Justus-Liebig-Universität Gießen

Interdisziplinäres Forschungszentrum
für biowissenschaftliche Grundlagen der Umweltsicherung

Institut für Bodenkunde und Bodenerhaltung

Stoffeigenschaften und Umweltverhalten von Ivermectin und anderen Antiparasitika im One Health-Kontext: Interdisziplinäre Herausforderungen für den Bodenschutz

Dissertation

vorgelegt von

Andre Patrick Heinrich

Gießen, 2025

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Abkürzungsverzeichnis

AS	Künstliches Bodensubstrat (*Artificial Soil*)
BVL	Bundesamt für Verbraucherschutz und Lebensmittelsicherheit
C_{org}	Organischer Kohlenstoff (*Organic Carbon*)
DT	Dissipationszeit (*Dissipation Time*), z. B. als DT_{50} oder DT_{90}
dw	Trockengewicht (*dry weight*)
EFSA	Europäische Behörde für Lebensmittelsicherheit (*European Food Safety Authority*)
EMA	Europäische Arzneimittel-Agentur (*European Medicines Agency*)
ERA	Umweltrisikobewertung (*Environmental Risk Assessment*)
EU	Europäische Union
FAO	Welternährungsorganisation (*Food and Agriculture Organization of the United Nations*)
HPLC	Hochleistungsflüssigkeitschromatographie (*High Performance Liquid Chromatography*)
K_D	Verteilungskoeffizient (Sorptionskoeffizient)
K_F	Freundlich-Koeffizient (Sorptionskoeffizient)
K_{OC}	Verteilungskoeffizient, normiert auf organischen Kohlenstoff
K_{OW}	n-Octanol-Wasser-Verteilungskoeffizient
LC_{50}	Halbmaximale letale Konzentration (*Lethal Concentration*), die bei 50 % der getesteten Organismen zur Mortalität führt
LUFA	Landwirtschaftliche Untersuchungs- und Forschungsanstalt (Speyer)
OECD	Organisation für wirtschaftliche Zusammenarbeit und Entwicklung (*Organisation for Economic Co-operation and Development*)
PEC	*Predicted Environmental Concentration*
PNEC	*Predicted No Effect Concentration*
QSAR	Quantitative Struktur-Wirkungs-Beziehung (*Quantitative Structure-Activity Relationship*)
RMM	Risikominderungsmaßnahme (*Risk Mitigation Measure*)
RQ	*Risk Quotient*
SD	Standardabweichung (*Standard Deviation*)
SDG	Ziel für nachhaltige Entwicklung (*Sustainable Development Goal)*
SPE	Festphasenextraktion (*Solid-Phase Extraktion*)
UBA	Umweltbundesamt
UN	Vereinte Nationen (*United Nations*)
UNEP	Umweltprogramm der Vereinten Nationen (*UN Environment Programme*)
WHO	Weltgesundheitsorganisation (*World Health Organization*)
WOAH	Weltorganisation für Tiergesundheit (*World Organisation for Animal Health*)

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Zusammenfassung

Die kumulative Dissertation untersucht die Stoffeigenschaften und das Umweltverhalten des Veterinär-Antiparasitikums Ivermectin und weiterer verwandter Wirkstoffe. Ziel ist es, die Umweltrisiken dieser Substanzen aus einer *One Health* Perspektive zu betrachten. Diese strebt die ganzheitliche Betrachtung der Zusammenhänge zwischen menschlicher Gesundheit, Tiergesundheit und Umweltschutz an. Die Wirkstoffe gehören zur Gruppe der makrozyklischen Laktone, die in Human- und Veterinärmedizin sowie im Pflanzenschutz zur Kontrolle von Schadorganismen verwendet werden. Zunehmend wird auch ein Einsatz in der Vektorkontrolle diskutiert. Der breite Einsatz der Wirkstoffe wirft daher Fragen nach der Vereinbarkeit von Gesundheitszielen und Umweltschutz im Sinne von *One Health* auf.

I) Sorptionsversuche ergaben, dass Ivermectin, Doramectin, Abamectin und Moxidectin stark in Böden und Sedimenten binden. Dies liegt an ihrer ausgeprägten Hydrophobie und ihrer hohen Bindungsaffinität zu organischer Substanz. Die auf den organischen Kohlenstoff normierten Sorptionskoeffizienten (K_{OC}-Werte) zeigten, dass die Wirkstoffe in der Umwelt nur eine geringe Mobilität aufweisen. Ein wichtiger Indikator für das Umweltverhalten von organischen Schadstoffen ist zudem der log K_{OW}-Verteilungskoeffizient, der Hinweise auf deren Verteilung und Mobilität in der Umwelt gibt. Für makrozyklische Laktone könnten diese K_{OW}-Werte teilweise zu niedrig eingeschätzt sein. Dies betrifft vor allem Fälle, in denen Bestimmungsmethoden verwendet wurden, die für sehr lipophile Substanzen weniger geeignet sind.

II) Die Bioakkumulation von Ivermectin in Regenwürmern wurde nach OECD-Testrichtlinie 317 untersucht. Das standardisierte Testverfahren mit dem Kompostwurm *Eisenia fetida* und künstlichem Testsubstrat deutete nur leichte Bioakkumulation an. In realistischeren Testszenarien (mit natürlichem Boden und den Regenwurmarten *Aporrectodea caliginosa* und *Lumbricus terrestris*) wurden moderat höhere Akkumulationsfaktoren festgestellt. Dies deutete darauf hin, dass das tatsächliche Risiko für Bioakkumulation in natürlichen Systemen höher sein könnte als bisher angenommen. Weiter wurde durch die Ergebnisse auf die geringe Bioverfügbarkeit und mögliche Persistenz von Ivermectin in Böden hingewiesen.

III) Der Einsatz von Ivermectin zur Malariavektorkontrolle durch behandelte Nutztiere wurde ebenfalls betrachtet. Vor allem in tropischen und subtropischen Regionen, in denen Tiere großflächig mit Ivermectin behandelt werden, könnten ökotoxikologische Risiken für Dung- und Bodenorganismen bestehen. Dieses Risiko ergibt sich aus den geringen Kenntnissen des Umweltverhaltens unter den dortigen klimatischen Bedingungen sowie begrenzten Daten zu regionalen Dung- und Bodenorganismen. Um diesen Risiken vorzubeugen, sind lokal angepasste Risikominderungsmaßnahmen nötig: beispielsweise die Lagerung von Dung unter Bedingungen, die den Abbau von Ivermectin fördern oder gezielte Behandlungsempfehlungen.

Die Ergebnisse bestätigen, dass Ivermectin und verwandte makrozyklische Laktone ein Risiko für Dung- und Bodenorganismen darstellen. Zudem könnte ihre tatsächliche Hydrophobie bislang unterschätzt sein, was systematische Neubestimmungen nötig macht. Vor diesem Hintergrund erscheint es sinnvoll, den *One Health*-Ansatz bei zukünftigen Bewertungen stärker zu berücksichtigen. Eine fachübergreifende Betrachtung ist vor allem bei schwer abbaubaren und bioakkumulierenden Stoffen von Bedeutung. Verlässliche Daten sind dabei die Grundlage für eine robuste Risikobewertung und eine wirksame Regulierung von Chemikalien.

Abstract

This cumulative dissertation investigates the substance properties and environmental behavior of the veterinary antiparasitic drug ivermectin and other related substances. The aim is to consider the ecological risks of these substances from a One Health perspective, which emphasizes the links between human health, animal health, and environmental protection. The active substances belong to the group of macrocyclic lactones, which are used in human and veterinary medicine as well as in plant protection. Their use in vector control is also being discussed. The widespread use of these active substances therefore raises questions about the compatibility of health objectives and environmental protection in the sense of One Health.

I) Sorption experiments confirmed that ivermectin, doramectin, abamectin, and moxidectin strongly bind in soils and sediments. Their strong sorption results from their pronounced hydrophobicity and affinity to organic matter. The measured organic carbon-normalized sorption coefficients (K_{OC}-values) suggest that the compounds exhibit only slight mobility in the environment. Another key indicator of the environmental behavior of organic pollutants is the log K_{OW} partition coefficient, which provides information on their distribution and mobility. For macrocyclic lactones, these values might currently be underestimated, particularly when less suitable test methods are applied.

II) The bioaccumulation of ivermectin in earthworms was investigated according to OECD test guideline 317. The standardized test method with the compost worm *Eisenia fetida* and artificial test substrate indicated only slight bioaccumulation. In more realistic test scenarios, using natural soil and the earthworm species *Aporrectodea caliginosa* and *Lumbricus terrestris*, moderately higher accumulation factors were observed. This suggests that the actual risk of bioaccumulation in natural systems could be higher than assumed. The limited bioavailability and potential persistence of ivermectin in soils were also highlighted.

III) The use of ivermectin for malaria vector control with treated livestock was also considered. Ecotoxicological risks for dung and soil organisms may occur, especially in tropical and subtropical regions where animals could be treated with ivermectin on a large scale. This risk arises from the limited knowledge of environmental behavior under local climatic conditions and limited data on regional soil and dung fauna. To reduce these risks, locally adapted risk mitigation measures are necessary, for example through appropriate storage of dung to promote ivermectin degradation or through targeted recommendations for livestock treatment.

The results confirm that ivermectin and other macrocyclic lactones may pose a risk to dung and soil organisms. In addition, their actual hydrophobicity is likely to be underestimated in some cases, which could make new assessments necessary. Therefore, it seems reasonable to integrate the One Health mindset in future risk assessments. An interdisciplinary approach is particularly important for substances that are potentially persistent or bioaccumulative. Reliable data is therefore the basis for sound risk assessment and effective chemical regulation.

1 Erweiterte Zusammenfassung

1.1 Allgemeine Einführung

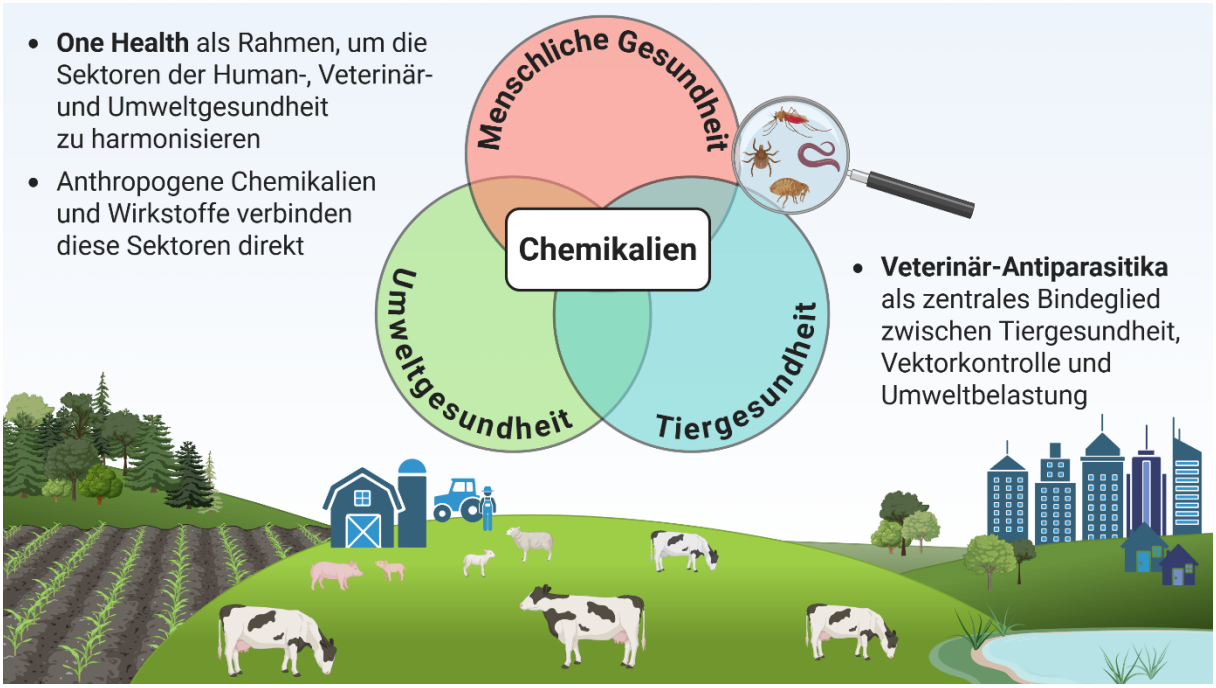
Veterinärmedizinische Antiparasitika sind essenziell für die Erhaltung der Tiergesundheit und die moderne Landwirtschaft. Sie werden weltweit zur Bekämpfung von Endo- und Ektoparasiten bei Nutztieren eingesetzt, da Parasiten schwerwiegende Infektionskrankheiten verursachen und erhebliche wirtschaftliche Schäden anrichten können (Deplazes et al., 2021). Besonders die Wirkstoffgruppe der makrozyklischen Laktone – wie Ivermectin, Doramectin oder Moxidectin – ist aufgrund ihrer hohen Wirksamkeit und ihres breiten Wirkspektrums seit über 40 Jahren von zentraler Bedeutung (Campbell et al., 1983; Omura, 2008; Deplazes et al., 2021). Nach der Verabreichung und Wirkung im Nutztier, dem Zielorganismus, gelangen viele Veterinär-Arzneimittel über Ausscheidungen behandelter Tiere in die Umwelt. Dort können sie verweilen und schädliche Auswirkungen auf Nichtzielorganismen haben (Díaz-Cruz et al., 2003; Hamscher und Mohring, 2012; Lim et al., 2013; Kaczala und Blum, 2016; Charuaud et al., 2019).

Diese unbeabsichtigte Wirkung der Substanzen in der Umwelt wird als ökotoxikologischer Effekt beschrieben (Fent, 2013). Während die ökotoxikologischen Auswirkungen der makrozyklischen Laktone auf Nichtzielorganismen in Teilen bekannt sind (Abschnitt 1.2.7), bestehen weiterhin Wissenslücken bezüglich ihrer Stoffeigenschaften und ihres langfristigen Umweltverhaltens (UBA, 2019). Dies ist besonders problematisch, da Veterinär-Antiparasitika eine zentrale Schnittstelle bilden: zwischen Tiergesundheit, sicheren tierischen Lebensmitteln, Risiken für Böden und Gewässer sowie der Kontrolle von auch für Menschen gefährlichen Krankheitserregern (Abb. 1). Ivermectin, das bekannteste Antiparasitikum aus der Gruppe der makrozyklischen Laktone, ist auch für die Anwendung bei Menschen zur Behandlung von Parasitenerkrankungen zugelassen (Larivière et al., 1987; Crump und Ōmura, 2011). Die Entdeckung der Avermectine – als Grundlage für die Entwicklung von Ivermectin – wurde zudem im Jahr 2015 mit dem Nobelpreis für Physiologie oder Medizin ausgezeichnet (Watts, 2015). Dies unterstreicht, wie breit der Einsatzbereich von Ivermectin sowohl in der Tier- als auch in der Humanmedizin ist. Weiter verdeutlicht es die enge Verbindung dieser Gesundheitssektoren im Sinne von *One Health*.

One Health und Veterinär-Antiparasitika im Kontext globaler Umweltprobleme

Die Umweltbelastung durch Chemikalien ist ein Bestandteil der *Triple Planetary Crisis*, die sich aus dem Klimawandel, Biodiversitätsverlust und der Umweltverschmutzung zusammensetzt (UN, 2021). Der Eintrag von Chemikalien aus Industrie, Landwirtschaft und Medizin in die Umwelt nimmt dabei weltweit zu und wirkt sich zunehmend negativ auf Ökosysteme und die menschliche Gesundheit aus (Fuller et al., 2022; Shetty et al., 2023). Die Umweltbelastung durch neuartige chemische Stoffe überschreitet zudem bereits heute die planetaren Belastungsgrenzen (*Planetary Boundaries*) (Persson et al., 2022).

Vor diesem Hintergrund wurde im Jahr 2023 das *Global Framework on Chemicals* geschaffen, um den nachhaltigen Umgang mit Chemikalien zu fördern und schädliche Umweltauswirkungen



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zu minimieren (UNEP, 2023). Der *One Health*-Ansatz betont diese komplexen Zusammenhänge. Er macht deutlich, dass die Gesundheit von Menschen, Tieren, Pflanzen und Ökosystemen miteinander verknüpft und voneinander abhängig ist (FAO, UNEP, WHO und WOAH, 2022). Dennoch steht die teils geringe Berücksichtigung ökologischer Aspekte im *One Health*-Kontext nicht im Einklang mit dem Ziel, Gesundheit tatsächlich ganzheitlich zu sehen (Essack, 2018). Ein verbindendes Element dieser Gesundheitssektoren sind zudem anthropogene Chemikalien, die alle Umweltmedien und Ebenen von *One Health* beeinträchtigen. Der Fokus in diesem Spannungsfeld liegt hier auf Veterinär-Antiparasitika, die durch ihre Stoffeigenschaften und ihr breites Wirkspektrum terrestrische und aquatische Ökosysteme durchdringen und belasten (Horvat et al., 2012; Charuaud et al., 2019; Chen et al., 2021). Gleichzeitig werden manche der als Arzneimittel verwendeten Wirkstoffe auch als Insektizide eingesetzt (Abschnitt 1.2.5), was die Anzahl möglicher Zielkonflikte erhöht (Alvarez et al., 2022; Hamid-Adiamoh et al., 2024).

