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REVIEW ARTICLE

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Surface distribution of pyrethroids following topical application to veterinary species: Implications for lateral transport

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Abstract

Pyrethroids like permethrin have been used as topical formulations for their ectoparasiticidal effects since the 1970s. There are numerous efficacy studies in dogs and livestock animals that indicate a fast spread of pyrethroids after topical administration onto rather confined areas of the skin. Some studies correlate the efficacy against ticks, fleas or lice with concentrations of pyrethroids in hair and, less frequently, *stratum corneum* samples. It is often stated that lateral transport is responsible for the distribution of the pyrethroids over the body surface. With this review, we attempt to demonstrate evidence for lateral transport of pyrethroids after topical administration in dogs, cattle and sheep and to present data gaps that should be addressed in follow-up studies.

KEYWORDS
lateral transport, pyrethroids

1 | INTRODUCTION

1.1 | General comment

Natural pyrethrins derived from extracts of the pyrethrum plant *Chrysanthemum cinerariifolium* and related species were discovered at the beginning of the last century, and their potential use in the control of insects was rapidly recognized. The refinement of the effective components led to the development of different synthetic pyrethroids like permethrin, that have been used as insecticides since the 1970s (Elliott et al., 1973). Pyrethroids are frequently utilized as insecticides in agriculture, in the impregnation of clothing and as ectoparasiticides, with permethrin being the most commonly used in the form of powders, shampoos, emulsions, impregnation sprays, ear clips, spot-on products and collars.

The type I pyrethroids such as permethrin (these lack an α-cyano group) bind to voltage-gated sodium channels of excitable cells such as nerve cells. Permethrin inhibits the sodium channel closure leading to long-lasting depolarization of the cells and consequently resulting in a nerve block. This causes paralysis of the organism and eventually death, which is the intended effect on arthropods (Bradberry et al., 2005). Spot-on products containing permethrin have been documented to be potent agents in the prevention of tick attachment and in the quick killing of attached ticks (Endris et al., 2002, 2003). The "knock-down effect" is the most important action of permethrin against fleas, and this is facilitated by the fast penetration of permethrin through the arthropod cuticle. However, this effect does not necessarily lead to immediate killing of the insect (Pfister & Armstrong, 2016).

Excretion and dermal penetration studies indicate that there is generally a poor dermal absorption of pyrethroids in humans of clearly below 10%, although this can be formulation dependent (Reifenrath, 2007). Baynes et al. (1997) reported low rates of absorption of permethrin in pig skin which is anatomically and biochemically similar to human skin. This is also true for permethrin, which is broadly used in human households as biocide or for impregnation

of clothes and carpets. Systemic poisoning with permethrin by dermal absorption is therefore very unlikely, and the risk is further reduced by a high intradermal metabolism (Bast et al., 1997) and rapid systemic degradation. However, there have been many reports and excellent reviews of several pyrethroids, especially permethrin, causing adverse effects in cats (Malik et al., 2010; Wismer & Means, 2018). One reason for the higher sensitivity of this species against pyrethroids may be a higher systemic exposure caused mainly by significant oral intake of a topically applied product during the cat's grooming activities and not so much by dermal absorption. In addition, several pyrethroids show a higher systemic stability in cats compared to other mammals which may further contribute to the observed cases of pyrethroid toxicity (Anadon et al., 2009). Toxicity of several of these pyrethroids is thought to be associated with deficiency in the phase 2 metabolism enzyme glucuronyltranferase (Court and Greenblatt, 2000). These factors explain why very few topical spot-on ectoparasiticides containing pyrethroids are approved and/or registered for use in cats. Regardless, the overall low toxic potential of permethrin in mammals leads to a wide distribution of permethrin preparations in veterinary medicine in species other than cats.

Manufacturers have proposed that pyrethroid containing products distribute evenly in the skin and the coat of dogs after application. This may be mainly achieved by the pyrethroid's high lipophilicity, whose $\log K_{ow}$ values range from 6.5 to 6.9 for the four pyrethroids listed in Table 1. However, the exact mechanism of lateral transport of pyrethroids like permethrin is not entirely clear. The absorption and distribution cannot be ruled out totally as small quantities of the substance can appear in the bloodstream following topical application associated with bypass of the first pass effect. However, these pyrethroids are rapidly cleared and are another argument against a prolonged persistence in the body.

