Parasitology Research (2022) 121:1065–1071
https://doi.org/10.1007/s00436-022-07460-4

TREATMENT AND PROPHYLAXIS - LETTER TO THE EDITOR

Drug dose and animal welfare: important considerations in the treatment of wildlife

Kate Mounsey[1,2] · Robert J. Harvey[1,2] · Victoria Wilkinson[3] · Kotaro Takano[1,2] · Julie Old[4] · Hayley Stannard[5] · Leanne Wicker[6] · David Phalen[7] · Scott Carver[3]

Received: 24 December 2021 / Accepted: 1 February 2022 / Published online: 11 February 2022

Abstract

A recent article published in Parasitology Research describes the use of high-dose moxidectin (Cydectin®) by wildlife carers for the treatment of sarcoptic mange in bare-nose wombats (*Vombatus ursinus*). We provide additional perspectives on this topic, including consideration of the pharmacokinetics, mode of action and efficacy of moxidectin. The volumes of moxidectin applied by some carers exceeded the manufacturer recommended dose by up to 100-fold, although there appeared to be no association between dose and clinical efficacy. The safety of these extremely high doses has not been scientifically evaluated and we raise concerns regarding the potential for severe adverse events that may be undetected in free-living animals. The inadvertent spillage of large volumes of pour-on acaricides may also have ecotoxic impacts. Reports of treatment failure prompting the perceived need for higher doses are also concerning. The causal factors behind treatment failures should be investigated as a matter of priority, as it is possible that moxidectin resistance is emerging in *Sarcoptes scabiei* mites infesting wombats. We welcome the insights of individuals actively engaged in the treatment of this debilitating disease of wombats and encourage further discourse, reflecting both the lived experience and evidence-based practice.

A recent publication in Parasitology Research by Old et al. (2021) raises the topical and often controversial issue of the treatment of wildlife by personnel with little or no formal scientific training (e.g. wildlife carers). In a valuable contribution to the subject, Old and colleagues document a wide range of topical (pour-on) application doses and frequencies of moxidectin (Cydectin®) administered in situ to bare-nosed wombats (*Vombatus ursinus*) by members of the wildlife carer/treater community in southeast Australia to treat sarcoptic mange disease. This treatment occurred under minor use permits issued by the Australian Pesticides and Veterinary Management Authority (APVMA). These permits do not require veterinary supervision, although carers are registered and are expected to comply with the guidelines of this permit.

The prevalence and severity of sarcoptic mange in wildlife is influenced by a variety of factors including mite biology, environmental conditions, population density, animal behaviour and immune susceptibility (Browne et al. 2021). In bare-nosed wombats, combinations of these elements play a substantial role in making the treatment of an already difficult disease more complex. Moroni et al. (2020) comment that any pharmacological treatment of free-ranging wildlife must consider these factors when assessing their feasibility and implications, especially in the context of emerging drug resistance and potential long-term ecological impacts. As individuals with significant interest in sarcoptic mange and

Handling Editor: Una Ryan

Kate Mounsey and Robert J. Harvey are joint first authors.

✉ Kate Mounsey
kmounsey@usc.edu.au

[1] School of Health and Behavioural Sciences, University of the Sunshine Coast, Maroochydore, QLD 4558, Australia

[2] Sunshine Coast Health Institute, Birtinya, QLD 4556, Australia

[3] School of Natural Sciences, University of Tasmania, Hobart, TAS 7005, Australia

[4] School of Science, Western Sydney University, Hawkesbury campus, Penrith, NSW 2751, Australia

[5] School of Agricultural, Environmental and Veterinary Sciences, Charles Sturt University, Wagga Wagga, NSW 2678, Australia

[6] Wildlife Conservation and Science, Zoos Victoria, Parkville, VIC 3052, Australia

[7] Sydney School of Veterinary Science, Faculty of Science, The University of Sydney, Sydney, NSW 2006, Australia

representing a range of professional research and veterinary expertise, we see value in providing expert commentary on this issue.

