Journal of
TRAVEL MEDICINE

REVIEW

Expert Review of the Evidence Base for Arthropod Bite Avoidance

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DOI: 10.1111/j.1708-8305.2010.00402.x

Bite avoidance measures are commonly recommended to international travelers to help reduce the risk of various arthropod-borne diseases. A key strategy is the use of repellents applied topically to skin or clothing which are considered in the first part of this review. Also advised are a variety of methods that employ the use of insecticides and physical barriers such as mosquito nets or oil preparations applied to the skin.

In the following document, the authors considered some of the most widely used bite avoidance methods and identified the strength and quality of evidence that determined efficacy. The overall purpose of the review is to provide the available evidence, in a graded format, upon which to base recommendations for the selection of appropriate repellents and other methods of bite avoidance in those traveling overseas.

Desired Outcomes and Methods

The authors were asked to consider the effectiveness of the most commonly used active ingredients (AIs) in repellent formulations and methods of bite avoidance. The evidence base considered protection against nuisance biting insects, reduction in the incidence of arthropod-borne diseases, and safety profile. Effectiveness of the repellent related to spectrum of activity against various mosquito species and other arthropods was examined as well as longevity of applied dose. Where possible, efficacy was compared to deet as being the accepted gold standard. All sections employed MEDLINE via PubMed in literature searches augmented by others depending on the subject area investigated. Details of the review process can be found at www.istm.org; click on "ISTM Committees" and then "Publications."

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Part 1: Repellents for Topical Use

Major Findings

N,*N*-diethyl-3-methylbenzamide (deet), (2-(2-hydroxyethyl)-piperidinecarboxylic acid 1-methyl ester (icaridin), *p*-methane 3, 8-diol (PMD), and ethyl butylacetylaminopropionate (IR3535)-based repellents all provide protection against biting arthropods, but volatile oils and other natural products are less reliable. On the strength of available evidence, the first-line choice for those visiting areas where malaria or other arthropod-borne diseases are endemic remains formulations with higher concentrations (20–50%) of deet. Higher concentration icaridin and PMD preparations are the most useful alternatives to deet where they are available. See Table 1 for a summary of the findings.

Diethyltoluamide (Other Name Deet; Chemical Name: *N*,*N*-Diethyl-3-Methylbenzamide, Former Nomenclature *N*,*N*-Diethyl-*m*-Toluamide)

Deet has been widely used in insect repellent products for use on human skin to protect against biting arthropods.[1–5] The majority of laboratory and field tests conducted to compare the efficacy of repellents use deet as the primary formulation or as a comparison. Deet is considered the most effective broad spectrum repellent AI against biting arthropods.[6]

The first laboratory tests against mosquitoes were reported by Gilbert and colleagues[7] who showed deet and dimethylphthalate were equally effective against *Anopheles quadrimaculatus*. Altman[8] reported field studies in Panama against *Anopheles albimanus* and showed 75% deet provided protection for at least 3 hours. Field studies undertaken in the last 20 years in Africa,[9,10] Australia,[11,12] Papua New Guinea,[13,14] Malaysia,[15] and Thailand[16] have shown that protection

Table 1 Summary of evidence base for topically applied repellents

Aspect of bite avoidance	Strength of evidence*	Quality of evidence†	Comments
Deet			
Dermal application to avoid mosquitoes	A	I	Deet provides shorter protection against *Anopheles* sp. mosquitoes than Culicine mosquitoes. Reapplication times will vary to maintain optimal effectiveness.
Dermal application to avoid ticks	B	I	Laboratory and field tests showed deet provides minimal protection, recent test showed adequate protection.
Application of deet to wristbands	E	I	Wristbands provide no protection for uncovered and untreated human skin.
Icaridin			
Dermal application to avoid mosquitoes	A	I	Icaridin provided good protection against *Anopheles* sp. mosquitoes in Africa and Asia, also effective against Culicine mosquitoes.
Dermal application of icaridin to humans to avoid ticks	B	I	Laboratory test showed icaridin provides protection for 1 h. Recent test showed adequate protection.
IR3535			
Dermal application to avoid mosquitoes	B	II	Based on limited field studies for mosquitoes. Not recommended in malaria endemic areas.
Dermal application to avoid sand flies	B	II	Based on one laboratory study.
PMD			
Dermal application to avoid mosquitoes	A	I	Can be highly recommended as an alternative repellent to deet at concentrations of >20% as a repellent for use in disease endemic areas. (Some evidence of efficacy against ticks.)
Citronella	C	III	Not recommended for use when engaging in vigorous activities, in disease endemic areas or areas with high densities of mosquitoes.
Neem	D	III	More studies should be conducted before it is recommended as a repellent.
Essential oils	D	III	Essential oils require careful formulation to be effective, and safety data suggest skin irritation is a factor.