In order to better demonstrate the surface distribution of permethrin, we provide details from studies that correlate efficacy data with data from samples from the skin, hair, blood and the *stratum corneum* of dogs and lateral transport studies for cypermethrin and deltamethrin in sheep and flumethrin in cattle.

The focus of this review is to highlight growing evidence for lateral transport as a mechanism of spread over the body which may support the efficacy data. We will include some more detailed *stratum corneum* data that have not been previously published (Lüssenhop, 2011).

2 | CHEMICAL RESIDUE EVIDENCE OF LATERAL TRANSPORT

2.1 | Drug transport mechanisms

Topically applied drugs or chemicals have several potential pathways for entry into the skin and/or subsequent transport into the systemic circulation. Although the latter is not the focus of this review paper, readers should recognize that chemical or drug transport will more likely be passive diffusion down a concentration gradient from the mixture or formulation applied to the skin surface. Shunt diffusion can occur in the skin via appendageal routes such as *diffusion* into the sweat gland, hair follicles and sebaceous. However, this is often more of a vertical transport mechanism via diffusion rather than a lateral transport mechanism that leads to deposition in the skin layers below the site of application and possible systemic absorption. The influence of various mixtures and formulations on pyrethroid absorption and skin disposition has been previously described (Baynes et al., 1997; Riviere et al., 2014), and we provide another example of solvent effects later in the paper.

Examples of veterinary topical products with limited skin absorption include products containing pyrethroid insecticides such as permethrin, cypermethrin, flumethrin and fenvalerate listed in Table 1. While molecular weight and $\log K_{ow}$ are important determinants of chemical penetration, vapour pressure could be an important factor in influencing surface distribution. The pyrethroids listed here are typically used in veterinary products and may be formulated with other insecticides such as neonicotinoids (e.g. imidacloprid) or insect growth regulators (e.g. pyriproxyfen).

Of the veterinary products that are applied topically, only a few are expected to have therapeutic effects following skin absorption into the systemic circulation ("transdermal" products), while most of the topically applied ectoparasiticidal products containing pyrethroids are expected to be therapeutic by working primarily on the skin surface. The disposition of veterinary drugs and insecticides following application to the skin has been widely reviewed in the open literature and in textbooks (Baynes & Riviere, 2010; Baynes et al., 2012; Magnusson et al., 2001; Riviere & Papich, 2001). This review is focused on evidence of lateral transport, while other publications cited above have focused on chemical/drug absorption and disposition.

TABLE 1 Some physicochemical properties[a] of the four pyrethroids reviewed

Pyrethroid	Molecular weight (gram/mol)	Log Octanol–Water coefficient (Log Ko/w)	Vapour pressure (mm Hg at 25°C)
Permethrin	391.29	6.5	2.18×10^{-8}
Flumethrin	510.39	7.6	1.7×10^{-9}
Cypermethrin	416.29	6.0	3.07×10^{-9}
Fenvalerate	419.91	6.2	1.5×10^{-9}

Note: LogKo/w = log octanol–water partition coefficient.

[a]Obtained from US EPA,https://comptox.epa.gov/dashboard/

2.2 | Lateral transport

Lateral transport could be defined as the lateral movement along the skin surface in any direction following topical application to a single spot on the skin. It has been postulated by work described later in this paper that eccrine skin secretions, hair follicles or a combination of both on the skin surface facilitates lateral transport of the drug. There is evidence that some topical acting compounds may bind to various regions of the hair shaft, and while there is significant evidence of vertical transdermal delivery via the transfollicular route (Knorr et al., 2009; Lauer et al., 1995), very little is known about the role of hair density and/or hair volume in the lateral transport and distribution of these chemicals. Further, there is some speculation that eccrine secretions to the skin surface may be involved in movement of chemicals away from the application site. Lloyd and Garthwaite (1982) reported that the surface topography of dog skin included a covering of a thin homogenous film of a sebaceous lipid that appeared to be oozing onto the surface as observed by scanning electron microscopy.

There is therefore limited understanding about how or whether the larger percentage of chemicals not absorbed by passive diffusion remain at the site of application and/or move laterally to other regions of the body via the above-mentioned sebaceous lipid.