Pharmacokinetics of moxidectin in wombats

Most mange treatments, including moxidectin, are not ovicidal, which means that a single-dose treatment will not clear infestation unless the drug is retained in the host at therapeutically active concentrations throughout the entire mite life cycle (at least 14 days) (Bernigaud et al. 2019). While moxidectin has prolonged retention compared to other macrocyclic lactones (e.g. ivermectin) in many host species (Bernigaud et al. 2016; Mounsey et al. 2016), this is not the case in southern hairy-nosed wombats (*Lasiorhinus latifrons*). The subcutaneous administration of a standard (0.2 mg/kg) dose of moxidectin in southern hairy-nosed wombats resulted in comparable plasma concentrations, but a considerably shorter plasma half-life (5 days, range 2–10) relative to other species (Death et al. 2011). This difference may be attributed to the low body-fat composition of wombats, as sequestration to adipose tissue contributes to the long half-life of this lipophilic drug in other animal species (Craven et al. 2002a, 2002b). Therefore, consistent with the observations of Old et al. (2021) and other studies (e.g., Martin et al. 2019), successful treatment of mange in bare-nosed wombats with moxidectin requires multiple treatments over many weeks. Importantly, the data from Death et al. (2011) and pharmacokinetic studies in other animals (Fazzio et al. 2019) show that higher plasma concentrations or administering higher subcutaneous doses did not change the elimination dynamics of moxidectin, suggesting that increasing dose volumes within therapeutic limits *will not extend the duration of therapeutic coverage* and *will not prevent reinfestation*.

The pharmacokinetics of topical moxidectin in bare-nosed wombats has not been investigated. While it is generally accepted that absorption is lower via the topical route, if pour-on treatments are administered to severely excoriated or fissured skin as occurs with severe mange, absorption could be much higher compared to that of intact skin. Conversely, the presence of hyperkeratotic crusts, another feature of severe disease, could be expected to impede topical absorption. These uncertainties mean there is a substantial risk of underdosing or overdosing with the currently employed topical treatment regimens, and caution is especially warranted with high doses due to the risk of toxicity. This uncertainty regarding dose volumes was expressed by the respondents in Old et al. (2021) and is further confounded by difficulties in dispensing accurate doses to free-living animals using current delivery methods.

Even if systemic absorption as measured by plasma concentrations is reduced with topical administration, several studies on non-blood feeding ectoparasitic mites and lice (including the mange mites *Psoroptes ovis* and *Chorioptes bovis* and chewing louse *Bovicola bovis*) demonstrate that topical administration of moxidectin was actually more efficacious than subcutaneous administration (Chick et al. 1993; Losson and Lonneux 1993), as high concentrations of moxidectin are retained in the skin (Lifschitz et al. 1999; Sallovitz et al. 2003). Clearly, the pharmacokinetics of moxidectin is complex, and more research is needed that is specific to bare-nosed wombats, including the effect of different routes of administration and skin lesion severity on plasma versus target tissue concentrations.

Do higher moxidectin volumes increase treatment efficacy?

The efficacy of the recommended dose (0.5 mg/kg every 4–6 weeks) of pour-on moxidectin against mange is well-established in the target species it was intended for (cattle and deer) (Virbac Animal Health 2021; Prichard et al. 2012). However, the scientific evidence for moxidectin's efficacy against sarcoptic mange in bare-nosed wombats suggests that this species likely requires doses to be administered at more frequent intervals over a prolonged period of time to achieve clinical resolution. The treatment of free-living wombats as detailed in Old et al. (2021) primarily utilised non-invasive methods such as "burrow-flaps" and "pole and scoop" to deliver moxidectin topically to the skin of infested wombats. Published field research from Tasmania (Martin et al. 2019) and unpublished field trials from New South Wales (Phalen, personal communication) showed that 4–5 mL of pour-on moxidectin (ca. 1 mg/kg in a 25 kg wombat), delivered weekly by burrow flap for a minimum of 8 to 12 weeks, resulted in the resolution of clinical signs of sarcoptic mange in free-living wombats. However, it is noteworthy that upon cessation of treatment, there was no evidence of a prophylactic effect against later reinfestation from a second exposure to *Sarcoptes* mites via direct contact or shared burrows.

Conversely, many of the respondents in Old et al. (2021) commented that dose volumes of 1 mg/kg applied topically were not effective and reasoned that lack of efficacy justified their decision to use much higher doses, despite this practice breaching minor use permits at the time. To our knowledge, the doses of moxidectin administered by carers as described in this report are the highest reported for the treatment of parasitic disease, in any other vertebrate species, globally. Put in context, delivery of 100 mL of Cydectin® equates to a dose of 20 mg/kg, and some carers utilised up to 200 mL of product per application. This is *exceptionally high* and

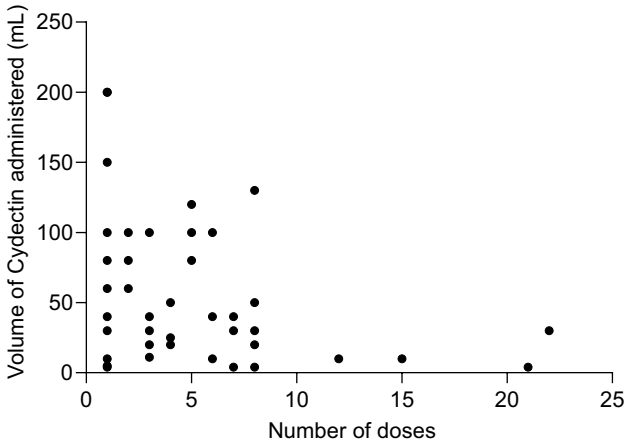

Fig. 1 The varied utilisation of Cydectin® by wildlife carers. Dose volume and number of doses administered in wombats with moderate and severe sarcoptic mange reported as successfully treated with moxidectin (Cydectin®) in Table 1 of (Old et al. 2021). Note that a single case may have received changing regimens over the course of treatment, so may be represented by more than one point on this graph

represents a 100-fold increase compared to the recommended regimen for this product (Virbac Animal Health, 2021).

