

# Cream formulations protecting against cercarial dermatitis by *Trichobilharzia*

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**Abstract** Dermatitis caused by penetrating bird schistosome cercariae is an emerging global public health problem. Infections may be prevented by the use of topical formulations that inhibit cercarial skin penetration. We evaluated nine water resistant formulations by exposing treated arms of volunteers to *Trichobilharzia szidati* cercariae. Six formulations protected from cercarial invasion. However, after immersion of the treated skin in water (2×20 min), only two formulations offered full protection: (1) Safe Sea™, a cream protecting against jelly fish, (2) niclosamide in water resistant sun protecting cream formulations at concentrations as low as 0.05%. In an in vitro system Safe Sea™ and a 0.1% niclosamide formulation caused a high damage rate in *T. szidati* (92% and 99% after 5 min; only niclosamide with lethal effect) but not in *Schistosoma mansoni* (1% and 72%; both formulations with lethal effect). However, a 1% niclosamide formulation damaged *S. mansoni* sufficiently (100% after 5 min) and might offer full penetration protection.

## Introduction

Human cercarial dermatitis (“swimmers’ itch”) is an immunologic cutaneous reaction associated with intense itching due to accidental penetration by bird schistosome larvae (cercariae), frequently members of the genus *Trichobilharzia* (Kolářová et al. 1997; reviewed by Horák et al. 2002). The disease occurs worldwide in cold, temperate and tropical environments and is considered as

an emerging public health problem in Europe (de Gentile et al. 1996; Chamot et al. 1998). Particularly known as an occupational disease of fishermen and fish farmers, it is gaining importance due to the increasing number of outbreaks among swimming tourists in recreational lake areas resulting in considerable economic damage to the tourism industry (de Gentile et al. 1996).

Transmission in freshwater occurs when water birds are actively invaded by cercariae that are released in high quantities from the snail intermediate host. Due to a similar lipid composition of avian and human skin, cercariae are not able to differentiate between humans and water birds and they accidentally invade human skin (Haas and van de Roemer 1998). Affected persons develop a distinctive inflammatory immune response. The intensity and time course of dermal symptoms depends on the degree of hypersensitivity induced by previous exposure (Hoeffler 1974). Even body parts covered by swimming suits develop such symptoms (Allerberger et al. 1994; Chamot et al. 1998). At present, there is no known prophylactic treatment against cercarial dermatitis. An easily applicable remedial measure is required to reduce the risk of infection when people get in contact with infested water. A simple approach is the use of a suitable topical and water resistant “anti-penetrant” cream. In the past, there were some attempts amongst researchers to develop a formulation that either prevents cercarial recognition or penetration of the human skin. Predominantly for human schistosomes, a series of substances was reported to have anti-penetrant or repellent potential, respectively (Pellegrino 1967). For example, the insecticide dimethylphthalate (MacFarlane 1949), its derivative dibutylphthalate (Yang et al. 1965) and the molluscicide niclosamide (Cherfas 1989; Abu-Elyazeed et al. 1993) were reported to inhibit cercarial skin penetration with varying efficiency. Encouraging results

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were also obtained with the insect repellent *N,N*-diethyl-*m*-toluamide (DEET); its observed loss of protection due to absorption into the systemic circulation was recently outflanked by incorporating the drug in liposomes (“Lipo DEET”) resulting in 100% protection (Salafsky et al. 1999; Ramaswamy et al. 2003). Studies with a novel human skin model indicate that a dimethicone-based cream offers a high level of protection (Ingram et al. 2002). Some data on substances interfering with cercarial proteases are also available (Cohen et al. 1991; Lim et al. 1999). Similar effects of such agents can be supposed for bird schistosomes. Yet, the insect repellent ethylbutylacetylaminopropionate (IR 3535) (Fradin and Day 2002) has already been reported to be not appropriate for the prevention of cercarial dermatitis (Caumes et al. 2003).

