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Pharmacokinetic and pharmacodynamic considerations for treating sarcoptic mange with cross-relevance to Australian wildlife

Kotaro Takano [a,b], Lachlan de Hayr [a,b], Scott Carver [c], Robert J. Harvey [a,b], Kate E. Mounsey [a,b,*]

[a] School of Health, University of the Sunshine Coast, Maroochydore, Queensland, Australia
[b] Sunshine Coast Health Institute, Birtinya, QLD, Australia
[c] Department of Biological Sciences, University of Tasmania, Hobart, Tasmania, Australia

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ABSTRACT

Sarcoptes scabiei is the microscopic burrowing mite responsible for sarcoptic mange, which is reported in approximately 150 mammalian species. In Australia, sarcoptic mange affects a number of native and introduced wildlife species, is particularly severe in bare-nosed wombats (*Vombatus ursinus*) and an emerging issue in koala and quenda. There are a variety of acaricides available for the treatment of sarcoptic mange which are generally effective in eliminating mites from humans and animals in captivity. In wild populations, effective treatment is challenging, and concerns exist regarding safety, efficacy and the potential emergence of acaricide resistance. There are risks where acaricides are used intensively or inadequately, which could adversely affect treatment success rates as well as animal welfare. While reviews on epidemiology, treatment strategies, and pathogenesis of sarcoptic mange in wildlife are available, there is currently no review evaluating the use of specific acaricides in the context of their pharmacokinetic and pharmacodynamic properties, and subsequent likelihood of emerging drug resistance, particularly for Australian wildlife. This review critically evaluates acaricides that have been utilised to treat sarcoptic mange in wildlife, including dosage forms and routes, pharmacokinetics, mode of action and efficacy. We also highlight the reports of resistance of *S. scabiei* to acaricides, including clinical and *in vitro* observations.

1. Introduction

Sarcoptes scabiei is the microscopic burrowing mite responsible for the globally occurring infectious skin disease, sarcoptic mange. *S. scabiei* is known to infest approximately 150 mammalian species including humans (where it is referred to as 'scabies') (Escobar et al., 2022). Infestation with *S. scabiei* causes a spectrum of immune responses in the host resulting in severe itching, inflammation, alopecia and skin lesions. Severe sarcoptic mange is associated with a proliferation of mites and the development of thick scaly crusts on the epidermis (hyperkeratosis and/or parakeratosis) (Alasaad et al., 2012; Oleaga et al., 2012). These epidermal changes can cause skin fissuring and scratching, which cause increased susceptibility to fly strike, secondary bacterial infections, dehydration, and difficulty in thermoregulation (DeCandia et al., 2019; Næsborg-Nielsen et al., 2022).

Scabies is globally endemic in humans, especially in indigenous and developing regions where it is recognised by the World Health Organization as a Neglected Tropical Disease (World Health Organisation, 2020). Infestations of domestic and livestock animals such as dogs (Pin et al., 2006) and cattle (Visser et al., 2013) are frequently reported. There are numerous case reports of sarcoptic mange infestations in wildlife including the red fox (*Vulpes vulpes*) (Pisano et al., 2019), Spanish ibex (*Capra pyrenaica*) (León-Vizcaíno et al., 1999), raccoon dog (*Nyctereutes procyonoides*) (Sugiura et al., 2018) and cheetah (*Acinonyx jubatus*) (Gakuya et al., 2012). Since the introduction of *S. scabiei* to Australia with European settlement, this parasite has affected a range of native and introduced Australian wildlife species, including the koala (*Phascolarctos cinereus*) (Obendorf, 1983), agile wallaby (*Macropus agilis*) (McLelland and Youl, 2005), bandicoot (*Isoodon obesulus* and *I. fusciventer*) (Wicks et al., 2007; Botten et al., 2022), common ringtail possum (*Pseudocheirus peregrinus*) (Gray, 1937), and dingo (*Canis lupus dingo*) (McCarthy, 1960).

Wombats, especially the bare-nosed wombat (*Vombatus ursinus*) are particularly affected by severe sarcoptic mange. Sarcoptic mange infestations of bare-nosed wombats have been observed throughout their geographic range at varied prevalence (Martin et al., 1998; Skerratt,

* Corresponding author. School of Health, University of the Sunshine Coast, Maroochydore, Queensland, Australia.
E-mail address: kmounsey@usc.edu.au (K.E. Mounsey).

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2005). Low prevalence (0–15%) in some areas can be owing to a range of environmental and host factors independent of immunity to past outbreaks. The presence of effective immunity is untested (Beeton et al., 2019) but is suggested to occur due to the removal of susceptible individuals from the populations due to high mortality of severely infected individuals and possible protective immunity of individuals that experienced slight or moderate infections (Skerratt, 2005). However, there are studies reporting much higher disease prevalence in wombat populations in New South Wales (Hartley and English, 2005), including the Wolgan Valley (Stannard et al., 2020). The population in Narawntapu National Park, Tasmania experienced a 94% population decline in six years since an outbreak of sarcoptic mange was confirmed (Martin et al., 2018, 2019).

There are a variety of acaricides available for sarcoptic mange which are generally effective in eliminating mites from humans and animals in captivity (Fig. 1). However, in wild populations it is often difficult to effectively treat animals, which can result in the unsuccessful elimination of mites from individuals or local populations (León-Vizcaíno et al., 2001; Menzano et al., 2007; Moroni et al., 2020). Single dose acaricide treatment is usually insufficient to eliminate mites from free-ranging host animals and their populations due to a lack of ovicidal activity and short plasma half-life. Follow-up administration is thus warranted, but difficult to implement in free-ranging wildlife. Another potential cause of control failure of *S. scabiei* is the possible emergence of drug resistance that has been reported in the treatment of scabies in humans, including ivermectin and permethrin resistance (Currie et al., 2004; Mounsey et al., 2010; Pasay et al., 2006). Acaricide resistance has also been reported in other ectoparasites such as head lice (*Pediculus humanus capitis*) (Diatta et al., 2016), cattle tick (*Rhipicephalus microplus*) (Stone et al., 2014) and sheep scab mite (*Psoroptes ovis*) (Doherty et al., 2018; Sturgess-Osborne et al., 2019, 2019van Mol et al., 2020).

Despite regular reports indicating high prevalence, sarcoptic mange is rarely given priority in health programs and research, perhaps because the disease complications are spread across a broad range of disciplines including parasitology, dermatology, immunology, infectious diseases, veterinary science and disease ecology. There is currently no review evaluating the use of specific acaricides in the context of their pharmacokinetic and pharmacodynamic properties, and subsequent likelihood of emerging drug resistance, particularly for Australian wildlife. An improved understanding and new advances in the treatment and control of sarcoptic mange would play a significant role in wildlife conservation and welfare.

2. Challenges to the treatment of sarcoptic mange in wombats

The average 14-day life cycle of the mite (Mellanby, 1944; Van Neste and Lachapelle, 1981) and the fact that few acaricides demonstrate ovicidal properties mean it is unlikely that single dose treatments will completely clear infestation. Development of acaricides that also target ovicidal stages is considered a research priority (Bernigaud et al., 2020). In the absence of ovicidal drugs, it would be favourable if a single dose acaricide was retained in the host at therapeutically active concentrations for the duration of the mite lifecycle, in order to provide coverage against any newly hatched eggs. Therefore, considering the host-specific pharmacokinetics of acaricide treatments is vital.

While few studies exist, most published reports of successful mange treatment in wildlife describe capture and multiple administration of subcutaneous ivermectin injection (Rowe et al., 2019). Alternative treatment methods reported included rifle darting or oral delivery in food. These modes of administration are not currently considered logistically or ethically viable for free-living wombat populations. Moreover, it is extremely difficult to treat free-ranging animals multiple times, as this usually requires a tracking or marking system to approach or recapture targeted individuals, or enclosures to keep them in captivity for a prolonged period during treatment. Recapture and re-administration of treated animals can be low (Skerratt et al., 2004; Ruykys et al., 2013), is expensive, and could result in stress-related treatment failure or illness (Munang'andu et al., 2010; Rowe et al., 2019). Therefore, treatment success rates are lower in free-ranging individuals, affirming the need for acaricides with a longer duration of activity to allow for single dose, or fewer doses of treatment, as well as development of non-invasive administration methods. In wombats, non-invasive methods currently employed include 'burrow flaps' where pour-on treatment is administered upon burrow entry or exit, or 'pole and scoop' type methods, where the wombat is approached from a distance and topical pour-on or spot-on treatments are directly administered. These methods can be labour intensive and require substantial engagement from wildlife volunteers (Old et al., 2021). Clinical guidelines for scabies treatment in both individual and community settings often emphasise that simultaneous treatment of 'close contacts' is critical for elimination of mites, which adds to the challenge of treating free-living wombats. Another consideration with this non-invasive, topical treatment approach is that it is uncertain how much drug is actually being absorbed, and how the presence of hyperkeratosis and other skin damage, along with the overall health of the wombat, affects