*A = good evidence to support use; B = moderate evidence to support use; C = poor evidence to support use; D = moderate evidence to support a recommendation against use; E = good evidence to support a recommendation against use.
†I = evidence from one or more properly randomized, controlled trial; II = evidence from one or more well-designed clinical trial without randomization, from case-controlled analysis of cohort study; III = consensus evidence, evidence from one authority or reports of expert committees, single case studies.

against *Anopheles* spp. is less than that provided against Culicine mosquitoes.

The response of different mosquito species to deet is variable.[17] Field tests of repellent formulations containing deet against biting *Culex* spp., *Aedes* spp., *Mansonia* spp., and *Verrallina* spp. have been reported.[5] The protection provided by deet was longer against these genera than provided against *Anopheles* spp.[12]

Studies have shown that deet provides only minimal or poor protection against ticks.[18–21] However, recently Carroll and colleagues[22] showed that a 33% deet, Extended Duration formulation provided high levels of protection for 12 hours.

Deet is recommended to be applied to the exposed skin of humans. However, alternative methods of using deet have been proposed and investigated. The application of deet to wide mesh cotton/nylon jackets provided good protection against mosquitoes and biting flies.[23] Deet-treated netting used as groundsheets were shown to provide significant protection against ticks.[24] Although application of deet to nylon/cotton fabrics has been shown to enhance protection against bites, the application of deet to some synthetic fibers and plastics may cause damage, and thus the use of deet applied to clothing is not widely accepted. The use of wristbands treated with deet and other AIs offered no protection against mosquitoes.[4]

There have been a number of reviews concerning the safety of deet,[25,26] and they have attested to its generally acceptable safety profile. There are few reports of systemic toxicity in adults following dermal application. The safety profile in the second and third trimester of pregnancy has been established through observation of very low placental cord concentrations after maternal application of deet,[27] and animal models do not indicate any teratogenic effects.[28] Recommendations for use in young children do vary between countries, with some recommending lower concentrations[29] and others suggesting that higher strengths can be used.[30] However, the causation between the few reported cases of encephalopathy in children and the topical use of deet cannot be supported by a good evidence base.[31]

The scientific evidence and continued use of deet for >50 years has shown this AI is the best broad spectrum repellent available for minimizing bites of mosquitoes, ticks, and other biting arthropods.

Icaridin (Formerly Picaridin; (2-(2-Hydroxyethyl)-Piperidinecarboxylic Acid 1-Methyl Ester; WHO Designation: Icaridin; Trade Name: Bayrepel; Development Reference Code: KBR 3023)

Independent field studies demonstrating the effectiveness of repellents containing icaridin against mosquitoes have been conducted in Malaysia[32,33] and Florida.[34] In Australia, a formulation containing 19.2% icaridin provided similar protection as 20% deet against *Verrallina lineata*.[35] In another study in Australia, the same formulation provided >95% protection against *Culex annulirostris* for 5 hours, but only 1 hour protection against *Anopheles* spp.[12] KBR 3023 at concentrations of 2% to 13% v/v in 90% ethanol provided better protection against Anophelines in Africa than comparable formulations containing deet.[10]

Field studies against mosquitoes in two locations in Australia showed that a 9.3% formulation only provided 2-hour protection against *V lineata*[35] and 5-hour protection against *C annulirostris*,[36] while 7% icaridin provided 5.7 hours of protection against *Aedes albopictus* in laboratory tests.[37] The use of lower concentrations of icaridin in commercial formulations may require the user to reapply repellent more often to maintain effectiveness than with the higher concentrations (>20%) of icaridin used in the field.