Heavy outbreaks of cercarial dermatitis at lake Bodensee in 2003 led to economic losses in tourism. As a consequence, the ecology and epidemiology of the parasite (*Trichobilharzia franki*) was studied in an inter-disciplinary research cooperation (Werner et al. 2005). The task of our group was to develop a cream, which prevents cercarial invasion into the skin. We integrated potentially cercaria-toxic substances into water resistant cream formulations and tested their effect on the skin of volunteers against invasion of *Trichobilharzia szidati* and in an in vitro system against *Schistosoma mansoni* cercariae. We found formulations protecting from *T. szidati* and potentially from *S. mansoni*.

## Materials and methods

### Parasites

Our strain of *T. szidati* (Neuhaus 1952) is synonymous with *Trichobilharzia ocellata* (La Valette 1855) as used by various European laboratories (Odening 1996; Kock 2001; Rudolfová et al. 2005). The stock was isolated from its host snail *Lymnaea stagnalis* taken from fish ponds near Höchststadt/Aisch (Germany) and maintained using laboratory-reared *L. stagnalis* as intermediate hosts and domestic ducks as final hosts. *S. mansoni* and its snail host, *Biomphalaria glabrata*, were isolated in Belo Horizonte (Brazil). The life cycle of the parasite was maintained using white mice infected by the paddling method.

### Topical agents

All formulations were prepared integrating the drug into a waterproof carrier cream, except for commercial products and dimethicones. Considering possible effects based on the differences in composition and water resistance, different waterproof carrier formulations were studied: (1) a hydrophobic base cream mixture manufactured by pharmacies, (2)

an expensive, rubbing resistant sun blocking formulation for infants, and (3) a low-cost common sunblocking lotion.

Experiments were performed using approved substances potentially suitable for blocking cercarial penetration (chemical details see Table 1): (1) niclosamide, a molluscicide and anti-helminthic for humans; (2) DEET, an obsolete insect repellent; (3) KBR 3023, a modern insect repellent; (4) IR 3535, intended to be an insect repellent; (5) dodecanoic acid, a fatty acid stimulating cercarial penetration, but toxic in high concentrations; (6) two dimethicones, DM 350 and TMS 3069, ingredients of commercial skin care or waterproof make up formulations, respectively; (7) “ParaRizol”, a naturopathic germicidal mixture of ozonised vegetable oils that kills human schistosome cercariae; (8) commercial milking grease, reportedly offering a high level of protection and (9) Safe Sea™, a commercial product against jellyfish.

Except for industry provided substances, the active agents were incorporated into the carrier formulations emulsifying them by sonication at 23°C. The resulting lotions had approximately the consistency of common sunscreen products. KBR 3023 was kindly provided by Bayer chemicals (Germany), dimethicones DM 350 and TMS 3069 by Wacker chemicals (Germany) and “ParaRizol” by Dr. G. Steidl (University of Erlangen-Nuremberg, Germany).

### Experimental conditions

**Volunteers** All 10 study participants (aged 23–64 years) were healthy members of our Parasitology section (University of Erlangen-Nuremberg). Before enrolment into the study, they received detailed information about the drugs to be tested and potential medical risks associated with repeated contacts to cercariae. All volunteers declared no history of allergies to the drugs or carrier formulations tested and no chronic medical problems or skin abnormalities.

**Exposing human skin to cercariae** Inhibitory effects of the drug formulations on cercarial penetration were investigated exposing the forearms of volunteers to *T. szidati* cercariae.

Defined skin areas (2 cm in diameter; 1 cm space in between) were pre-treated with mixtures containing the drug (20 µl per area). Water resistance and persistence of protection were evaluated by two test series: Volunteers exposed their skin to cercariae (1) immediately 5 min after application of the cream and (2) after 40 min of water contact using a protocol for testing the water resistance of sunscreen products (U.S. Food and Drug Administration, Sec. 352.76; 2003). In detail, 5 min after application of the cream, the volunteers immersed their arms into 10 l fresh water containers at 23°C for 20 min. The water was bubbled via air stones simulating moderate activity in water. This procedure was repeated after a 20 min resting period during which the skin was strictly air-dried.