1.2 Kontext der Fragestellungen

1.2.1 Anwendung von Veterinär-Antiparasitika

Antiparasitika gehören zu den umsatzstärksten Produktgruppen unter den Veterinär-Arzneimitteln. Besonders in der Nutztierhaltung tragen sie zur Gesunderhaltung von Tieren bei, indem sie die Krankheitslast durch Parasiten verringern und so die Produktivität der Tierproduktion sichern (Taylor et al., 2016; Deplazes et al., 2021). Der europäische Markt für Veterinär-Arzneimittel wird dabei etwa zur Hälfte von Produkten für Haustiere dominiert, während rund 25 % auf Nutztiere (Rinder, Schweine, Schafe) entfallen sowie etwa 10 % auf Geflügel

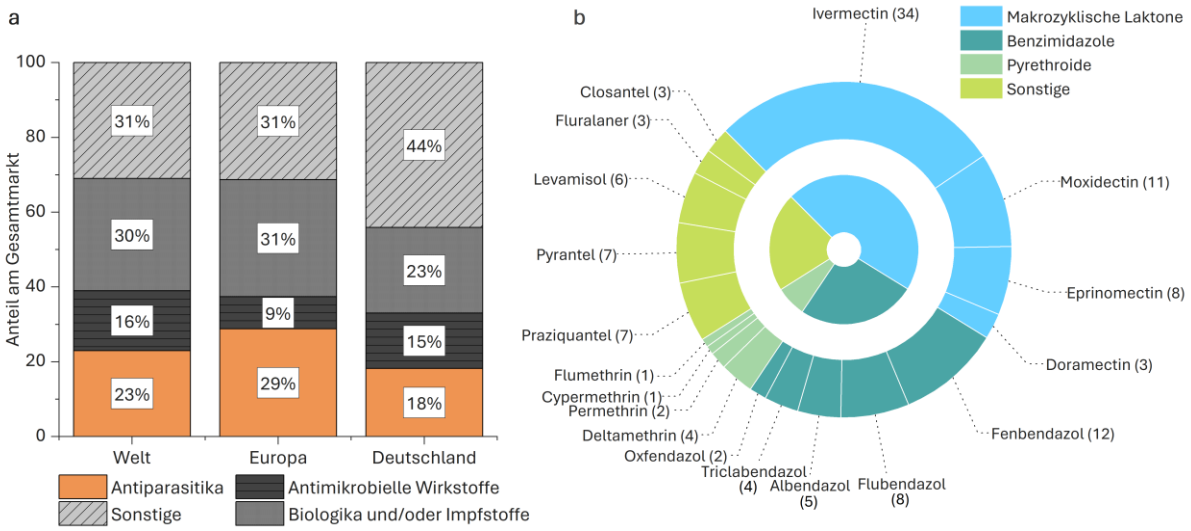

Abbildung 2 | Marktübersicht Veterinär-Arzneimittel. **a**, Näherungsweise Marktaufteilung der verschiedenen Produktkategorien im Tierarzneimittelmarkt, weltweit (Selzer und Epe, 2021), in Europa (AnimalhealthEurope, 2024) und in Deutschland (BfT, 2024); vereinfachte Darstellung. **b**, Maßgeblich relevante Veterinär-Antiparasitika (nach Taylor et al. (2016), Deplazes et al. (2021), Selzer und Epe (2021)), ohne spezifische Antiprotozoika, für Nutztiere (Rinder, Schweine, Schafe, Ziegen, Pferde, Hühner). Zahlen im Klammern zeigen die Anzahl der in Deutschland verkehrsfähigen Arzneimittel, abgerufen im öffentlichen Teil der Arzneimitteldatenbank des Bundes mit der Rechercheoberfläche AMIce (BfArM, 2025). n = 121, enthält acht Kombinationsprodukte mit je zwei der aufgeführten Wirkstoffe. **a–b**, Eigene Darstellungen.

(AnimalhealthEurope, 2024). Die näherungsweise Verteilung nach Produktkategorien ist in Abb. 2a dargestellt. Obwohl die Erhebungsmethoden variieren, zeigt sich, dass Antiparasitika 18–29 % der verkauften Veterinär-Arzneimittel ausmachen. Innerhalb der Veterinär-Antiparasitika etablierten sich makrozyklische Laktone als eine der bedeutendsten Wirkstoffgruppen. Seit der Markteinführung von Ivermectin in den 1980er Jahren wurden weitere Vertreter entwickelt und kommerzialisiert, die eine hohe Wirksamkeit und lange Wirkdauer vereinen (Shoop et al., 1995). Werden Antiparasitika zur Behandlung von parasitären Wurmerkrankungen eingesetzt, spricht man von Anthelminthika (*griech.* „helmins“ = Wurm), z. B. bei Magen-Darm-Strongyliden oder Lungenwürmern (*Dictyocaulus* spp.). Obwohl Anthelminthika in fast allen Tierarten eingesetzt werden, liegt der Schwerpunkt auf der Behandlung von Wiederkäuern (Taylor et al., 2016).

Avermectine und Milbemycine

Die makrozyklischen Laktone werden in Avermectine und Milbemycine unterschieden (Tab. 1). Beide Stoffklassen sind für eine Vielzahl von Anwendungen zugelassen (Shoop et al., 1995; Prichard et al., 2012). Doch die hohe Relevanz der Wirkstoffe (Abb. 2b) zeigt sich nicht nur im Nutztierbereich: so konnten im öffentlichen Teil der Arzneimitteldatenbank des Bundes insgesamt 56 in Deutschland verkehrsfähige Arzneimittel mit den Wirkstoffen Ivermectin, Moxidectin, Eprinomectin und Doramectin für diese Tierarten ermittelt werden (BfArM, 2025). Gleichzeitig existieren 87 verkehrsfähige Arzneimittel mit Selamectin als Wirkstoff, allerdings nur für Hunde und Katzen. Auch die fluorierten Substanzen der Gruppe der Isoxazoline, die Wirkstoffe Lotilaner, Afoxolaner und Sarolaner sind nur für Hunde und Katzen verfügbar mit 60, 57 bzw. 51 verkehrsfähigen Arzneimitteln (BfArM, 2025). Für diese Tiere werden Eprinomectin, Selamectin, und Moxidectin dennoch als wichtige Wirkstoffe (*major use*) angesehen (EMA, 2023).

Herkunft und Unterscheidung der Wirkstoffe

Avermectine wurden erstmals 1979 aus dem Bakterium *Streptomyces avermitilis* isoliert (Burg et al., 1979). Viele Arten der hauptsächlich in Böden vorkommenden Gattung *Streptomyces* können zahlreiche bioaktive Naturstoffe synthetisieren. Neben den als Antiparasitika genutzten Avermectinen und Milbemycinen gehören auch andere makrozyklische Verbindungen zu den von *Streptomyces*-Arten produzierten Stoffen, darunter Makrolidantibiotika wie Erythromycin und Spiramycin (Aigle et al., 2014; Alam et al., 2022). Milbemycine wurden bereits 1967 in einer Fermentationskultur von *Streptomyces hygroscopicus* identifiziert (Prichard et al., 2012). Während einige dieser Wirkstoffe für den humanmedizinischen Einsatz weiterentwickelt wurden, finden makrozyklische Laktone zusätzlich breite Anwendung in der Veterinärmedizin (Omura, 2008; Taylor et al., 2016). Der Begriff *makrozyklische Laktone* wird hier für die als Antiparasitika verwendeten Wirkstoffe dieser Gruppe verwendet. Zur weiteren Übersicht sind die im Rahmen der eigenen Veröffentlichungen betrachteten Stoffe und weitere in Tab. 1 aufgeführt.

Tabelle 1 | Übersicht der makrozyklischen Laktone. Die Wirkstoffe sind ursprünglich Fermentationsprodukte verschiedener *Streptomyces*-Arten. Mischungsverhältnisse der Bestandteile sind in Produktspezifikationen und Zulassungsunterlagen festgelegt, basierend auf der Ausbeute der Fermentation und Reinigungs- und Standardisierungsprozessen. Typischer Hauptbestandteil sind 70–90 % der B_{1a}- bzw. A4-Verbindung.

Avermectine					
Wirkstoff	**Ursprung**	**Bestandteile**	**Summenformel**	**CAS-Nr.**	***M*** **(g/mol)**
Eprinomectin	*S. avermitilis*	Eprinomectin B_{1a}	$C_{50}H_{75}NO_{14}$	133305-88-1	914,14
		Eprinomectin B_{1b}	$C_{49}H_{73}NO_{14}$	133305-89-2	900,12
Abamectin	*S. avermitilis*	Avermectin B_{1a}	$C_{48}H_{72}O_{14}$	65195-55-3	873,09
		Avermectin B_{1b}	$C_{47}H_{70}O_{14}$	65195-56-4	859,06
Ivermectin	*S. avermitilis*	Ivermectin B_{1a}	$C_{48}H_{74}O_{14}$	71827-03-7	875,11
		Ivermectin B_{1b}	$C_{47}H_{72}O_{14}$	70209-81-3	861,08
Emamectin (Benzoat)	*S. avermitilis*	Emamectin B_{1a}	$C_{56}H_{81}NO_{15}$	138511-97-4	1008,26
		Emamectin B_{1b}	$C_{55}H_{79}NO_{15}$	138511-98-5	994,23
Doramectin	*S. avermitilis*[a]	Doramectin	$C_{50}H_{74}O_{14}$	117704-25-3	899,13
Selamectin	*S. avermitilis*[a]	Selamectin	$C_{43}H_{63}NO_{11}$	220119-17-5	769,97
Milbemycine					
Milbemycinoxim	*S. hygroscopicus*	Milbemycin A4 Oxime	$C_{32}H_{45}NO_7$	93074-04-5	555,71
		Milbemycin A3 Oxime	$C_{31}H_{43}NO_7$	114177-14-9	541,69
Milbemectin	*S. hygroscopicus*[b]	Milbemycin A4	$C_{32}H_{46}O_7$	51596-11-3	542,71
		Milbemycin A3	$C_{31}H_{44}O_7$	51596-10-2	528,69
Moxidectin	*S. cyanogriseus*[c]	Moxidectin	$C_{37}H_{53}NO_8$	113507-06-5	639,83

Quellen: Konsensinformationen nach Shoop et al. (1995), Nonaka et al. (2000), Prichard und Geary (2019) sowie CAS Common Chemistry (2025) und ChemSpider (2025)
[a] genetische Mutation von *S. avermitilis*; [b] subsp. *aureolacrimosus*; [c] subsp. *noncyanogenus*

1.2.2 Bodengesundheit und Bodenschutz

In Deutschland bildet das Bundes-Bodenschutzgesetz (BBodSchG) die rechtliche Grundlage für den Bodenschutz. Zweck dieses Gesetzes ist, die Bodenfunktionen nachhaltig zu sichern oder wiederherzustellen. Die natürlichen Funktionen unbelasteter Böden sind dabei die essenzielle Lebensgrundlage des Menschen. Dazu zählen auch die Bereitstellung von Pflanzennährstoffen oder die Regulierung des Wasserhaushalts sowie Funktionen als Puffer und Filter gegenüber Schadstoffen. Widerstandsfähige und gesunde Böden tragen so dazu bei, die ökologischen und wirtschaftlichen Auswirkungen von intensiver Landnutzung und Bodenerosion zu verringern (BBodSchG; EEA, 2023). „Bodengesundheit" beschreibt daher die Fähigkeit eines Bodens, seine zentralen Funktionen nachhaltig zu erfüllen. Ein gesunder Boden steht so für einen Zustand, in dem dieser seine Funktionen und Dienstleistungen vollständig erbringen kann (EEA, 2023). In diesem Zusammenhang kann „Umweltgesundheit" als ein Maß für das Gesundheits- und Funktionsniveau der gesamten Umwelt verstanden werden (FAO, UNEP, WHO und WOAH, 2022).

Die Bundes-Bodenschutz- und Altlastenverordnung (BBodSchV) regelt hierzu weiter Vorsorgemaßnahmen gegen schädliche Bodenveränderungen. Zu diesen zählen in § 3 auch ausdrücklich Stoffeinträge, die „[...] den Bodenzustand irreversibel verändern und dadurch die Bodenfunktionen erheblich [beeinträchtigen]". Auch der Funktionsverlust durch Versiegelung wird als große Herausforderung im Bodenschutz betrachtet (Deutscher Bundestag, 2023). Im Fall des Stoffeintrags von veterinärmedizinischen Wirkstoffen gelangen diese vor allem über Ausscheidungen behandelter Tiere auf landwirtschaftlich genutzte und angrenzende Böden (Boxall et al., 2004; Hamscher und Mohring, 2012; Wohde et al., 2016b).

Bodenschutz ist auch ein wichtiges Anliegen der *Sustainable Development Goals* (SDGs) der Vereinten Nationen (UN, 2015). Insbesondere SDG 15 „Leben an Land" fordert, Böden vor Degradation zu schützen und ihre nachhaltige Nutzung sicherzustellen. Eine reduzierte Chemikalienbelastung steht auch im Zusammenhang mit SDG 6 „Sauberes Wasser und Sanitäreinrichtungen", da Umweltschadstoffe durch Erosion und Auswaschung über Böden in aquatische Ökosysteme gelangen. Weiter betont SDG 3 „Gesundheit und Wohlergehen", dass Todesfälle und Erkrankungen aufgrund gefährlicher Chemikalien und kontaminierter Böden bis 2030 verringert werden sollen. Zuletzt definierte SDG 12 „Nachhaltiger Konsum und Produktion" das Teilziel, bis 2020 die schädlichen Auswirkungen von Chemikalien auf Menschen und Umwelt zu reduzieren. Obwohl dieses Ziel unerreicht blieb, wurden dessen Kernpunkte verstärkt im *Global Framework on Chemicals* verankert (UNEP, 2023). Zusätzlich sind Böden mit vielen der planetaren Grenzen und deren Überschreitungen verbunden, wodurch ihr Schutz besondere strategische Beachtung verdient (Kopittke et al., 2021).

1.2.3 Begriffsbestimmungen und Hintergrund zum K_{OW}-Wert

Kenntnisse über die Affinität eines Stoffs zu unterschiedlichen Umweltmedien dienen der Abschätzung seiner Mobilität, Persistenz und Bioverfügbarkeit. Der **Verteilungskoeffizient K_D** beschreibt das Gleichgewichtsverhältnis zwischen der Konzentration eines Stoffs, der an einen Feststoff (Boden oder Sediment) sorbiert ist, und der Konzentration desselben Stoffs in einer wässrigen Phase (Formel 1). Er wird gemäß OECD-Richtlinie 106 durch Batch-Equilibrium-

Experimente bestimmt (OECD, 2000). Der K_D-Wert ist spezifisch für die untersuchte Matrix und unterliegt Variationen durch Bodenparameter wie dem organischen Kohlenstoff (C_{org}), pH-Wert oder der Textur. Hier ist $C_s^{ads}(eq)$ die Stoffkonzentration in der festen Phase bzw. $C_{aq}^{ads}(eq)$ die Stoffkonzentration in der wässrigen Phase, bei angenommenem Sorptionsgleichgewicht:

$$K_D = \frac{C_s^{ads}(eq)}{C_{aq}^{ads}(eq)} \quad \left[\frac{L}{kg}\right] \tag{1}$$

Da die Sorption hydrophober organischer Verbindungen stark mit dem Gehalt an organischer Bodensubstanz korreliert (Baker, 1997; OECD, 2000), wird zur besseren Vergleichbarkeit der **Verteilungskoeffizient K_{OC}** berechnet (Formel 2). Die Einbeziehung des f_{OC} (*fraction of organic carbon*) als Masseanteil des C_{org} der Probe erlaubt eine vergleichende Einschätzung der Sorptionseigenschaften, unabhängig vom individuellen C_{org}-Gehalt:

$$K_{OC} = \frac{K_D}{f_{OC}} \quad \left[\frac{L}{kg}\right] \tag{2}$$

Als weiterer relevanter Parameter beschreibt der **n-Octanol-Wasser-Verteilungskoeffizient K_{OW}** das Gleichgewicht zwischen der Konzentration eines Stoffs in *n*-Octanol und in Wasser und dient als Maß für die Hydrophobie (bzw. Lipophilie) einer Verbindung (Formel 3):

$$K_{OW} = \frac{C_{n-Octanol}}{C_{Wasser}} \tag{3}$$

Die experimentelle Bestimmung des K_{OW}-Werts ist definiert in OECD-Richtlinien 107 (OECD, 1995) und 123 (OECD, 2006). Für stark hydrophobe Substanzen ermittelt die neuere, in OECD-Richtlinie 123 beschriebene *Slow-Stirring*-Methode genauere K_{OW}-Werte. Dennoch wird für diese Substanzen manchmal auf K_{OW}-Werte aus der älteren und ungeeigneten *Shake-Flask*-Methode zurückgegriffen. Sowohl K_{OW}- als auch K_{OC}-Werte werden oft in der Form des dekadischen Logarithmus als log K_{OW} bzw. log K_{OC} angegeben. Zur K_{OW}-Bestimmung können auch *Quantitative Structure-Activity Relationship* (QSAR) Modelle herangezogen werden, die K_{OW}-Werte basierend auf molekularen Strukturparametern ermitteln (Cappelli et al., 2015). Weiter ist die Abschätzung K_{OW}-basierter K_{OC}-Werte möglich, da die Sorption organischer Stoffe innerhalb bestimmter Grenzen stark mit ihrer Hydrophobie korreliert (Sabljić et al., 1995; Baker, 1997; Doucette, 2003).

Hinsichtlich des Verbleibs in der Umwelt beschreibt die **Dissipationszeit** (*Dissipation Time*, DT) die Zeit (üblicherweise in Tagen), in der sich die Ausgangskonzentration eines Stoffes in einer Umweltmatrix (z. B. Boden) durch alle relevanten Prozesse reduziert. Dies beinhaltet neben dem Abbau (*Degradation*) auch Prozesse wie Sorption, Volatilisierung oder Auswaschung. Eine klare Trennung zwischen tatsächlichem Abbau und anderen Prozessen ist dabei unter praxisnahen Bedingungen oft nicht möglich, wodurch der Begriff Dissipation zielführender sein kann (Beulke und Brown, 2001). Dann bezeichnet **DT_{50}** die Zeit, in der 50 % und **DT_{90}** die Zeit, in der 90 % der initialen Konzentration dissipiert sind. Diese Zeiträume dienen zur Charakterisierung der Persistenz und können mittels OECD-Richtlinie 307 (OECD, 2002) für Stoffe in Böden durch

standardisierte Inkubationsexperimente abgeschätzt werden. Gemäß Anhang XIII der REACH-Verordnung (Verordnung (EG) Nr. 1907/2006) wird die Persistenz eines Stoffes anhand der DT_{50}-Werte beurteilt (beschrieben als Abbau-Halbwertszeit). Hiernach gilt ein Stoff als persistent, wenn der DT_{50}-Wert im Boden, Süßwasser- oder Flussmündungssediment 120 Tage übersteigt.

1.2.4 Stoffeigenschaften und Wirkmechanismus makrozyklischer Laktone

Die Gefährdung von Böden durch Veterinär-Antiparasitika, und im vorgestellten Fall durch makrozyklische Laktone, ergibt sich aus ihrem Wirkmechanismus und ihren Stoffeigenschaften: Avermectine und Milbemycine zeichnen sich durch chemische Stabilität und eine hohe Lipophilie aus (Shoop et al., 1995; Prichard et al., 2012). Diese Eigenschaften beeinflussen sowohl ihre Wirksamkeit als auch ihr Umweltverhalten. Aufgrund ihrer Hydrophobie besitzen sie eine hohe Affinität zu lipidhaltigen Geweben; dies führt zu langen Halbwertszeiten in behandelten Tieren. Diese hohe Gewebeverteilung verlängert die Wirkdauer im Zielorganismus, beeinflusst aber auch die Persistenz der Wirkstoffe nach der Exkretion. Zudem wird je nach Tierart und Verabreichungsform ein erheblicher Anteil der Dosis von Nutztieren unmetabolisiert und hauptsächlich über den Kot ausgeschieden (González Canga et al., 2009). Von dort aus können die Wirkstoffe wie Ivermectin langsam in die Umwelt übergehen (Liebig et al., 2010; Römbke et al., 2010; Wohde et al., 2016a). In Bezug auf ihr Umweltverhalten bestehen für makrozyklische Laktone jedoch teilweise Wissenslücken, beispielsweise bezüglich ihrer Stoffeigenschaften wie dem Grad der Lipophilie oder der Persistenz in Böden (UBA, 2019).