While there was a strong perception from sections of the wildlife carer/treater community that higher volumes enhanced recovery by reducing treatment time, objective interpretation of the relationship between moxidectin dose and treatment success in wombats was limited. The authors acknowledged that they found "no relation between dose volume and overall length of treatment for mild, moderate and severe sarcoptic mange", although no statistical analysis was presented. The ability to analyse the effect of dosing regimen on clinical outcome was complicated by the ad hoc nature of dose volumes given, mode of delivery, treatment period, number of repeat doses given, and peri- and post-treatment monitoring. Regardless, to better understand these associations, we plotted drug volume versus number of doses administered in recovered wombats (Fig. 1). When visualising the data from Old et al. (2021) in this way, it is apparent that there was no difference in dose numbers between volumes under pre-existing minor use permits (20 mL, ca. 4 mg/kg) from the APVMA and higher doses (100 mL, ca. 20 mg/kg) described in this paper. However, this analysis does suggest that dose volumes below 5 mL (ca. 1 mg/kg) were associated with more repeat doses and longer treatment duration in accordance with recommended guidelines, although not with a higher likelihood of treatment failure. Additionally, it is important to recognise other pertinent factors influencing data interpretation, acknowledged by Old et al. (2021). The definition of treatment success is broad, with an absence of physical examination by veterinarians, and a lack of diagnostic testing (such as microscopic examination of skin scrapings or histopathological examination of skin biopsies) to support the assertion that treatment resulted in "cure". Thus, recovery may not be accurately captured in all cases and may be subject to reporting biases toward cases that were more likely called "successful" by the survey respondents.

Mode of action and selectivity of macrocyclic lactones

Macrocyclic lactones such as moxidectin and ivermectin are irreversible agonists of ligand-gated chloride channels, where their binding causes hyperpolarisation and paralysis in the target organism. Certain families of ligand-gated chloride channels are only found in invertebrates, such as the glutamate-gated chloride channels (GluCls), in which the macrocyclic lactones bind with high affinity at low concentrations. This potent activity of moxidectin against the GluCls is often cited as the reason for its high selectivity and safety. However, it is less well communicated that other ligand-gated ion channels are also widely distributed in the mammalian central nervous system and that macrocyclic lactones are also agonists of these receptors. For example, both ivermectin and moxidectin are active against $GABA_A$ receptors (Menez et al. 2012) and ivermectin can activate glycine receptors (GlyRs) at relatively low concentrations (Shan et al. 2001). While the concentrations of ivermectin or moxidectin required to open mammalian receptors are generally higher than their invertebrate GluCl counterparts, they become relevant in the case of high and/or frequent doses. It is important to acknowledge that while moxidectin and ivermectin are structurally related and share the same mode of action, differences do exist between the drugs (reviewed in Prichard et al. 2012), which are still incompletely understood—moxidectin especially is not well characterised.

Safety of high-dose macrocyclic lactone treatment

We emphasise that no published safety data on moxidectin exists in wombats, and there have been few safety studies in any species on the topical application of moxidectin beyond 5–10 mg/kg, as higher doses are not normally used nor required to achieve the desired clinical effect. Most published doses are between 0.2 and 0.5 mg/kg, with higher doses less common and only for certain species (Schraven et al 2021). The macrocyclic lactones are generally considered to have a wide safety margin, due to the expression of P-glycoproteins at the blood–brain barrier which prevents their entry to the CNS and binding to mammalian receptors.

However, the potential for neurotoxicity from macrocyclic lactone treatment does exist when high doses are administered, and moxidectin was found to accumulate in the brain of *both* P-glycoprotein deficient and wild-type mice (Menez et al. 2012), meaning that high concentrations could theoretically enter the brain and cause CNS effects. Concerns regarding safety of macrocyclic lactones in wombats have been raised by others previously, even at "standard" doses. Ruykys et al. (2013) reported that two free-living southern hairy-nosed wombats with mange lost body weight over a period of > 30 days following a single treatment with ivermectin (0.2 mg/kg subcutaneous injection), before body weight was eventually regained. While this could be related to recovery or diet changes, it may also indicate that ivermectin could cause adverse off-target effects to southern hairy-nosed wombats, which would reasonably be expected to be greater at higher drug doses.