As is typical of many skin *in vivo* animal studies, there are many technical challenges associated with accurately assessing parameters such as dermal bioavailability, chemical disposition within the epidermis and dermis and chemical or drug transfer to regions distal from the site of application. Therefore, another mechanism that could explain lateral transport of the substance is by a mechanical means such as rubbing and grooming. Several studies described later in this review report an attempt to control this animal activity; however, this activity may be difficult to control depending on the animal restraint methods in these *in vivo* trials. Toutain et al. (2012) demonstrated that allo- and self-grooming behaviour among cattle treated with ivermectin pour-on product could account for the inter- and intra-animal variability in pharmacokinetic and pharmacodynamic response. Another technical challenge in many of these studies is to prevent chemical's vehicle straying over the skin surface from the application site to adjacent skin areas, that is the researcher does not often provide detailed information regarding the ability to restrict the formulation to a defined dose area. In addition, there is the opportunity for the chemical to be lost with *stratum corneum* shedding which has been well characterized in human skin (Lin et al., 2012) and in some pets can occur every 20–30 days (Baker et al., 1973), depending on the animals' health and environmental conditions.

The actual process of obtaining hair clippings and *stratum corneum* samples can result in erroneous transfer or loss of the chemical during sampling. The many advantages and challenges associated with using tape stripping to obtain *stratum corneum* samples have been well documented (Escobar-Chavez et al., 2008; Lademann et al., 2009), and it is well-recognized that the method of applying the tape and the number of tape strips can add significant experimental error to the measured chemical mass in *stratum corneum* samples. Our review of the literature revealed that not all of the studies measured all the various skin layers such as *stratum corneum*, epidermis and dermis as expected in a mass balance study, and the majority of the studies were focused on assaying limited samples such as hair and/or skin surface which may bias determination of lateral transport.

2.3 | Evidence of lateral transport

Pfister and Armstrong (2016) reviewed the lateral transport of permethrin in dogs that was reported by Lüssenhop et al. (2012). However, in the short communication of Lüssenhop et al. (2012) not all study details were provided; thus, we add some helpful details about methods and results in this review (Lüssenhop, 2011). In this study, six beagle dogs were exposed to permethrin (50 mg/kg body weight) formulated in either one of four commercially available products [Exspot® (Intervet Deutschland GmbH (MSD Tiergesundheit), Unterschleißheim, Germany); Fletic® (IDT Biologika GmbH, Dessau/Roslau, Germany); Preventic® (Virbac Tierarzneimittel GmbH, Bad Oldesloe, Germany); and Advantix® (Bayer Vital GmbH, Leverkusen, Germany)] and allowing for at least 12 weeks washout period between application of each of the four formulations. Skin, hair and *stratum corneum* samples (biopsy, hair collection, tape strip) were collected from locations distal from the application site which was a spot-on application between the shoulder blades directly to the skin. During each test period, dogs were kept in individual cages to avoid cross-contamination, but grooming behaviour was not prevented by measures like Elizabethan collar. Initial samples were taken 24 hr after treatment to assess the speed of distribution from the application site to all other areas of the body. Further sampling was performed 14 days and 28 days after treatment, which allowed an evaluation of the progression of the products' distribution. Hair was collected on the back about 5–10 cm left of the application site and a second area on the left hind leg.

Hair samples contained measurable permethrin concentrations from the two body regions. Across all four formulations, the median concentrations in hair on the back ranged from 399 to 521 μg/g at day 1 and declined to median concentrations ranging from 52 to 190 μg/g at 28 days. For the hind leg, concentrations declined from the median range of 406–1038 μg/g at day 1 to 29–32 μg/g at day 28 (Table 2). The decline in hair concentrations over time can plausibly be attributed to desquamation of the *stratum corneum* and/or self-grooming behaviours.

Within this study, blood samples were taken 24 hr, 14 days and 28 days after topical administration of the spot-on formulations. Plasma was analysed by HPLC, and the limit of quantification was 100 ng/ml plasma (limit of detection was 50 ng/ml). None of the blood samples taken produced signals above the limit of detection (Lüssenhop, 2011; Lüssenhop et al., 2012).

To address the contribution of *stratum corneum* lipids on reservoir function and lateral transport, adhesive tape stripping was performed in Lüssenhop (2011) and Lüssenhop et al (2012), which is

TABLE 2 Median concentration of permethrin in hair samples of back and leg (μg/g hair) for each product at days 1, 14 and 28 after application. Samples from six dogs were obtained for each product

	Day 1		Day 14		Day 28	
	Back	Leg	Back	Leg	Back	Leg
Exspot© Median	521	406	184	56	52	32
Fletic© Median	520	636	223	60	71	42
Preventic© Median	839	1038	360	157	109	32
Advantix© Median	399	581	341	153	190	29

known to be a simple, efficient and chemical-specific method and which is commonly used in the examination of topical drugs (Löffler et al., 2004). The area of the part of the adhesive tape strip that was analysed was approximately 9.5 cm^2.