Protection from biting by ticks provided by 20% lotions of KBR 3023 was reported to be short.[38] Carroll and colleagues[22] showed that Bayrepel (10 and 20% icaridin) repellent provided high levels of protection for 12 hours when applied to human volunteers against *Amblyomma americanum* under simulated field-contact conditions.

IR3535 [Also known as 3535 or EBAAP (Ethyl Butylacetylaminopropionate)]

Five field studies were identified, all testing IR3535 against mosquitoes.[10,34,39–41] These indicated that IR3535 is as effective as deet in repelling mosquitoes of the *Aedes* and *Culex* genera but may be less effective than deet in repelling anopheline mosquitoes. A number of laboratory studies were also identified, testing IR3535 against a variety of other arthropods, including blackflies and ticks.[42] An uncontrolled field study of a new, controlled-release formulation of IR3535 reported that these formulations may provide complete protection against mosquito biting for 7.1 to 10.3 hours.[41] IR3535 may be more effective than deet in protecting against phlebotomine sandfly biting (10.4 h mean protection vs 8.8 h, respectively).[42]

*PMD: Lemon Eucalyptus (*Corymbia citriodora*) Extract*

The principal repellent component of lemon eucalyptus extract is PMD, which is the main by-product of lemon eucalyptus hydrodistillation.[43] The active component is prepared through acid modified extraction of leaves or a synthetic version of PMD is used in the majority of commercially available preparations. Importantly, PMD has been proven to prevent malaria in a clinical trial in the Bolivian Amazon.[44]

Studies carried out both in the laboratory and the field using rigorous methodology have shown PMD to be a repellent of equal efficacy and longevity as deet.[45] At 30% AI, PMD provided almost complete protection for 4 hours in South America[46] and complete protection for 6 hours at 50% AI in Sub-Saharan Africa against malaria vectors.[47] In both of these studies, the protection time was equivalent to the deet controls. A well-designed laboratory trial of PMD against a further African malaria vector showed complete protection for 4 to 5 hours using PMD impregnated towlettes,[48] again comparable with deet. Laboratory trials using the main vectors of dengue fever have shown good protection, which is important for travelers as the vector bites in the day-time.[45,49] Against the tick vectors of Lyme disease and Rocky Mountain spotted fever, PMD reduces attachment and feeding success by around 77%, and PMD is highly effective against the Highland Midge.[50] PMD has not been tested against the vectors of leishhmaniasis in vivo, although in vitro results suggest that it may be effective.[51]

Citronella

Citronella is one of the essential oils obtained from the leaves and stems of different species of *Cymbopogon* grasses. From the available literature and information, we can conclude that the complete protection time for citronella-based repellents is <2 hours[4,49,52] because the repellent is highly volatile, but this can be prolonged by careful formulation and the addition of fixatives like vanillin.[53]

Neem

Neem is a vegetable oil pressed from the fruits and seeds of neem (*Azadirachta indica*). Several field studies from India have shown very high efficacy of neem-based preparations.[54–56] However, these studies have used questionable methodologies and their results contrast strongly with several others that have shown medium-range protection from neem products being inferior to deet.[46,49,57] Neem has a low dermal toxicity but can cause skin irritation such as dermatitis.[58] However, caution should be taken as neem is a proven reproductive toxicant and long-term subchronic exposure could impair fertility.[59]

Essential Oils

Many commercial repellents contain a number of plant essential oils either for fragrance or as repellents. The most effective of these include thyme oil, geraniol, peppermint oil, cedar oil, patchouli, and clove.[52,60,61] Most of these essential oils are highly volatile and this contributes to their poor longevity as mosquito repellents. They can be irritating to the skin[49,62] and their repellent effect is variable, dependent on formulation and concentration.

Conclusions

The largest body of evidence for effectiveness in terms of spectrum of activity and longevity relates to deet that remains as a gold standard to which newer repellents are compared in reducing nuisance bites from arthropods. Icaridin and PMD are reasonable alternatives to deet for those visiting areas where arthropod-borne diseases are endemic, whereas IR3535 has shown reduced efficacy against *Anopheles* mosquitoes and should not be advised for malaria endemic areas. When advising a formulation, the concentration of AI and the expected application rate of AI should always be considered because these will greatly influence longevity of the applied dose. There are, for instance, some icaridin formulations containing suboptimal concentrations. Apart from the repellent choice, the following factors will determine the duration of any repellent product.