Avermectine und Milbemycine besitzen denselben grundlegenden Wirkmechanismus, obwohl sie hinsichtlich der Wechselwirkungen mit spezifischen Ionenkanälen Unterschiede in Wirksamkeit und Selektivität aufweisen (Prichard et al., 2012). Strukturell besitzen sie einen 16-gliedrigen makrozyklischen Laktonring, der dreidimensional mit einer Benzofuran- (C-2 bis C-8) sowie einer Spiroketalgruppe (C-17 bis C-25) verbunden ist (Abb. 3). Die Avermectine zeichnen sich durch eine Disaccharidgruppe an der C-13-Position aus; die Milbemycine sind an der C-13-Position unsubstituiert (Shoop et al., 1995; Lespine, 2013).

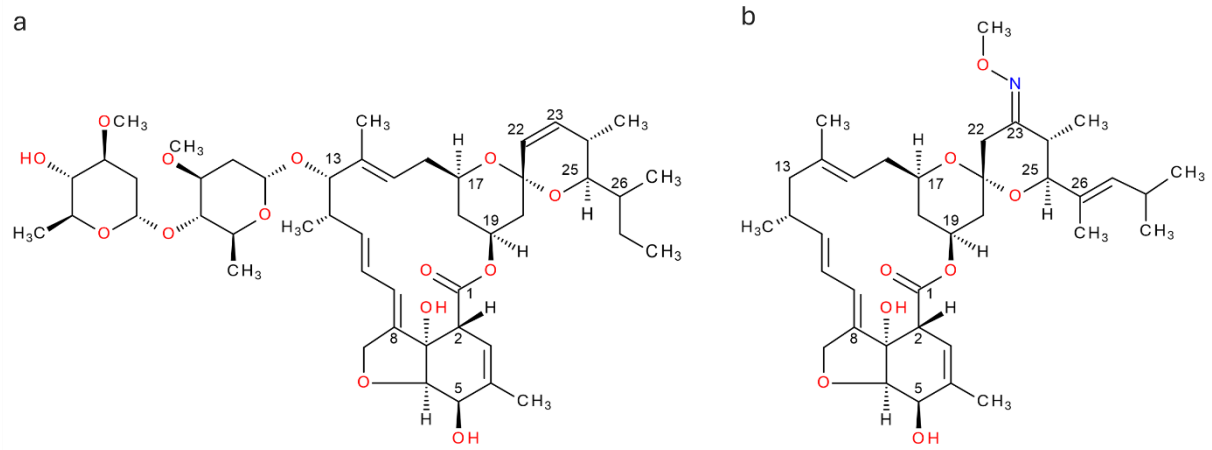

Abbildung 3 | Grundstrukturen der makrozyklischen Laktone. **a**, Struktur von Avermectin B_{1a} ($C_{48}H_{72}O_{14}$, Hauptbestandteil von Abamectin) als Vertreter der Avermectine, gekennzeichnet durch das makrozyklische Laktongerüst und die Disaccharid-Seitenkette. Variationen innerhalb der Avermectine ergeben sich hauptsächlich durch die Substitution an C-25 und die Bindung zwischen C-22 und C-23 (Einzel- oder Doppelbindung); **b**, Struktur von Moxidectin ($C_{37}H_{53}NO_8$) als Vertreter der Milbemycine. **a–b**, Strukturen nach Shoop et al. (1995) und Martin et al. (1997), eigene Darstellungen (erstellt mit BIOVIA Draw 25.1).

Der exakte Wirkmechanismus der Avermectine und Milbemycine ist nicht vollständig aufgeklärt. Wegen ihrer Wirkung gegen Endoparasiten und Ektoparasiten werden sie als Endektozide bezeichnet. Aufgrund ihrer hohen Aktivität gegen parasitäre Würmer, Spinnentiere und Insekten sowie ihrer geringen Toxizität für Säugetiere sind sie von großem Interesse für die Medizin und die Landwirtschaft (Prichard et al., 2012; Taylor et al., 2016). Für Ivermectin ist beschrieben, dass es auf das Nervensystem von Nematoden wirkt, indem es die Signalübertragung über den Neurotransmitter γ-Aminobuttersäure (GABA) an mindestens zwei Stellen beeinflusst. Einerseits stimuliert es die Freisetzung von GABA aus den Nervenenden, andererseits verbessert es die Bindung von GABA an spezifische Rezeptoren auf der postsynaptischen Membran. Durch diese verstärkte GABA-Bindung kommt es zu einem erhöhten Einstrom von Chlorid-Ionen in die Zelle, was zur Hyperpolarisation führt. Die Folge ist eine Lähmung der Muskulatur, die den Tod des Parasiten bedingt. Im Gegensatz dazu beschränkt sich die GABA-Signalübertragung bei Säugetieren auf das zentrale Nervensystem. Da Ivermectin bei therapeutischen Konzentrationen kaum die Blut-Hirn-Schranke passiert, ist die Wirkung auf das Nervensystem von Säugetieren in der Regel minimiert. Weitere Erkenntnisse zeigen zudem, dass makrozyklische Laktone in die Zellmembran eingebettet werden und an glutamatgesteuerte Chloridkanäle binden können. Auch diese Bindung führt zu einem vermehrten Einstrom von Chlorid-Ionen sowie der Lähmung des Parasiten (Shoop et al., 1995; Taylor et al., 2016). Unabhängig von strukturellen Unterschieden zeigen die Wirkstoffe der makrozyklischen Laktone lipidähnliche Eigenschaften, beispielsweise eine hohe Lipophilie, den Transport durch Lipoproteine in Lymphe und Plasma sowie die Speicherung im Fettgewebe (Lespine, 2013).

Umweltgefährdung durch Stoffeigenschaften

Während andere Arzneimittelgruppen – wie Antibiotika (Havelkova et al., 2016; Zhi et al., 2020) oder nichtsteroidale Antirheumatika (Parolini, 2020) – ebenfalls ökotoxikologische Effekte auf Invertebraten bewirken, ist dies nicht ihre klinische Zielsetzung und als Nebeneffekt zu sehen. Die Daseinsberechtigung der makrozyklischen Laktone als Arzneimittel erschließt sich jedoch aus ihrer toxischen Wirkung auf Invertebraten. Ihre selektive Sicherheit für Säugetiere gefährdet so auch eine Vielzahl ökologisch relevanter Nichtzielorganismen, darunter Dunginsekten, Regenwürmer (Lumbricidae), Springschwänze (Collembola), aber auch aquatische Invertebraten (Strong, 1992; Liebig et al., 2010; Lumaret et al., 2012; Finch et al., 2020; Junco et al., 2021).

Die ausgeprägte Hydrophobie (bzw. Lipophilie) der Wirkstoffe führt maßgeblich zu ihrer starken Bindung an feste Ausscheidungen (González Canga et al., 2009) sowie organische Bodenbestandteile (Krogh et al., 2008; Dionisio und Rath, 2016). Dies führt dazu, dass sie nur eingeschränkt für den mikrobiellen Abbau zur Verfügung stehen, welcher als einer der Hauptabbaupfade für z. B. Eprinomectin (Litskas et al., 2013) und Ivermectin (Lagos et al., 2022) in Böden identifiziert wurde. Gleichzeitig erhöht ihre starke Lipophilie das Risiko einer Bioakkumulation in Organismen. So gelten Substanzen mit einem log K_{OW}-Wert > 4 tendenziell als besonders bioakkumulationsfähig, da sie bevorzugt in lipophilen Kompartimenten von Organismen gespeichert werden können (Arnot et al., 2010; EMA, 2016; Proc et al., 2021). Für Ivermectin ist dieser Übergang in Nichtzielinvertebraten bereits für sedimentbewohnende

Glanzwürmer (*Lumbriculus variegatus* (Slootweg et al., 2010), Dungkäfer (*Thorectes lusitanicus* (Verdú et al., 2020)) oder Stechmücken (*Culex pipiens* (Lorente et al., 2023)) dokumentiert.

1.2.5 Einsatz als Insektizid und zur Vektorkontrolle

Makrozyklische Laktone finden nicht nur als Veterinär-Antiparasitika Anwendung, sondern auch als Pflanzenschutzmittel oder Insektizide im Sinne von *One Health* im Gesundheitswesen. Bei der Verwendung im Pflanzenschutz wird zwischen verschiedenen Anwendungen unterschieden, wobei Avermectine als insektizid und akarizid (gegen Milben und Zecken) wirkende Stoffe gelten (Jansson und Dybas, 1998). Ihre insektizide Aktivität ist eng mit ihrem Wirkmechanismus verknüpft, der sie für viele Invertebraten toxisch macht (Rugg et al., 2005). Ob sie als Antiparasitika, Insektizide oder Akarizide eingestuft werden, hängt dabei weniger von ihrer biologischen Wirkung, sondern mehr von der regulatorischen Einordnung ab.

Abamectin

Der Wirkstoff (als Gemisch aus Avermectin B_{1a} und Avermectin B_{1b}) wird in insektiziden und akariziden Pflanzenschutzmitteln eingesetzt. Er wirkt durch Kontakt und Aufnahme und zeigt eine translaminare Bewegung innerhalb der Pflanze, wodurch Schädlinge effektiv bekämpft werden (Beers et al., 1997; Pohanish, 2015). In Deutschland zugelassen sind nur Kombinationsprodukte die Abamectin und Pyrethrine enthalten (BVL, 2025). Abamectin wird vor allem zur Kontrolle von Milben und Thripsen in verschiedenen Zierpflanzen, Zitruspflanzen und Sonderkulturen wie Erdbeeren oder Tomaten verwendet (Jansson und Dybas, 1998; Alvarez et al., 2022). Der Wirkstoff ist in 18 EU-Ländern zur Verwendung in Pflanzenschutzmitteln zugelassen (EU Pesticides Database, 2025a). Hierbei handelt es sich um ein dynamisches Anwendungsfeld: beispielsweise wurde die Zulassung des Pflanzenschutzmittels Vertimec Pro, das Abamectin enthält, im Dezember 2022 durch das Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL) teilweise widerrufen (BVL, 2023a). Für den Einsatz an Zierpflanzen folgte ein weiterer teilweiser Widerruf (BVL, 2023b). Diese Widerrufe betrafen Anwendungen im Freiland und auf Balkonen aufgrund von Bedenken hinsichtlich des Schutzes von bestäubenden Insekten wie Bienen (Alvarez et al., 2022). Im Auftrag der Europäischen Behörde für Lebensmittelsicherheit (EFSA) wurden zudem mehrere Datenlücken bezüglich der Wirkung auf Nichtzielorganismen und dem Verbleib in der Umwelt identifiziert (Alvarez et al., 2022).

Emamectin

Der Wirkstoff ist in 17 EU-Ländern, jedoch nicht in Deutschland, zur Verwendung in Pflanzenschutzmitteln zugelassen (EU Pesticides Database, 2025b). Für Emamectin konnten somit keine in Deutschland verwendeten Pflanzenschutzmittel identifiziert werden. Die Substanz ist jedoch als im Jahr 2023 ausgeführter Wirkstoff gelistet (BVL, 2024). Die Anwendung im Pflanzenschutz erfolgt oft als thermisch stabileres und besser wasserlösliches Emamectin Benzoat (Jansson und Dybas, 1998). Die Verwendung in Form von Emamectin Benzoat führt überdies in vielen Fällen zu einer erhöhten Wirksamkeit (Rugg et al., 2005). Der Einsatz in Feld- und Gewächshausanwendungen richtet sich dabei insbesondere gegen blattfressende Lepidopteren-Larven an Sonderkulturen wie Weinreben, Tomaten oder Paprika (EFSA, 2012).

Milbemectin

Aus der Gruppe der Milbemycine ist Milbemectin (als Gemisch aus Milbemycin A4 und Milbemycin A3) in akariziden Pflanzenschutzmitteln in Deutschland zugelassen. Diese Mittel werden ebenfalls als bienengefährlich eingestuft (BVL, 2025). Wie für Abamectin wurden auch für Milbemectin im Auftrag der EFSA mehrere Datenlücken festgestellt, beispielsweise hinsichtlich des Verbleibs und Verhaltens in natürlichen Gewässern und Sedimenten. Zudem fehlten Studien zur Dissipation in Böden unter EU-relevanten Boden- und Klimabedingungen, obwohl diese erforderlich gewesen wären, da für Milbemycin A4 DT_{90}-Werte von bis zu 272 Tagen ermittelt wurden (Álvarez et al., 2023). Der Wirkstoff ist in 21 EU-Ländern sowie in Norwegen zur Verwendung in Pflanzenschutzmitteln zugelassen (EU Pesticides Database, 2025c).

Ivermectin und Eprinomectin

Für beide Stoffe sind keine Anwendungen als Insektizide im Pflanzenschutz bekannt, jedoch existieren Szenarien, in denen sie aufgrund ihrer insektiziden Wirkung eingesetzt werden. Speziell für Ivermectin wird ein Einsatz in der Vektorkontrolle zunehmend erörtert (Chaccour et al., 2013; Billingsley et al., 2020; Ahmad et al., 2022; WHO, 2022). Dabei spielt der *One Health*-Gedanke eine tragende Rolle, bei dem die Behandlung von Nutztieren (*endectocide-treated livestock*) zur Kontrolle von Krankheitsvektoren genutzt wird (Pooda et al., 2015; Imbahale et al., 2019). Die Behandlung zielt beispielsweise darauf ab, Moskitos (*Anopheles* spp.) zu bekämpfen, die sich vom Blut behandelter Tiere ernähren und an der mit dem Blut aufgenommenen Dosis sterben (Chaccour et al., 2018; Pooda et al., 2023). Auch die direkte Gabe von Ivermectin an Menschen zur Reduktion der Malariaübertragung wird erprobt (Billingsley et al., 2020; Chaccour et al., 2023).

Für Eprinomectin sind vergleichbare Überlegungen seltener, jedoch wird auch dieser Wirkstoff als potenzielles Vektorkontrollwerkzeug im Nutztierbereich diskutiert. Berichte zeigen, dass Eprinomectin im Bereich therapeutischer Plasma-Konzentrationen ebenfalls letal auf bestimmte Vektoren wirken kann, wenn es über das Blut aufgenommen wird (Poché et al., 2015; Ruiz-Castillo et al., 2022). Beim Einsatz an Nutztieren die sowohl zur Vektorkontrolle als auch zur Lebensmittelgewinnung gehalten werden, müssen zudem Wartezeiten von der Applikation bis zur sicheren Verwendung von z. B. Milch oder Fleisch beachtet werden. Für Ivermectin können diese bei bis zu 122 Tagen nach Verabreichung liegen (FAO/WHO, 2016).

1.2.6 Regulierung von Veterinär-Antiparasitika

In der EU unterliegen Veterinär-Arzneimittel, insbesondere Antiparasitika, einer umfassenden Umweltbewertung im Rahmen der Europäischen Tierarzneimittelverordnung (Verordnung (EU) 2019/6). Zentrales Instrument ist das zweistufige *Environmental Risk Assessment* (ERA), bei dem Veterinär-Arzneimittel einer Umweltrisikobewertung unterzogen werden müssen, die auf ihrer voraussichtlichen Verwendung basiert. Konkrete Anforderungen an die Durchführung des ERA sind in Leitlinien der Europäischen Arzneimittel-Agentur (*European Medicines Agency*, EMA) geregelt; in VICH GL6 für Phase I und VICH GL38 für weiterführende Prüfungen in Phase II. Die Berechnung eines *Risk Quotient* (RQ) bildet die Grundlage: Hierbei wird das Verhältnis zwischen der vorhergesagten Umweltkonzentration (*Predicted Environmental Concentration*, PEC) und der

ökotoxikologisch abgeleiteten Konzentration ohne erwartete schädliche Wirkung (*Predicted No Effect Concentration*, PNEC) gebildet. Die PNEC ist dabei ein ermittelter Schwellenwert, der nicht alle potenziellen Effekte ausschließen kann. Ein RQ ≥ 1 weist auf ein mögliches Umweltrisiko hin und kann weitere Prüfungen oder Risikominderungsmaßnahmen erfordern (EMA, 2016).

In **Phase I** des ERA wird die potenzielle Exposition des Arzneimittels in der Umwelt anhand von Wirkstoff, Hilfsstoffen, Anwendungsart, Zieltierart und Nutzungsumfang abgeschätzt. Liegt die berechnete Umweltkonzentration z. B. im Boden unter einem bestimmten Schwellenwert, kann die Bewertung dort enden. Für systemisch wirksame Antiparasitika besteht dabei eine Besonderheit: aufgrund ihres breiten Einsatzes und ihrer direkten Exposition von Böden und Gewässern über Dung, Urin oder Hautkontakt werden diese Wirkstoffe standardmäßig als besonders prüfpflichtig eingestuft und direkt in Phase II überführt (EMA, 2000). Die Leitlinie für **Phase II** folgt erneut einem zweistufigen Ansatz: in Tier A erfolgt eine erste konservative Risikobewertung auf Basis einfacher und kostengünstiger Studien zu Exposition und Wirkung. Führt diese Bewertung zu einem möglichen Umweltrisiko, wird die Prüfung in Tier B mit detaillierteren Daten und verfeinerten Methoden fortgesetzt, um die Einschätzung zu präzisieren. Beispielsweise wird Substanzen mit einem log K_{OW}-Wert > 4 im ERA eine potenzielle Bioakkumulation unterstellt. Für solche Stoffe empfiehlt es sich, in Tier B an Fischen eine Biokonzentrationsstudie durchzuführen, sofern dies aufgrund der Stoffeigenschaften sinnvoll erscheint. Bei Substanzen mit einem log K_{OW}-Wert > 5 wird der ermittelte RQ vorsorglich um das Zehnfache erhöht, um eine mögliche Aufnahme über Sedimente zu berücksichtigen (EMA, 2005). Da bislang keine standardisierten Sicherheitsfaktoren für die terrestrische Bioakkumulation etabliert sind, kommt der Auswahl realistischer Versuchsbedingungen besondere Bedeutung zu.