**Table 1** Effects of cream formulations on cercarial penetration into the skin of human volunteers

|                                     | Concentration | Exposure to cercariae             |                         |                                   |                         |
|-------------------------------------|---------------|-----------------------------------|-------------------------|-----------------------------------|-------------------------|
|                                     |               | No water resistance test          |                         | Water resistance test             |                         |
|                                     |               | Penetration rate<br>% ( $\pm$ SE) | Number of<br>replicates | Penetration rate<br>% ( $\pm$ SE) | Number of<br>replicates |
| <b>Insect repellents</b>            |               |                                   |                         |                                   |                         |
| Un-treated                          | –             | 32.5 (+3.0/–2.9)                  | 4                       | 40.8 (+10.8/–10.1)                | 6                       |
| Cream base                          | –             | 16.3 (+10.9/–7.6)                 | 4                       | 35.0 (+7.5/–7.0)                  | 6                       |
| DEET <sup>a</sup>                   | 1%            | 2.5 (+1.9/–1.0)                   | 4                       | –                                 | –                       |
|                                     | 10%           | 0.0 (+0.0/–0.0)*                  | 4                       | 28.3 (+7.6/–6.8)                  | 6                       |
| IR 3535 <sup>b</sup>                | 1%            | 8.8 (+5.7/–3.9)                   | 4                       | –                                 | –                       |
|                                     | 10%           | 0.0 (+0.0/–0.0)*                  | 4                       | 22.5 (+7.0/–6.1)                  | 6                       |
| KBR 3023 <sup>c</sup>               | 1%            | 13.8 (+9.2/–6.4)                  | 4                       | –                                 | –                       |
|                                     | 10%           | 0.0 (+0.0/–0.0)*                  | 4                       | 30.0 (+14.7/–11.9)                | 6                       |
| <b>Other chemicals</b>              |               |                                   |                         |                                   |                         |
| Un-treated                          | –             | 32.5 (+8.0/–7.4)                  | 6                       | 46.0 (+7.6/–7.4)                  | 5                       |
| Cream base                          | –             | 31.7 (+12.0/–10.5)                | 6                       | 22.0 (+5.1/–4.6)                  | 5                       |
| Dodecanoic acid                     | 20 mM         | 0.8 (+0.4/–0.1)*                  | 6                       | –                                 | –                       |
|                                     | 50 mM         | 1.7 (+0.9/–0.3)*                  | 6                       | –                                 | –                       |
|                                     | 100 mM        | 0.0 (+0.0/–0.0)*                  | 6                       | 13.3 (+7.6/–5.3)                  | 6                       |
| Ozonide mixture <sup>d</sup>        | 1%            | 2.5 (+1.9/–1.0)                   | 4                       | 18.0 (+9.9/–7.5)                  | 5                       |
| Dimethicone DM 350 <sup>e</sup>     | 100%          | 27.5 (+7.7/–6.9)                  | 4                       | –                                 | –                       |
| Dimethicone TMS 3069 <sup>e</sup>   | 100%          | 30.0 (+9.2/–8.2)                  | 4                       | –                                 | –                       |
| Milking grease                      | 100%          | –                                 | –                       | 23.0 (+13.6/–10.1)                | 5                       |
| <b>Protecting formulations</b>      |               |                                   |                         |                                   |                         |
| Un-treated                          | –             | 32.5 (+3.0/–2.9)                  | 4                       | 45.0 (+6.8/–6.6)                  | 5                       |
| Cream base                          | –             | 16.3 (+10.9/–7.6)                 | 4                       | 33.0 (+4.1/–4.0)                  | 5                       |
| Safe Sea <sup>TM</sup> <sup>f</sup> | 100%          | 0.0 (+0.0/–0.0)*                  | 4                       | 0.0 (+0.0/–0.0)*                  | 6                       |
| Niclosamide <sup>g</sup>            | 0.01%         | –                                 | –                       | 32.0 (+3.9/–3.7)                  | 5                       |
|                                     | 0.05%         | –                                 | –                       | 0.0 (+0.0/–0.0)*                  | 5                       |
|                                     | 0.1%          | –                                 | –                       | 0.0 (+0.0/–0.0)*                  | 5                       |
|                                     | 0.5%          | –                                 | –                       | 0.0 (+0.0/–0.0)*                  | 5                       |
|                                     | 1.0%          | 3.8 (+2.2/–1.6)                   | 4                       | 0.0 (+0.0/–0.0)*                  | 5                       |
|                                     | 10%           | 0.0 (+0.0/–0.0)*                  | 5                       | –                                 | –                       |