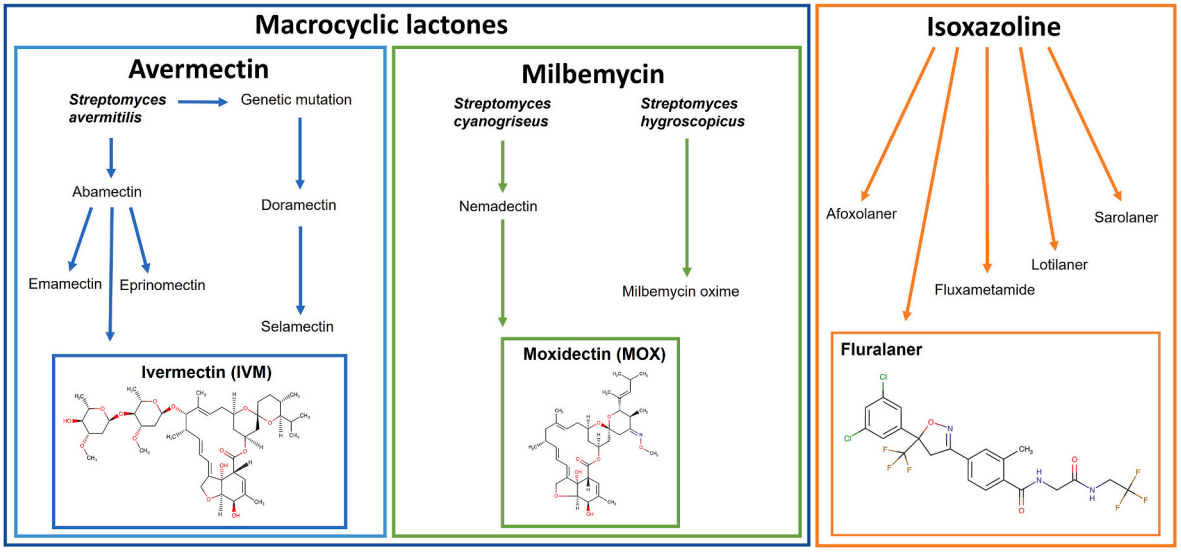

Fig. 1. Structural organisation of avermectins, milbemycins, isoxazolines, with the chemical structures of ivermectin, moxidectin, fluralaner (adapted from Prichard and Geary, 2019; Gonçalves et al., 2021).

effective drug concentration (Bains et al., 2022). Thus, there is a substantial likelihood of underdosing or overdosing with topical administration, depending on the amount administered.

As wombats are relatively solitary, but switch burrows frequently (every four to ten days) and share burrows asynchronously, environmental transmission is likely the main source of transmission (Skerratt et al., 2004; Evans, 2008; Martin et al., 2019). This is in contrast to the typical scenario of transmission by skin contact in human scabies. The environmental transmission mechanism is supported by theory and empirical observations (Beeton et al., 2019; Martin et al., 2018; Hindle et al., 2022).

Studies document female mites surviving off-host for over a week when held at 15 °C with 75% humidity, and up to 19 days at 16 °C with 97% relative humidity (reviewed in Arlian and Morgan, 2017). The conditions of low, stable temperatures and high humidity inside wombat burrows facilitate prolonged off-host survival of mites, with mites estimated to survive in wombat burrows for up to 16 days in winter compared to only five days in summer (Browne et al., 2021). This environmental reservoir, combined with short acaricide treatment half-lives in hosts suggests that even if treatment is effective at an individual level, reinfection from burrows hampers individual- and population-level control efforts.

3. Invertebrate ligand-gated chloride channels as acaricide targets

Ligand-gated chloride channels (LGCCs) in invertebrates form a superfamily including γ-aminobutyric acid (GABA) (ffrench-Constant et al., 1993), glutamate (Cully et al., 1994), histamine (Zheng et al., 2002) and pH-sensitive channels (Schnizler et al., 2005). These LGCCs have a pentameric structure, with each subunit bearing a large N-terminal extracellular ligand-binding domain, four hydrophobic α-helical transmembrane-spanning regions (TM1-TM4), with TM2 lining the ion channel pore, an intracellular loop connecting TM3 and TM4, and a small C-terminal extracellular region (Nakata et al., 2017) (Fig. 2).

LGCCs are present in the nervous system and muscle of invertebrates and play a range of critical roles in biological functions through mediation of inhibitory neurotransmission (Ortells and Lunt, 1995). Among the LGCCs in arthropods, GABA-gated chloride channels are particularly well studied as the major inhibitory receptors involved in various physiological roles including locomotion (Bloomquist, 2003), olfactory learning (Liu et al., 2007) and regulation of sleep (Agosto et al., 2008). GluCls are another well-studied member of the LGCCs. They are only found in invertebrates and involved in a range of important functions including controlling locomotion, mediating sensory input and regulating feeding via pharyngeal pumping (Wolstenholme, 2012).

LGCCs are utilised as the target site of a variety of acaricides including the macrocyclic lactones (e.g., ivermectin and moxidectin) (Forrester et al., 2002; Chen and Kubo, 2018), cyclodiene insecticides (e.g., dieldrin) (Nagata and Narahashi, 1994), phenylpyrazole-type compounds (e.g., fipronil) (Ikeda et al., 2003) and isoxazolines (e.g., fluralaner) (Weber and Selzer, 2016). Thus, understanding the LGCC gene complement and receptor-ligand interactions is highly relevant when considering the activity of these acaricides in *S. scabiei* and their potential contribution to treatment failure and drug resistance. In the following section, we will discuss relevant treatments for sarcoptic mange in wildlife, and what is known about the interactions of these treatments with corresponding LGCC targets.

4. Acaricides targeting LGCCs used for the treatment of sarcoptic mange in wildlife

Acaricides that have been used to treat sarcoptic mange in Australian wildlife include malathion (Barker, 1974), amitraz (Brown et al., 1982), ivermectin (Skerratt, 2003), moxidectin (Martin et al., 2019), selamectin (McLelland and Youl, 2005) and fluralaner (Wilkinson et al., 2021). While ivermectin has been frequently used as highlighted by Rowe et al. (2019), moxidectin and fluralaner are the currently approved acaricides for sarcoptic mange in wombats by the Australian Pesticides and Veterinary Management Authority (APVMA). This

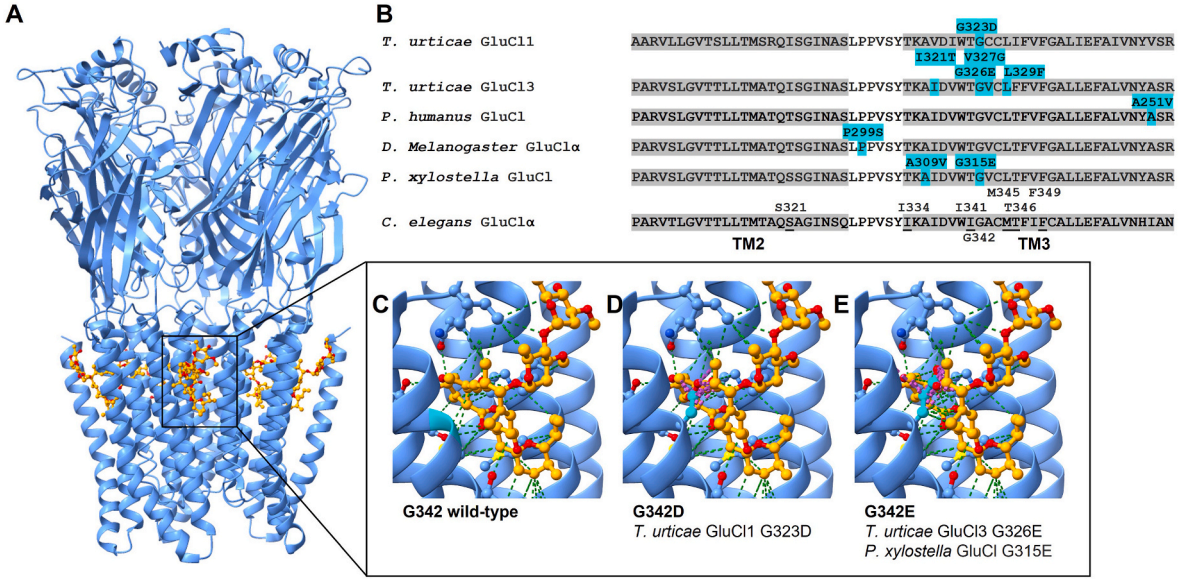

Fig. 2. A, Crystal structure of *Caenorhabditis elegans* glutamate-gated chloride channel (GluCl), side view, bound to ivermectin (Hibbs and Gouaux, 2011; PDB: 3RHW) visualised using ChimeraX. B, Multiple sequence alignment of transmembrane domains 2 and 3 (grey shading) showing resistance-associated mutations (blue highlighting) in GluCls from selected arthropods including *Tetranychus urticae* GluCl1 (XP_025018486.1) and GluCl3 (NP_001310061.1); *Pediculus humanus* GluCl (EEB17068); *Drosophila melanogaster* GluClα (NP_001163656.2), *Plutella xylostella* GluCl (XP_011555227.1), aligned to *C. elegans* GluClα (AAA50785.1). *T. urticae* and *P. xylostella* have several mutations clustered around the TM3 residues associated with IVM binding (underlined). C, The G342 site (cyan) in the wild-type *C. elegans* GluCl crystal structure is close to the ivermectin binding pocket. D and E, Substitution of this corresponding residue with the resistance-conferring substitutions G323D or G326E results in side-chain protrusion and resulting clashes with ivermectin (pink dashes) that are predicted to disrupt binding. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

section evaluates dosage forms and routes, efficacy, mode of action, and pharmacokinetics of the most common acaricides currently used.

4.1. Macrocyclic lactones

The macrocyclic lactones are a class of broad spectrum antiparasitic drugs with medical, veterinary and agricultural use globally. The family of macrocyclic lactones is divided into the avermectins and milbemycins, which share a similar chemical structure (Fig. 1). The parent compound avermectin was first isolated in 1978 from *Streptomyces avermitilis* sampled from the soil in Japan (Crump and Ōmura, 2011). The discovery and subsequent synthesis of ivermectin by Satoshi Ōmura of Kitasato University and William Campbell of Merck resulted in the 2015 Nobel Prize in Physiology or Medicine for use in the treatment of river blindness and lymphatic filariasis, as well as broad spectrum parasiticidal activities (Crump and Ōmura, 2011). Since ivermectin was introduced onto the market as Ivomec® (1% w/v ivermectin) in 1981, a number of other avermectin-based products have been developed, including doramectin, abamectin and selamectin. Second generation macrocyclic lactones include the milbemycins, consisting of moxidectin, nemadectin and mibemycin. Of the macrocyclic lactones, ivermectin and moxidectin are of the highest relevance to the treatment of sarcoptic mange in wombats.