In humans, the accumulation of ivermectin in brain tissue due to greater than 100-fold overdoses via oral ingestion has resulted in coma and death (Chung et al. 1999; Sung et al. 2009). Severe illness resulting from the inappropriate use of ivermectin for the prevention and treatment of COVID-19 is also being reported (Centers for Disease Control and Prevention, 2021). Most studies of macrocyclic lactone safety and pharmacokinetics consider the usual modes of treatment, where low concentrations and less frequent treatment are customary. However, there are some diseases such as disseminated strongyloidiasis, severe crusted scabies and demodicosis where more intensive treatments are required, and these are relevant to the discussion of the treatment of sarcoptic mange in wombats. While rare, reports exist of encephalopathy after repeated ivermectin treatment in *Strongyloides* hyperinfection (reviewed in Donadello et al. 2013). Fluctuations in plasma ivermectin concentrations including substantial increases post treatment were observed, indicating that careful monitoring of patients receiving frequent treatments is required. Accumulation of ivermectin in the brain, coma and death were noted in a patient 14 days after the cessation of daily ivermectin treatment (van Westerloo et al. 2014). Notably, these patients had no known impairment of P-glycoprotein function. In severe disease, other comorbidities such as impairment to liver function and hypoalbuminemia may also result in unpredictable drug absorption, pharmacokinetics and treatment response. In severe sarcoptic mange of wombats (Martin personal communication; Rukys et al. 2013.) and other mammalian species (Espinosa et al. 2017; Nakagawa et al. 2009), secondary bacterial infections, elevated liver enzymes, septicaemia and systemic amyloidosis are common causes of organ dysfunction that are not treated by macrocyclic lactones and which may be expected to alter plasma pharmacokinetics and drug clearance, so this is an important consideration.

While moxidectin appears to have a lower affinity for mammalian $GABA_A$ receptors and a wider safety margin compared to ivermectin (Menez et al. 2012), this drug is not immune from safety and neurotoxicity concerns. Mouse model studies have observed moxidectin toxicity at routine topical doses for the treatment of fur mite (*Myocoptes musculinus*). Like the reports of ivermectin neurotoxicity in strongyloidiasis, there was a substantial accumulation of moxidectin in the brain relative to plasma and no observable P-glycoprotein deficit (Lee et al. 2009). Because there have been limited studies of high-dose moxidectin in animals, the clinical signs and physiological impacts of overdose in wombats cannot be predicted. Adverse events have been reported at high and/or inappropriate doses of moxidectin in dogs and horses warranting caution in their use (Khan et al. 2002; Mueller 2004). Adverse effects in dogs include salivation, lethargy, vomiting, and loss of appetite as well as neurological signs including ataxia (abnormal, uncoordinated movements), tremor, and nystagmus (repetitive abnormal eye movements). In horses, overdose leads to ataxia, depression, drooping of the lower lip, tremor, decreased respiratory rate, stupor, and coma (Dowling 2012).

We note with concern the report of one death of a wombat receiving two high doses (200 mL followed by 100 mL) and a second death at lower doses (6 × 30–40 mL). With no clinical examination of these cases, both may be potentially related to CNS toxicity. Any deaths following acaricide treatment should be followed up by gross post-mortem examination including histological review of tissues and appropriate toxicity screening. Investigations should include the collection of brain tissue to test for drug accumulation and liver tissue to assess hepatic function, which could impair normal drug clearance. These documented mortality incidents raise further concerns due to the commonality of treated wombats avoiding re-observations despite rigorous post-treatment monitoring (Wilkinson, personal communication). In such cases, it is a real possibility that adverse effects related to moxidectin dose (as well as mange severity, secondary infections and other factors), including mortality, may go undetected and therefore be under-recognised and under-reported. The experience with ivermectin-related encephalopathy in strongyloidiasis and complex pharmacokinetic properties of both drugs suggest that adverse neurological effects may not arise until well after treatment has ceased, meaning that longer-term monitoring is likely required, especially when high doses are administered repeatedly. Furthermore, transient or less overt clinical signs such as lethargy and reduced respiratory rates are unlikely to be identified in the absence of clinical examination.

The difficulties associated with appropriately monitoring treated animals at sufficiently regular intervals were cited as the key issue by the interviewees and are a well-known barrier to the successful treatment of sarcoptic mange in

wildlife (Rowe et al. 2019). Thus, empirical assessment of the safety of high-dose moxidectin, including monitoring for neurotoxicity events, using data gathered by non-veterinary trained carers alone is not possible. Owing to the complexities of definitively identifying cause and effect in free-living wombats, it is possible that death from treatment may be incorrectly attributed to death from mange-related complications or other causes.