Skin areas were exposed to 20 *T. szidati* cercariae 5 min after product application and after concluding a water resistance test.

Data obtained from 20 cercariae/replicate. Cream base containing the active agents: “Ombia Sun, Sonnenmilch, Lichtschutzzfaktor 8, wasserfest”, E. Kiessling, Georgensgmünd, Germany. Dimethicones, milking grease and Safe Sea<sup>TM</sup> were applied purely.

\* $P < 0.001$  vs un-treated (Tukey's multiple *t*-test).

<sup>a</sup> *N,N*-diethyl-*m*-toluamide.

<sup>b</sup> Ethylbutylacetylaminopropionate (IR 3535).

<sup>c</sup> 1-piperidinecarboxylic acid, 2-(2-hydroxyethyl)-, 1-methylpropylester (“Bayrepel”).

<sup>d</sup> Contents: ozonide 70%, wormwood oil 10%, walnut oil 10%, clove oil 10%.

<sup>e</sup> Dimethicones provided by Wacker chemicals, Germany.

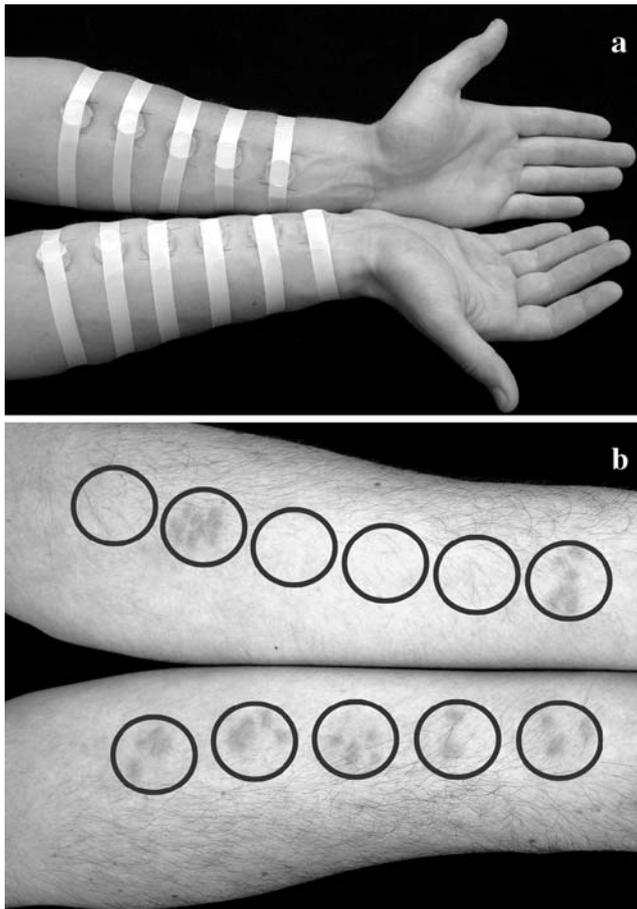
<sup>f</sup> Patented cream protecting against jelly fish: “Quallen+Sonnenschutz Canea” for children by Nidaria Technology, M.P. Jordan Valley, Israel.