4.1.1. Ivermectin

4.1.1.1. Mode of administration and clinical efficacy. Ivermectin is a semi-synthetic, chemically modified avermectin. Originally developed for subcutaneous administration for control of cattle nematode parasites, it is also available as oral and topical formulations (Crump and Ōmura, 2011). Ivermectin is generally used at concentrations ranging from 200 to 500 μg/kg for *S. scabiei* and is available in a range of formulations.

Orally-administered ivermectin was first used on compassionate grounds in humans with crusted scabies, a condition similar to sarcoptic mange in wombats, where treatment failures were commonly observed with topical therapies (Currie et al., 2004). Several studies show the inadequacy of single-dose oral ivermectin, due to a lack of ovicidal effect (Rosumeck et al., 2018; Bernigaud et al., 2020). Multiple doses are thus required for crusted scabies, and even in mild cases a second dose, one week after the first dose, is recommended to cover the life cycle of mites (Currie and McCarthy, 2010). Ivermectin has been extensively used for community-scale control of human scabies and in institutional settings. A trial using 200 μg/kg of oral ivermectin in Fiji showed a 94% reduction in scabies prevalence in the 716 participants (Romani et al., 2015). These results are consistent with the other mass treatment programs in Papua New Guinea and the Solomon Islands, both resulting in a significant and sustained decline in the scabies prevalence (Bockarie et al., 2000; Lawrence et al., 2005). Mass drug administration to control scabies using ivermectin has also been conducted in Aboriginal communities in Northern Territory, Australia. As reported in Kearns et al. (2015), the administration of two doses of oral ivermectin in up to 1000 participants, resulted in a reduction in scabies prevalence from 4% to 1% at six months post-administration, but increased to 9% at 12-months post administration. This failure to achieve sustained reduction in prevalence is in contrast to the Fiji experience. This discrepancy may be due to high population mobility between communities or the effect of localised outbreaks potentially involving “core transmitter” crusted scabies patients. However, ivermectin is now increasingly used in the treatment of scabies globally and has been shown to be effective in patients with permethrin-resistant scabies (Balestri et al., 2022). Such experiences can be informative to the design and/or interpretation of population control strategies for sarcoptic mange in wombats.

A systematic review by Rowe et al. (2019) found that subcutaneous injection of ivermectin at a dose of 200–400 μg/kg, with a median of two doses, has been the most commonly used administration route for sarcoptic mange treatment in captive and free-ranging animals. This review found little consensus between dose concentration (e.g., 200 vs 400 μg/kg) and overall treatment success. However, multiple treatments increased the recovery rate of infected animals, especially for severely infested animals, which is in line with the use of ivermectin in humans with crusted scabies (Rowe et al., 2019; Davis et al., 2013). Skerratt (2003) found that experimentally infested bare-nosed wombats treated with three subcutaneous injections of ivermectin at a dose of 300 μg/kg with 10-day intervals had a complete recovery from sarcoptic mange by day 63 post-treatment. Successful treatments of sarcoptic mange using the same treatment regimen have been reported in several other species of Australian fauna including the agile wallaby (McLelland and Youl, 2005), koala (Speight et al., 2017), and Southern hairy-nosed wombat (*Lasiorhinus latifrons*) (Ruykys et al., 2013).

4.1.1.2. Pharmacodynamics. The macrocyclic lactones act as agonists of LGCCs, where they bind irreversibly, leading to an influx of chloride ions and hyperpolarization. Ivermectin has high affinity for glutamate-gated chloride channels (GluCls), which are specific to invertebrates and abundant in nematode pharyngeal muscle cells and arthropod motor neurons (Bloomquist, 2003). GluCls are expressed in tissues showing a high sensitivity to low ivermectin doses, and recombinant GluCls have a high sensitivity to ivermectin (the EC_{50} in nematodes is in the nanomolar range) (Cully et al., 1994). GluCl mutants also result in reduced ivermectin sensitivity (Kwon et al., 2010; Ghosh et al., 2012; Wolstenholme and Rogers, 2005). In *Caenorhabditis elegans*, the interactions of ivermectin with GluCls have been demonstrated through inhibition of pharyngeal pumping and related-muscle paralysis mediated through GluCls in the motor and pharynx and motor nerves (Dent et al., 1997, 2000; Cook et al., 2006). Similar results indicating that GluCls are the major ivermectin target site have been reported in arthropods including spider mites (*Tetranychus urticae*) (Kwon et al., 2010) and the diamondback moth (*Plutella xylostella*) (Liu et al., 2014). Hibbs and Gouaux (2011) were the first to model the molecular interaction of ivermectin by solving the 3D structure of a *Caenorhabditis elegans* GluCl subunit (Hibbs and Gouaux, 2011; PDB: 3RHW, Fig. 2). This structure demonstrated that ivermectin inserts into the ion channel pore lined by transmembrane domains between subunits, with most contact with residues in the TM2 and TM2-TM3 loop regions. The binding of ivermectin is proposed to open the space between TM2 and TM3, displacing TM2 and resulting in a permanently open ion channel conformation (Fig. 2).

Although ivermectin is understood to mainly act on GluCls, it also interacts with invertebrate GABA-gated chloride channels. In fact, initial studies suggested that the main target site of ivermectin was GABA receptor (reviewed in Xu et al., 2017) prior to the molecular characterisation of GluCls. For instance, in Fritz et al. (1979), excitatory and inhibitory postsynaptic potentials in *Homarus americanus* (American lobster) were observed to be blocked by abamectin, suggesting that GABA-gated chloride channels were involved in the inhibitory effect. Irreversible inhibition of GABA-activated currents by ivermectin was also observed in *C. elegans*, which also emphasised the role of GABA-gated chloride channels as a secondary target site of the drug (Hernando and Bouzat, 2014). A more recent study found that ivermectin and milbemycin act as agonists on the *D. melanogaster Resistance to dieldrin* (Rdl) GABA-R subunit (Nakao et al., 2015). RNAi experiments that silenced multiple Rdl GABA-R versus GluCl genes independently in *Tetranychus cinnabarinus* suggested that both receptor subtypes were associated with the acaricidal activity of abamectin (Xu et al., 2017). Electrophysiological assays suggested that GluCls were the more likely target, with 10 μM of abamectin or ivermectin activating GluCls, but not GABA-Rs (Xu et al., 2017). However, higher concentrations of these drugs were not tested in this system.

These results strongly support the hypothesis that ivermectin can activate both glutamate- and GABA-gated chloride channels in

invertebrates. As well as GluCl and GABA-Rs, macrocyclic lactones are also known to interact with other invertebrate ligand-gated chloride channels including histamine-gated chloride channels (HisCls; Zheng et al., 2002) and the pH-gated chloride channels (pHCls; Nakatani et al., 2016). In *S. scabiei* a pHCl has been functionally characterised and found to be irreversibly activated by ivermectin (Mounsey et al., 2007). Recent genome sequencing has revealed a broad range of LGCCs in *S. scabiei,* including several GluCls and Rdl-like GABA-Rs (Korhonen et al., 2020). Due to the apparent variation in responses between channels of different target organisms, specific functional analysis of *S. scabiei* LGCCs will be required to fully elucidate which of these LGCCs represent the major targets for known acaricides.

The high safety margin of ivermectin is often attributed to the fact that the drug is selective to invertebrate LGCCs. However, it is important to recognise macrocyclic lactones can indeed potentiate vertebrate LGCCs. Ivermectin was found to potentiate recombinant human glycine receptors at low concentrations and was an irreversible agonist at concentrations >0.3 μM (Shan et al., 2001). Ivermectin also binds to and potentiates several mammalian $GABA_AR$ subtypes, including the major isoform α1β2γ2L at low micromolar concentrations (Adelsberger et al., 2000; Dawson et al., 2000; Ménez et al., 2012; Estrada-Mondragon and Lynch, 2015), which may be relevant in the case of high doses and/or impairment of the mammalian blood brain barrier.

4.1.1.3. Pharmacokinetics. Ivermectin is highly lipophilic and has poor solubility in water. Ivermectin is metabolised in the liver by cytochrome P450 and metabolites excreted in faeces (Zeng et al., 1998). The pharmacokinetics of ivermectin has been studied in humans and several domestic and livestock species (Table 1), but not in wombats. Considerable variation is observed between species and route of administration (oral, topical or subcutaneous injection). Absorption of orally administered ivermectin, as determined by maximum concentration in plasma (C_{max}) was similar between humans, dogs and cattle (ranging from 28.7 to 132.6 ng/mL following a standard 150–300 μg/kg dose). Compared to cattle and dogs, humans absorb and eliminate ivermectin more rapidly (half-life ($T_{1/2}$) of 15–27 h (0.21–1.53 days) in humans, compared to 198 h (3.44 days) in cattle. The pharmacokinetics of ivermectin administered via feed were recently evaluated in Iberian ibex *(C. pyrenaica)* with a $T_{1/2}$ of <48 h (Moroni et al., 2022). Thus, while ivermectin generally shows the high efficacy against *S. scabiei,* due to its short retention time, multiple treatments are needed to ensure the elimination of newly hatched mites (Rosumeck et al., 2018).

Administration of subcutaneous injection of ivermectin at 200 μg/kg results in a significantly longer half-life compared to the oral route (Table 1). Subcutaneous injection of ivermectin has been well studied in cattle, with substantial variation observed. This may be possible due to the differences in breed, smaller sample size or erratic absorption from

Table 1
Comparative pharmacokinetic parameters of ivermectin, moxidectin and fluralaner in selected species.