Ecotoxicity potential with indiscriminate use of pour-on moxidectin

The interviewees in Old et al. (2021) note that substantial spillage of moxidectin can occur during drug administration. Moxidectin has recently been identified by the European Union as persisting in the environment and bio-accumulating in fish (European Medicines Agency, 2017). In cattle, moxidectin is preferable to ivermectin in that it is generally less lethal to arthropods, such that concentrations persisting in faeces do not adversely affect dung beetle populations (Lumaret et al. 2012). However, moxidectin is highly toxic to aquatic organisms, such that inadvertent spillage of high volumes of product that ultimately enter waterways could have profound impacts, especially on fish. These may manifest as both acute toxicity and reproductive changes such as reduced egg hatching that could affect population dynamics in the longer term (Lumaret et al. 2012; Mesa et al. 2018; Muniz et al. 2021). While more research into the ecotoxicological impacts of moxidectin are needed, in the short term, it would be prudent to clearly communicate to end-users that moxidectin pour-on should not be used near waterways, in volumes that inevitably lead to spillage, or during rain events that may lead to moxidectin being washed off the wombat or flooding of burrows. Another consideration is that high doses of moxidectin in burrow flaps may be dispensed to non-target animals utilising burrows.

Drug resistance

A key concern of the interviewees in Old et al. (2021) was regarding the potential emergence of mite resistance to moxidectin. We share these sentiments. Acknowledging the difficulties in objectively assessing treatment responses in these settings, if carers are reporting a potential lack of moxidectin efficacy at conventional dose volumes, then formal investigations to gather evidence of treatment failure(s), including the underlying mechanisms, are warranted. The usage patterns reported in this study have raised strong suspicions that moxidectin resistance may already exist in mites from some of these treated populations, which may explain the high variation in reported treatment efficacy at different doses.

Resistance is known to emerge in *Sarcoptes* mites following intensive exposure to acaricides. Important lessons can be learned from the treatment of crusted scabies, which is the human equivalent to severe sarcoptic mange where similar treatment regimens are utilised. Oral ivermectin has been used for crusted scabies for more than two decades with varied success. Early studies showed that single-dose therapy was not effective, and even three doses at 14-day intervals failed to achieve cure in some cases (Huffam and Currie 1998). Genetic analysis revealed that some of these cases were likely to be recrudescent infections rather than reinfection (Walton et al. 1999). In a further report, two severe crusted scabies patients did not respond to oral ivermectin despite five doses being administered over a period of one month. Large numbers of live mites were still observed post-treatment, and these mites were found to have a diminished response to ivermectin in vitro (Currie et al. 2004). A later study confirmed that selection for ivermectin-tolerant mites can occur quickly, with increased in vitro survival times noted in mites obtained from a patient 8 days post ivermectin treatment (Mounsey et al. 2009). These observations led to the recommendation that ivermectin treatment should be supplemented with topical acaricides and keratolytic therapy to aid the removal of crusts and limit the future emergence of resistance (Currie and McCarthy 2010). Unfortunately, such intensive regimens are not possible in free-living wombats. Notably, there have been several cases of apparent moxidectin treatment failure in orphaned bare-nosed wombats in care, with live mites and eggs still observed in skin scrapings despite multiple doses of subcutaneously administered moxidectin (Wicker, personal communication). It is unknown whether these cases represent *bona fide* resistance, or whether these suboptimal responses to treatment were related to other factors such as impaired drug bioavailability.

While ivermectin resistance is widespread in nematodes and arthropods, reports of moxidectin resistance have been less common until recently. It now appears that many years of indiscriminate pour-on treatment with moxidectin has led to resistance in the closely related *Psoroptes ovis* mite, the causative agent of psoroptic mange in sheep and cattle (Doherty et al. 2018; Sturgess-Osborne et al. 2019; van Mol et al. 2020). Based on this experience, there is a very high potential of selecting for moxidectin resistance in *S. scabiei* mites with repeated doses of moxidectin. Due to the uncertainties surrounding drug concentration in the skin, it is possible that mites are frequently exposed to sub-therapeutic levels of moxidectin, and continual increases of drug dose are likely to escalate the selection for resistance. Empirical investigations of this would involve testing of mites for in vitro and molecular evidence of moxidectin resistance (Doherty et al. 2018; Mounsey et al. 2009, 2017). Collection of skin scrapings and analysis of mites in non-responding

animals could provide rich insights and may be a relevant consideration for wombats in care. This should be complemented by a thorough health assessment to understand underlying issues which may be contributing to poor treatment response.