1. Product concentration: In general, the higher percentage of AI, the greater the protection time will be, although this tends to plateau at 50% w/v in the case of deet.[63]
2. The rate of application that is applied to the exposed human skin is also variable.[64] And travelers have been shown to apply relatively low doses of AI on treated skin.[65]
3. Activity level of the user: The effectiveness of a repellent is reduced by evaporation and absorption from the skin surface and wash-off by sweat.
4. Environmental conditions: Rain or water, washing the repellent off the body, wind, and high ambient temperatures will reduce a product's effectiveness.
5. User's overall attractiveness to blood-feeding arthropods, such as mosquitoes.
6. Number and species of blood-feeding arthropods (biting density).

Part 2: Area and Barrier Methods

Major Findings

The strongest level of evidence exists for the use of insecticide-treated mosquito nets, and these are to be advised for all travelers visiting disease endemic areas at risk from biting arthropods on retiring. Insecticide-treated clothing and other fabrics would also be a useful adjunct to dermal applied repellents. Electric insecticide vaporizers, essential oil candle, and coils to burn do reduce bites from arthropods, but there is little evidence on the efficacy of knockdown insecticide sprays. There is some concern regarding the potential adverse effects of burning coils. There is less evidence that these technologies reduce the incidence of malaria. There is only weak evidence regarding the efficacy of oils used on the skin. See Table 2 for a summary of the findings.

Fabric Impregnation With Insecticides

The use of fabric impregnated with insecticides, particularly insecticide-treated bed nets, has become an important tool or method of personal protection against arthropod bites and disease-transmitting vectors. Some of the insecticides that are recommended and used for treatment of fabrics are permethrin, deltamethrin, lambda-cyhalothrin, alpha-cypermethrin, cyfluthrin, and etofenprox.[66] However, the insecticide most commonly used for fabric impregnation is permethrin [3-(phenoxyphenyl) methyl (±)-*cis*, *trans*-3-(2,2-dichloroethenyl)-2,2-dimethyl-cyclopropanecarboxy late].

Permethrin is a synthetic pyrethroid insecticide derived from crushed dried flowers of the plant *Chrysanthemum cinerarifolium*. Although permethrin's primary mode of action is contact toxicity against a wide variety of biting arthropods, it is also unique in that it serves both as a contact insecticide and as an insect repellent. Permethrin-impregnated clothing provides good protection against mosquitoes,[67–77] ticks,[78–84] chigger mites,[85,86] fleas,[87] lice,[88,89] sand flies,[90,91] kissing bugs,[92,93] and tsetse flies.[94] Thus, the use of permethrin-treated clothing will decrease the biting frequency and transmission of arthropod-borne diseases among civilian travelers and deployed military personnel. Today, military personnel from many countries use permethrin to repel and kill arthropods that land on many kinds of treated surfaces, including field uniforms, tents, bed nets, and helmet covers.[95]

Impregnated-treated fabrics such as bed nets, curtains, chaddars (veils or wraps worn by Muslim women), top sheets, and blankets have also been found to be effective in reducing the burden of malaria and other vector-borne diseases[96–100] and have been used in the Roll Back Malaria Program by the World Health Organization for tropical countries. However, due to the development of pyrethroid resistance in mosquito vectors, the use of impregnating fabrics with insecticide mixtures, a combination of a repellent and insecticide-treated bed nets or mixtures of repellents and non-pyrethroid–treated fabrics have become new promising tools for disease vector control.[101,102]

The development and use of long-lasting insecticide nets such as Olyset Net and Perma Net has also been proven to be effective in reducing or eliminating the need for insecticide retreatment of insecticide-treated nets.[103–107] In addition, recently, the use of tent barrier treatments with bifenthrin and permethrin is another effective method of personal protection against biting arthropods.[108–111]

Electric Insecticide Vaporizers

An insecticide vaporizer, which are mains- or battery-operated electrical devices releasing a pyrethroid insecticide, will clear a room of insects in around 30 minutes and will remain effective for over 6 hours.[112]

Ten field and laboratory studies were identified, testing a variety of insecticides and devices in different settings, against a range of flying insects, including various mosquito species.[113–122]