The concentration of permethrin in the successively taken strips generally decreased exponentially from the first to the last strip (Figure 1), which indicates that most of the permethrin was deposited in the upper layers of the *stratum corneum*.

The comparison of the concentrations of permethrin on the back and on the leg 24 hr after application of the spot-on products showed no significant differences, either in the adhesive strips or in the hair samples (Table 2 and Figure 2). This leads to the conclusion that the distribution over the body surface was fast and homogenous.

This may be explained by the high lipophilicity of permethrin, which facilitates a quick distribution within the lipids that are present around the hair, on the skin surface and within the bilayers of the *stratum corneum*. Furthermore, the added solvents in the spot-on formulations are all known to be enhancers of percutaneous penetration and might also support lateral transport (Thong et al., 2007).

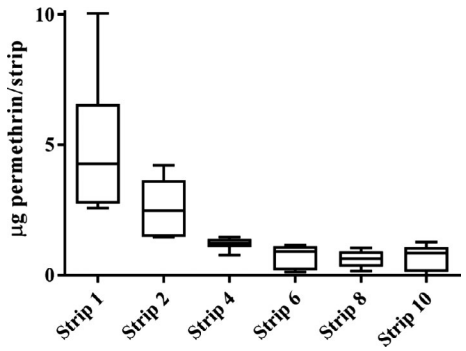

FIGURE 1 Box plot diagram illustrating a representative profile of permethrin concentrations of adhesive tape strips (μg/strip) of six dogs treated with Preventic®. On study day 0, Preventic® was applied to six dogs at a dose of 50 mg/kg. The median of the concentrations of the strips successively taken from the leg on study day 1 is shown as well as the 25% and 75% percentile and the minimum and maximum (previously unpublished data from Lüssenhop, 2011)

The mechanism of 1-methoxypropan-2-ol, which is contained in Exspot® and which is also known as propylene glycol, is described as occupying the hydrogen bonding sites and thereby reducing drug–tissue binding interactions on the skin surface that could determine vertical into or lateral transport along the skin (Thong et al., 2007). The pyrrolidone derivates which are contained in Fletic® (N-methylpyrrolidone) and Advantix® (1-methyl-2-pyrrolidone) interact with keratin in the *stratum corneum* primarily as a humectant (Kilpatrick-Liverman & Polefka, 2006) and generally with lipids in the skin. Isopropyl myristate, which is part of the Preventic® formulation, acts directly on the *stratum corneum* by permeating into liposome bilayers and thereby increasing fluidity (Thong et al., 2007).

The statistically equal distribution over the whole body could also be observed in adhesive tape strips from day 14 and day 28. However, some of the hair samples from the back showed significantly higher values than samples from the leg on day 14 and on day 28 in some of the products, which indicates that concentrations in the hair decreased faster on the legs than on the trunk.

Overall permethrin concentrations decreased over the course of the study, both in the hair and in the *stratum corneum*. This decrease in concentration very likely resulted from several factors, including natural desquamation of the *stratum corneum* which would result in permethrin being scaled off together with the corneocytes. This implication is supported by the finding that on day 28 after treatment, no permethrin was found in the lower layers of the *stratum corneum* (Figure 2). New corneocytes that did not serve as reservoir for permethrin were formed from the living epidermis. Also, dog grooming and the general abrasion by contact with the environment induced a loss of active ingredient. Metabolism in the body may have contributed to a decrease of concentration over time, although systemic bioavailability was limited.

Although the concentrations have been low towards the end of the study, a sufficient acaricidal effect could be shown in a study with ticks which was simultaneously conducted on the same dogs (Lüssenhop et al., 2011). In this part of the study, ticks of the species *Dermacentor reticulatus* were exposed to the dogs for six hours on study days 1, 14 and 28. Twenty ticks were put in specially built chambers which were attached to the back and to the hind leg in order to compare efficacy of the products on the two body parts. The chambers were always attached to the right side, and samples for the analysis of concentrations were taken from the left side. The results of this efficacy study showed an increase of attached ticks and a decrease of dead ticks over time. The median range of dead ticks in the leg chamber was 17.0–19.5 (depending on product) on day 1 and decreased to 12.5–15.0 on day 28 (Lüssenhop et al., 2011).

