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Uptake and elimination of permethrin related to the use of permethrin treated clothing for forestry workers

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HIGHLIGHTS

- Uptake of permethrin from treated clothing is assessed in an experimental setting.
- Internal exposure kinetics is tracked by determination of urinary metabolites.
- Metabolite excretion kinetics suggest dermal uptake of permethrin.
- Make of clothing, external climate conditions and physical workload affect exposure.

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ABSTRACT

Wearing of permethrin treated clothing usually implicates an uptake of permethrin by the user. Aim of our study was to examine the kinetics of internal permethrin exposure in volunteers during and after a single 8 h-use of treated clothing as well as factors potentially influencing permethrin uptake. 28 male volunteers (age: 20–34 years) were equipped with permethrin treated jackets and pants from two different suppliers. The clothing was worn for 8 h, simulating differing external conditions, including comfort conditions as well as conditions of increased temperature and humidity without and with additional physical workload. Internal permethrin exposure was monitored by determination of permethrin metabolites (DCCA and 3-PBA) in a set of 12 urine samples, covering a period of 504 h from the beginning of the wearing interval. Time–concentration curves showed an increase of internal exposure associated with wearing of the clothing (individual maximum: 109.5 μg/L) followed by a first-order like decay (mean half-life: 38.5 h). Metabolite excretion was affected by the make of clothing, which could be explained by differing permethrin contents of the garment. Furthermore, internal exposure increased with increasing temperature/humidity and additional physical workload. Assuming dermal uptake of permethrin, this may be ascribed to an alteration of the barrier function of the skin.

1. Introduction

For more than a decade, treatment of clothing with the pyrethroid permethrin is a WHO-recommended personal protective measure for persons at risk of contracting vector borne diseases transmitted by arthropods, (Rozendaal, 1997; WHO, 2001a,b). This approach aimed initially at prevention of tropical diseases such as malaria or dengue fever. Meanwhile, it has been refined and transferred for prevention of tick borne diseases such as lyme disease or tick borne encephalitis, which are found in temperate zones. Contemporary tick protective clothing is mostly equipped with a factory based long lasting permethrin impregnation. Respective garments are commercially available from several producers for quite some time now. Major target groups for their use are forestry and other outdoor workers but also leisure time users such as hikers.

The active ingredient permethrin, (±)-3-phenoxybenzyl 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate, is usually a mixture consisting of *cis*- and *trans*-isomers. Permethrin toxicity is largely determined by the *trans*/*cis* ratio, with the *cis*-isomer being more toxic than the *trans*-isomer (WHO, 1990, 1999). Uptake of permethrin is possible by inhalation, oral intake and/or dermal absorption. Experimental studies suggest dermal absorption rates of about 2% of the applied dose (WHO, 1990; ATSDR, 2003; Appel

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et al., 2008). Permethrin is quickly metabolized into *cis*- and *trans*-3-(2,2-dichlorvinyl)-2,2-dimethylcyclopropancarboxylic-acid (*cis*-DCCA and *trans*-DCCA) and 3-phenoxabenzylalcohol (3-PBOH) after absorption. The latter is subsequently oxidized to 3-phenoxybenzoic-acid (3-PBA). Both DCCA isomers and 3-PBA are considered as main metabolites of permethrin (WHO, 1990). Determination of internal exposure by biological monitoring is usually based on quantification of their urinary concentrations using in particular DCCA excretion for quantitative assessment of permethrin uptake (Appel et al., 2008; Hardt and Angerer, 2003; Tomalik-Scharte et al., 2005).

Though being a potent neurotoxin in target organisms, the mammalian toxicity of permethrin and other pyrethroids is generally considered as low, promoting a widespread use for pest control but also in veterinary and human medicine (WHO, 2005, for review on toxicology see also: ATSDR, 2003; Appel et al., 2008). An acceptable daily intake (ADI) of 50 μg/kg body weight was published by the WHO (1999). However, the classifications of permethrin with respect to potential carcinogenicity are heterogeneous at present. The compound is classified as “likely to be carcinogenic to humans by the oral route” by the US EPA (2009) (US Environmental Protection Agency), whereas permethrin was labelled as group 3 (“not classifiable as to its carcinogenicity to humans”) by the IARC (1991) (International Agency for Research on Cancer). Insecticide treatment of uniforms is among others blamed for health impairments of soldiers in the first Gulf War (Ishøy et al., 1999). Permethrin in particular has been mentioned as a potential cause for the so called “gulf war syndrome” (Abou-Donia et al., 1996; Plapp, 1999).