Notwithstanding our above concerns regarding the safety and paucity of evidence supporting the use of high moxidectin doses, these observations from experienced carers represent the lived experience of treating sarcoptic mange. Such insights are highly valuable and eloquently highlight the "grand challenges" of this debilitating disease in bare-nosed wombats and wildlife more generally. Key issues include the following:

1. A need for more effective acaricides with sufficient host retention, preferably needing only a single or small number of doses.
2. Improved delivery methods that are non-invasive, accurate and feasible for treating free living populations.
3. Extreme caution with the use of higher doses, including frequent monitoring of animals and thorough investigation of adverse events.
4. Carers/treaters should be familiarised with the risks of using acaricides near waterways.
5. A better understanding of the pharmacokinetics, safety and efficacy of new and existing drugs.
6. Deeper investigations into treatment failures, including testing for drug resistance and investigating other underlying factors which may contribute to poor treatment responses.

In summary, the successful treatment of sarcoptic mange requires partnerships among stakeholders, including wildlife carers and treaters, veterinarians and research scientists. We encourage continued conversations, supported by both individual experiences and scientific evidence. We recognise that debate and discourse about knowledge, experience, strength of evidence and interpretations of that can at times be difficult and emotive. Nonetheless, it is our experience that the goals of all stakeholders are broadly aligned and keeping perspective of common ground, i.e. the welfare of an iconic Australian animal, is of significant value to all.

Funding Scott Carver, David Phalen, Kotaro Takano, Victoria Wilkinson and Kate Mounsey are involved in recent research on the safety, pharmacokinetics and efficacy of Fluralaner (Bravecto®) to treat wombats for *S. scabiei*, supported by an Australian Research Council Linkage Project LP180101251. The original article discussed (Old et al. 2021) was funded by the Wombat Protection Society of Australia.

References

Bernigaud C, Fang F, Fischer K, Lespine A, Aho LS, Dreau D, Kelly A, Sutra J, Moreau F, Lilin T, Botterel F, Guillot J, Chosidow O (2016) Preclinical study of single-dose moxidectin, a new oral treatment for scabies: efficacy, safety, and pharmacokinetics compared to two-dose ivermectin in a porcine model. PLoS Negl Trop Dis 10(10):e0005030. https://doi.org/10.1371/journal.pntd.0005030

Bernigaud C, Samarawickrama GR, Jones MK, Gasser RB, Fischer K (2019) The challenge of developing a single-dose treatment for scabies. Trends Parasitol 35(11):931–943. https://doi.org/10.1016/j.pt.2019.08.002

Browne E, Driessen MM, Cross PC, Escobar LE, Foley J, López-Olvera JR, Niedringhaus KD, Rossi L, Carver S (2021) Sustaining transmission in different host species: the emblematic case of *Sarcoptes scabiei*. Bioscience. https://doi.org/10.1093/biosci/biab106

Centers for Disease Control Health Advisory (2021). Rapid increase in in ivermectin prescriptions and reports of severe illness associated with the use of products containing ivermectin to prevent or treat COVID-19. CDHHAN-00449. 26th August 2021, https://emergency.cdc.gov/han/2021/pdf/CDC_HAN_449.pdf.

Chick B, McDonald D, Cobb R, Kieran PJ, Wood I (1993) The efficacy of injectable and pour on formulations of moxidectin against lice on cattle. Aus Vet J 70(6):212–213

Chung K, Yang CC, Wu ML, Deng JF, Tsai WJ (1999) Agricultural avermectins: an uncommon but potentially fatal cause of pesticide poisoning. Ann Emerg Med 34(1):51–57. https://doi.org/10.1016/s0196-0644(99)70271-4

Craven J, Bjorn H, Hennessy DR, Friis C (2002a) The effects of body composition on the pharmacokinetics of subcutaneously injected ivermectin and moxidectin in pigs. J Vet Pharmacol Ther 25(3):227–232

Craven J, Hennessy DR, Friis C (2002b) Does the rate of fat deposition influence the pharmacokinetic disposition of subcutaneously administered moxidectin and ivermectin in pigs? J Vet Pharmacol Ther 25(5):351–357

Currie BJ, McCarthy JS (2010) Permethrin and ivermectin for scabies. N Engl J Med 362(8):717–725. https://doi.org/10.1056/NEJMct0910329

Currie BJ, Harumal P, McKinnon M, Walton SF (2004) First documentation of *in vivo* and *in vitro* ivermectin resistance in *Sarcoptes scabiei*. Clin Infect Dis 39(1):e8-12. https://doi.org/10.1086/421776

Death CE, Taggart DA, Williams DB, Milne R, Schultz DJ, Holyoake C, Warren KS (2011) Pharmacokinetics of moxidectin in the southern hairy-nosed wombat (*Lasiorhinus latifrons*). J Wildl Dis 47(3):643–649. https://doi.org/10.7589/0090-3558-47.3.643