Drug	Host	Route	Dose (μg/kg)	C_{max} (ng/ml)	T_{max} (days)	$T_{1/2}$ (days)	AUC (ng.day/ml)
Ivermectin	**Human**	Oral[b,c,d,e]	150-300[a]	30.4–81	0.14–0.43	0.21–1.53	36.9–229.2
		Topical[f]	185	0.2	0.66	2.10	0.3
	Dog	Oral[g,h,i]	100–250	44.3–132.6	0.17–0.23	3.32–3.35	41.7–236.8
		Subcutaneous injection[i]	200	66.8	1.40	3.19	349.2
	Cattle	Oral[j]	200	28.7	1.62	3.44	132
		Topical[k]	500	12.2	3.4	5.3	121.5
		Subcutaneous injection[l]	200	44.49	6.25	6.17	590.3
Moxidectin	**Human**	Oral[m,n,o,p]	100-600[a]	53.6–296	0.08–0.22	20.20–47.46	126–624
	Dog	Oral[h,q,r]	200–1000	95.8–649	0.08–0.2	12.7–25.89	45.5–191.3
	Cattle	Topical[s]	500	2.3	5	8.95	21.7
		Subcutaneous injection[t,u]	200–1000	39.4–136	0.32–0.4	9.18–14.5	164.0–88
	Southern Hairy-nosed wombat	Subcutaneous injection[v]	200	98.6	0.56	5.03	377
Fluralaner	**Dog**	Oral[w]	25	3948	1	12	46115
		Topical[x]	25–50	727–1698	25	17–21	41243-85852
	Bare-nosed wombat	Topical[y]	25–85	6.2–16.4	3–3.75	40.10–166.5	152.9–516.8

C_{max}: Peak plasma concentration; T_{max}: Time to reach C_{max}; AUC: Area under curve; $T_{1/2}$: Time to reach half of C_{max}.

[a] Dose converted to μg/kg, presumed at 65 kg.
[b] Krishna and Klotz (1993).
[c] Edwards et al. (1988).
[d] Baraka et al. (1996).
[e] Smit et al. (2019).
[f] Hazan et al. (2013).
[g] Daurio et al. (1992).
[h] Al-Azzam et al. (2007).
[i] Gokbulut et al. (2006).
[j] Canton et al. (2018).
[k] Gayrard et al. (1999).
[l] Gotardo et al. (2020).
[m] Cotreau et al. (2003).
[n] Tan et al. (2022).
[o] Korth-Bradley et al. (2012a).
[p] Korth-Bradley et al. (2012b).
[q] Lespine et al. (2006).
[r] Vanapalli et al. (2002).
[s] Sallovitz et al. (2002).
[t] Fazzio et al. (2019).
[u] Lanusse et al. (1997).
[v] Death et al. (2011).
[w] Kilp et al. (2014).
[x] Kilp et al. (2016).
[y] Wilkinson et al. (2021).

the injected area (González-Canga et al., 2009). There is currently one study documenting the pharmacokinetics of topical ivermectin in cattle. Although it showed similar pharmacokinetic characteristics to those of subcutaneous injection, significantly lower absorption was reported, reflected by a three-fold lower mean C_{max} (12.2 ng/ml) and five-fold lower AUC (115.5 ng.day/ml) (Gayrard et al., 1999) (Table 1). However, an increased absorption of topical administration due to licking behaviour of cattle can lead to oral ingestion of topical ivermectin, which can result in neurotoxicity (Laffont et al., 2001).

The correlations between mode of administration, drug serum levels and efficacy are not straightforward. Due to the lipophilic nature of macrocyclic lactones, these drugs can deposit in adipose tissue and skin, and be redistributed to blood over time (McKellar and Gokbulut, 2012). Thus, differences in pharmacokinetics between species may reflect different levels of deposition in subcutaneous fat, which may explain persistence in cattle compared to humans and dogs. In humans, bioavailability of oral ivermectin is enhanced when consumed with a fatty meal (Miyajima et al., 2016). While most pharmacokinetic studies only measure plasma levels, when considering the efficacy of an acaricide, it is also important to take other body sites into consideration (Prichard et al., 2012). *S. scabiei* mites reside in the stratum corneum of skin and do not directly feed off blood. Thus, the distribution of, and concentrations of drug in the skin is of relevance as well as the levels circulating in the blood (Lifschitz et al., 2018; Bernigaud et al., 2018). One study on a limited number of scabies patients confirmed that oral administration of ivermectin resulted in distribution to the skin surface at concentrations equivalent to plasma (Haas, 2002). Concentrations increased in oiler regions of skin owing to the lipophilic nature of ivermectin. While the above studies concur that injection, followed by oral, then topical administration resulted in the highest plasma C_{max}, for some ectoparasites topical pour-on administration may be preferential due to higher concentrations observed in the skin relative to plasma (Chick et al., 1993). Indeed, one study found *S. scabiei* var. *bovis* were more effectively controlled by pour-on formulations of ivermectin (Benz et al., 1989).

4.1.1.4. Safety. The macrocyclic lactones have a high safety margin, primarily due to the expression of mammalian P-glycoproteins (P-gps), of which ivermectin is a substrate. P-gps normally prevent ivermectin crossing the blood-brain barrier and binding to $GABA_A$Rs, where it could otherwise cause neurotoxicity (Dawson et al., 2000; Finch and Pillans, 2014). While billions of doses of ivermectin have been administered with relatively few severe adverse events, there are reports of neurotoxicity of ivermectin in mammals receiving high doses, or in those with P-gp deficiency. P-gps are encoded by the *mdr1* gene, and the association between P-gps and ivermectin toxicity was first observed in *mdr1a* deficient mice receiving ivermectin for mite infestation (Schinkel et al., 1994). Dog breeds with a 4-bp deletion mutation in the *mdr1* gene such as the Collie and Australian Shepherd express a non-functional P-gps, thus dogs carrying the homozygous mutation are susceptible to neurotoxicity due to the increased penetration and accumulation of macrocyclic lactones into the brain. P-gp deficient dogs administered with standard 0.2 mg/kg dose of ivermectin show severe clinical signs of neurotoxicosis including ataxia, depression, tremor and somnolence (Hopper et al., 2002; Geyer and Janko, 2012).

In humans, reports of neurotoxicity are rare, even with administration up to 10-times the usual oral dose (Guzzo et al., 2002). However, the accumulation of ivermectin in the brain tissue due to intensive overdoses (over 100-fold of the standard dose) can result in coma and death (Chung et al., 1999; Sung et al., 2009). For some filarial infections such as *Loa loa,* adverse events following ivermectin treatment primarily relate to an immune hypersensitivity response to release of parasite antigens, referred to as 'Mazzotti' reactions (Boussinesq et al., 2003). There are isolated reports of Mazzotti-type reactions occurring in crusted scabies patients (Ito, 2013). Interestingly, severe adverse events unrelated to Mazzotti reactions (confusion, lethargy, incontinence and coma) were also observed after standard ivermectin treatment (0.15 mg/kg) in a small number of individuals with *Loa loa* infection, that was suggested to be associated with *mdr-1* polymorphism possibly altering drug distribution (Bourguinat et al., 2010). Recently, there have been cases of inappropriate ivermectin use for the treatment of COVID-19 infection, which resulted in neurotoxicity in a patient after being exposed to oral (5 tablets of 3 mg ivermectin every 8 h) and intravenous ivermectin (20 mg/2 mL of veterinary ivermectin) (Porubcin et al., 2022). Due to the overdose of ivermectin, the patient required admission to the intensive care unit.

Most studies of ivermectin safety and pharmacokinetics consider the usual modes of treatment for nematodes, where low concentrations and infrequent treatment (e.g., annual or biannual) is customary. However, there are some diseases such as disseminated strongyloidiasis, severe crusted scabies and demodicosis where more intensive treatments are required. There are several reports of encephalopathy after repeated ivermectin treatment in *Strongyloides* hyperinfection (Donadello et al., 2013). Fluctuations in plasma ivermectin concentrations, namely increases post treatment, were observed, indicating that careful monitoring of plasma concentrations was required. Significant accumulation of ivermectin in the brain (30 ng/g), coma and death were noted in a patient 14 days post daily ivermectin treatment (van Westerloo et al., 2014). Notably, this patient did not have any *mdr1* mutations to suggest impairment to P-gp function.

4.1.2. Moxidectin

4.1.2.1. Mode of administration and clinical efficacy. Moxidectin is a semi-synthetic milbemycin macrocyclic lactone derived from nemadectin, which was obtained from fermentation of *Streptomyces cyanogriseus* (Fig. 1) (Shoop et al., 1995). Like ivermectin, moxidectin has broad spectrum activity against nematodes and arthropods, including *S. scabiei.* Originally developed as an injectable formulation for cattle in 1989, moxidectin is now globally marketed as Advocate® spot on (imidacloprid 10% and moxidectin 1%), Equest® oral paste (19.5 mg/g moxidectin and 121.7 mg/g of praziquantel) and Cydectin® pour on (5 mg/mL moxidectin) (Williams et al., 1992; Pullium et al., 2005; Cobb and Boeckh, 2009; Le Sueur et al., 2010). Oral moxidectin is currently undergoing phase II clinical trials as an alternative to ivermectin for human scabies (ClinicalTrials.gov, 2022).

Early studies documented the high efficacy of a single moxidectin subcutaneous injection at 0.2 mg/kg against *S. scabiei* in cattle, achieving a 100% recovery rate at day 14 (Losson and Lonneux, 1993). In sheep, two moxidectin injections at 0.2 mg/kg were required to achieve complete elimination of mites, with a single dose resulting in 75–92% of mite reduction (Fthenakis et al., 2000; Hidalgo Argüello et al., 2001). Bernigaud et al. (2016) compared the efficacy of orally administrated ivermectin (0.2 mg/kg, twice) and moxidectin (0.3 mg/kg once) in pigs experimentally infested with *S. scabiei,* with moxidectin demonstrating 100% efficacy, compared to 62% efficacy with ivermectin. This result was consistent with *in vitro* assays showing a lower EC_{50} (concentration required to kill of 50% of mites) of moxidectin relative to ivermectin (Mounsey et al., 2017). While the studies above show that one or two doses of moxidectin were sufficient to clear infestation, in llamas, alpacas, and camelids, multiple administrations were required over many weeks to achieve complete elimination of mites (Beck, 2020). Similarly, in Wagner and Wendlberger (2000), 41 dogs with sarcoptic mange were treated with moxidectin at 0.2–0.25 mg/kg weekly either orally or subcutaneously with most requiring three to six administrations to clear infestation. These results are consistent with the fact that like ivermectin, moxidectin has no demonstrated ovicidal activity against the eggs of *S. scabiei* (Bernigaud et al., 2020).