With respect to these toxicological issues, detailed data on potential permethrin uptake from clothing seems to be a prerequisite for accurate risk assessment. Recent biomonitoring studies in soldiers showed, that a regular use of permethrin treated battle dress uniforms (BDUs) is associated with increased internal permethrin exposure of the wearers (Appel et al., 2008; Rossbach et al., 2010; Kegel et al., 2014). However, little is known about other fields of application, factors influencing uptake of permethrin from treated clothing or the kinetics of permethrin uptake and elimination. Thus, it was the objective of this study to examine the time course of internal permethrin exposure in volunteers during and after a single 8 h-use of permethrin treated protective clothing for forestry works, taking into account climate conditions, physical work load and the make of clothing as potential factors of influence on permethrin uptake.

2. Material and methods

2.1. Study design

30 healthy male volunteers aged between 20 and 34 years (median 25 years) were equipped with permethrin treated forestry work clothing (jackets and pants either with or without cut protective lining) obtained from two different producers. We requested the subjects to wear the clothing for 8 h each (=exposure) under three differing external conditions. The wearing conditions were in detail: (I) comfort conditions without any further restrictions regarding the subjects' whereabouts over the whole 8 h period, (II) a minimum stay of 4 h under conditions of increased temperature and humidity (≤25 °C and ≤60% relative humidity (RH)), and (III) like (II) but with additional simulation of intermittent physical workload using a bicycle ergometer (six 10 min-intervals at a heart rate of 140–150 min^{-1}). The participants underwent the three wearing conditions in randomized order with a gap of at least three weeks between two exposures. Conditions of increased temperature and RH were generated in a 16 m^3 stainless steel chamber and monitored continuously every 5 min during the experiments. The mean values (±SD) of temperature and RH calculated from monitoring data were 26.9 ± 0.7 °C and 60.3 ± 4.4% for exposure condition (II) and 26.9 ± 0.8 °C and 61.8 ± 2.9% for exposure condition (III), respectively.

The subjects' health status was assessed before their inclusion into the study by taking a detailed medical history focusing in particular on pre-existing diseases (in particular skin diseases and allergies), a medical examination, routine blood analysis (blood count, electrolytes, creatinine, alanine transaminase, glutamic oxaloacetic transaminase, γ-glutamyltranspeptidase, alkaline phosphatase, glucose, C-reactive proteine, INR, erythrocyte sedimentation-rate), urine analysis with a test strip (Combur 10®, F. Hoffmann-LaRoche, Basel, Switzerland), body plethysmography and exercise electrocardiography.

The diet of the experimental subjects was not restricted during the study. Potential additional permethrin exposure (e.g. medical use of permethrin containing agents, use of permethrin formulations for pet treatment or pest control) was assessed by questionnaire.

2.2. Clothing

All clothing used was commercially available. Factory based permethrin treated pants with or without cut protection lining were obtained from two different producers (designated as “A” or “B” in the following). Pants equipped with cut protection lining were either waistband trousers (producer A) or bib and brace overalls (producer B). Waistband trousers were provided as pants without cut protection by both producers. Both producers also provided permethrin treated long sleeved jackets, which were worn in combination with the pants of the respective producer. According to the specifications of the producers, initial permethrin content in all types of treated pants and jackets was between 1250 and 1500 mg/m^2 with a *trans*/*cis* isomeric ratio of 3:1. Both producers state resistance of pants' impregnations towards laundering associated loss of protective efficacy for at least 50 launderings. Pants provided by producer B were treated by the so called polymer coating method (Faulde et al., 2003). No further details are available on the treatment process used by producer A. Counting initially on the reliability of the manufacturers' information we did only exemplary measurements of the permethrin content in samples of virgin clothing after completion of the study. Quadruplicate determinations were conducted in two pants of each supplier, using a GC/MS-procedure as outlined by Faulde et al. (2003). Contrary to our expectations, mean permethrin concentrations of 202 (*trans*/*cis* ratio 3.1:1; supplier A) and 1278 mg/m^2 (*trans*/*cis* ratio 3.0:1; supplier B) were found, suggesting an about six-fold concentration difference dependent on the make of the clothing. Unfortunately, these numbers could not be verified by a larger number of determinations due to limited availability of respective virgin clothing.

Treated clothing was used three times by each participant and washed before use and after use under condition (II) and (III) according to the recommendations of the suppliers. All participants wore standardized virgin long sleeved cotton T-shirts and briefs or boxer shorts as undergarments during the experiments. T-shirts were provided inside with pre-weighted absorbing nursing pads in the breast and lower back area to assess perspiration of the participants. The nursing pads were removed immediately after exposure and the amount of sweat absorbed was determined gravimetrically. The averaged relative increase in weight of both pads was calculated as a measure for the extent of sweating.

2.3. Urine sampling

Internal permethrin exposure was determined in urine samples of the subjects. In total twelve samples were collected before, during,