<sup>g</sup> WR046234, 2',5-dichloro-4'-nitrosalicylanilide.

Subsequently, the test sites were incubated 30 min with 20 cercariae suspended in 1.5 ml fresh water in petri dishes (1 cm in diameter) being fixed with plaster strips (Fig. 1a). Exposed skin areas were then examined for appearing skin eruptions (Fig. 1b), usually fully developing after 12–24 h. Penetration rates were recorded by counting the number of papules and penetrated skin was treated with a commercial cortisone-based product. The carrier formulation without

drugs served as a placebo control. The data were compared with those obtained from un-treated skin.

*Effect of niclosamide and Safe Sea<sup>TM</sup> on cercariae* The mode of action of the efficient formulations was studied by exposing them to *T. szidati* and *S. mansoni* cercariae in vitro. Approximately 100 cercariae of *T. szidati* and *S. mansoni* in 365  $\mu$ l fresh water were placed on a microscopic cavity slide



**Fig. 1** Exposure of a volunteer's forearms to *T. ocellata* cercariae. **a** 30 min incubation with 20 cercariae per skin site. **b** Forearms of a sensitised subject 20 h after exposure. Un-treated skin and sites pretreated with non-efficient lotions developed distinctive skin reactions

(cavity 2 cm in diameter). The cavity contained 20  $\mu$ l of the drug-based formulation, equally spread with a cotton bud and let dry for 30 min. The carrier formulation without drug served as a control. The particular effect on cercariae was observed microscopically for 60 min and (1) tail shedding, (2) impairment (no locomotion possible; minimal body and sucker contractions but still protonephridial activity) and (3) mortality (complete immobilisation; no protonephridial activity) were recorded. Affected cercariae (impaired and dead) were pooled in a damage rate and the average time during which 50% of the larvae were expected to be affected ( $DT_{50}$ ) or dead ( $LT_{50}$ ) was calculated.

All experiments were performed using a letter-coded protocol unknown to the investigators and data were evaluated before the medication identity was revealed.

#### Statistical methods

Statistical analysis of penetration rates was performed using arcsine transformation of the values to allow for non-

normal distribution of values expressed as percentages. Mean values and standard errors (SE) were computed from transformed data and re-transformed for display. Differences among means were determined using the Tukey's multiple *t*-test procedure with a significance level of 0.001.

## Results

### Lotions inhibiting penetration

Penetration rates into un-treated skin varied and reached up to 49%. Characteristic skin reactions initially appeared as red spots (approximately 2 mm in diameter) within 2 h after exposure to the cercariae. Depending on the sensitisation of the individual, typical cutaneous manifestations (macules, papules, swelling and pruritus) developed within 2 days (Fig. 1b). The symptoms persisted for about 5 to 10 days.