1.2.7 Verbleib in der Umwelt und ökotoxikologische Effekte

Die Wirkstoffkonzentrationen in festen Ausscheidungen behandelter Tiere schwanken stark, je nach Tierart und Applikationsform (Steel, 1993; González Canga et al., 2009). Für Doramectin, Eprinomectin und Ivermectin sind bei Rindern – je nach zugelassenem Produkt – die typischen Dosen 0,2 mg/kg Körpergewicht (*body weight*, bw) bei subkutaner Injektion sowie 0,5 mg/kg bw bei dermaler (*pour-on*) Verabreichung (EMA, 2004b, 2004a, 2009; UBA, 2019). Im Beispiel subkutaner Ivermectin-Injektionen bei Rindern sind dokumentierte Wirkstoffrückstände im Dung in Tab. 2 dargestellt. Die daraus gemittelte Konzentration von 1898 ng/g im trockenen Rinderdung (*dry weight*, dw) zeigt die Größenordnung, in der Ivermectin nach therapeutischer Verwendung für Nichtzielorganismen verfügbar sein kann. Diese Exposition betrifft zunächst Dung- und anschließend auch Bodenorganismen. Im Kontrast dazu steht die sehr hohe Empfindlichkeit vieler Dungkäfer (Finch et al., 2020) und Dungfliegen (Blanckenhorn et al., 2013b) gegenüber makrozyklischen Laktonen. Die halbmaximale letale Konzentration (LC_{50}), die bei 50 % der Organismen in standardisierten Toxizitätstests zur Mortalität führt, ist oft vielfach niedriger als die Umweltkonzentration. Besonders empfindlich sind dabei Dungfliegen und deren Larven, die innerhalb der Dungfladen Entwicklungszyklen durchlaufen. LC_{50}-Werte können bereits im Bereich von 0,6–176 ng/g dw liegen (Blanckenhorn et al., 2013a) und sind damit um mehrere Größenordnungen niedriger als Konzentrationen, die im Dung behandelter Rinder vorkommen.

Tabelle 2 | Ivermectin-Konzentrationen im Dung behandelter Rinder. Vereinheitlicht dargestellt in ng/g dw (des Trockengewichts) nach Verabreichung von 0,2 mg Ivermectin / kg Körpergewicht durch subkutane Injektion. Angabe als Mittelwert ± Standardabweichung (SD), sofern ermittelbar.

T_{max} (d)	C_{max} (ng/g dw)	Referenz
2,0	3926 ± 53 [a]	Sommer et al. (1992)
6,0	2380 (bei Getreidemast)	Cook et al. (1996)
8,0	1110 (bei Weidehaltung)	Cook et al. (1996)
3,0	1200 ± 300	Herd et al. (1996)
5,6	872 ± 153	Fernandez et al. (2009)

T_{max} = Zeit bis zum Erreichen der maximalen Konzentration nach einmaliger Injektion
C_{max} = maximale Konzentration
[a] Wert ausgelesen aus Abb. 2 in Sommer et al. (1992) mittels PlotDigitizer™ (https://plotdigitizer.com/)

Der Übergang der Rückstände vom Dung in Böden erfolgt langsam und ist abhängig von den klimatischen Bedingungen. Punktuelle Höchstkonzentrationen in Böden befinden sich dabei besonders im Bereich der Dungablagerungen und wenige cm unterhalb der Bodenoberfläche (Römbke et al., 2010; Wohde et al., 2016a; Iglesias et al., 2018). In bestimmten Szenarien wurde auch ein verlangsamter Abbau der organischen Substanz durch Dungorganismen dokumentiert (Sommer und Bibby, 2002; Iglesias et al., 2006). Die Dissipation im Boden wird dann vor allem durch Niederschlag und Temperatur beeinflusst (Wohde et al., 2016a). Die DT_{50}-Werte von Ivermectin in Böden liegen zwischen 10 (Oliveira Ferreira et al., 2019) und 240 Tagen (Dubroca et al., 2003), abhängig von Bodentyp und klimatischen Bedingungen. Einträge in Gewässer erfolgen primär über Oberflächenabfluss oder Erosion, wobei der Transport aufgrund der starken Sorption gering bleibt (Bair et al., 2017). In natürlichen Fließgewässern können Ivermectin-Konzentrationen im Bereich von wenigen ng/L auftreten (Charuaud et al., 2019) und dort in Sedimente übergehen (Chen et al., 2021). Auch die schnelle Dissipation aus der Wasserphase innerhalb weniger Stunden (Prasse et al., 2009) ist durch die Hydrophobie der Stoffe bedingt.

Umweltrelevanz

Umfassende Forschungsarbeiten weisen seit über 30 Jahren kontinuierlich auf die toxischen Wirkungen von Ivermectin, Moxidectin und anderen makrozyklischen Laktonen auf Dung- und Bodenorganismen hin (Strong, 1992; Liebig et al., 2010; Jochmann und Blanckenhorn, 2016; Verdú et al., 2018a; Junco et al., 2021; Souza und Guimarães, 2022; Vokřál et al., 2023). Auch unter Freilandbedingungen gibt es kritische Betrachtungen zum Verbleib in der Umwelt (Iglesias et al., 2018; Mesa et al., 2020) sowie zu Effekten auf Nichtzielorganismen (Jochmann et al., 2016; Mesa et al., 2018). Eine aquatische Mesokosmos-Studie (Sanderson et al., 2007) zeigte zudem Umweltauswirkungen von Ivermectin über einen Zeitraum von 265 Tagen. Trotz der schnellen Dissipation aus der Wasserphase verblieb Ivermectin persistent im Sediment mit negativen Auswirkungen auf Sedimentorganismen. Zudem werden zunehmend auch negative Effekte auf Populations- und Ökosystemebene dokumentiert (Verdú et al., 2018b; Ambrožová et al., 2021; Backmeyer et al., 2023). Das Ziel der vorliegenden Dissertation ist es, die Befunde zur Umweltrelevanz der makrozyklischen Laktone systematisch einzuordnen und zu erweitern.

1.3 Zielsetzung und Hypothesen

Das Umweltverhalten und die ökotoxikologischen Risiken makrozyklischer Laktone wie Ivermectin, Abamectin, Doramectin und Moxidectin sind bislang trotz ihres breiten Einsatzes nur unzureichend erfasst. Auch Jahrzehnte nach ihrer Markteinführung ist für viele dieser Veterinär-Antiparasitika keine vollständige Umweltbewertung möglich, da Daten zu grundlegenden Stoffeigenschaften wie Persistenz, Bioakkumulation und Toxizität fehlen (UBA, 2019). Insbesondere ihre Sorption in Böden und Sedimenten, ihre potenzielle Bioakkumulation in terrestrischen Organismen sowie die Folgen ihrer großflächigen Anwendung im *One Health*-Kontext werfen wissenschaftliche und regulatorische Fragen auf. Daraus ergibt sich die übergeordnete Zielsetzung dieser Arbeit:

> Ziel dieser Arbeit ist es, die Sorptionseigenschaften und die potenzielle Bioakkumulation von Ivermectin und anderen Antiparasitika zu untersuchen, um deren langfristige Auswirkungen auf Bodenökosysteme regulatorisch und in einem *One Health*-Kontext besser bewerten zu können.

Aus dieser zentralen Zielsetzung leitet sich die folgende Hypothesenbildung ab. Jede Hypothese adressiert dabei einen spezifischen Aspekt der Umweltinteraktion dieser Stoffe (insbesondere Ivermectin) und entspricht thematisch den veröffentlichten Untersuchungen. Fünf aus den Veröffentlichungen abgeleitete Forschungsfragen (A–E) werden am Ende der Abschnitte 1.4.1 bis 1.4.3 formuliert. In den Abschnitten 2.1 bis 2.3 werden die Kernergebnisse der jeweiligen Veröffentlichungen zusammengefasst. Die Hypothesen werden im Diskussionsteil adressiert.

Hypothese 1: Sorption und Stoffeigenschaften

> Die Antiparasitika Abamectin, Doramectin, Ivermectin und Moxidectin zeigen starke Sorption in Böden und Sedimenten, bedingt durch ausgeprägte Lipophilie und daraus resultierende hohe Affinität zu organischer Bodensubstanz. Dies spricht für hohe log K_{OW}-Werte, die in der Fachliteratur und Regulatorik teilweise unklar dokumentiert oder zu niedrig eingeschätzt sind.

Hypothese 2: Bioakkumulation und ökotoxikologische Relevanz

> Ivermectin birgt aufgrund seiner hohen Lipophilie ein potenzielles Risiko der Bioakkumulation in Regenwürmern. Standardisierte Versuche mit dem Kompostwurm *Eisenia fetida* in künstlichem Testsubstrat (gemäß OECD-Richtlinie 317) erfassen dieses Risiko möglicherweise unzureichend und sind nicht repräsentativ für reale Expositionsszenarien.

Hypothese 3: Interdisziplinäre Perspektive und Umweltrisikominderung

> Die flächenhafte Verabreichung von langwirksamen Ivermectin-Präparaten an Nutztiere zur Malariavektorkontrolle birgt ein Risiko für die Bodenökologie in tropischen und subtropischen Regionen. Gezielte regionalspezifische Risikomanagementmaßnahmen sind erforderlich, um negative Auswirkungen auf die Umweltgesundheit zu minimieren.

1.4 Forschungsansätze und Methoden

1.4.1 Sorptionseigenschaften von Antiparasitika in Böden und Sedimenten

Bodenproben aus Deutschland wurden vom Hessischen Landesamt für Naturschutz, Umwelt und Geologie (HLNUG) bereitgestellt und deckten eine Bandbreite an physikalisch-chemischen Eigenschaften, Bodentypen, Beprobungstiefen sowie Weide- und Kulturstandorten in Hessen ab. Marokkanische Boden- und Sedimentproben stammten aus der Gharb-Ebene im Nordwesten des Landes; jeweils aus den obersten 20 cm. Sedimente wurden entlang der Flüsse Sebou und Loukos in 1,5–2 m Uferentfernung beprobt. Proben aus Marokko gehörten zum bereits laufenden FETCH-Projekt und wurden hier weiterverwendet. Alle Proben wurden luftgetrocknet, auf <2 mm gesiebt und physikochemische Parameter, insbesondere der C_{org}-Gehalt, wurden bestimmt.

Für Sorptionsversuche wurden insgesamt 20 Boden- und 6 Sedimentproben verwendet. Das Protokoll folgte im Verlauf der OECD-Richtlinie 106 „*Test No. 106: Adsorption -- Desorption Using a Batch Equilibrium Method*“ (OECD, 2000). Für jede Probe wurde 1 g Boden oder Sediment in 45 mL Zentrifugengläsern mit 30 mL 0,01 mol/L $CaCl_2$-Lösung suspendiert (Abb. 4a). Das Probe-zu-Lösung-Verhältnis von 1:30 (w/v) basierte auf eigenen Voruntersuchungen und vergleichbaren Sorptionsstudien (Dionisio und Rath, 2016; Rath et al., 2019). Da bei sehr hydrophoben Substanzen wie Avermectinen ein Sorptionsgleichgewicht zugunsten der festen Phase erwartet wird, ist ein größeres Flüssigkeitsvolumen erforderlich, um ausreichende Analytkonzentrationen in der wässrigen Phase und eine robuste Quantifizierung zu gewährleisten (OECD, 2000).

Testsubstanzen waren vier makrozyklische Antiparasitika: Abamectin (bestimmt als Avermectin B_{1a}), Doramectin, Ivermectin (bestimmt als Ivermectin B_{1a}) sowie Moxidectin. Die Substanzen wurden als pulverförmige, analytische Standards in Acetonitril gelöst, um konzentrierte Arbeitslösungen herzustellen. Vor der Dotierung wurden die Feststoffproben 24 h in $CaCl_2$-Lösung vorgeschüttelt. Jeder Suspension wurden 30 µL einer Arbeitslösung mit allen vier Testsubstanzen hinzugefügt. Dies geschah für deutsche Proben als Duplikat und für marokkanische Proben als Triplikat. In unterschiedlichen Aufteilungen lagen die in den Proben angesetzten Testkonzentrationen zwischen 100–500, 100–1.000 und 500–2.500 µg/L je Substanz.

Nach der Dotierung wurden die Proben 48 h lang geschüttelt bis zum erwarteten Sorptionsgleichgewicht. Kontrollen enthielten Boden-/Sedimentproben mit $CaCl_2$-Lösung oder ausschließlich $CaCl_2$-Lösung, die mit Analyten versetzt war. Die Versuchsdauer von 48 h, um ein scheinbares Sorptionsgleichgewicht zwischen den Konzentrationen im Boden/Sediment und in der wässrigen Phase zu erreichen, beruhte auf Vorversuchen und wird durch vergleichbare Experimente gestützt (Krogh et al., 2008; Dionisio und Rath, 2016). Eine beispielhafte Bewertung der Desorption wurde nach weiteren 72 h Schüttelzeit für ausgewählte Proben durchgeführt.

Das analytische Protokoll basierte auf Vorarbeiten (Wohde et al., 2016a; Wohde et al., 2017) und wurde für die Versuche angepasst. Nach dem Schütteln und anschließender Zentrifugation wurde zur Durchführung einer Festphasenextraktion (*Solid-Phase Extraktion*, SPE; Abb. 4b)

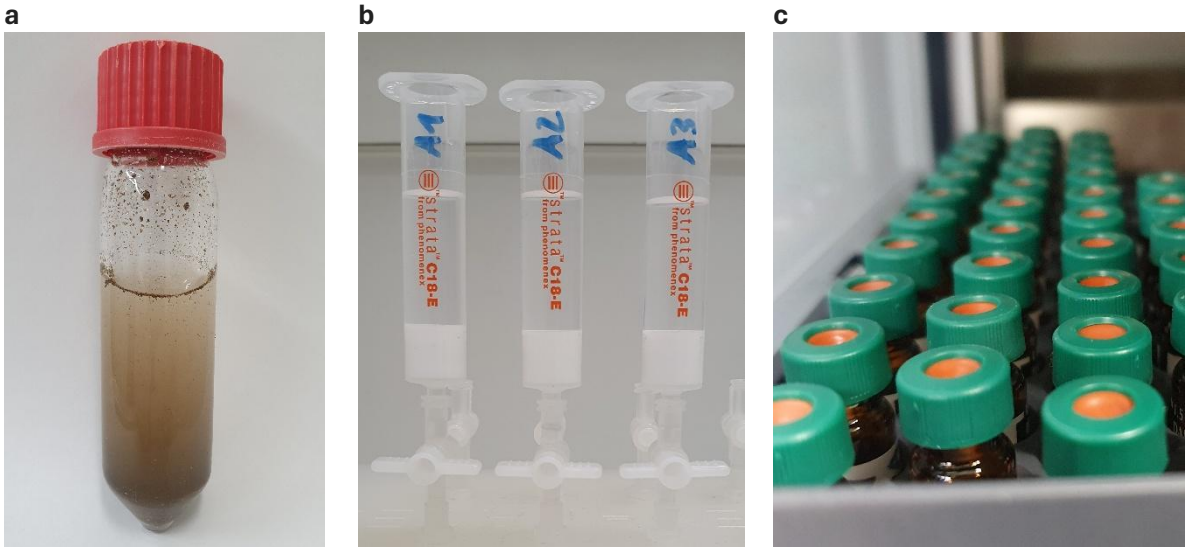

Abbildung 4 | Schritte der Sorptionsversuche. **a**, Ansatz in 45 mL Zentrifugenglas mit 30 mL 0,01 mol/L $CaCl_2$-Lösung für die Suspensionen der Boden- oder Sedimentprobe. **b**, SPE-Kartuschen zur Festphasen-Extraktion (Phenomenex Strata C18-E, 500 mg, 6 mL). **c**, Derivatisierte Proben in 1,8 mL Braunglas-Vials zur Quantifizierung der Analyten mittels Hochleistungsflüssigkeitschromatographie (HPLC) mit anschließender Fluoreszenzdetektion im Agilent 1200 HPLC-System. **a–c**, Eigene Aufnahmen (A. Heinrich).

jeweils ein Aliquot von 25 mL des Überstands überführt. Die mit hydrophobem C-18 Material befüllten SPE-Kartuschen (Phenomenex Strata C18-E, 500 mg, 6 mL) wurden zuvor schrittweise mit Propan-2-ol und Milli-Q® Reinstwasser konditioniert. In einem auf die SPE-Kartuschen befestigten Reservoir wurde der Überstand mit 8,333 mL Propan-2-ol und 25 µL Triethylamin versetzt. Nach der SPE und nachfolgender Elution mit Propan-2-ol wurde dieses unter N_2 abgedampft und der Rückstand in 1.000 µL Acetonitril rekonstituiert. Die Quantifizierung der Analyten erfolgte basierend auf der von Wohde et al. (2016a) vorgestellten Methode mittels Hochleistungsflüssigkeitschromatographie (HPLC) und anschließender Fluoreszenzdetektion nach Derivatisierung (Abb. 4c; Details in Abschnitt 1.4.4).

Die Sorptionskoeffizienten K_D und K_{OC} sowie die prozentuale Desorption wurden entsprechend OECD-Richtlinie 106 (OECD, 2000) ermittelt. Die Koeffizienten wurden, basierend auf Chappell et al. (2020), über lineare Sorptionsisothermen bestimmt. Da lineare Ansätze keine Konkurrenz um Bindungsplätze betrachten (Sparks, 2003) und von konstanter Steigung ausgehen, eignen sie sich so für niedrige und umweltrelevante Konzentrationsbereiche (Rao und Jessup, 1983). Die Auswertung und Kontextualisierung der Daten enthielt auch die Berechnung von K_{OC}-Werten über zwei Wege (linear und als Mittelwert) sowie deren näherungsweise Umrechnung in log K_{OW}-Werte. Die Interpretation der K_{OW}-Werte mittels empirischer Ansätze (Karickhoff, 1981; Gerstl, 1990; Sabljić et al., 1995; Baker, 1997) diente der Validierung der Sorptionsdaten und der Abschätzung, ob bisherige Standardwerte die tatsächliche Lipophilie der Substanzen angemessen abbilden.

Thematische Forschungsfrage

A) Wie verhalten sich die Antiparasitika Abamectin, Doramectin, Ivermectin und Moxidectin in Böden und Sedimenten hinsichtlich ihrer Sorptionseigenschaften und welche Schlüsse über ihren K_{OW}-Wert lassen sich ableiten?