It is plausible that permethrin could only be detected in the hair, and the *stratum corneum* as its high lipophilicity does not enable it to be transdermally absorbed and reach detectable concentrations in the lower skin layers or even the systemic circulation (Bast & Kampffmeyer, 1996, Bast et al., 1997; Woollen et al., 1992), which was supported by a lack of any positive blood sample for permethrin in the study (Lüssenhop, 2011; Lüssenhop et al., 2012).

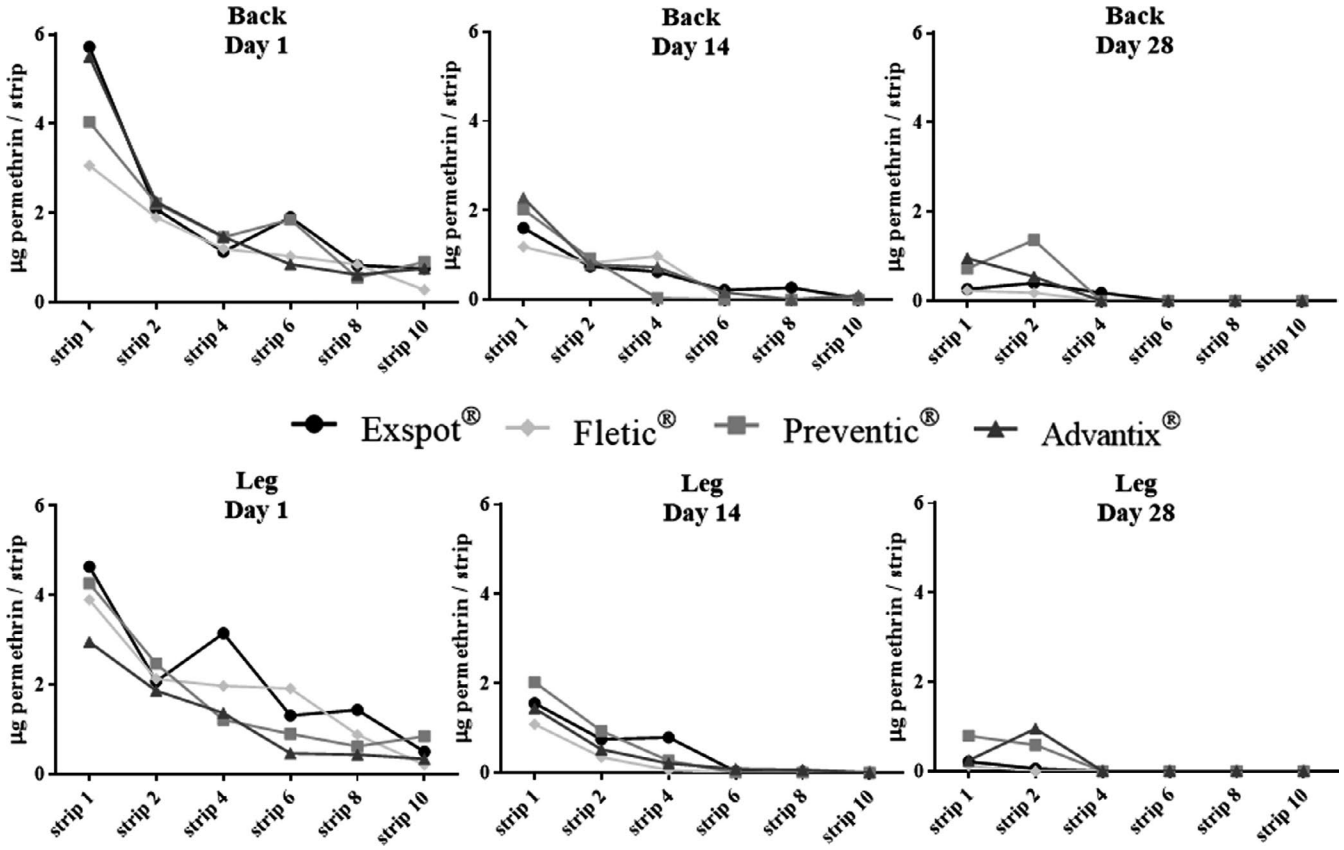

FIGURE 2 Permethrin concentration profiles of successively taken adhesive tape strip samples (µg/strip) for all permethrin containing ectoparasiticides tested. Medians (n = 6) for each commercial product on days 1, 14 and 28 post-treatment (previously unpublished data from Lüssenhop, 2011)