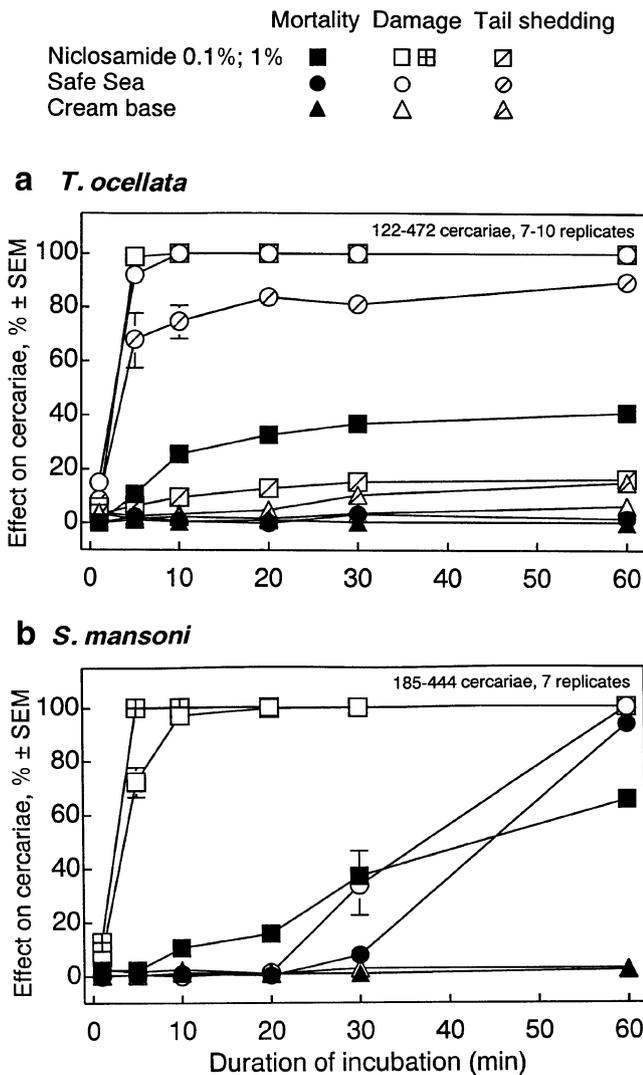
All three carrier formulations used for integrating drugs yielded comparable results. Application of the cream alone gave some protection against cercarial penetration, yet this observation was quite erratic in the different test series (data not shown). However, penetration rates were clearly decreased by most drug-based lotions when skin was exposed to the cercariae 5 min after application. Particularly in high concentrations, common insecticides (DEET, KBR 3023 and IR 3535), niclosamide and dodecanoic acid fully inhibited cercarial penetration (Table 1). However, after the water resistance test protocol, protective effects disappeared in most of the cases. Complete protection was only achieved by (1) a commercial product against jellyfish (Safe Sea™) and (2) mixtures containing niclosamide in concentrations as low as 0.05% (Table 1).

None of the volunteers reported any dermatological or systemic side effects for any of the drugs tested during and after the experimental period.

### Effect of niclosamide and Safe Sea™ on cercariae

In vitro tests on the particular effects of the two efficient penetration inhibitors revealed that Safe Sea™ was not lethal to *T. szidati* cercariae, but quickly decreased their motility ( $DT_{50}$  2.8 min), accompanied by a high tendency to tail shedding (68% after 5 min) (Fig. 2a). However, Safe Sea™ had a fully different effect on *S. mansoni* cercariae. Although it finally killed *S. mansoni* ( $LT_{50}$  45.9 min), it caused no tail shedding and damaged the cercariae much slower ( $DT_{50}$  37.8 min) as *T. szidati* (Fig. 2b).

The 0.1% niclosamide formulation decreased cercarial motility drastically ( $DT_{50}$  2.8 min for *T. szidati* and 3.8 min for *S. mansoni*) and had a weak lethal effect on both species. A higher niclosamide concentration of 1% reached the same toxicity in *S. mansoni* ( $DT_{50}$  2.8 min) as the



**Fig. 2** Effect of niclosamide and Safe Sea™ on **a** *T. ocellata* and **b** *S. mansoni* cercariae. *S. mansoni* cercariae did not shed their tails

proven protective 0.1% formulation in *T. szidati* and could therefore protect against penetration of the *S. mansoni* cercariae.

## Discussion

The precise public health significance of cercarial dermatitis, mainly defined by clinical reports and outbreaks, still remains obscure. Findings on the survival of schistosomula in experimentally infected mammals are alarming. Though not maturing in mammalian hosts, schistosomula of *Trichobilharzia* sp. and other bird schistosomes can migrate along blood vessels or the nervous system to internal organs in a similar manner to that observed in avian hosts, thus reaching the lungs, nervous tissue and other organs (Olivier 1953; Appleton and Brock 1986; Haas and Pietsch

1991; Horák et al. 1999; Horák and Kolářová 2000; Bayssade-Dufour et al. 2001). Recent studies on the nasal species *T. regenti* revealed that this parasite may cause histopathological changes, leading to clinical symptoms such as leg paralysis and balance and orientation disorders (Horák et al. 1999; Hrádková and Horák 2002). Such properties justify continued attention to the development of convenient methods for the control and prevention of cercarial dermatitis.