Moxidectin is approved by the Australian Pesticides and Veterinary Medicines Authority (APVMA) under a minor use permit for the

treatment of sarcoptic mange in wombats, although there have been no formal studies evaluating either clinical efficacy or safety in this species. Moxidectin has recently been utilised for a population-scale control program of sarcoptic mange in bare-nosed wombat in Narawntapu National Park, Tasmania (Martin et al., 2018, 2019). In this study, 'burrow flaps' were deployed to dispense 5 mL of moxidectin (~0.6–1 mg/kg) topically onto animals on burrow entry or exit. This study concluded that although the treatment showed success against sarcoptic mange in individuals and in the population during and after the 12 week-treatment program, it was ineffective as a long-term method at either an individual or population scale, due to reinfection from burrows, possible incomplete treatment coverage, and insufficient bioavailability in animals over the mite life cycle. Considering the epizootic events occurring at Narawntapu National Park, it is likely the environmental load of mites was high during this trial.

In addition to the burrow flap method, direct 'pole and scoop' application of moxidectin is utilised extensively by wildlife volunteers, with a recent survey undertaken to capture usage patterns and perceptions of efficacy (Old et al., 2021). Treatment regimens varied dramatically with regards to both dose volume (4–200 mL) and numbers of doses (1–21 treatments). Respondents identified concerns regarding treatment failure using low doses and noted the difficulty of administering repeated treatment of animals that are frequently lost to follow up. Despite perceptions of suboptimal treatment response, the study authors found no association between increased dose volumes and improved treatment outcome. Recently, the APVMA approved additional minor use permits for increased dose volumes from 20 mL (~4 mg/kg) to 100 mL (~20 mg/kg in a 25 kg animal). The use of the latter exceptionally high dose in wombats has raised questions regarding safety, environmental toxicological impacts, and whether mite resistance is emerging in these populations (Lumaret et al., 2012; Mesa et al., 2018; Mounsey et al., 2022).

4.1.2.2. Pharmacodynamics. Although the efficacy of milbemycins have been studied for over two decades, there is only a limited knowledge on their specific mode of action, compared to that of the avermectins (Shoop et al., 1995; Cobb and Boeckh, 2009). Although both ivermectin and moxidectin act on GluCls, there are differences in the manner of their interaction with these channels, and these vary between target organisms and the presence or absence of the endogenous ligand (reviewed in Prichard et al., 2012). It is therefore difficult to make inferences on the activity of moxidectin due to substantial variation between target organisms. Numerous studies report cross-resistance to ivermectin and moxidectin in nematode species including, *Cooperia* spp. (Geurden et al., 2015), *C. elegans* (Ménez et al., 2016), and *Teladorsagia circumcincta* (Paraud et al., 2016). On the other hand, there are studies documenting the effectiveness of moxidectin in a range of ivermectin-resistant parasites including *Haemonchus contortus* (Craig et al., 1992; Prichard and Geary, 2019) suggesting different binding sites, receptor sequences, and/or number of receptor targets may exist in these species. Molecular modelling suggests that some, but not all binding sites on the *C. elegans* GluCl are retained when moxidectin was substituted for ivermectin (Hibbs and Gouaux, 2011), which may explain why cross resistance is not always observed between these drugs.

In arthropods, differences between the activities of moxidectin and ivermectin are more apparent. Moxidectin has limited activity against ivermectin-sensitive mosquito species including *Anopheles farauti* (Pasay et al., 2019), *Anopheles arabiensis* and *Anopheles gambiae* (Fritz et al., 2009, 2012; Butters et al., 2012). The low efficacy of moxidectin is also reported in bed bugs (*Cimex lectularius*) (Zha et al., 2017). It is well established that moxidectin has limited activity against ivermectin-sensitive dung beetles (Hempel et al., 2006, Verdú et al., 2018) making it a preferable choice for the treatment of cattle to minimise ecological impacts on beneficial arthropods. In contrast to these findings in some arthropods, moxidectin has efficacy on the *S. scabiei* mite both *in vivo* (summarised above) and *in vitro* (Mounsey et al., 2017) There have been virtually no studies looking that the comparative distribution of LGCCs in different arthropods to account for these differences in moxidectin sensitivity, or functional expression of arthropod LGCCs with moxidectin.

Ivermectin and moxidectin are known to have a different degree of interaction with P-gps as well as other multidrug resistance transporters (Prichard et al., 2012). While ivermectin is a potent substrate of P-gp and interferes with its transport activity, moxidectin is proposed to be a poor substrate of this transporter, and thus may be less susceptible to elimination from the target parasite, when compared to ivermectin (Lespine et al., 2007; Ballent et al., 2014). This is evidenced by the lower transport rate of radiolabelled moxidectin, compared to ivermectin and selamectin in canine peripheral lymphocytes and human intestinal epithelial cell cultures (Lespine et al., 2007). Kiki-Mvouaka et al. (2010) compared the brain concentration, plasma kinetics and intestinal excretion of ivermectin, eprinomectin and moxidectin in wild-type and P-gp deficient mice. In the P-gp deficient mice, increased plasma concentrations of ivermectin and eprinomectin were observed, whereas that of moxidectin was unchanged, suggesting P-gp independent transport mechanism for moxidectin. These results are consistent with Lespine et al. (2007) demonstrating a lower transport rate of moxidectin.

4.1.2.3. Pharmacokinetics. Moxidectin has a superior pharmacokinetic profile compared to ivermectin in most animals, including humans, due to its rapid absorption, high volume of distribution and longer half-life (Table 1). In cattle, topical moxidectin was documented to have a significantly lower systematic bioavailability compared to that of subcutaneous injection, reflected by a decreased C_{max} (2.3 ng/ml) and AUC (21.7 ng d/ml). Although there is no significant difference in the mean C_{max} between the subcutaneous injection of moxidectin and ivermectin in cattle, the half-life of moxidectin is substantially longer. This prolonged retention relates to the formation of drug deposits in skin and adipose tissue, followed by sustained release into the circulation. This is supported by Bernigaud et al. (2016) where moxidectin remained detectable in the skin and plasma of pigs for 47 days post-administration, whereas ivermectin was undetectable after 12 days.

Like the experience with ivermectin, pour-on moxidectin shows higher efficacy for ectoparasites compared to other routes of administration in several host animals. Losson and Lonneux (1996) found that pour-on moxidectin had higher efficacy than subcutaneous administration against skin feeding *Psoroptes ovis, Damalinia. bovis* and *Chorioptes bovis.* In contrast, both pour-on (0.5 mg/kg) and injectable formulations were equally efficacious on blood-feeding lice (*Linognathus vituli*) (Chick et al., 1993). This shows that regardless of lower systemic absorption, pour-on formulations were effective against these ectoparasites and were likely retained at sufficiently therapeutic concentrations in the skin. The impact of pour-on delivery and drug distribution to highly keratotic skin crusts have not been determined but is of considerable relevance for the treatment of severe sarcoptic mange.

Death et al. (2011) examined pharmacokinetics of a single subcutaneous injection of 0.2 mg/kg moxidectin in Southern hairy-nosed wombats. In this study, moxidectin was readily absorbed in the plasma shown by the C_{max} (98.6 ng/ml), with a half-life of five days. Although the C_{max} was higher compared to that of other mammals (Table 1), the considerably shorter half-life indicates that multiple administrations of moxidectin in wombats with sarcoptic mange are required to cover the life cycle of mites and achieve complete elimination of infestation. However, interpretation of this study is limited in that subcutaneous injection is not the routinely used administration method for wombats, and concentrations of moxidectin in the skin were not evaluated.

4.1.2.4. Safety. Moxidectin has a wider margin of safety than ivermectin, primarily due to its reduced interactions with P-gp and apparent reduced affinity for mammalian CNS $GABA_A$Rs. On recombinant α1β2γ2 $GABA_A$Rs, maximum potentiation caused by ivermectin and moxidectin relative to GABA alone was approximately 414% versus 257%, demonstrating that ivermectin causes a greater potentiation for this subtype (Ménez et al., 2012). In P-gp deficient dogs showing a high sensitivity to oral ivermectin at 120 μg/kg, a similar molar concentration of oral moxidectin showed no toxicological signs (Paul et al., 2000). Furthermore, P-gp-deficient dogs observed to be ivermectin sensitive demonstrated no signs of toxicosis even after repeated exposure at 100 μg/kg for seven days (Geyer et al., 2005). Moxidectin has been used as a safe treatment in P-gp-deficient collies administered up to 6.5 mg/kg in a topical spot-on solution (Paul et al., 2004). Even though moxidectin is detected in brain tissue, the difference in the risk of neurotoxicity between the two drugs is most likely associated with their differential interactions with the mammalian $GABA_A$Rs and differences in the accumulation of ivermectin and moxidectin in the brain (Ménez et al., 2012).