Table 2 Summary of evidence base for area and barrier methods

Effect	Strength of evidence*	Quality of evidence†	Comments
Insecticides			
Effectiveness of insecticides on clothing	A	I	Strong evidence from numerous authorities or reports of expert committees supporting the use of impregnated insecticides (permethrin) on clothing as an important method of personal protection against arthropod bites.
Effectiveness of net impregnation	A	I	Numerous studies have shown good personal protection against arthropod bites with the use of nets impregnated with insecticides.
Effectiveness of use on tents	B	II	Consistent evidence from studies showing good personal protection against arthropod bites with the use of impregnated tents with insecticides.
Vaporizing insecticide mats			
Inhibition of nuisance biting by mosquitoes	B	II	Consistent evidence that insecticide vaporizers cause mosquito bite inhibition, mosquito repellence, mosquito knockdown, and mosquito death.
Malaria prevention	D	II	No evidence from three studies
Mosquito coils			
Inhibition of nuisance biting by mosquitoes	B	II	Good evidence of protection against mosquito bites
Malaria prevention	C	III	Consensus that mosquito coils could be a useful measure to prevent malaria
Lung cancer	D	II	Prior exposure to mosquito coil smoke was more common in lung cancer patients than in controls. Lung cancer risk was higher in frequent burners of mosquito coils than in non-burners.[125]
Other adverse effects	D	III	Breathlessness,[132] chest irritation,[114] eye and nose irritation.[120,132,147]
Essential oil candles			
Inhibition of nuisance biting by mosquitoes	C	II	Two studies demonstrating significant repellency compared to control.[73,134]
Inhibition of nuisance biting by other insect species	C	II	Essential oil, linalool, and geraniol but not citronella candles repelled significantly more sandflies than did the control candle.[135]
Mosquitoes knockdown sprays			
Inhibition of nuisance biting by mosquitoes and other insect species	C	III	Anecdotal evidence only.
Malaria prevention	D	II	Two studies showed no significant reduction in malaria incidence.[119,137]
Prevention of other insect-transmitted infections	D	III	No studies.
Oil-based products			
Inhibition of nuisance biting by midges	C	I	Evidence for bath oils only.
Inhibition of nuisance biting by mosquitoes	C	II	Evidence for chemical base oils only. Inhibition was observed mostly in culicine mosquitoes.[148]
Soybean oil inhibition of nuisance biting by mosquitoes and black fly	D	III	More studies (field trials) needed to establish the efficacy of soybean oil as a repellent, although initial studies are very promising. Toxicity very low.
Garlic and vitamin B	E	II	Do not confer protection against haematophagous arthropods and this notion should be discouraged.

*A = good evidence to support use; B = moderate evidence to support use; C = poor evidence to support use; D = moderate evidence to support a recommendation against use; E = good evidence to support a recommendation against use.
†I = evidence from one or more properly randomized, controlled trial; II = evidence from one or more well-designed clinical trial without randomization, from case-controlled analysis of cohort study; III = consensus evidence, evidence from one authority or reports of expert committees, single case studies.

Electric insecticide vaporizers using pyrethrins or pyrethroids inhibit nuisance biting by mosquitoes, and vaporized pyrethrins kill house flies. There is no direct evidence that the technology does prevent malaria or any other insect-transmitted infection.[119,120,122] Exposure to pyrethrins and/or pyrethroids may present a low-level health hazard to humans,[123] and so vaporizers containing these classes of insecticide should be used by travelers with caution. Vaporized neem oil is an effective inhibitor of mosquito landing and appears safe to humans.[121] It should be investigated further for its potential usefulness in preventing malaria and other mosquito-transmitted infections.

Mosquito Coils

Mosquito coils are made from a paste of powdered insecticide, usually a pyrethrin or pyrethroid which when lit will smolder at a steady rate. Burning one mosquito coil releases the same amount of particulate matter as does burning 75–137 cigarettes[124] and emits formaldehyde equivalent to 51 cigarettes.[125]

Historically, some authorities have advised international travelers to burn mosquito coils in their room at night, in order to discourage mosquito biting and so help prevent mosquito-transmitted infection, notably malaria. These authorities include some national expert bodies.[126–130]

Consistent evidence from a systematic review indicated that coils cause mosquito bite inhibition, mosquito repellence, mosquito deterrence, mosquito knockdown, and mosquito death. Inhibition of nuisance biting is seen in all mosquito species: *Aedes*, *Anopheles*, *Culex*, and *Mansonia*.[131] There has been little evidence that this technology prevents malaria transmission[120,131,132] or other mosquito-transmitted infection. However, the expert group considers that they would be effective in preventing malaria in the light of as yet unpublished data.[133] Exposure to mosquito coil smoke could be hazardous to humans due to its potential association with lung cancer, but this should be taken in context of the amount likely to be inhaled over an evening and the very occasional use by travelers. In many countries, such coils are licensed for outdoor use only due to these concerns.