1.4.2 Verknüpfung der Sorption, Desorption und Bioakkumulation von Ivermectin

Für diese Untersuchung wurden ein künstliches Testsubstrat und ein natürlicher Boden sowie verschiedene Regenwurmarten eingesetzt. Der primäre Bioakkumulationsversuch mit dem Kompostwurm *E. fetida* erfolgte in OECD-konformem Testsubstrat (*Artificial Soil*, AS) aus Quarzsand, Kaolin und Torf (OECD, 1984). Zwei weitere Versuche wurden mit *Aporrectodea caliginosa* und *Lumbricus terrestris* im Referenzboden LUFA 2.2, einem sandigen Lehmboden, durchgeführt. Der untersuchte und dotierte Analyt war Ivermectin (als Ivermectin B_{1a}).

Die Bioakkumulationsversuche folgten dem Aufbau in OECD-Richtlinie 317 (OECD, 2010). *E. fetida* wurde als typischer Modellorganismus in Standardtests verwendet, während *A. caliginosa* und *L. terrestris* aufgrund ihres Vorkommens in mineralischen Bodenschichten ausgewählt wurden (Edwards, 2022). Vor der Exposition im jeweiligen Testsubstrat wurden die Regenwürmer unter kontrollierten Bedingungen kultiviert. Für die Dotierung mit Ivermectin wurde eine Zielkonzentration von 0,5 mg/kg dw gewählt, um etwa 1 % des LC_{50}-Werts für *E. fetida* nicht zu überschreiten. Mit diesem Ansatz sollten eine Ivermectin-induzierte Mortalität vermieden und gleichzeitig eine ausreichende Konzentration zur quantitativen Analytik sichergestellt werden (OECD, 2010; Wang et al., 2010). Nach der Einstellung des Wassergehalts und Homogenisierung der Substrate wurden die Bioakkumulationsexperimente über 21 Tage in einem Klimaschrank durchgeführt (21 ± 1 °C, 16/8 h Licht/Dunkel-Zyklus). Nach Abschluss der Exposition erfolgte für *E. fetida* zusätzlich eine Eliminationsphase von weiteren 21 Tagen in unbelastetem AS.

Die Probenahme erfolgte gestaffelt. Bei *E. fetida* wurden während der Aufnahme- und der Eliminationsphase jeweils neun Entnahmezeitpunkte realisiert. Für *A. caliginosa* und *L. terrestris* erfolgten drei Entnahmezeitpunkte während der Aufnahmephase. Nach der Entnahme wurden die Würmer über Nacht auf feuchtem Filterpapier entleert und anschließend gefriergetrocknet. Die Extraktion von Ivermectin aus Boden- und Wurmproben erfolgte mit Acetonitril unter Zusatz von Doramectin als internem Standard. Je Probenahme wurden n = 3 Behälter beprobt. Die Substratmenge und Wurmanzahl folgten den Vorgaben in OECD-Richtlinie 317 (OECD, 2010). Der Wassergehalt betrug 22,7 % im AS-Substrat und 23 % in LUFA 2.2 und wurde wöchentlich geprüft. Ergänzend wurde eine Sorptionsstudie durchgeführt, um die Affinität von Ivermectin zu den einzelnen Komponenten des künstlichen Substrats (Quarzsand, Kaolin und Torf) sowie zum Gesamtgemisch zu bestimmen. Die Versuche basierten auf einem 1:30 (w/v) Verhältnis von Feststoff zu Lösung (0,01 mol/L $CaCl_2$), wobei die Methode aus OECD-Richtlinie 106 (OECD, 2000) Anwendung fand. Das Protokoll basierte auf der in Abschnitt 1.4.1 verwendeten Methodik. Nach der Adsorptionsphase (48 h) wurde die Desorption durch Ersetzen des Überstandes und erneutes Schütteln (72 h) bewertet.

Zur Auswertung der Bioakkumulation wurden die Aufnahme sowie die kinetischen Bioakkumulationsfaktoren (BAF_k) für *E. fetida* anhand einer Kinetik erster Ordnung berechnet. Darüber hinaus wurden ein Ein- sowie ein Zwei-Kompartiment-Modell zur Abbildung der Eliminationsmuster genutzt (Bruns et al., 2002). Dies geschah, da hydrophobe Substanzen wie Avermectine häufig einen schnellen und einen langsameren Eliminationsabschnitt zeigen (Belfroid und Sijm, 1998). Der Einfluss des Lipidgehalts von *E. fetida* sowie durch den C_{org} im AS

wurde ebenfalls berücksichtigt mit der Ermittlung des *Biota-Soil Accumulation Factor* (BSAF). Für *A. caliginosa* und *L. terrestris* wurden aus den Konzentrationen der Wurm- und Bodenproben der Aufnahmephase reine Akkumulationsfaktoren (C_{Wurm}/C_{Boden}) gebildet. Die Quantifizierung von Ivermectin und Doramectin in Boden- und Wurmproben sowie in den Sorptions- und Desorptionsversuchen erfolgte mittels HPLC-Fluoreszenzdetektion nach Derivatisierung. Die Auswertung beinhaltete neben der Bestimmung von BAF_k, BSAF, K_D- und K_{OC}-Werten auch die Bestimmung des DT_{50}-Werts für Ivermectin im künstlichen Testsubstrat. Weiter wurde der nichtlineare Sorptionskoeffizient K_F (Sparks, 2003) für die Sorption im AS bestimmt.

Thematische Forschungsfragen

- **B)** In welchem Ausmaß sorbiert Ivermectin an organischem Material in Böden, und wie beeinflusst dies dessen Bioverfügbarkeit und Bioakkumulation in Regenwürmern?
- **C)** Welche Bioakkumulationsrisiken bestehen für Regenwürmer durch die Anwendung von Ivermectin in der Tiermedizin?

1.4.3 Ökotoxikologische Betrachtung von Ivermectin in der Malariavektorkontrolle

Das interdisziplinäre *One Health*-Projekt wurde gemeinsam mit Partnern aus Burkina Faso und Frankreich durchgeführt und verband die Felder Vektorkontrolle mit Ivermectin, Umweltchemie und Ökotoxikologie. Die Projektpartner übernahmen die Durchführung der Feldversuche mit Rindern und die Modellierung der Moskitopopulationen (*Anopheles coluzzii*). Ergänzend dazu konzentrierten sich die Arbeiten in Deutschland auf die ökotoxikologische Abschätzung und die umweltanalytische Laborarbeit im Rahmen der *One Health*-Perspektive.

Der Schwerpunkt lag auf der Bestimmung der Ivermectin-Gehalte in Blutplasma und Dung der behandelten Rinder sowie der Beurteilung der ökotoxikologischen Relevanz der Ivermectin-Rückstände im Dung. Die Pharmakokinetik in Plasma und Dung wurde über einen Zeitraum von bis zu 211 Tagen erfasst; nach Verabreichung eines langwirksamen Ivermectin-Depotpräparats (IVM-BEPO) sowie einer kommerziellen Vergleichsformulierung (IVOMEC-D). Dabei wurde IVM-BEPO einmalig und IVOMEC-D monatlich verabreicht. Die Dungproben wurden nach Entnahme teilweise direkt eingefroren und teils unter kontrollierten Bedingungen im Labor (26 ± 2 °C) oder unter Freilandbedingungen (17,9–39,6 °C) gelagert. Im Anschluss erfolgten die Extraktion und Quantifizierung der Ivermectin-Rückstände im Labor. Zur Ermittlung der Dissipation wurden Konzentrationsänderungen im gelagerten Dung über 90 Tage erfasst. Ergänzend wurden Sorptionsversuche mit 30 Bodenproben aus drei Dörfern der Provinz Tuy (im südwestlichen Burkina Faso) durchgeführt, um die Sorption von Ivermectin unter regionaltypischen Bedingungen zu charakterisieren. Auch diese Sorptionsstudie folgte OECD-Richtlinie 106 (OECD, 2000). Der Verteilungskoeffizient K_D wurde mit bodenspezifischen Parametern korreliert.

Zur ökotoxikologischen Abschätzung wurden die gemessenen Ivermectin-Gehalte im Dung mit Literaturdaten zur Toxizität gegenüber Nichtzielorganismen (Dungkäfer und Dungfliegen) verglichen. Ein weiterer Schritt war die Entwicklung praxisnaher Risikominderungsmaßnahmen zur Reduzierung der Umweltbelastung. Hierbei wurden bestehende Empfehlungen für Veterinär-Antiparasitika angepasst und mit landwirtschaftlichen Praktiken in Burkina Faso verknüpft. Die

analytische Quantifizierung von Ivermectin (als Ivermectin B_{1a}) erfolgte mittels HPLC-Fluoreszenzdetektion nach Derivatisierung. Die Ergebnisse wurden in die *One Health*-Fragestellung der Vektorkontrolle mit Ivermectin-basierten Maßnahmen integriert.

Thematische Forschungsfragen

- **D)** Wie lassen sich Umweltrisiken durch den Einsatz von Ivermectin-behandelten Rindern zur Vektorkontrolle beschreiben und managen?
- **E)** Wie können Umweltanalytik und ökotoxikologische Expertise in Endektozid-basierte Vektorkontrollmaßnahmen für *One Health*-Ansätze integriert werden?

1.4.4 Analytische Bestimmung der Wirkstoffe mittels HPLC-Fluoreszenzdetektion

Dieser Schritt basierte auf der Methode von Wohde et al. (2016a) und wurde entsprechend der neuen Fragestellungen angepasst. Das Protokoll zur Extraktion von Rinderplasma wurde ergänzt durch Informationen von Polson et al. (2003) und Xu et al. (2011). Die quantitative Bestimmung von Abamectin (als Avermectin B_{1a}), Doramectin, Ivermectin (als Ivermectin B_{1a}) sowie Moxidectin erfolgte durch HPLC-Fluoreszenzdetektion nach Derivatisierung. Dies geschah für Extrakte der Boden-, Regenwurm-, Dung- und Plasmaproben sowie für die Sorptions- und Desorptionsversuche. Die Derivatisierung der aufbereiteten Extrakte erfolgte nach matrixspezifischer Anpassung mit einer Mischung aus N-Methylimidazol/Acetonitril (1:1, v/v), Triethylamin, Trifluoressigsäureanhydrid/Acetonitril (1:1, v/v) und Trifluoressigsäure. Verwendete Chemikalien (Tab. A 1) sowie exakte Volumina (Tab. A 2) sind im Anhang gelistet. Das Injektionsvolumen betrug 40 µL mit einem Agilent 1200 HPLC-System. Als mobile Phasen der Gradientenelution wurden A (Reinstwasser) und B (Acetonitril) eingesetzt; Flussrate: 0,3 mL/min; Gradient: 0–10 min, 88 auf 100 % B; 10–11 min, 100 % B; 11,01–20 min, 88 % B. Die stationäre Phase war eine *Reversed-Phase* C18-Säule (150 mm, 3 µm Partikelgröße; Acclaim™ PolarAdvantage II, Thermo Fisher Scientific). Die Temperatur des HPLC-Systems betrug 30 °C. Der Fluoreszenzdetektor war auf 364 nm (Anregung) und 463 nm (Emission) eingestellt. In Abb. 5 dargestellt ist ein ausgegebenes HPLC-Chromatogramm der Laborarbeiten, für das zusätzlich Eprinomectin B_{1a} dotiert wurde.

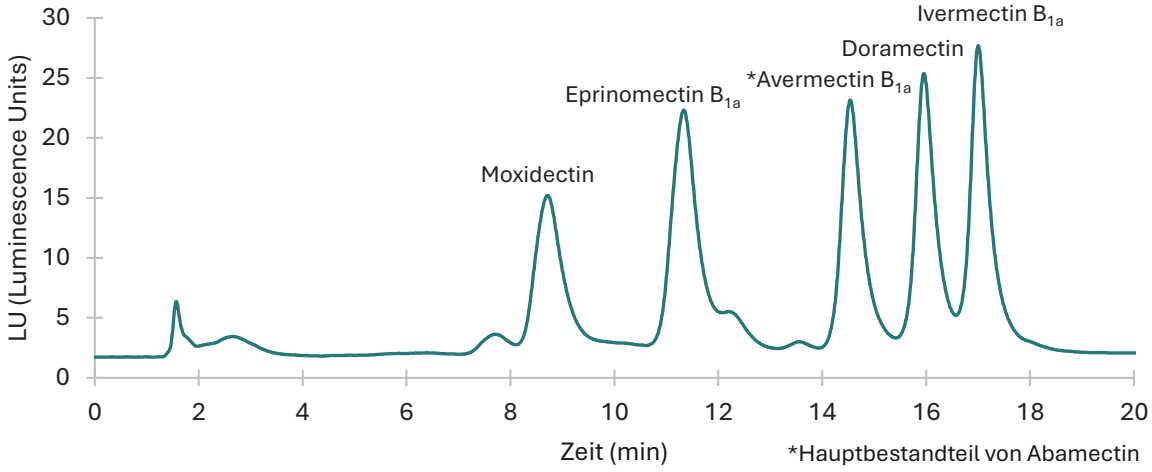

Abbildung 5 | HPLC-Chromatogramm. Nachgewiesen wurden Moxidectin, Eprinomectin B_{1a}, Avermectin B_{1a}, Doramectin und Ivermectin B_{1a}. Die HPLC-Methode wurde hier abgeändert mit erhöhtem Wasseranteil (20 % statt 12 % zu Beginn auf einer C18-Säule) zur besseren gemeinsamen Darstellung der fünf Analyten.

2 Zusammenfassung der Ergebnisse

2.1 Sorption der untersuchten Antiparasitika in Böden und Sedimenten

In Böden variierten die K_D-Werte zwischen 38 und 642 mL/g für Abamectin, Doramectin und Ivermectin. Für Moxidectin zeigten sich höhere K_D-Werte zwischen 166 und 3.123 mL/g. Die Sorption korrelierte stark positiv mit dem C_{org}-Gehalt, wobei in Proben mit weniger als 0,3 % C_{org} die K_D-Werte von der linearen Regression abwichen, was einen stärkeren Einfluss mineralischer Sorbenten andeutet. Diese Böden wurden, angelehnt an OECD-Richtlinie 106 (OECD, 2000) und Krahe et al. (2006), von der K_{OC}-Berechnung ausgeschlossen. Die K_{OC}-Werte folgten dem Trend Moxidectin >> Ivermectin > Doramectin > Abamectin, mit log K_{OC}-Werten für Moxidectin von 4,74 (entsprechend 54.721 mL/g) und für Ivermectin von 4,12 (13.139 mL/g). Im Vergleich niedriger waren die log K_{OC}-Werte für Doramectin (3,93 mL/g) und Abamectin (3,63 mL/g). Diese Ergebnisse lagen im Bereich veröffentlichter Werte zu makrozyklischen Laktonen (Krogh et al., 2008; Dionisio und Rath, 2016). Die Gesamtheit der K_D- und K_{OC}-Werte unterstreicht die sehr starke Sorption in Böden und in deren organischer Substanz, insbesondere für die hydrophoberen Stoffe Ivermectin und Moxidectin. Nach einer Box-Cox-Transformation der K_D-Werte zeigte eine multiple lineare Regression, dass der C_{org}-Gehalt signifikant mit den K_D-Werten von Abamectin, Doramectin und Ivermectin assoziiert war ($p < 0,05$). Zusätzlich erwiesen sich das C/N-Verhältnis und der pH-Wert als signifikante Prädiktoren für die K_D-Werte von Abamectin und Doramectin ($p < 0,05$).

In Sedimenten aus Marokko zeigte sich eine ähnliche Sorptionsreihenfolge, jedoch mit einer größeren Variation. Hier lagen die K_D-Werte für Abamectin, Doramectin und Ivermectin im Bereich 22–915 mL/g und für Moxidectin zwischen 87 und 2.326 mL/g. Generell lagen K_{OC}-Werte in den Sedimenten über denen in Böden, was sich in einem Verhältnis von etwa 1,2–2,4 je nach Substanz ausdrückte. Dies bestätigt vorherige Erkenntnisse zur stärkeren Retention hydrophober Substanzen in Sedimenten im Vergleich zu Böden. Eine mögliche Ursache hierfür ist, dass der Sedimentationsprozess in Gewässern die organischen Bestandteile fraktioniert. Dadurch können polarere bzw. wasserlöslichere organische Bestandteile abgetrennt werden, während weniger polare organische Bestandteile im Sediment verbleiben (Chiou und Kile, 2000). Auch für Albendazol, ein Benzimidazol-Anthelminthikum, wurden in Sedimenten höhere K_{OC}-Werte als in Böden dokumentiert (Mutavdžić Pavlović et al., 2018). Die Sorption in Böden und Sedimenten ist anhand der K_{OC}-Werte gemeinsam in Abb. 6 illustriert. Die durchgeführten Desorptionsversuche, beispielhaft am Referenzboden LUFA 2.2, belegten eine minimale Rücklösung der Wirkstoffe aus dem Boden: so wurden für alle Stoffe Desorptionsraten im Bereich von 2,6–4,6 % bestimmt. Damit liegt die Desorption deutlich unterhalb der Schwelle von 75 %, ab der eine reversible Sorption definiert wird (OECD, 2000). Entsprechend der häufig verwendeten Einstufung nach McCall et al. (1980) zur Mobilität in Böden kann anhand der K_{OC}-Werte eine weitere Bewertung erfolgen: Abamectin kann in Böden als gering mobil (*slight mobility*) betrachtet werden, während Doramectin, Ivermectin und Moxidectin mit einem K_{OC}-Wert > 5.000 mL/g als immobil gelten.