Despite the higher safety margin of moxidectin demonstrated in ivermectin-sensitive dog breeds, there are several studies documenting neurotoxicity in collie and other breeds of dogs exposed to oral moxidectin contained in equine dewormer, which has palatability to dogs. Moxidectin overdose in dogs causes similar symptoms of neurotoxicity to ivermectin (Ménez et al., 2012). Beal et al. (1999) reported ataxia, lethargy and seizures in a Border Collie that orally ingested an unknown volume of moxidectin. Another case study described vomiting and the development of tremors, ataxia and hyperaesthesia due to the ingestion of moxidectin at a concentration of at least 25 mg/kg (Snowden et al., 2006). Three dogs with no *mdr-1* mutation were reported to show clinical signs of neurotoxicity including muscle tremors, ataxia, disorientation, salivation and temporal blindness after ingestion of moxidectin at low doses of 1.9–2.8 mg/kg (See et al., 2009). Beagle dogs orally administered with moxidectin at 2–4 mg/kg every 24-h showed clinical signs of neurotoxicity including depression, ataxia and tremor within five days, with some long-term effects including salivation, tremor, lacrimation and depression (Joint FAO/WHO Expert Committee on Food Additives, 1996). Thus, these studies suggest moxidectin can also cause neurotoxicity in dogs when administered at high doses, and caution is advised in its use where the safety of high doses has not been assessed, including in wombats. Moxidectin toxicosis in dogs has been successfully treated with lipid infusion (Crandell and Weinberg, 2009; Bates et al., 2013).

4.2. Isoxazolines

Isoxazolines are a potent new class of insecticide, first described in 2010 (A1443, fluralaner) by Nissan Chemical Industries (Ozoe et al., 2010) and DuPont (afoxolaner, Shoop et al., 2014). Their development has been described as a "groundbreaking success story of the 21st Century" (Selzer and Epe, 2021). The isoxazoline family currently includes four marketed compounds, listed in order of commercial development - afoxolaner (NexGard®), fluralaner (Bravecto®), sarolaner (Simparica®) and lotilaner (Credelio®). These are available alone or in combination with other products such as with milbemycin (Nexgard spectra®), or moxidectin (Bravecto plus®). The isoxazolines are structurally related to the phenylpyrazole compound fipronil, with incorporation of an isoxazoline moiety increasing activity against LGCCs, with potent ectoparasiticidal qualities (Ozoe et al., 2010). Importantly however, although the isoxazolines share their mode of action (LGCC antagonism) with both the organochlorines (dieldrin, lindane) and phenylpyrazoles, they have been shown to target a distinct binding site, reducing the chance of cross-resistance (Asahi et al., 2015). While all isoxazolines have demonstrable activity against mites, it is afoxolaner and fluralaner that have been studied most intensively, demonstrating high efficacy against *S. scabiei* and *Demodex canis.* However, *in vitro* assays of egg hatchability found no ovicidal effect of afoxolaner or sarolaner (Bernigaud et al., 2020).

4.2.1. Fluralaner

4.2.1.1. Mode of administration and clinical efficacy. Among the isoxazolines, fluralaner is the most well-studied for *S. scabiei*. Fluralaner is formulated as a chewable oral tablet (25 mg/kg) or topically administrated spot-on (25–56 mg/kg in dogs, 40–94 mg/kg in cats) and has been marketed in North America, Europe, Australia, New Zealand and a number of countries in Asia (Ozoe et al., 2010; Gassel et al., 2014). Safety has been evaluated for a range of animals, including dogs, cats, rabbits, black bear and wombats (Gassel et al., 2014; Rohdich et al., 2014; Van Wick et al., 2020; Wilkinson et al., 2021). In Taenzler et al. (2016) and Romero et al. (2016), a single dose of oral or topical fluralaner administrated at 25 mg/kg to dogs exhibited 100% efficacy against *S. scabiei* within four weeks of treatment. A similar case is documented in pet rabbits treated with a single dose of oral fluralaner at 25 mg/kg, resulting in clinical resolution of sarcoptic mange by day 30 post-treatment (Singh et al., 2022). Afoxolaner is also effective against *S. scabiei* infestation of pigs, with a single oral dose of 2.5 mg/kg showing 100% efficacy at day 8 post treatment (Bernigaud et al., 2018). Similar results with 2.5 mg/kg oral afoxolaner were observed in dogs with generalised demodicosis, with 100% efficacy at day 28 post treatment (Beugnet et al., 2016).

High efficacy of single dose of fluralaner against *S. scabiei* has also been observed in wildlife. In bare-nosed wombats, topical fluralaner at 25 mg/kg resulted in a complete clinical resolution by day 19 and 30 for mild and moderate sarcoptic mange infections, respectively (Wilkinson et al., 2021). Although the sample size of this study was small (n = 3), large field trials are ongoing and Bravecto® has now been approved by the APVMA for the treatment of sarcoptic mange in the bare-nosed wombat. One potential factor limiting utility raised by some wildlife carers is the difficulty administering a small volume of spot-on product accurately to the wombat in field conditions. As the product is insoluble in water, the need for appropriate diluents has been proposed to ease dispensing of treatment using burrow flap and pole and scoop methods (Wilkinson et al., 2021). Fluralaner has also been used to treat sarcoptic mange in an American Back Bear (*Ursus americanus*) with oral treatment resulting in clinical resolution by week five post-treatment (Van Wick and Hashem, 2019).

4.2.1.2. Pharmacodynamics. Fluralaner is an antagonist of LGCCs of arthropods, blocking the influx of chloride ions and disrupting inhibitory functions of the neurotransmitter (Zhao and Casida, 2014; Asahi et al., 2015). Consequently, depolarisation and hyperexcitation are induced, causing flaccid paralysis and the death of target arthropods (Weber and Selzer, 2016). Functional studies revealed that the main target of fluralaner in cattle ticks was GABA-Rs, with the compound inhibiting channels at very low concentrations (IC_{50} 2.8 nM). Fluralaner also exhibited activity against *Rhipicephalus microplus* GluCl in nanomolar ranges, albeit at higher concentrations (IC_{50} 80 nM) (Gassel et al., 2014). Similarly in the head louse (*P. humanus*) the related compound lotilaner was active against GABA-Rs (IC_{50} 40.7 nM) but showed no activity against GluCls (Lamassiaude et al., 2021). Notably, fluralaner retains activity in both dieldrin and fipronil resistant GABA-Rs, suggesting that the compounds bind to distinct sites (Gassel et al., 2014). This differential binding of isoxazolines with other GABA antagonists was also demonstrated in spider mites (*T. urticae*), which are not intrinsically sensitive to fipronil and plant hoppers (*Laodelphax striatellus*) with a fipronil resistance mutation (Asahi et al., 2015; Mermans et al., 2022).

The binding sites of fluralaner were further investigated using electrophysiological analysis of artificial mutants in the transmembrane domains of a *M. domestica* Rdl-like GABA-R subunit. Substitutions at

Q271 in TM1 resulted in a 68-fold reduced fluralaner sensitivity compared to the wild type, and G333M and G333S in TM3 completely abolished fluralaner activity (Yamato et al., 2020). These sites are distinct from A299 and/or A302 in TM2 that have been associated with decreased dieldrin and fipronil sensitivity in other organisms. Interestingly, substitution at L315 in a *Musca domestica* GluCl, which corresponds to position 336 in the GABA-R dramatically *increased* the sensitivity of the GluCl to fluralaner, reinforcing the importance of this TM3 region in fluralaner binding (Nakata et al., 2017). Thus, fluralaner is highly selective for invertebrate Rdl-like GABA-Rs, showing no activity against rat α1β2γ2 $GABA_A$ receptors at the highest concentration tested (30 μM) (Gassel et al., 2014). Similarly, lotilaner showed no inhibitory effect on a canine $GABA_AR$ at the highest concentration tested (10 μM) (Rufener et al., 2017). The evaluation of higher concentrations would be useful to assess the potential impact of overdose and mammalian toxicity.

4.2.1.3. Pharmacokinetics. A substantial advantage of the isoxazolines is a notably longer duration of effectiveness at a single dose compared to the macrocyclic lactones. The prolonged effectiveness of fluralaner is demonstrated by pharmacokinetic studies in dogs with a $T_{1/2}$ of 12 days after a single oral dose of 12.5–56 mg/kg (Table 1). Orally administrated fluralaner in dogs at a single dose of 25 mg/kg remained detectable until day 112 post treatment (Kilp et al., 2014). Topical application also exhibits a long duration of persistence, suggested by a $T_{1/2}$ of 21 days in dogs and 12 days in cats, following a single dose at 25 mg/kg and 40 mg/kg, respectively (Kilp et al., 2016). The shorter persistence of topical fluralaner in cats compared to dogs supports its higher minimum recommended dose in cats to achieve 12 weeks of protection.

The prolonged efficacy of fluralaner is recognised as a distinct advantage for the treatment of sarcoptic mange in free-living wombats and other animals, overcoming shortfalls of ivermectin and moxidectin. A single dose is theoretically feasible for full treatment across the entire mite life cycle, although multiple doses are likely to be needed in practice. A pilot pharmacokinetic and safety study of topical fluralaner at two concentrations (25 and 85 mg/kg) was recently undertaken in bare-nosed wombats (Wilkinson et al., 2021). While the mean C_{max} in wombats was approximately 100 times lower than that of dogs and cats, the mean $T_{1/2}$ was prolonged relative to these species, (40 days for 25 mg/kg and 167 days for 85 mg/kg, Table 1). Pharmacokinetic studies for the related compound afoxolaner showed an increased C_{max} and longer duration of persistence in pig skin relative to plasma after a single oral dose, with a skin:plasma AUC ratio of 9.2 (Bernigaud et al., 2018). These pharmacokinetic parameters combined with its high activity at low concentrations suggest that one to three fluralaner applications should provide protection from the mite reinfection for an extended duration, in contrast to the experience with moxidectin. Field studies are in currently progress that will fully assess treatment frequency and duration of effectiveness.

4.2.1.4. Safety. Neurotoxicity appears to be a rare event in treatment with isoxazolines, however the relatively recent development of these products is noteworthy. In safety studies, orally administered fluralaner at three times the recommended dose to P-gp deficient collies revealed no adverse events, suggesting that the treatment was well tolerated in this cohort (Walther et al., 2014). There has been one case report of transient neurological adverse events in a dog 24 h post treatment with oral Bravecto, with clinical signs suggesting interactions with $GABA_ARs$ (Gaens et al., 2019). This dog was not found to possess *mdr1* mutations, but other blood-brain barrier disruption cannot be ruled out.