Doherty E, Burgess S, Mitchell S, Wall R (2018) First evidence of resistance to macrocyclic lactones in *Psoroptes ovis* sheep scab mites in the UK. Vet Rec 182(4):106. https://doi.org/10.1136/vr.104657

Donadello K, Cristallini S, Taccone FS, Lorent S, Vincent JL, de Backer D, Jacobs F (2013) Strongyloides disseminated infection successfully treated with parenteral ivermectin: case report with drug concentration measurements and review of the literature. Int J Antimicrob Agents 42(6):580–583. https://doi.org/10.1016/j.ijantimicag.2013.07.015

Dowling PM (2012) Ivermectin and moxidectin toxicosis. In: Wilson DA (ed) Clinical Veterinary Advisor: The Horse. Elsevier Saunders, St Louis

Espinosa J, Ráez-Bravo A, López-Olvera JR, Pérez JM, Lavín S, Tvarijonaviciute A, Cano-Manuel FJ, Fandos P, Soriguer RC, Granados JE, Romero D, Velarde R (2017) Histopathology, microbiology and the inflammatory process associated

with *Sarcoptes scabiei* infection in the Iberian ibex. Capra Pyrenaica Parasit Vectors 10(1):596. https://doi.org/10.1186/s13071-017-2542-5

European Medicines Agency (2017). Moxidectin-containing veterinary medicines used in cattle, sheep and horses. https://www.ema.europa.eu/en/medicines/veterinary/referrals/moxidectin-containing-veterinary-medicines-used-cattle-sheep-horses. Accessed 16/11/2021.

Fazzio L, Moreno L, Galvan W, Canton C, Alvarez L, Streitenberger N, Sánchez R, Lanusse C, Sanabria R (2019) Pharmacokinetic profile and anthelmintic efficacy of moxidectin administered by different doses and routes to feedlot calves. Vet Parasitol 266:73–79. https://doi.org/10.1016/j.vetpar.2018.12.016

Huffam SE, Currie BJ (1998) Ivermectin for *Sarcoptes scabiei* hyperinfestation. Int J Infect Dis 2(3):152–154. https://doi.org/10.1016/s1201-9712(98)90118-7

Khan SA, Kuster DA, Hansen SR (2002) A review of moxidectin overdose cases in equines from 1998 through 2000. Vet Hum Toxicol 44(4):232–235

Lee VK, Tiwary AK, Sharma-Reddy P, Lieber KA, Taylor DK, Mook DM (2009) Moxidectin toxicity in senescence-accelerated prone and resistant mice. Comp Med 59(3):227–233

Lifschitz A, Virkel G, Imperiale F, Sutra JF, Galtier P, Lanusse C, Alvinerie M (1999) Moxidectin in cattle: correlation between plasma and target tissues disposition. J Vet Pharmacol Ther 22(4):266–273

Losson B, Lonneux JF (1993) Field efficacy of injectible moxidectin in cattle naturally infested with *Chorioptes bovis* and *Sarcoptes scabiei*. Vet Parasitol 51(1–2):113–121

Lumaret JP, Errouissi F, Floate K, Römbke J, Wardhaugh K (2012) A review on the toxicity and non-target effects of macrocyclic lactones in terrestrial and aquatic environments. Curr Pharm Biotechnol 13(6):1004–1060. https://doi.org/10.2174/138920112800399257

Martin AM, Richards SA, Fraser TA, Polkinghorne A, Burridge CP, Carver S (2019) Population-scale treatment informs solutions for control of environmentally transmitted wildlife disease. J Appl Ecol 56:2363–2375

Menez C, Sutra JF, Prichard R, Lespine A (2012) Relative neurotoxicity of ivermectin and moxidectin in Mdr1ab (-/-) mice and effects on mammalian GABA(A) channel activity. PLoS Negl Trop Dis 6(11):e1883. https://doi.org/10.1371/journal.pntd.0001883

Mesa LM, Hörler J, Lindt I, Gutiérrez MF, Negro L, Mayora G, Montalto L, Ballent M, Lifschitz A (2018) Effects of the antiparasitic drug moxidectin in cattle dung on zooplankton and benthic invertebrates and its accumulation in a water-sediment system. Arch Environ Contam Toxicol 75(2):316–326. https://doi.org/10.1007/s00244-018-0539-5

Moroni B, Valldeperes M, Serrano E, López-Olvera JR, Lavín S, Rossi L (2020) Comment on: "The treatment of sarcoptic mange in wildlife: a systematic review." Parasit Vectors 13(1):471. https://doi.org/10.1186/s13071-020-04347-0

Mounsey KE, Holt DC, McCarthy JS, Currie BJ, Walton SF (2009) Longitudinal evidence of increasing *in vitro* tolerance of scabies mites to ivermectin in scabies-endemic communities. Arch Dermatol 145(7):840–841. https://doi.org/10.1001/archdermatol.2009.125