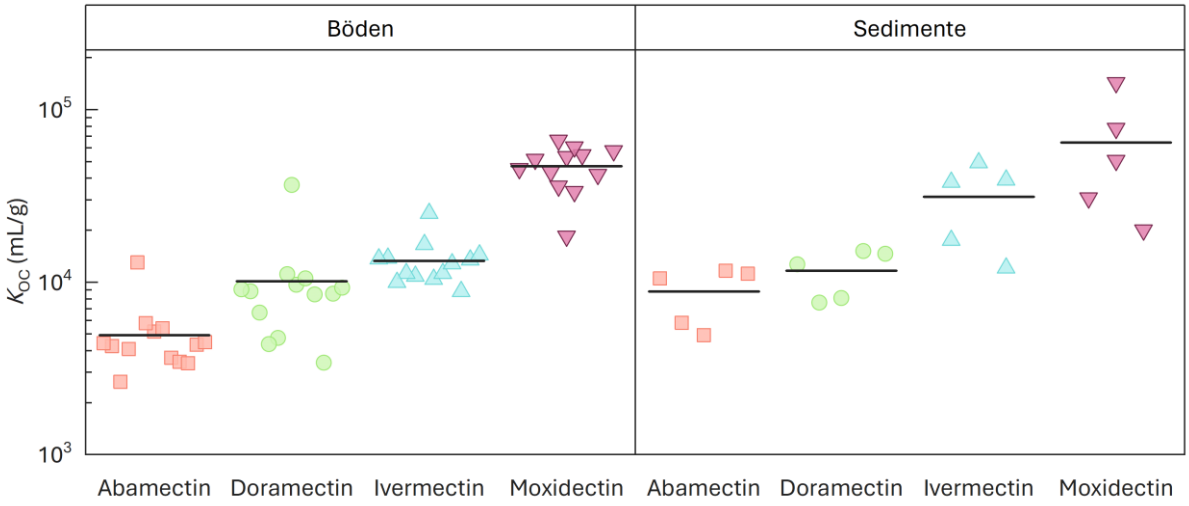

Abbildung 6 | Übersicht Sorption. K_{OC}-Werte der untersuchten Antiparasitika in Böden und Sedimenten. Bestimmung von Abamectin als Avermectin B_{1a} und von Ivermectin als Ivermectin B_{1a}. Die horizontalen Linien im Streudiagramm zeigen die Mittelwerte je Substanz und Matrix.

Aus den über die lineare Regression ermittelten K_{OC}-Werten wurden weiter K_{OW}-Werte mittels empirischer Ansätze abgeleitet. Zur Darstellung sind diese K_{OW}-Werte kombiniert für alle Böden und Sedimente (als log K_{OW}) und arithmetisches Mittel ± Standardabweichung (SD) aufgeführt: Abamectin (4,5 ± 0,4), Doramectin (4,7 ± 0,3), Ivermectin (5,3 ± 0,5) sowie Moxidectin (5,8 ± 0,4). Die erweiterte Betrachtung hierzu erfolgt zusammenfassend im Diskussionsteil (Abschnitt 3.5).

In Bezug auf die Forschungsfrage (→ Fragestellung A) zeigten die Ergebnisse eine starke Sorption der vier Antiparasitika in Böden und Sedimenten sowie geringe Desorption, was auf geringe Mobilität und potenzielle Persistenz hinweist. Die Sorption korrelierte stark positiv mit dem C_{org}-Gehalt und variierte substanzspezifisch. Die abgeleiteten log K_{OW}-Werte zwischen 4,5 und 5,8 bestätigen die ausgeprägte Lipophilie als zentrale Einflussgröße und Stoffeigenschaft.

2.2 Sorption, Bioakkumulation und Bioverfügbarkeit von Ivermectin in Boden-Regenwurm-Systemen

Die Ergebnisse zeigten die starke Sorption von Ivermectin an organische Bodenbestandteile, insbesondere an den Torf im künstlichen Testsubstrat. In diesem AS-Substrat wurde für Ivermectin ein K_D-Wert von 180 mL/g und ein log K_{OC}-Wert von 3,7 (entsprechend 5.002 mL/g) bestimmt. Der Freundlich-Koeffizient K_F betrug 79,9 $\mu g^{1-1/n} \cdot (mL)^{1/n} \cdot g^{-1}$ mit einem Exponenten von n = 1,62. Damit wies Ivermectin eine deutlich nichtlineare Sorption auf. Die beobachtete Abnahme der Sorption bei höheren wässrigen Konzentrationen kann teilweise auf die für Adsorptionsprozesse typischen Sättigungseffekte an Tonmineralien zurückgeführt werden. Dieses Verhalten ähnelt der Langmuir-Sorption, bei der Bindungsstellen nach und nach besetzt werden, was die weitere Sorptionsleistung verringert (Sparks, 2003). Im Vergleich der Einzelbestandteile des AS ergab sich die stärkste Sorption in der Torffraktion. Dagegen zeigte sich im Kaolin nur leichte und im Sand nahezu keine Sorption. Parallel dazu ergab die Desorptionsstudie die geringste Rücklösung aus Torf (0,7 ± 0,6 %), gefolgt von Kaolin (20,2 ± 9,2 %) und Sand (72,1 ± 18,8 %). Die Kombination aus starker Sorption und geringer

Desorption deutet darauf hin, dass Ivermectin in organischen Fraktionen zurückgehalten wird und so dessen Bioverfügbarkeit eingeschränkt sein kann (Alexander, 1995; Carter et al., 2016).

In den Bioakkumulationsexperimenten mit *E. fetida* zeigte sich für Ivermectin ein niedriges Akkumulationspotenzial. Der BAF_k (± Standardfehler) lag je nach Berechnung im Bereich von 0,505 ± 0,30 bis 0,727 ± 1,40 g Boden (dw) pro g Regenwurm (dw). Unter Einbeziehung des Lipid- und C_{org}-Gehalts wurden für den BSAF Werte zwischen 0,280 ± 0,17 und 0,403 ± 0,78 bestimmt. Beide Kennzahlen liegen unter dem in der Literatur oft als kritisch betrachteten Schwellenwert von 1 (Proc et al., 2021). Zudem wurde per Definition (OECD, 2010) kein Gleichgewicht (*Steady State*) in der Aufnahmephase erreicht. Dies deutete auf eine fortschreitende Aufnahme auch über 21 Tage hinaus hin. Die Elimination von Ivermectin in *E. fetida* folgte einem biphasischen Muster mit einer schnellen und einer langsameren Phase, was charakteristisch für lipophile Substanzen ist (Belfroid und Sijm, 1998). Der berechnete DT_{50}-Wert für den Konzentrationsrückgang von Ivermectin im AS betrug 142 Tage, was auf eine relevante Persistenz und damit auf eine potenziell verlängerte Bioverfügbarkeit hinweist. Dies steht im Zusammenhang mit der hohen Sorption in Böden und der intrinsischen Stabilität der Avermectine. Trotz geringer Akkumulation im Versuch spricht dies für ein potenziell anhaltendes Expositionsrisiko bei wiederholter Umweltbelastung.

Für *A. caliginosa und L. terrestris* zeigten sich während der Aufnahmephase leicht höhere Akkumulationsfaktoren als bei *E. fetida*, wobei auch hier kein Gleichgewicht erreicht wurde. Jedoch unterschieden sich die reinen Akkumulationsfaktoren (C_{Wurm}/C_{Boden}) signifikant zwischen den drei Arten (Kruskal-Wallis-Test, $p < 0{,}001$). Ein Dunn-Post-hoc-Test zeigte, dass *A. caliginosa* und *L. terrestris* höhere Akkumulationsfaktoren aufwiesen als *E. fetida* ($p < 0{,}05$), während zwischen *A. caliginosa* und *L. terrestris* kein signifikanter Unterschied festgestellt wurde ($p > 0{,}05$). Dies lässt sich auf artspezifische physiologische Unterschiede (Li et al., 2024) und die Retention von Ivermectin im Boden zurückführen. In LUFA 2.2, einem Boden mit geringerem C_{org}-Gehalt, kann die Bioverfügbarkeit aufgrund geringerer Sorption erhöht sein, was zu einer moderat stärkeren Aufnahme in den Regenwürmern führt. Die geringe Bioverfügbarkeit wird weiter begründet durch Einschätzungen, dass Ivermectin trotz dessen Lipophilie nur eingeschränkt biologische Membranen durchdringen kann (Escher et al., 2007; Arnot et al., 2010). Als komplexe Invertebraten verfügen Regenwürmer zusätzlich über Mechanismen, mit denen sie den Eintrag von Xenobiotika wie Ivermectin begrenzen oder kompensieren können. Hierzu gehören artspezifische Entgiftungskapazitäten, wie z. B. durch Carboxylesterase-Aktivität im Darm von *L. terrestris* und *A. caliginosa* (Sanchez-Hernandez et al., 2009; Sanchez-Hernandez et al., 2014).

Die Ergebnisse verdeutlichen, dass die starke Sorption von Ivermectin in organischem Material die Bioverfügbarkeit für Regenwürmer verringern kann (→ Fragestellung B). Dennoch könnte bei wiederholter und andauernder Belastung sowie artabhängiger Exposition das Risiko für eine stärkere Akkumulation bestehen. Dies könnte auch Spezies betreffen, die tiefere Bodenschichten besiedeln (→ Fragestellung C). Die niedrigen BAF_k-Werte in *E. fetida* aus dem zentralen Bioakkumulationsversuch sollten daher nicht isoliert interpretiert werden. Vielmehr ist eine systematische Betrachtung und Bewertung notwendig, auch im Rahmen regulatorischer Risikoabschätzungen und im Kontext realer terrestrischer Ökosysteme.

2.3 Ivermectin in der Malariavektorkontrolle: Ökotoxikologische Herausforderungen und Perspektiven im *One Health*-Kontext

Die Bestimmung der Ivermectin-Gehalte in Blutplasma und Dung der behandelten Rinder belegte eine langanhaltende systemische Verfügbarkeit des Wirkstoffs nach einmaliger Applikation des Depotpräparats IVM-BEPO. Die Qualität und Anwendbarkeit dieser Formulierung lagen im Fokus der Auswertung. Im Vergleich zur klassischen Handelsformulierung IVOMEC-D wurde für IVM-BEPO ein über 211 Tage quantifizierbarer Ivermectin-Gehalt im Dung festgestellt. Für IVM-BEPO lag die maximale mittlere Konzentration im Dung bei über 500 ng/g dw. Über den gesamten Zeitraum betrug die mittlere Konzentration ± SD im Dung 337 ± 185 ng/g dw. Dieser längere Expositionszeitraum gegenüber dem mehrfach verabreichten Vergleichspräparat zeigte sich auch im Plasma deutlich: die mittlere Konzentration für mit IVOMEC-D behandelte Tiere betrug 81 ± 24 ng/mL im Plasma (an Tag 2 nach der ersten Injektion) und sank innerhalb von 28 Tagen nach der Injektion auf 3,9 ± 2,4 ng/mL. Diese rasche Kinetik wurde für die nachfolgenden Injektionen wiederholt beobachtet. Nach der Behandlung mit der langwirksamen Formulierung wurde hingegen ein stabilerer Konzentrationsverlauf ermittelt. Hier wurde die maximale mittlere Plasmakonzentration im ersten Monat an Tag 7 (23 ± 8,9 ng/mL) und insgesamt an Tag 204 (33 ± 6,2 ng/mL) nach Injektion dokumentiert. Über den gesamten Zeitraum lag die mittlere Plasmakonzentration des Depotpräparats bei 19 ± 9,2 ng/mL.

Zur Charakterisierung des Umweltverhaltens wurden die Konzentrationsverläufe im gelagerten Dung untersucht. Der ermittelte DT_{50}-Wert von 182 Tagen (auf Basis der Tage 30, 60 und 90 unter Laborbedingungen) wies auf eine hohe Persistenz des Wirkstoffs im Dung hin. Bei Einbezug des Initialwerts von Tag 0 lag der DT_{50}-Wert bei 478 Tagen. Dies belegt, dass Ivermectin in der Praxis über längere Zeit im Dung verbleiben könnte, insbesondere wenn dieser unter trockenen Bedingungen gelagert wird. Grundlage dafür ist, dass unter semi-Freiland Bedingungen nach 90 Tagen kein signifikanter Konzentrationsrückgang beobachtet wurde (paarweiser Tukey-Test, $p > 0,05$). Die Sorptionsversuche mit Böden aus der Tuy Provinz ergaben mittlere K_D-Werte zwischen 55 und 123 mL/g sowie log K_{OC}-Werte zwischen 3,82 und 4,04 (entsprechend 6.630–10.870 mL/g). Die Sorption korrelierte signifikant positiv mit dem C_{org}-Gehalt und dem pH-Wert der Böden (jeweils Pearson's $r = 0,86$; $p < 0,05$). Diese Werte bestätigten die starke Sorption und limitierte Mobilität von Ivermectin auch unter den spezifischen Bedingungen Burkina Fasos.

Zur ökotoxikologischen Abschätzung wurde ein Vergleich der gemessenen Konzentrationen im Dung mit publizierten LC_{50}-Werten für Nichtzielorganismen wie Dungkäfern und Dungfliegen durchgeführt. Die über eine lineare Regression abgeschätzten Konzentrationen im Dung der mit IVM-BEPO behandelten Rinder überstiegen diese ökotoxikologisch relevanten Schwellenwerte teils deutlich, was auf ein potenziell hohes Risiko für Dung-assoziierte Insekten schließen lässt. Diese Einschätzung wurde durch Freilandstudien zu Ivermectin (Jochmann und Blanckenhorn, 2016; Verdú et al., 2018b) gestützt und durch spezifische Literaturdaten zu langfristigen Auswirkungen ergänzt. Dies ist besonders relevant, da es kaum veröffentlichte Erkenntnisse über ökologische Auswirkungen von langwirksamen, injizierbaren Ivermectin-Formulierungen gibt. Weiter bestehen Wissens- und Datenlücken hinsichtlich der in Westafrika vorherrschenden

Nichtzielorganismen-Gemeinschaften. Jüngste Erkenntnisse von Ruhinda et al. (2025) unterstützen diese Einschätzung: in einer Freilandstudie unter tropischen Bedingungen wurde ein Rückgang der Abundanz dungbewohnender Insekten festgestellt, insbesondere bei Termiten und Käfern, nachdem Rinder mit Ivermectin behandelt wurden. Die Effekte hielten über mehrere Wochen an und betrafen sowohl den Dungabbau als auch die Larvenentwicklung. Hinsichtlich der zunehmenden Diskussion um Endektozid-Behandlungen zur Vektorkontrolle unterstreicht dies die Notwendigkeit, potenzielle Umweltauswirkungen differenzierter zu bewerten.

Im Projektabschnitt zur Vektorkontrolle, basierend auf Feld- und Modellierungsergebnissen, zeigte sich eine hohe Wirksamkeit beider Formulierungen gegenüber *An. coluzzii*. Modellierungen zeigten, dass die Kombination aus Ivermectin-behandelten Rindern und Moskitonetzen zu einer Reduktion der infektionsrelevanten Moskitopopulation um bis zu 95 % führen kann. Dies war jedoch abhängig von Parametern wie dem Verhältnis von Rindern zu Menschen oder der Wirtspräferenz der Vektoren. Besonders effektiv erwies sich das IVM-BEPO Depot, welches eine kontinuierliche Moskitoreduktion über sechs Monate erzielte, während wiederholte IVOMEC-D-Injektionen nur eine zyklische Reduktion ermöglichten.

Vor diesem Hintergrund wurden Maßnahmen zur Risikominderung (*Risk Mitigation Measures*, RMMs) abgeleitet (Abb. 7). Damit wurden Ansätze entwickelt, um Umweltrisiken durch den Einsatz von Ivermectin-behandelten Rindern zur Vektorkontrolle zu managen (→ Fragestellung D). Gleichzeitig zeigte sich, dass die Integration von Umweltchemie und Ökotoxikologie in derartige Vektorkontrollstrategien bislang vernachlässigt ist. Diese Expertisen müssen künftig im Sinne eines proaktiven und vollständigen *One Health*-Ansatzes gestärkt werden (→ Fragestellung E). Dies sollte insbesondere durch die Betrachtung der Umweltauswirkungen unter klimatisch angepassten Bedingungen erfolgen. Auch RMMs müssen regional angepasst werden.

Abbildung 7 | Regionalspezifische Maßnahmen zur Umweltrisikominderung. Während die Ableitung der RMMs auf existierenden Konzepten (Liebig et al., 2014; UBA, 2019) basiert, muss sie kontextsensitiv weiterentwickelt werden. Die Erfassung des Umweltrisikos durch Endektozid-basierte Vektorkontrollmaßnahmen erfordert sowohl ortsspezifische Informationen zum Umweltverhalten der Wirkstoffe (*Environmental Fate*) als auch zur ökotoxikologischen Wirkung auf lokale Nichtzielorganismen. Eigene Darstellung (erstellt mit BioRender.com).

3 Diskussion im weiteren Problemkreis

3.1 Bodenschutz im *One Health*-Kontext

Angelehnt an den interdisziplinären *One Health*-Ansatz ist Bodenschutz weit mehr als nur das Vermeiden chemischer Belastungen. Neben dem flächendeckenden Eintrag von anthropogenen Schadstoffen wie Antiparasitika oder anderen Arzneimitteln stellen insbesondere strukturelle Eingriffe wie Bodenverdichtung und Bodenversiegelung eine große Herausforderung dar. Insbesondere die Versiegelung führt dazu, dass Böden essenzielle Funktionen verlieren. In der Folge gehen Ökosystemdienstleistungen verloren, die nicht nur die Umwelt, sondern auch unmittelbar die Gesundheit von Menschen und Tieren betreffen. So fördern degradierte Böden z. B. die Belastung von Oberflächengewässern durch Schadstoffe oder beeinträchtigen die Lebensmittelproduktion (UBA, 2004; KBU, 2025). Im Bodenschutz kann der Verlust der Bodenfunktionen durch Versiegelung daher als eines der größten Probleme angesehen werden. Auch in Bezug auf die UN-Ziele für nachhaltige Entwicklung ist sie relevant: Versiegelung steht hier im direkten Widerspruch zu SDG 15 „Leben an Land“, das den Schutz und die Wiederherstellung von Ökosystemen und Böden fordert. Auch SDG 13 „Maßnahmen zum Klimaschutz“ ist betroffen, da die Fähigkeit von Böden, insbesondere von Mooren, zur Kohlenstoffspeicherung gemindert wird (UBA, 2018). Im Sinne eines integrierten Bodenschutzes erfordert der Umgang mit diesen Problemen daher eine ganzheitlichere Sichtweise.

Da die Gesetzgebung im BBodSchG als unzureichend betrachtet wird, ist eine Anpassung an zukünftige Herausforderungen notwendig (Deutscher Bundestag, 2023). Das Umweltbundesamt (UBA) empfiehlt in der *Kommission Bodenschutz*, dass Bodenschutz durchführbarer gemacht werden muss für Umweltschadstoffe, für die bislang noch keine Vorsorgewerte existieren. Als Beispiel werden per- und polyfluorierte Alkylverbindungen (PFAS) genannt (KBU, 2025). Auch die Verwendung von Pflanzenschutzmitteln und deren Vorkommen in Böden hat weltweit besorgniserregende Ausmaße angenommen (Sabzevari und Hofman, 2022). Jedoch hat die Belastung durch Arzneimittel, insbesondere Veterinär-Antiparasitika, bislang noch nicht dieselbe Aufmerksamkeit wie andere Stoffgruppen erlangt. Der Schutz der Bodengesundheit benötigt daher umfassende Maßnahmen zur Reduzierung der Chemikalienbelastung.