In contrast to other studies indicating the safety of isoxazolines, Palmieri and colleagues (2020) described a comparatively high number of adverse events reported to the US FDA and European Medicines Authority (EMA), and additionally conducted a survey of veterinarians and pet owners regarding adverse events. The most commonly reported adverse event to the FDA was vomiting/nausea (43.6% of reports), with 3.6% reporting neurological events (shaking/tremors/ataxia) and 2.8% seizure. The EMA reported a higher number of neurological events, with 18.7% seizures of all adverse events recorded. While these are seemingly high, such reports are very difficult to interpret in contrast to randomised controlled trials, as underlying clinical conditions are not known and these numbers are based on voluntary self-reports which could be subject to bias. In light of these findings, more studies are needed, and caution is still warranted with the use of isoxazolines, especially in dogs with pre-existing neurological conditions such as epilepsy. Isoxazolines are also contraindicated in pregnant animals, as developmental abnormalities in puppies have been reported (cited in Zhou et al., 2022).

5. Acaricide resistance in *S. scabiei*

Despite the high prevalence of scabies across the world, there are only limited studies documenting treatment failures, although these reports have increased in recent years. In most cases, scabies treatments when used correctly remain effective. Treatment failures are frequently attributed to inadequate use of acaricides (for example only giving a single dose which fails to eliminate eggs) or reinfestation through direct or indirect contact with untreated individuals or contaminated environments (Currie et al., 2004). These difficulties are confounded in free-living animals where treatment application and follow-up are difficult to evaluate empirically (Mounsey et al., 2022; Rowe et al., 2019). Despite these acknowledged difficulties in assessing treatment failures, there is a growing concern about the potential emergence of acaricide resistance in *S. scabiei.*

5.1. Clinical and in vitro reports of resistance

5.1.1. Macrocyclic lactones

Treatment failure of ivermectin for *S. scabiei* var. *hominis* infestation, linked with resistance was first reported in 2000 (Currie et al., 2004). In this study, persisting crusted scabies after multiple doses of ivermectin were observed in two patients, who had previously been administered ivermectin 30 and 58 times since 1995 and 1996, respectively. In these cases, live mites were microscopically confirmed at day 26 post commencement of ivermectin treatment (five doses of 0.2 mg/kg on days 1, 2, 15, 16, and 29). *In vitro* assays confirmed increased mite survival time, with some mites surviving for 9 h of ivermectin exposure, compared to 1–2 h survival in ivermectin susceptible mites. Increased clinical severity was observed post treatment in both cases. This study showed that ivermectin resistance in *S. scabiei* could develop as a result of intensive use of the acaricide.

Mounsey et al. (2009) investigated longitudinal data of *in vitro* ivermectin sensitivity of *S. scabiei* var. *hominis* collected from skin scrapings of 16 crusted scabies patients hospitalised between 1997 and 2006. This analysis demonstrated a doubling of mite survival times to ivermectin over the ten years. Additionally, sequential data showed increased mite survival in a single patient over a routine course of ivermectin treatment which suggests that selection for tolerant mites can occur rapidly, which may promote development of resistance. A further case report also describes clinical persistence of crusted scabies despite six doses of ivermectin, although *in vitro* confirmation was not undertaken (Fujimoto et al., 2014). To prevent future recurrences of resistance, it is recommended that treatment protocols for crusted scabies are guided by clinical grading (Davis et al., 2013) and incorporate a combination of topical acaricides and keratolytic therapy with ivermectin (Currie and McCarthy, 2010). Such protocols are not possible in free-living animals, and thus it is possible that resistance could emerge quickly with suboptimal monotherapy. There is only one other published study of possible resistance to ivermectin in *S. scabiei* in animals. Two dogs in the same household in Japan showed clinical signs of sarcoptic mange and no response to treatment, despite two doses of oral ivermectin within 14 days (Terada et al., 2010). They were then treated

with fipronil spray three times with 14-day intervals, which resulted in rapid clinical resolution in both dogs.

Macrocyclic lactone resistance has emerged as a significant issue in a range of nematode and arthropod species in sheep, goats, and cattle, often linked with intensive use (Shoop, 1993; Sangster, 1999). For example, cattle infested with sheep scab mite (*P. ovis*) were treated with repeated subcutaneous injections of ivermectin with no clinical resolution or reduction in mite density, although adequate concentrations of drug in the skin were confirmed (Lifschitz et al., 2018). The continuous use of ivermectin has resulted in the development of resistance in *R. microplus* (cattle tick) mainly in Brazil. Klafke et al. (2006) examined ivermectin resistance in this species with a 10-year history of ivermectin exposure using a larval immersion test (LIT) technique, which found them to be up to 3.78-fold resistant compared to non-exposed tick populations. It has also been shown that intensive ivermectin exposure can result in the development of resistance in fruit fly (*D. melanogaster*) (Kane et al., 2000), horn fly (*Haematobia irritans*) (Byford et al., 1999), and head lice (*P. humanus*) (Diatta et al., 2016).

There has been growing concern regarding the inadequate outcomes with moxidectin for the treatment of sarcoptic mange in wombats. A recent survey revealed that the use of topically applied moxidectin by some wildlife carers had exceeded "standard" doses (~0.5 mg/kg) for sarcoptic mange by up to 100-fold (Old et al., 2021). The use of these treatment regimens suggests that moxidectin resistance might already exist in *S. scabiei* in these wombat populations, which may in part explain the highly variable treatment outcomes reported in some areas. In addition, there are several cases of treatment failures in orphaned bare-nosed wombats in care despite multiple doses of moxidectin (Mounsey et al., 2022). Although moxidectin resistance is less common compared to ivermectin resistance, several studies have recently documented clinical and *in vitro* moxidectin resistance in *P. ovis* (Sturgess-Osborne et al., 2019). *In vitro* assay on *P. ovis* collected from sheep farms in the UK also demonstrated the significantly lower mortality rates from moxidectin exposure compared to those of sensitive mites (Doherty et al., 2018). Clinically, two or more doses of moxidectin administered via subcutaneous injections with weekly intervals failed to eliminate *P. ovis* in cattle in beef farms in Belgium and Netherlands (van Mol et al., 2020).

5.1.2. Resistance of S. scabiei to other acaricides

The emergence of resistance to lindane (γ-hexachlorocyclohexane) in *S. scabiei* var. *hominis* has been reported globally (Taplin et al., 1986; van den Hoek et al., 2008). Most cases of reported resistance were linked to inadequate or intensive use of the drug. Treatment failures in Panama were attributed to the emergence of lindane resistance resulting from the five years of intensive use in an island community (Meinking, 1999). In response to the widespread lindane resistance in *S. scabiei* and *P. capitis* and the emergence of safer alternatives, lindane became banned in 52 countries and restricted in 33 others by 2006 (Humphreys et al., 2008).

Permethrin has been widely used as the first-line treatment option for human scabies in the UK, the USA and Australia, where it has been deployed extensively in community control programs (Carapetis et al., 1997). Anecdotal reports of varied success of permethrin for crusted scabies in northern Australia, combined with early *in vitro* data showing slower killing time, and possible increasing tolerance (Walton et al., 2000), but to date this appears not to have materialised in this region. Conversely, permethrin resistance is now strongly suspected across Europe (Sunderkötter et al., 2019; Soerensen et al., 2021; Mang et al., 2021; Balestri et al., 2022; Lee et al., 2022; Meyersburg et al., 2022; Ertugrul and Aktas, 2022). As permethrin is not used widely in animals and is not practical for wildlife, discussions of resistance are less relevant, although permethrin resistance has been reported in laboratory selected *S. scabiei* var. *canis* (Pasay et al., 2008). There is no published use of permethrin in wombats.

5.2. Mechanisms of acaricide resistance

Development of resistance in both endo and ectoparasites is proposed to occur via three overarching mechanisms. These include: (i) target site alteration, (ii) increased metabolic detoxification, and (iii) increased drug efflux. The relative contribution of these mechanisms may differ according to the species and drug in question. Compared to permethrin resistance which is commonly associated with mutations in voltage-gated sodium channels, the molecular mechanisms of macrocyclic lactone resistance appear multifactorial. Despite concerted efforts over the years, specific mechanisms have been difficult to clearly define. This may be due to the interactions of these drugs with multiple ion channel targets, and different efflux transporters within the target organism. In this section we will discuss resistance mechanisms of specific relevance to treatments used for sarcoptic mange in wildlife.

5.2.1. Alteration to drug metabolism and efflux

Increased metabolism and clearance of drugs is a commonly reported resistance mechanism in arthropods (Feyereisen, 2015). There are various multi-functional detoxification enzymes reported in arthropods, including Esterases, Glutathione-S-Transferases (GSTs), Cytochrome P450s and UDP-glucosyltransferases (UGTs). GSTs are a multi-functional family of enzymes that play a crucial role in detoxification of endogenous compounds and xenobiotic toxins including insecticides and acaricides by converting them into the less toxic and water-soluble substrates to be excreted via multidrug-resistance-related proteins (MRP) (Pavlidi et al., 2018). Pyrethroids, macrocyclic lactones, organophosphates and DDT are known to have detoxification pathways involving GSTs (Lumjuan et al., 2005). GST-associated drug resistance has been reported in various insects and acari. In particular, the association between pyrethroid resistance and increased GST activity is well studied in acari such as *R. sanguineus* (Duscher et al., 2014), the citrus red mite (*Panonychus citri*) (Liao et al., 2013) and two-spotted spider mite *Tetranychus urticae* (Zhang et al., 2022). Increased Cytochrome P450 expression has also been linked to abamectin resistance in *T. urticae* (Xu et al., 2021).

