian Gulf War, it is recognized that the average personal use of pesticides in that theater of operation was low and is unlikely to be associated with induction of chronic disease.[48]

Conclusion

From all available data and the data review of several committees, the personal protective DOD Insect Repellent System consisting of the concurrent use of DEET and permethrin is safe and effective when used at recommended application rates. It is imperative that DOD leaders, at all levels, understand and endorse the need for and the use of these protective measures. The U.S. military will be tasked to respond around the globe, but U.S. troops need not suffer the psychological or physical stresses associated with insect bites and the possible exposure to disease agents. To maintain the strength and readiness of military forces, both deployed and on station, the use of personal protective measures needs to be encouraged and monitored for compliance. This is one battle that can be won with minimal effort, yielding maximal results and preserving the strength of the force.

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