Bodenschutz im Anthropozän

Auch die Ausrufung des Anthropozäns ändert, wie Menschen mit Böden umgehen müssen. Das Anthropozän – als Erdzeitalter, in dem menschliche Aktivitäten zu einem dominanten Faktor wurden – verändert die Perspektive auf Bodenschutz grundlegend. Böden gelten nicht mehr nur als natürliche, sondern als zunehmend menschengemachte Systeme. Deren Eigenschaften und Funktionen werden verändert durch Landwirtschaft, Urbanisierung, Chemikalieneinträge und Erosion (Richter, 2020). Besonders im Kontext des *One Health*-Ansatzes wird dabei deutlich, dass Böden zentrale ökologische Funktionen erfüllen, deren Verlust negative Auswirkungen auf Umwelt- und Gesundheitsbereiche hat (Guo et al., 2023). Der Schutz von Böden und deren nachhaltige Nutzung erfordern daher auch im Anthropozän einen vorsorgenden Ansatz. Dies ist

insbesondere aufgrund von Stoffeinträgen wie Human- und Veterinär-Arzneimitteln erforderlich, die zwar der öffentlichen Gesundheit dienen, aber gleichzeitig die Umwelt- und Bodengesundheit beeinträchtigen können.

Einordnung der Dissertation

In Hinblick auf die veröffentlichten Arbeiten (Heinrich et al., 2021; Heinrich et al., 2025) wurde die ausgeprägte Sorptionsfähigkeit der makrozyklischen Laktone und deren Risiko zur Persistenz in Böden und Sedimenten unterstrichen. Im globalen Kontext wurde die Bedeutung von Ivermectin zur Malaria-Vektorkontrolle betrachtet (Heinrich et al., 2024). In diesem Feld wurden Maßnahmen zum Schutz von landwirtschaftlich genutzten Böden sowie der Dung- und Bodenfauna erörtert. Die Umsetzung solcher Maßnahmen und das Monitoring der Veterinär-Antiparasitika in Böden bleiben von zentraler Relevanz (Römbke und Duis, 2018; UBA, 2019). Der Einsatz von Veterinär-Antiparasitika wie Ivermectin oder Eprinomectin zur Vektorkontrolle schafft jedoch zusätzliche Zielkonflikte zwischen Human- und Umweltgesundheit. Diese gilt es, im Sinne des in der Ökotoxikologie verankerten Vorsorgeprinzips systematisch zu adressieren.

3.2 Aquatische Risiken und Eintragspfade

Neben Böden sind auch aquatische Lebensräume zentrale Senken für Stoffeinträge wie Veterinär-Antiparasitika. In vielen Untersuchungen wurden entsprechende Wirkstoffe in Gewässern und Feuchtgebieten nachgewiesen und mit Nutztierhaltungen in Verbindung gebracht (Horvat et al., 2012; Charuaud et al., 2019; Mesa et al., 2020; Chen et al., 2021).

Die Rolle von Aquakulturen

Ein wachsender Aspekt der Tierproduktion und veterinärmedizinischen Versorgung sind auch Aquakulturen. Die EU sieht in nachhaltiger Aquakultur zudem ein zentrales Element der „blauen Wirtschaft“ mit Potenzial für ressourcenschonende Eiweißversorgung (EPRS, 2024). In Europa entfallen etwa 2,5 % der Verkäufe von Veterinär-Arzneimitteln auf aquatische Tiere (AnimalhealthEurope, 2024). Obwohl der Eintrag von Veterinär-Antiparasitika in Gewässer auch landwirtschaftlichen Quellen zugeordnet wird, ist der Stoffeintrag im Fall aquatischer Nutzungen unmittelbarer. Avermectine werden in Aquakulturen besonders zur Behandlung von Infektionen mit ektoparasitären Ruderfußkrebsen eingesetzt. Insbesondere Ivermectin und Emamectin Benzoat finden dabei Verwendung (Horsberg, 2012). Andere Antiparasitika für Aquakulturen sind beispielsweise Diflubenzuron, Teflubenzuron oder Praziquantel (Norbury et al., 2022; Rigos et al., 2024). Im Fall der Avermectine wurden im Kontext von Aquakulturen bereits potenzielle Umweltbelastungen für Ivermectin (Grant und Briggs, 1998), Abamectin (Hong et al., 2020) und Emamectin Benzoat (Horsberg, 2012) beschrieben. Beim Einsatz zur Bekämpfung von Seeläusen (Caligidae) konnte Ivermectin zudem in niedrigen Konzentrationen im marinen Sediment um Fischfarmen nachgewiesen werden (Cannavan et al., 2000). In Sediment-Wasser-Systemen wurden für Ivermectin DT_{50}-Werte von < 6 (Prasse et al., 2009) bis 15,9 Stunden (Wohde et al., 2017) gemessen, was auf eine rasche Dissipation aus der Wasserphase durch Bindung an Schwebstoffe und Sedimentpartikel hindeutet. Daher ist die Bewertung des Verbleibs und der Wirkung makrozyklischer Laktone in Sedimenten von großer Bedeutung.

Einordnung der Dissertation

Im Rahmen der Dissertation wurden erstmals Sedimente als Umweltkompartimente für makrozyklische Laktone in Sorptionsversuchen untersucht (Heinrich et al., 2021). Damit leistet die Arbeit einen Beitrag zum unzureichend verstandenen Verbleib dieser Wirkstoffe im Übergang zwischen terrestrischen und aquatischen Systemen. Zusätzlich wurde erstmals die Bioakkumulation von Ivermectin im Modellorganismus *E. fetida* zur Ableitung von BAF_k- und BSAF-Werten betrachtet (Heinrich et al., 2025). Dieser Ansatz erweitert das Verständnis von Bioakkumulationsprozessen jenseits aquatischer Organismen. Während in der regulatorischen Umweltbewertung die Bioakkumulation primär in aquatischen Organismen geprüft wird (mit einem Biokonzentrationsfaktor von 2000 als Schwelle (Verordnung (EG) Nr. 1907/2006)), bleiben terrestrische Akkumulationspfade größtenteils unberücksichtigt. In Kombination mit Befunden von Slootweg et al. (2010) die eine Bioakkumulation im Glanzwurm *L. variegatus* dokumentierten, ergibt sich ein differenzierteres Bild der Akkumulationspotenziale in Oligochaeta. Neben Effekten auf aquatische Nichtzielorganismen (Muniz et al., 2023) ist auch die Exposition aquatischer Krankheitsvektoren relevant. So wurden Bioakkumulation und toxische Effekte von Ivermectin in aquatischen Lebensstadien von Stechmücken beschrieben (Lorente et al., 2023). Im Kontext der Vektorkontrolle mit Endektoziden erhält dies zusätzliche Relevanz.

3.3 Resistenzen gegen Veterinär-Antiparasitika

Resistenzen gegen Ivermectin und Moxidectin wurden bei verschiedenen parasitären Würmern und in mehreren Tierarten dokumentiert (Geurden et al., 2015; O'Shaughnessy et al., 2019). Auch für Doramectin sind Resistenzen bekannt (Borgsteede et al., 2007; Conde et al., 2021). Die weltweite Zunahme der Resistenzen gegen Veterinär-Antiparasitika ist allerdings nicht auf makrozyklische Laktone beschränkt (Taylor et al., 2016). In Arthropoden entwickeln sich Resistenzen gegen Avermectine zumeist langsam und bilden sich ohne Selektionsdruck schnell zurück. Hauptmechanismus ist dabei die metabolische Resistenz, die auf dem Abbau der Wirkstoffe beruht. Die potenzielle schnelle Rückbildung macht Avermectine daher geeignet für Programme zum Resistenzmanagement. Um die Wirksamkeit der Wirkstoffe zu sichern, wird empfohlen, den Selektionsdruck durch Wirkstoffrotation, integrierte Bekämpfungsstrategien und gezieltes Resistenzmanagement zu minimieren (Rugg et al., 2005). Auch Refugia-Strategien, bei denen bewusst ein Anteil der Tier- bzw. Parasitenpopulation unbehandelt bleibt, gelten als Maßnahme zur Verzögerung von Resistenzen (van Wyk, 2001).

Ein zusätzlich hochrelevanter Aspekt ist der mögliche Effekt von Ivermectin und Moxidectin auf mikrobielle Gemeinschaften. Aufgrund ihrer makrolidähnlichen Struktur wurden neue Hinweise gefunden, dass beide Wirkstoffe auch das Wachstum bestimmter Bakterien beeinflussen können. Bei wiederholter Exposition zeigten einige bakterielle Isolate zudem vereinzelt eine verringerte Empfindlichkeit gegenüber ausgewählten Antibiotika (Dommann et al., 2024). Daher gewinnt das Vorsorgeprinzip im Bereich der Veterinärmedizin weiter an Bedeutung. Resistenzen von Pathogenen und Vektoren betreffen nicht nur die Tiergesundheit, sondern sind eng mit der Gesundheit von Böden und auch der menschlichen Gesundheit verknüpft.

Einordnung der Dissertation

Für Veterinär-Antiparasitika existieren bereits Konzepte zur Risikominderung. Diese Strategien wirken dabei nicht nur ökotoxikologischen Risiken entgegen, sondern reduzieren auch das Resistenzrisiko bei Parasiten (Heinrich et al., 2024). Zudem könnte der Eintrag tendenziell persistenter Wirkstoffe wie Ivermectin zu einer langfristigen Exposition von in Böden lebenden Parasiten führen. Dies gilt insbesondere für bodenübertragene parasitäre Würmer (*soil-transmitted helminths*). Bei diesen Organismen könnte ein großflächiger Eintrag makrozyklischer Laktone Resistenzrisiken schaffen (Vercruysse et al., 2011; Hürlimann et al., 2023). Der anschließende Stoffeintrag in angrenzende Gewässer führt weiter zur Exposition aquatischer Lebensstadien, z. B. Moskitolarven, was zusätzlichen Selektionsdruck riskiert (WHO, 1981; Sagna et al., 2023). Das bessere Verständnis über die Stoffeigenschaften von Veterinär-Antiparasitika und deren Verbleib in Böden ist daher essenziell. Es schafft eine fundierte Grundlage, um Expositionspfade und Resistenzrisiken abzuschätzen und zu vermeiden, insbesondere durch Berücksichtigung lokaler Umwelt- und Bodenbedingungen.

3.4 Umweltrisiken durch Haustierbehandlungen

Ein in der Dissertation nicht betrachteter und zusätzlich problematischer Aspekt sind die Ausscheidungen von Veterinär-Arzneimitteln durch Haustiere. Die Anzahl von Hunden und Katzen ist weltweit ansteigend, ebenso wie die Verwendung entsprechender Präparate, insbesondere langwirksamer Spot-on-Produkte zur Ektoparasitenkontrolle. Diese enthalten häufig aus Umweltsicht kritische Wirkstoffe wie Fipronil, Imidacloprid oder die fluorierten Isoxazoline Fluralaner und Afoxolaner (Diepens et al., 2023; Giannelli et al., 2024). Trotz hoher Persistenz und nachgewiesener Toxizität für Nichtzielorganismen unterliegen diese Produkte einer reduzierten Umweltprüfung. So wird angenommen, dass die Zulassung von Arzneimitteln für nicht lebensmittelliefernde (*non-food*) Tiere mit weniger Umweltbedenken verbunden ist, weil insgesamt auch geringere Produktmengen eingesetzt werden (EMA, 2000).

Allerdings werden Haustierprodukte nicht nur individuell, sondern auch häufig routinemäßig zur ganzjährigen Prophylaxe eingesetzt (Perkins, 2020). Angesichts ihrer hohen Toxizität und verschiedener Eintragspfade (z. B. über Hausstaub oder das Waschen von Tieren) liegt daher ein relevanter Umwelteintrag nahe. Auch die Ausscheidungen der lipophilen und chemisch stabilen Wirkstoffe, wie Fluralaner oder Selamectin, durch Haustiere werden zunehmend kritisch diskutiert (Wells und Collins, 2022). Ein zusätzlich relevanter Expositionspfad sind Zecken- oder Parasitenschutzhalsbänder (*collars*). Diese können z. B. Deltamethrin, Flumethrin, Imidacloprid, oder Diazinon enthalten. Die Wirkstoffe können unter anderem in die Umwelt gelangen, wenn die Halsbänder bei Hunden nicht abgenommen werden, bevor sie Gewässer betreten oder darin schwimmen (Diepens et al., 2023). Ergänzend dazu entfällt fast die Hälfte der in Europa verkauften Veterinär-Arzneimittel auf den Haustierbereich (AnimalhealthEurope, 2024). Auch auf europäischer Ebene wird daher zunehmend hinterfragt, ob Veterinär-Arzneimittel für Haustiere tatsächlich nur eine vernachlässigbare Umweltrelevanz haben. Aktuelle Daten legen nahe, dass diese Annahme nicht mehr uneingeschränkt tragfähig ist (EMA, 2023).

3.5 Stoffeigenschaften im regulatorischen Kontext

Im Fall von Ivermectin wird seit über 30 Jahren ein log K_{OW}-Wert von 3,22 kommuniziert (Bloom und Matheson, 1993; Escher et al., 2007; Krogh et al., 2008; Bair et al., 2017). Während teils Sekundärquellen angegeben werden, führt die Angabe auf Halley et al. (1989) zurück, die dokumentierten *„Ivermectin is not expected to accumulate in fish based on an octanol-water coefficient of 1651 (S.H.L. Chiu and R. Sestokas, personal communication).“* Dies entspricht dem gerundeten log K_{OW}-Wert von 3,22. Dieser Wert findet sich auch in früheren Unterlagen zur Umweltrisikobewertung des IVOMEC-D Präparats (Merck & Co., Inc., 1990). Die ausgeprägte Hydrophobie, beispielsweise erkennbar durch experimentell ermittelte Sorptionskoeffizienten, steht jedoch nicht im Zusammenhang mit diesem niedrigen log K_{OW}-Wert. Am Beispiel von Ivermectin und Selamectin wurde daher eine Neubestimmung des K_{OW}-Werts durchgeführt mit der angemesseneren *Slow-Stirring*-Methode (OECD, 2006). Dies geschah in einem durch das UBA koordinierten Projekt (UBA, 2019). Die experimentell bestimmten log K_{OW}-Werte betrugen 5,6 für Ivermectin und 6,0 für Selamectin. Zur Einordnung in der Dissertation wurden für ausgewählte Avermectine und Milbemycine rechnerisch ermittelte K_{OW}-Werte in Abb. 8 zusammengestellt. Diese Datenbankabfragen basieren auf Berechnungen beispielsweise aus empirischen Ansätzen oder QSAR-Abschätzungen (Tetko et al., 2005; ChEMBL, 2024b, 2024a; ChemSpider, 2024; EPI Suite, 2024; Fu et al., 2024; PubChem, 2024). Auch die nach Heinrich et al. (2021) abgeleitete K_{OW}-Werte wurden dort eingefügt. Im Beispiel von Ivermectin liegt der aus den Sorptionsdaten ermittelte log K_{OW}-Wert von 5,3 deutlich näher am experimentell bestimmten (5,6) sowie dem rechnerisch ermittelten (5,8) Wert.

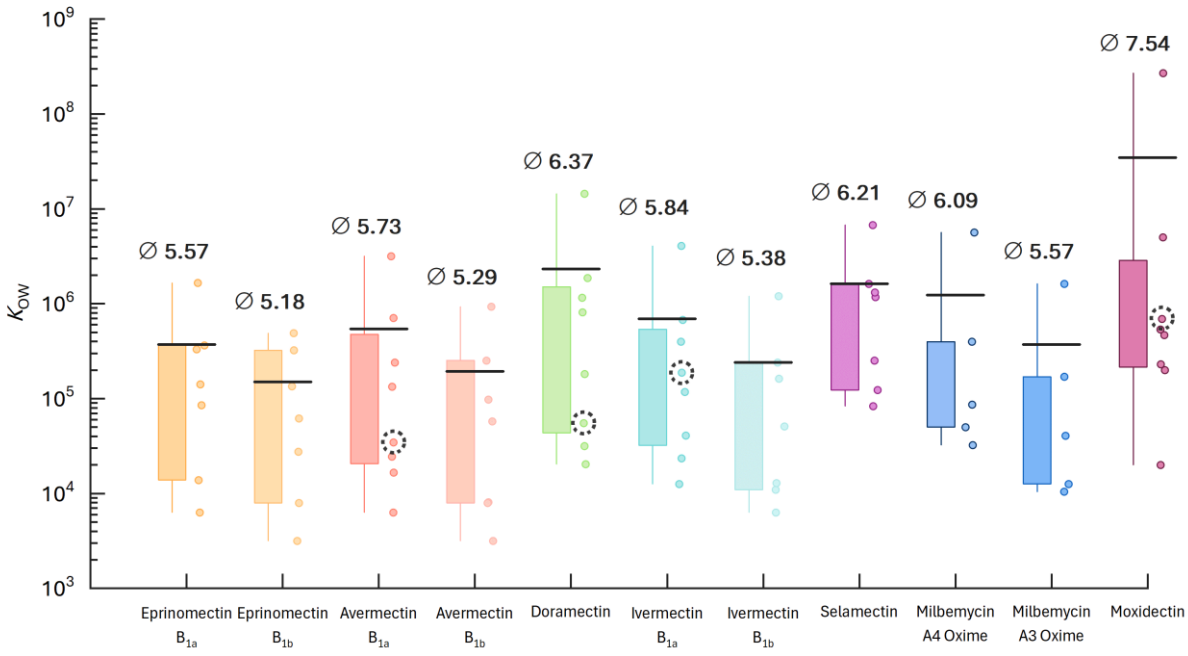

Abbildung 8 | Berechnete Verteilungskoeffizienten (K_{OW}-Werte). Boxplots der K_{OW}-Verteilungskoeffizienten ausgewählter Avermectine und Milbemycine basierend auf Berechnungen aus Online-Datenbanken (ChemSpider, PubChem, VCCLAB, ChEMBL, EPI SUITE, ADMETlab; aus Tab. A 3). Mittelwerte, als log K_{OW}-Werte, sind oberhalb der Boxplots (Q1–Q3) angegeben. Die horizontalen Linien zeigen die Mittelwerte. Die vier innerhalb der Kreise markierten Werte sind abgeleitet aus Heinrich et al. (2021). Eigene Darstellung.