Mounsey KE, Bernigaud C, Chosidow O, McCarthy JS (2016) Prospects for moxidectin as a new oral treatment for human scabies. PLoS Negl Trop Dis 10(3):e0004389. https://doi.org/10.1371/journal.pntd.0004389

Mounsey KE, Walton SF, Innes A, Cash-Deans S, McCarthy JS (2017) *In vitro* efficacy of moxidectin versus ivermectin against *Sarcoptes scabiei*. Antimicrob Agents Chemother 61(8) https://doi.org/10.1128/aac.00381-17

Mueller RS (2004) Treatment protocols for demodicosis: an evidence-based review. Vet Dermatol 15(2):75–89. https://doi.org/10.1111/j.1365-3164.2004.00344.x

Muniz MS, Halbach K, Alves Araruna IC, Martins RX, Seiwert B, Lechtenfeld O, Reemtsma T, Farias D (2021) Moxidectin toxicity to zebrafish embryos: bioaccumulation and biomarker responses. Environ Pollut 283:117096. https://doi.org/10.1016/j.envpol.2021.117096

Nakagawa TL, Takai Y, Kubo M, Sakai H, Masegi T, Yanai T (2009) A pathological study of sepsis associated with sarcoptic mange in raccoon dogs (*Nyctereutes procyonoides*) in Japan. J Comp Pathol 141(2–3):177–181. https://doi.org/10.1016/j.jcpa.2009.05.003 (Epub 2009 Jun 18 PMID: 19539304)

Old JM, Skelton CJA, Stannard HJ (2021) The use of Cydectin® by wildlife carers to treat sarcoptic mange in free-ranging bare-nosed wombats (*Vombatus ursinus*). Parasitol Res 120(3):1077–1090. https://doi.org/10.1007/s00436-020-07012-8

Prichard R, Ménez C, Lespine A (2012) Moxidectin and the avermectins: consanguinity but not identity. Int J Parasitol Drugs Drug Resist 2:134–153. https://doi.org/10.1016/j.ijpddr.2012.04.001

Virbac Animal Health (2021) Product insert: Cydectin Pour-on for Cattle and Red Deer.

Rowe ML, Whiteley PL, Carver S (2019) The treatment of sarcoptic mange in wildlife: a systematic review. Parasit Vectors 12(1):99. https://doi.org/10.1186/s13071-019-3340-z

Ruykys L, Breed B, Schultz D, Taggart D (2013) Effects and treatment of sarcoptic mange in southern hairy-nosed wombats (*Lasiorhinus latifrons*). J Wildl Dis 49(2):312–320. https://doi.org/10.7589/2012-10-256

Sallovitz JM, Lifschitz A, Imperiale F, Virkel G, Lanusse C (2003) A detailed assessment of the pattern of moxidectin tissue distribution after pour-on treatment in calves. J Vet Pharmacol Ther 26(6):397–404

Schraven AL, Stannard HJ, Old JM (2021) A systematic review of moxidectin as a treatment for parasitic infections in mammalian species. Parasitol Res 120(4):1167–1181. https://doi.org/10.1007/s00436-021-07092-0

Shan Q, Haddrill JL, Lynch JW (2001) Ivermectin, an unconventional agonist of the glycine receptor chloride channel. J Biol Chem 276(16):12556–12564. https://doi.org/10.1074/jbc.M011264200

Sturgess-Osborne C, Burgess S, Mitchell S, Wall R (2019) Multiple resistance to macrocyclic lactones in the sheep scab mite *Psoroptes ovis*. Vet Parasitol 272:79–82. https://doi.org/10.1016/j.vetpar.2019.07.007

Sung YF, Huang CT, Fan CK, Lin CH, Lin SP (2009) Avermectin intoxication with coma, myoclonus, and polyneuropathy. Clin Toxicol (phila) 47(7):686–688. https://doi.org/10.1080/15563650903070901

van Mol W, De Wilde N, Casaert S, Chen Z, Vanhecke M, Duchateau L, Claerebout E (2020) Resistance against macrocyclic lactones in *Psoroptes ovis* in cattle. Parasit Vectors 13(1):127. https://doi.org/10.1186/s13071-020-04008-2

van Westerloo DJ, Landman GW, Prichard R, Lespine A, Visser LG (2014) Persistent coma in *Strongyloides* hyperinfection syndrome associated with persistently increased ivermectin levels. Clin Infect Dis 58(1):143–144

Walton SF, McBroom J, Mathews JD, Kemp DJ, Currie BJ (1999) Crusted scabies: A molecular analysis of *Sarcoptes scabiei* variety *hominis* populations from patients with repeated infestations. Clin Infect Dis 29(5):1226–1230. https://doi.org/10.1086/313466