Several attempts to limit cercarial dermatitis by interrupting the schistosome life cycle were described. This was conducted with chemical, mechanical or biological approaches targeting either the intermediate or definitive host with variable success (reviewed by Horák et al. 2002). Besides inconsistent results, most approaches lack applicability, may reduce the recreational attractiveness of popular lakes and thus, do not really represent viable options. Also, considering the tourism industry, the establishment of local public safety instructions when the parasites have already appeared within a particular water body does not represent an economically justifiable answer to the problem. And it is known that such warning restrictions are rarely respected by bathers (Chamot et al. 1998). It appears that the easiest solution of this common summertime problem is to develop a topical barrier formulation as we show in our present study that allows safe contact with infested waters of recreational areas.

We found only two of nine formulations to be effective: (1) Safe Sea™, a lotion against jellyfish stings. Cercariae of *T. ocellata* are immediately immobilised by this formulation and this may explain its protective effect. However, *S. mansoni* cercariae are poorly affected for a long period. As they can penetrate human skin within a period of time as short as 90 s (Haas and Haeberlein, unpublished results), Safe Sea™ does not represent a protective option against infection with human schistosomes. The observed cercaricidal effect of Safe Sea on *T. szidati* cercariae may, at least in part, be related to the H1-antihistamine diphenhydramine contained in the product. H1-antihistamines seem to interfere with cercarial histaminergic mechanisms, leading to a complete immobilisation and death (Ercoli et al. 1985). (2) Niclosamide in low dosages highly damaged both species, though cercariae of *S. mansoni* are more resistant to the agent. Our results confirm earlier findings: a 1% niclosamide-based lotion guarantees a high level of cercarial impairment and significantly reduces the likelihood of infection (Bruce et al. 1992; Abu-Elyazeed et al. 1993).

The poor inhibitory effects of dimethicones and DEET might be related to species-specific differences in susceptibility. Contrary to previous findings on *S. mansoni* cercariae (Ingram et al. 2002), dimethicones appeared to stimulate cercariae of *T. szidati* to penetrate into human skin (data not shown). It is not known whether this difference

originates from stimulatory properties of the agent itself or is related to physiological features of *T. szidati* cercariae (e.g. body size, protease amount) that nevertheless enable them to penetrate skin with rather thick mechanical barriers. Similarly, it just can be speculated whether the poor effect of DEET (10%) was parasite, concentration and carrier related. Liposomal DEET (20%), however, was shown to provide complete protection against infection with *S. mansoni* (Salafsky et al. 1999; Ramaswamy et al. 2003). The inhibitory value of other agents decreasing penetration rates to a certain extent is hardly assessable. Such agents could be studied further using more suitable carrier formulations.

In conclusion, low-dosed niclosamide-based lotions can be recommended for the prevention of cercarial dermatitis. The toxicology of this drug, which is widely used as a human anti-helminthic (Yomesan<sup>TM</sup>), was well-investigated in the past (Andrews et al. 1982). No skin irritation or sensitising effects were noted during skin contact and it is considered to be safe in the context of several medical purposes. The estimated material costs for our 0.1% niclosamide-based formulation would not exceed 1€/200 ml and it could be easily manufactured in large quantities by local pharmacists. We made our results public and a method to prepare a cream based on the anti-helminthic Yomesan<sup>TM</sup> has already been published (Fischer and Reimann 2006). Due to easy production and low manufacturing costs even when needed in higher concentrations, such formulations might also help control human schistosomiasis in developing countries. Further studies will have to confirm whether and to which extent the encouraging formulations described can be successfully applied in the field.

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