Additionally, Bäumer et al. (2012) reported that after six beagle dogs were exposed to a collar, impregnated with 4.5% flumethrin and 10% imidacloprid, shaved areas 5 cm from the collar and on the left hind leg were tape stripped at 24 hr, 14 and 28 days after applying the collar. At 24 hours, 20–140 ng flumethrin was recovered, but this increased to 1,000–1,200 ng in both regions after 14 and 28 days (Bäumer et al., 2012). These data are evidence of lateral transport and also continued release of the pyrethroid over time.

The above-mentioned data obtained with the collar containing flumethrin and imidacloprid confirm the comprehensive study with permethrin containing products, making lateral transport most likely for the movement of pyrethroids over the skin and coat of animals.

While there are no other related permethrin studies in the open literature for related pyrethroid lateral transport in companion animals, there are at least six other pyrethroid studies conducted in livestock animals that demonstrate lateral transport. The details of these studies are provided in Table 3 for cypermethrin, deltamethrin and flumethrin and are now discussed.

Jenkinson et al. (1986) were among the first to report the rate of movement of a pyrethroid, cypermethrin, across sheepskin (Jenkinson et al., 1986) using autoradiography of skin biopsies. This study involved the use of four sheep where ^{14}C cypermethrin was applied at a point close to the midline. Although there was significant variability between the four sheep, cypermethrin was detected in the *stratum corneum* of samples 8 cm away from the site of application at 45 and 90 min. The authors proposed that this was evidence of movement within the *stratum corneum* and that there may be involvement of the lateral movement of sweat and sebum emulsion that facilitated the transport of cypermethrin. Variability in secretions between individual sheep due to differences in skin physiology and/or epidermal structure could also support this hypothesis (Lloyd et al., 1979). The lack of vertical, systemic absorption and redistribution was supported by lack of ^{14}C detection in the dermis by autoradiography.

Further support of lateral transport is given by Johnson et al. (1996) where an aqueous formulation of α-cypermethrin (50 mg/ml) was applied to dorsal midline from neck to tail of five sheep. Data for days 14 to 98 showed that a sample site 50 mm from dorsal midline consistently had the highest concentrations (5–30 times higher) of α-cypermethrin (approximately 50–360 ppm) compared to the other two lower regions (<50 ppm). It should be noted that these five sheep were not housed individually but kept in field conditions which could explain some of the high variability reported and the apparent lateral transport of α-cypermethrin to various regions of the sheep's body.

Johnson et al. (1995) conducted a study similar to the α-cypermethrin study described above (Johnson et al., 1996); however, a xylene-based or water-based ^{14}C deltamethrin formulation (10 mg/

TABLE 3 Experimental details and results for sheep topically treated with cypermethrin or deltamethrin and cattle topically treated with flumethrin