Essential Oil Candles

Three field studies were identified, demonstrating the effectiveness of essential oil candles in repelling mosquitoes and sand flies.[134–136]

Burning essential oil candles is likely to prevent biting by both mosquitoes and by sandflies. They may also prevent biting by other insect species. While there is no evidence that this technology prevents malaria, leishmaniasis, or any other insect-transmitted disease, this is an aspect which should be investigated. Candles containing 5% essential oil of geraniol appear to hold the most promise.

Knockdown Insecticide Sprays

Knockdown insecticides are aerosol sprays which are designed to be sprayed indoors and into the air, to eliminate flying insects by killing them as they fly through the room.[128]

Two individual studies were identified which failed to demonstrate that knockdown insecticide sprays prevented malaria in travelers to Africa.[119,132] Only anecdotal evidence supports the assumption that knockdown sprays inhibit nuisance biting by flying insects. There is an obvious, but mostly unquantified health risk to humans, from inhaling any insecticide vapor.[137] In the absence of persuasive evidence on the benefits of this technology, the use of knockdown insecticide sprays should be discouraged, in favor of vector avoidance strategies of proven effectiveness.[138]

Bath Oils and Chemical Base Oils

Bath oils, and chemical base oils also, seem to protect against insect biting not by a repellant action but by forming a physical barrier between the human target and the insect.[139] They are reported to be especially effective against small flying insects, creating an oily layer which traps these insects on the sticky surface of the skin.[140] Some studies have suggested that small flying insects, such as biting midges and sandflies, are not efficiently repelled by conventional repellants (deet and pyrethroid insecticides).[141,142]

One small randomized controlled trial (nine adult volunteers) tested a commercial bath oil preparation (Avon Skin-so-Soft, SSS)[140] and found that deet formulations were significantly more effective in preventing midge biting than was SSS.

Soybean Oil

Two well-designed laboratory evaluations of Bite Blocker, a commercial preparation containing 2% soybean oil in addition to other oils and emulsifiers, have shown that it is competitive with deet, against a dengue vector and nuisance biting mosquitoes in one study[49] and equivalent to that of low-concentration deet in a second study.[4] A field trial showed 3.5-hour protection under intensive biting pressure of nuisance mosquitoes, but this was not conducted by independent researchers.[143] In a similar study against black flies, soybean oil provided complete protection from black fly bites of 9.7 hours as compared to 6.6-hour protection provided by deet.[144]

Garlic and Vitamin B

It is still commonly believed and reported in magazines that ingestion of garlic or B vitamins makes the human skin unpalatable to blood feeding and biting arthropods which have been refuted.[145,146] Garlic and B vitamins must never be suggested as a natural method of bite prevention.

Conclusions

The use of insecticide-treated mosquito nets and clothing is well supported by the data and is to be recommended to travelers visiting malaria endemic areas. Electric insecticide vaporizers and essential oil candles inhibit nuisance biting, but there is little evidence that they help prevent malaria. Mosquito coils are effective and may help to reduce the risk of malaria, although safety concerns have been raised. The use of bath oils and other oils should be discouraged in travelers until further effective personal protection evidence is available.[127]

Acknowledgment

The authors dedicate this review to the memory of Dr Nigel Hill who died suddenly in January 2010.

Declaration of Interests

L. I. G. is director of Nomad Medical that produces deet and permethrin based products. A. M. C., N. H., S. M., and P. S. state that they have no conflict of interest. The opinions expressed herein are those of the authors and do not necessarily reflect those of the UK Ministry of Defence, the United States Department of Defense, and the Joint Health Command of the Australian Defence Force or any current defense policy.

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