Increased GST, esterases and P450s were observed in permethrin resistant *S. scabiei* var. *canis* via direct enzyme measurement, as well as the addition of enzyme inhibitors which restored permethrin susceptibility to mites *in vitro* (Pasay et al., 2009). Transcriptional upregulation of GSTs has also been observed in tolerant and/or resistant scabies mites. These include the laboratory model of permethrin resistant mites, mites obtained from a crusted scabies patient post ivermectin treatment, and mites exposed to ivermectin *in vitro* (Mounsey et al., 2010).

ATP-binding cassette (ABC) transporters are found in a wide range of organisms. These transporters play a crucial role in the detoxification and export of chemical compounds. Among several types of proteins in those subfamilies, the one most commonly associated with macrocyclic lactone resistance is the ABC-B transporter P-glycoprotein (P-gp). Over expression of P-gps has been consistently implicated in ivermectin resistant nematodes such as *Teladorsagia circumcincta* and *H. contortus* (Xu et al., 1998; Bartley et al., 2009; Raza et al., 2016; Maté et al., 2018; Laing et al., 2022), but at times the modest upregulation observed does not fully correlate with the extent of resistance, suggesting multiple mechanisms are involved. It has also been difficult to pinpoint a reliable genetic marker for measuring the contribution of P-gps to macrocyclic lactone resistance in nematodes.

Over-expression of a P-gp has been identified in *S. scabiei* var. *hominis* mites with decreased ivermectin sensitivity *in vitro*, which were obtained from a crusted scabies patient undergoing ivermectin treatment (Mounsey et al., 2010). Over expression of P-gp has also been observed in ivermectin resistant *R. microplus* (Pohl et al., 2011), and in abamectin exposed or resistant *T. cinnabarinus* and diamondback moth (*Plutella xylostella*) (Tian et al., 2013; Xu et al., 2016). Relative to other mechanisms such as metabolic detoxification and target site alteration in resistant arthropods, the contribution of P-gps is less frequently

reported.

5.2.2. Target site alterations

Ligand gated chloride channels represent the primary target site for the major classes of acaricides currently used for the treatment of sarcoptic mange in wildlife - the macrocyclic lactones and isoxazolines. Therefore, target site insensitivity rendered by genetic alterations to these channels is proposed as a major resistance mechanism.

5.2.2.1. Glutamate-gated chloride channels. As the interaction of ivermectin with GluCls is well understood (Fig. 2), GluCl alterations have been the subject of many investigations of resistance in both nematodes and arthropods. Early studies in the model organism *C. elegans* showed that mutations in GluCl conferred ivermectin resistance, although the extent of resistance has been inconsistent between studies. (Dent et al., 2000; Ghosh et al., 2012). This potentially reflects the fact that the native assembly of GluCl subunits is still not well understood. The importance of GluCl genes to resistance has been recently confirmed in genome-wide association studies of both *C. elegans* and *H. contortus* (Evans et al., 2021; Khan et al., 2020), however in both studies associations with additional loci and metabolic genes such as P450s were also identified.

Several variants in GluCl subunits have been identified in ivermectin resistant *Cooperia oncophora* isolated from the UK. These mutations were characterised by functional expression in *Xenopus laevis* oocytes. This resulted in the identification of a key alteration - L256F, located in the N-terminal extracellular ligand-binding domain, which had a 2.5-fold reduction in sensitivity to ivermectin and moxidectin, as well as reduced sensitivity to glutamate (Njue et al., 2004). Apart from this study, there are surprisingly few reports of field resistance being directly linked to GluCl channel mutations in nematodes, despite the clear existence of genetic association.

The association of GluCl alteration with macrocyclic lactone resistance is clearer in arthropods. The first study to demonstrate this was in laboratory-selected *D. melanogaster* where a mutation in the GluCl TM2 region was associated with a reduction in ivermectin and glutamate sensitivity when expressed in *Xenopus* oocytes (Kane et al., 2000). Since then, several GluCl mutations have been associated with resistance in laboratory and field resistant arthropods (Fig. 2). These include abamectin resistant plant mites *T. urticae* (two-spotted spider mite). Comparison of isogenic *T. urticae* strains with and without selection for abamectin resistance identified a G323D (reannotated as G314D in Dermauw et al., 2012) mutation in TM3 of GluCl1 (Kwon et al., 2010). A residue at the equivalent position in GluCl3 (G326E) was also identified together with the G323D/G314D GluCl1 mutation in a highly resistant (2000-fold) field strain, suggesting that an accumulation of mutations could contribute high levels of resistance (Dermauw et al., 2012). Functional expression confirmed that GluCl3 G326E resulted in a complete loss of agonist activity by both abamectin and milbemycin (Mermans et al., 2017). Both GluCl1 G323D and GluCl3 G326E mutations are seen with high frequency in abamectin-resistant spider mite populations (Ilias et al., 2017). Recently, additional mutations have been identified in field resistant *T. urticae,* including I321T in TM3 in GluCl3 (Xue et al., 2020), which confers modestly reduced abamectin potentiation in functional studies. However, the ability of this mutant channel to form cell-surface GluCls in *Xenopus* oocytes was also diminished relative to the wild-type subunit (Xue et al., 2021). Along with I321T, additional mutations in TM3 have been identified in some populations, including V327G and L329F (Xue et al., 2020).

In the diamondback moth, *P. xylostella*, GluCl variants that mediate insecticide sensitivity have been extensively characterised. Many of these mutations are at equivalent residues to those documented in *T. urticae.* For example, G315E corresponds to G314D/G323D in GluCl1, and G326E in GluCl3 (Fig. 2, Wang et al., 2017). From these studies it is clear that this region in TM3 is a “hotspot” for resistance, which is plausible due to the modelled interactions with ivermectin at this site (Hibbs and Gouaux, 2011), where the G314D/E or G326E substitutions are predicted to block ivermectin binding in the *C. elegans* structure (Fig. 2). Recent analysis of ivermectin resistant *P. humanus* have identified three variants in a GluCl subunit: S46P in the N-terminal extracellular domain, A251V in TM3, and H272R in the TM3-TM4 intracellular loop (Amanzougaghene et al., 2018). Functional expression analysis of these variants, which is currently lacking, will be important to understand their effects on ivermectin sensitivity.

While variants in GluCl genes associated with avermectin resistance have been well studied, studies on the effects of these changes on the milbemycin class of macrocyclic lactones are more limited. Cross resistance and decreased sensitivity to milbemectin was observed for the *T. urticae* GluCl3 G326E mutation (Mermans et al., 2017). Yamaguchi et al. (2012) determined that two previously identified GluCl mutations in *H. contortus,* L256F and P316S, resulted in a 37- and 100-fold decreased susceptibility to milbemycin compared to wild-type GluCls, suggesting some shared binding and potential for cross resistance. As the emergence of resistance to the milbemycins is somewhat more recent, mutations in laboratory selected or field resistance isolates are yet to be fully characterised.

5.2.2.2. GABA receptors and other LGCCs. The macrocyclic lactones are most commonly associated with activity against the GluCls, however interactions with Rdl-like GABA-Rs are also noted. While laboratory models of resistant *D. melanogaster* and *M. domestica* show that alterations in the TM2 and TM3 region of *Rdl* alter ivermectin sensitivity (Kane et al., 2000, Nakao et al., 2015, Fuse et al., 2016, it is noted that no *Rdl* mutations associated with macrocyclic lactone resistance have been identified in field-resistant isolates to date.

In contrast to the somewhat mixed understanding of the interaction of macrocyclic lactones with insect and mite Rdl-like GABA-Rs, it is well established that the isoxazolines are antagonists of these channels, although as they bind to a site distinct from other GABA receptor channel blockers, cross-resistance may evolve more slowly. The isoxazolines are a relatively new class of drug, and resistance has not yet been reported. The functional studies detailed in section 4.2.1.2 highlight key residues of interest in *Rdl*-like subunits should resistance emerge.

There is a considerable body of knowledge supporting that the GluCls and *Rdl*-like GABA-Rs are the main targets of the macrocyclic lactones and isoxazolines respectively, and resistance-associated mutations have been identified in these LGCCs. However, resistance is complex, and it is known that other LGCCs are also targeted by these drugs and theoretically could be implicated in resistance. In insects, ivermectin is known to interact with histamine- and pH-gated chloride channels, with the latter being functionally characterised in *S. scabiei* and shown to be activated by ivermectin (Georgiev et al., 2002; Schnizler et al., 2005; Mounsey et al., 2007; Nakatani et al., 2016).

6. Research priorities and conclusions

This review has highlighted the challenges of controlling mange disease, especially in free-living populations such as the bare-nosed wombat, where the disease has significant impacts. Key barriers to effective treatment include difficulties in application to free-living animals, complexities in population versus individual disease control, and the challenges of administering multiple doses to the same animal. These challenges are further confounded by insufficient understanding of both the pharmacokinetic and pharmacodynamic interactions between acaricide, parasites and their hosts. There is no standardised assessment for investigating treatment failures in either animals or humans, and further *in vitro* studies, as is routinely conducted in other parasites, would provide helpful information on phenotypic responses to treatment. We would also strongly suggest the prospective collection of mites

with suspected acaricide resistance for molecular genetic investigations.

There are fundamental knowledge gaps regarding acaricide treatment of sarcoptic mange, and the physiological LGCC targets of these drugs in *S. scabiei* remain uncharacterised. The recent availability of a high-quality genome of *S. scabiei* (Korhonen et al., 2020) will facilitate genetic and functional characterisation of these scabies mite LGCCs, allowing researchers to assess their potential contribution to altered treatment responses and the emergence of acaricide resistance. With limited availability of effective treatment options to control sarcoptic mange in wombats, this could support therapeutic guidance and allow proactive resistance management in the future.

Declaration of competing interest

The authors hereby declare no conflict of interest.

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