Reference	Animal species; details on restrainment	Details on active ingredients (a.i.s)	Study group composition	Application area	Test method; sampling material	Sampling time points	Results
Cypermethrin							
Jenkinson et al. (1986)	Sheep (adult); in metabolism cage	^{14}C cypermethrin (Barricade®); 180 µl/animal	One group à four animals all treated with a.i.	Point application in centre of 40 × 20 cm clipped area at dorsal surface	Autoradiography of skin biopsies, histopathology 9 skin samples	45 and 90 min p.t. at 8 cm from application site margin and in centre of application site (only 90 min p.t.)	^{14}C a.i. in stratum corneum, around hair follicles, sebaceous glands at application site; 45 min p.t. ^{14}C a.i. in *stratum corneum*, some in hair follicle canals and epidermis at 8 cm; no presence of a.i. in dermis other than adjacent to the epidermis or hair follicles, in a few instances found more widely spread throughout *stratum papillare*, not traced in deeper dermis
Johnson et al. (1996)	Sheep (19 months; 70 mm wool staple length)	Aqueous α-cypermethrin (Vanquish®); 20 ml/animal (50 mg/ml)	One group à five animals all treated with a.i.	dorsal midline application (neck to butt of tail; 120 mm width)	high pressure liquid chromatography wool samples at 9 locations (3 × 3 cm, 50 mm from dorsal midline (backline), upper body, lower body), partly split into tip, middle and base	Days 1, 2, 4, 8, 14, 21, 28, 42, 70, 98 p.t.	Some movement from back to lower body parts 24 h p.t., wide variation in concentration; backline data most often higher than other sampling sites; partly significant differences in concentrations of tip, middle and base segments in different regions, great variation
Deltamethrin							
Johnson et al., 1995	Sheep (6–12 months; after shearing) unrestrained	^{14}C xylene-based deltamethrin (Clout®), water-based deltamethrin (Clout-S®)	Three groups à five animals, lice infested or free treated with different a.i.s	Dorsal midline according to manufacturer	high pressure liquid chromatography wool samples at 9 locations (3 × 3 cm; 10 mm from application side (backline), upper body, lower body), partly split into tip and base, skin biopsies (1 or 2), blood samples	wool samples: Days 1, 2, 4, 6, 8, 10, 14, 21, 28, 35, 42, 98 p.t. (xylene-based treatment); Days 1, 2, 4, 8, 12, 16, 21, 28, 35, 42, 56, 70, 98 p.t. (xylene-based treatment); Days 1, 2, 4, 7, 11, 14, 21, 28, 35, 42, 56, 70, 98 p.t. (water-based treatment) skin samples: first group as in wool samples; second group Days 1, 12, 28, 35, 42, 56, 70, 98	Movement of a.i. from back to lower body within 24 hr; maximum concentrations 4–5 days to develop on fleece in xylene-based treatment group, 11 days in water-based treatment group; difference in a.i. concentration at dorsal midline between different formulations; water-based formulation lower concentrations at all sites; concentrations in fleece tip significantly greater

(Continues)

TABLE 3 (Continued)

Reference	Animal species; details on restrainment	Details on active ingredients (a.i.s)	Study group composition	Application area	Test method; sampling material	Sampling time points	Results
Flumethrin							
Stendel et al. (1992)	Cattle (~400 kg, 1–2 cm hair length); unrestrained	Flumethrin (Bayticol®); 1 mg/kg b.w.	Four groups à two animals all treated with a.i.	Backline (from withers to tailbase)	Reverse phase high pressure liquid chromatography 32 hair samples (16/side) from 16 sites, 5 g hairs per analysis	Days 1, 3, 5, 10 p.t.	>0.01 µg a.i./cm^2 in general; highest concentration dorsally and ears at 1 day p.t.; decrease from lateral and ventral to distal; overall decrease on Day 3; Days 5 and 10 uniform pattern
Hamel and Van Amelsfoort (1986)	Bulls; restrained	Flumethrin in 1:1 mixture with fluorescent naphthalimide derivate; 1 mg/kg b.w.	Two individuals both treated with a.i.	Backline (from withers to tailbase)	Fluorescence, photographs; thorax, abdomen, hind quarters	2, 4, 10 hrs p.t.	Radial transport from application site; widespread fluorescence within 2–4 hrs p.t.; 2 h p.t. staining on backline, thoracal and abdominal parts, 4 h p.t. augmenting on thorax, and abdomen, plus tail brush and ears, 10 h p.t. no further spreading, but glimmer all over on back, hindquarters and shoulders
Stendel (1986)	Cattle (~440 kg, 2.5–3.5 years, 0.5 cm hair length), restrained vs. unrestrained	Flumethrin; 1 mg/kg b.w.; 21 days post-tick infestation	Two groups of *Boophilus microplus* infested cattle all treated with a.i.	Left body side, in a line 5 cm below midline	Acaricidal efficacy treated side vs. opposite side tick removal at different time points, evaluation of efficacy criterion 3–4 weeks p.t., criterion: inhibition of fertile egg deposition	1, 2, 4, 8 until 512 min p.t.	Unrestrained cattle: acaricidal efficacy within 1 min on treated side, within 4–8 min in regions with head and tail contact, within 32–64 min in regions without head and tail contact; restrained cattle: acaricidal efficacy within 1 min on treated side, within 128–256 min on untreated side

Abbreviations: a.i., active ingredient; b.w., body weight; p.t., post-treatment.

ml per formulation) was applied to the dorsal midline of fine-wool Merino sheep housed as a group in covered pens, and these sheep were shorn prior to application (Johnson et al., 1995). Instead of obtaining samples 50 mm from dorsal midline as the Johnson et al (1996) study, samples were obtained 10 mm from the midline. Deltamethrin concentrations in the blood were negligible, and there was 20–25 times more deltamethrin in the wool than the skin biopsy after 24 hr. Deltamethrin concentrations in the wool were significantly lower with the water-based formulation than the xylene-based formulation across different days, and this was the general trend across other regions of the body. This is probably the first study to demonstrate a formulation influence on the rate of lateral transport across skin.

Earlier in this review, lateral transport of flumethrin was described in dogs (Bäumer et al., 2012). Similar flumethrin lateral distribution has been reported in cattle in either restrained or unrestrained housing. Hamel and Van Amelsfoort (1986) applied flumethrin (1.0 mg/kg) to the backline of two bulls that were restrained in a squeeze chute. Using a fluorescence technique, photographs at 2, 4 and 10 hr demonstrated lateral transport from the site of application to thorax, abdomen and hindquarters. Stendel et al. (1992) applied flumethrin in the concentration of 1 mg/kg body weight along the backline of eight Holstein cattle (400 kg), housed in groups of two unrestrained cattle in boxes to allow contact. While this housing protocol could have confounded determination of lateral transport by inter-animal interaction, it did show that flumethrin was distributed to various body regions including the legs based on hair samples from 16 defined body areas 10 days after initial application (Stendel et al., 1992). Stendel (1986) similarly treated restrained cattle, but the product was applied to an area on the left side that was 5 cm below midline. Based on the acaricidal activity, flumethrin appeared to have been transported to the right side of the cattle. It should be noted that Stendel et al. (1992) in an unpublished report demonstrated that after oral or IV administration to cattle, flumethrin was not efficacious, which is strongly suggestive that activity is locally on the skin coat and not systemic.

3 | CONCLUSION

Topical pyrethroid products have been shown to be effective ectoparasiticides in veterinary species, and the scientific community hypothesized that for these products to be effective after a single topical application, there could be other mechanisms such as lateral distribution from site of application for the product to be effective at distal anatomical sites. To support a hypothesis of systemic distribution, pyrethroids must be found in the circulation postapplication. However, the data presented in this paper demonstrated that very little if any of the pyrethroids were present in the bloodstream for the various veterinary species investigated. The livestock studies demonstrated that no deltamethrin, flumethrin or α-cypermethrin was detected in the blood of respective sheep and cattle, and the canine studies demonstrated that no positive blood samples for permethrin were found at any study time point. This is also the case for flumethrin in a collar matrix, where systemic exposure was not seen or was seen in only very low levels at single time points in dogs and cats (internal data provided by Bayer Animal Health). Overall, there is a common understanding that pyrethroids in general do not necessarily penetrate through skin in a relevant amount and are not stable enough in the body to serve as systemic ectoparasiticide. Although there are potential vehicle effects that could increase or decrease skin permeation, systemic bioavailability may be limited to small percentage uptake as described earlier. A similar transport behaviour was found for flumethrin in cats, dogs and cattle, and again no or negligible concentrations of the pyrethroid were found in serum (Bäumer et al., 2012; Stendel et al., 1992). Similarly, in one of the sheep studies which used autoradiography of the skin, α-cypermethrin was not detected in the dermis and deeper skin layers or blood, but on the surface distal to site of application.

Although the above-discussed studies strongly suggest a lateral transport of pyrethroids, there is still limited conclusive evidence of the relative contributions of the *stratum corneum*, hair and eccrine secretions if a relatively small amount of topically applied pyrethroids (e.g. 715 mg permethrin in 1 ml for dogs up to 15 kg) spread to distant sites of the body within 24 hours. There is need of a better understanding of the rate of sebum movement across the skin of veterinary species and how this is affected by disease or nutritional status, assess the contribution of added solvents like pyrrolidone derivatives or isopropyl myristate and the influence of grooming behaviour. Hopefully, future studies can shed light on these data gaps for pyrethroids and other chemical classes which can be used to predict lateral transport and possible efficacy of current and new ectoparasiticides.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

The individual contributions each author, WB and RB, are specified a follows: WB involved in Abstract, Introduction, Chemical Residue Evidence of Lateral Transport, Conclusion. Figures and References. RB involved in Chemical Residue Evidence of Lateral transport, further studies supporting the view of a lateral transport, Tables and References. WB and RB have read and approved the final manuscript.

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