Im Vergleich der rechnerisch ermittelten K_{OW}-Werte erscheinen diese Mittelwerte realistischer hinsichtlich der häufig dokumentierten Hydrophobie der Substanzen und deren Neigung zur Persistenz. Obwohl für Ivermectin, trotz eines log K_{OW}-Werts > 4, kein akutes Akkumulationsrisiko bestand (Heinrich et al., 2025), war diese Prüfung dennoch notwendig. Nur die Kenntnis über die Stoffeigenschaften von Arzneimitteln und Pestiziden erlaubt deren sichere Verwendung.

Auch zu anderen makrozyklischen Laktonen lassen sich Unsicherheiten über deren Stoffeigenschaften identifizieren. So nennen beispielsweise Zulassungsunterlagen eines Moxidectin-Präparats einen log K_{OW}-Wert von 4,77 (Fort Dodge Animal Health, 1997). Doch auch 1997 bestand noch keine Möglichkeit der exakten Bestimmung mittels *Slow-Stirring*-Methode. Zudem deuten die log K_{OW}-Ableitungen aus den Sorptionsversuchen mit 5,8 (Heinrich et al., 2021) sowie aus den berechneten Werten mit 7,5 (Abb. 8) eine deutlich höhere Hydrophobie an. Auch in aktuelleren Unterlagen wird weiter auf den Wert von 4,77 verwiesen (EMA, 2017).

In einem weiteren Beispiel wird für Abamectin oft ein log K_{OW}-Wert von 4,4 angeführt (BVL, 2015; Dionisio und Rath, 2016). Doch findet sich auch in Zulassungsunterlagen der Hinweis, dass dieser Wert auf der *Shake-Flask*-Methode (OECD, 1995) basiert. Dies mit dem Hinweis „*GLP. Although abamectine is a surface active substance and the shake flask method is usually not suitable for high logKow values, the study is found acceptable, because the found value is comparable with the values found in literature and KOWWIN calculations.*" (BVL, 2013) Auch wenn dieses Vorgehen methodisch nicht ideal ist, wird es in der regulatorischen Praxis akzeptiert. Diese pragmatische Herangehensweise ist nötig, ersetzt jedoch keine belastbare Datenbasis. Obwohl die Abweichungen zum aus den Sorptionsversuchen abgeleiteten log K_{OW}-Wert (4,5) minimal sind, erscheinen sie im Vergleich zum berechneten Mittelwert (5,7) deutlich größer. Um regulatorische Entscheidungen noch zielgerichteter unterstützen zu können, sind belastbare und systematisch erhobene Daten zu zentralen Stoffeigenschaften nötig. Dies gilt insbesondere bei der Bewertung potenziell persistenter und bioakkumulierender Substanzen wie Avermectinen.

Chemikalienbelastung als interdisziplinäre *One Health*-Herausforderung

Eine umfassende Sicht auf menschliche Gesundheitsvorsorge macht deutlich, wie wichtig gesunde Böden sind: beispielsweise für sauberes Wasser, stabile Klimabedingungen und sichere Lebensmittel (Romano und Zelikoff, 2024). Auch wenn Umweltverschmutzung dabei kein neues Problem darstellt, gehört die globale Chemikalienbelastung zu den größten Risiken für die menschliche Gesundheit. Dieses Risiko verschärft sich, weil viele industrielle Prozesse, aber auch die regulatorische Verantwortung, global ungleich gewichtet sind (Shetty et al., 2023). Weiter gibt es für eine Vielzahl der verwendeten Chemikalien keine kompletten Datensätze über beispielsweise Reproduktions- und Immuntoxizität, die Auswirkungen langfristiger Exposition oder die Risiken von Chemikaliengemischen (Fuller et al., 2022). Damit die Regulierung von Chemikalien dennoch wirksam bleibt, braucht es systematische Forschung, die gezielt in Entscheidungsprozesse überführt wird. Damit auch der Einsatz von Veterinär-Antiparasitika verantwortungsvoll erfolgen kann, sind robuste und regulatorisch verwertbare Daten zu ihren Stoffeigenschaften unerlässlich.

3.6 Schlussfolgerung

Die Dissertation liefert wichtige Beiträge zur Stärkung der Umweltgesundheit im *One Health*-Zeitalter, indem sie Umweltchemie und Ökotoxikologie kombiniert und das Verständnis der Umweltwirkungen von Ivermectin und den verwandten Wirkstoffen erweitert. Anhand der drei Hypothesen konnte zunächst bestätigt werden, dass Abamectin, Doramectin, Ivermectin und Moxidectin aufgrund ihrer hohen Lipophilie starke Sorptionseigenschaften in Böden und Sedimenten aufweisen. Dies deutet auf hohe log K_{OW}-Werte hin, die in der Literatur und regulatorischen Dokumenten teilweise unterschätzt sein könnten (Hypothese 1 ist akzeptiert).

Das Bioakkumulationsrisiko von Ivermectin in Regenwürmern wurde eingeschränkt bestätigt. Die Ergebnisse zeigten eine geringere Bioakkumulation als aufgrund der hohen Lipophilie vermutet. Dennoch wurde deutlich, dass standardisierte Testmethoden nicht alle realistischen Expositionsszenarien abbilden können. Unterschiedliche Kombinationen von Regenwürmern und Substraten könnten geeigneter sein (Hypothese 2 ist mit Einschränkungen akzeptiert).

Das *One Health*-Projekt zur Malariavektorkontrolle in Burkina Faso verdeutlichte, dass die flächenhafte Anwendung langwirksamer Ivermectin-Präparate erhebliche Risiken für die Bodengesundheit tropischer und subtropischer Regionen bergen könnte. Regionalspezifische Risikomanagementmaßnahmen sind zwingend nötig, um Umweltauswirkungen zu minimieren. Weiter müssen umweltchemische und ökotoxikologische Expertise eine umfangreichere Rolle in Endektozid-basierter Vektorkontrolle einnehmen (Hypothese 3 ist akzeptiert).

Aus den Ergebnissen und der erweiterten Diskussion ergibt sich eine interdisziplinäre Relevanz der makrozyklischen Laktone im Sinne von *One Health*. Die Wirkstoffe veranschaulichen, wie eng Umweltgesundheit mit Tiergesundheit und öffentlicher Gesundheit verknüpft ist. Um diese Herausforderungen zu bewältigen, ist eine nachhaltige und durch Wissenschaft gestützte Nutzung der Wirkstoffe entscheidend. Gleichzeitig besteht weiterer Forschungsbedarf, z. B. hinsichtlich der Langzeitwirkung und Mischtoxizität der Substanzen. Auch Anwendungen in Aquakulturen oder im Haustierbereich sollten aufmerksamer betrachtet werden. Die vom UBA seit Langem geforderte Einführung von Wirkstoff-Monographien ist hierzu ein vielversprechender Ansatz (UBA, 2024). Diese harmonisierten Datensätze könnten helfen, Umweltdaten und Stoffeigenschaften systematisch zu bündeln, um Datenlücken bei älteren Wirkstoffen zu schließen und zukünftige Umweltrisikobewertungen zu verbessern.

Schlussgedanke

Ein vorsorgender Bodenschutz ist mehr als reine Schadensvermeidung. Er ist die Grundlage für funktionierende Ökosysteme und sichere Lebensmittel. Wenn Menschen den Boden entschlossener vor chemischen Belastungen wie Arzneimitteln, Pflanzenschutzmitteln und anderen Chemikalien schützen, handeln sie nicht nur selbstlos im Sinne der Umweltgesundheit. Ein sorgsamer Umgang mit natürlichen Ressourcen stärkt auch die menschliche Gesundheit und gesellschaftliche Resilienz. Bodenschutz ist damit immer auch Vorsorge für die Zukunft: gleichermaßen für Menschen, Tiere, Umwelt und den Planeten.

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5 Sorption ausgewählter Antiparasitika in Böden und Sedimenten

5.1 Veröffentlichung

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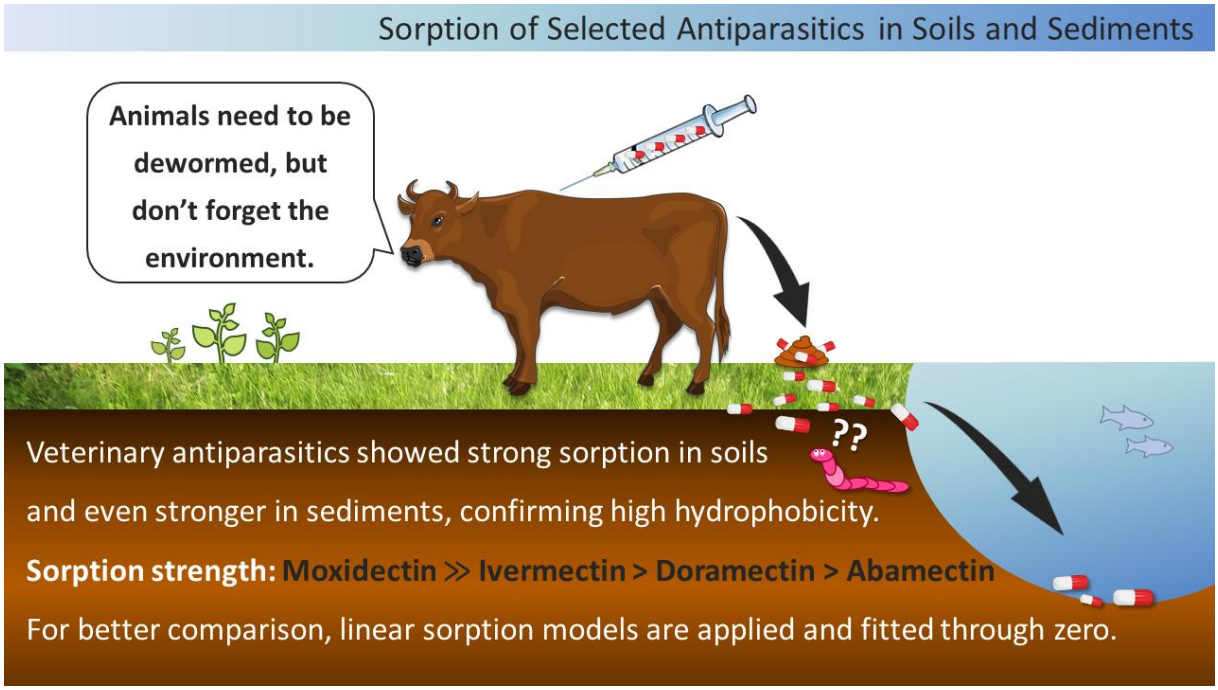
Graphical Abstract



Abstract

Background

Veterinary pharmaceuticals can enter the environment when excreted after application and burden terrestrial and aquatic ecosystems. However, knowledge about the basic process of sorption in soils and sediments is limited, complicating regulatory decisions. Therefore, batch equilibrium studies were conducted for the widely used antiparasitics abamectin, doramectin, ivermectin, and moxidectin to add to the assessment of their environmental fate.

Results

We examined 20 soil samples and six sediments from Germany and Morocco. Analysis was based on HPLC-fluorescence detection after derivatization. For soils, this resulted in distribution coefficients K_D of 38–642 mL/g for abamectin, doramectin, and ivermectin. Moxidectin displayed K_D between 166 and 3123 mL/g. Normalized to soil organic carbon, log K_{OC} coefficients were 3.63, 3.93, 4.12, and 4.74 mL/g, respectively, revealing high affinity to organic matter of soils and sediments. Within sediments, distribution resulted in higher log K_{OC} of 4.03, 4.13, 4.61, and 4.97 mL/g for the four substances. This emphasizes the diverse nature of organic matter in both environmental media. The results also confirm a newly reported log K_{OW} for ivermectin which is higher than longstanding assumptions. Linear sorption models facilitate comparison with other studies and help establish universal distribution coefficients for the environmental risk assessment of veterinary antiparasitics.

Conclusions

Since environmental exposure affects soils and sediments, future sorption studies should aim to include both matrices to review these essential pharmaceuticals and mitigate environmental risks from their use. The addition of soils and sediments from the African continent (Morocco) touches upon possible broader applications of ivermectin for human use. Especially for ivermectin and moxidectin, strong sorption further indicates high hydrophobicity and provides initial concern for potential aquatic or terrestrial ecotoxicological effects such as bioaccumulation. Our derived K_{OW} estimates also urge to re-assess this important regulatory parameter with contemporary techniques for all four substances.

Keywords

Sorption, Pharmaceuticals, Environmental fate, Environmental distribution, K_D, K_{OC}, Moxidectin, Avermectin, Desorption, Africa

Background

Discovery of the anthelmintic, actinomycete-derived macrocyclic lactones in the 1970s and their advancement into widely available antiparasitic agents came as nothing less than a medical and economic revelation [1, 2]. Grouped into avermectins and milbemycins, the efficient broad-spectrum endectocides for humans and animals revolutionized treatment of parasitic infestations [3]. Hailed as the 'wonder drug from Japan' [4], the avermectin derivative ivermectin was added to the World Health Organization model list of essential medicines [5]. A valued antiparasitic and safe for human use, ivermectin is also considered as a new malaria vector control tool [6, 7]. Almost unparalleled in its benefits for human health [8], ivermectin (IVM) was initially developed as a veterinary drug. Similar macrocyclic lactones include the avermectins abamectin (ABA), doramectin (DOR), and eprinomectin (EPR) as well as moxidectin (MOX), a milbemycin agent [3].

The use of pharmaceuticals for animals and humans can be accompanied by the release of drug residues into many environmental compartments. Particularly veterinary medicinal products (VMPs) for livestock, poultry or aquaculture come with the risk of direct drug excretion onto agricultural soils, involuntary application via manure fertilization, and release via runoff or erosion into surface waters. Exposure routes also include drug manufacturing and disposal, and all exposure scenarios raise the question of potential ecotoxicological effects and environmental fate of VMPs [9]. In this regard, sorption of VMPs and contaminants in soils and sediments is a fundamental process which governs the interdependence of fate, bioavailability, and ecotoxicity of a substance [10, 11]. Monitored by the European Medicines Agency (EMA), VMPs set to be registered in the European Union (EU) must undergo environmental risk assessments [12, 13]. Unfavorable, in this context, for avermectins and MOX is that animals excrete them largely unmetabolized, mainly within days after application, and primarily bound to feces. This feature is ascribed to their hydrophobic nature and an active excretion process via P-glycoprotein [14, 15]. Despite their extensive use as VMPs, only a limited number of sorption studies exist for macrocyclic lactones. In contrast, hundreds of soil sorption observations are available for major plant protection products, such as atrazine [16]. Reflecting the medical significance of IVM, most studies investigating soil sorption focus on this drug [17,18,19]. Others investigate ABA [20], EPR [21, 22], or multiple agents at once [23]. To varying degrees, the overarching observation is the tendency of these substances to strongly bind to soil organic matter. This is indicated by a high organic carbon–water partition coefficient (K_{OC}). However, with sorption as a fundamental process in soil chemistry [24], the data situation on the fate of these VMPs seems insufficient.

Another complication for environmental risk assessments of the four antiparasitics is the lack of reliable and transparent octanol–water partition coefficients (K_{OW}). A routinely assumed order of hydrophobicity (as log K_{OW}) appears to be: IVM (3.2 [25], presumably used in a marketing request [26]), ABA (4.0 [27] to 4.4 [28]), DOR (4.4 [29]), MOX (4.77 [30], presumably referred to by the EMA [31]). However, the reported methodology behind these values can be deficient or absent. This is reiterated by the EMA [32] which also cites 4.4 as log K_{OW} for DOR, but addresses the inappropriately used shake-flask method. This methodology is also stated for the 4.4 value of ABA [28] and for MOX [30]. Furthermore, a report funded by the German Environment Agency on environmental properties of antiparasitics, compiled by Römbke et al. [13], concluded that a log K_{OW} of 3.22 underestimates this key hydrophobicity indicator for IVM. While this value by Halley et al. [25] is cited frequently [17, 33, 34], the 2019 report implicates at least a 240-fold increase in hydrophobicity when expressed as log K_{OW}. In 1989, a method to determine the log K_{OW} of potentially highly hydrophobic substances like IVM had not been standardized. It was only introduced in 2006 by the Organisation for Economic Co-operation and Development (OECD) with guideline 123 [35]. Compared to the shake-flask method, this slow-stirring technique is considered more reliable for highly hydrophobic substances [12]. The technique was applied by the Fraunhofer-Institute for Molecular Biology and Applied Ecology (Schmallenberg, Germany), yielding a new log K_{OW} of 5.6 (± 0.3) for IVM [13]. This assessment is backed by curated data from the U.S. Environmental Protection Agency predicting a median log K_{OW} of 5.41 for IVM's main component IVM B_{1a} [36].

From a regulatory perspective, a log K_{OW} > 4 for VMPs indicates a potential for bioaccumulation to occur in the

environment, although multiple criteria need to be considered [12, 37]. In this context, the EMA's Committee for Medicinal Products for Veterinary Use concluded that MOX-containing VMPs for cattle, sheep, and horses might harbor persistent, bioaccumulative, and toxic properties [38]. Fabrega and Carapeto [39] compiled that as a result of environmental concerns, 20 referral procedures of VMPs have been triggered to re-assess environmental risks post-authorization. Six of these products were antiparasitics. It is noteworthy that the European Union is committed to identify knowledge gaps and to address potential environmental risks of pharmaceutical residues and investigate their fate [40].

Non-target effects of macrocyclic lactones

Extensive reviews by Liebig et al. [33], Lumaret et al. [41], Finch et al. [42], and Junco et al. [43] summarize environmental risks accompanying the unintentional release of macrocyclic lactones and are cause for concern. Acute and chronic effects are observed especially for coprophagous species. Though well documented, knowledge about fate and toxic effects of these drugs on non-target organisms is ever-evolving. Beyond dung and soil, aquatic biota can also be harmed if antiparasitics enter surface waters and sediments [44,45,46].

How would antiparasitics end up in sediments?

Compelling evidence for this pathway is presented in a field study by Mesa et al. [47] who treated cow herds with IVM and monitored drug concentrations in the wetlands used for grazing. IVM was detected in manure, water, sediment, and macrophytes as well as in wetland invertebrates and fish. Environmental IVM loads increased with animal count and injection frequency. For DOR, Kumirska et al. [48] reported field-concentrations in water, sediment, and fish at a sampled river, with DOR in water exceeding predicted no effect concentrations for *Daphnia magna*. Since ABA is also used as a pesticide, runoff or erosion from treated fields can enter adjacent water bodies [49, 50], enabling transport into sediments. Discharge of antiparasitics into water and sediment, besides direct excretion or transfer from fields, may also be relevant in aquaculture. There, concerns for environmental exposure have been raised for IVM [51], ABA [52], and the ABA derivative emamectin benzoate [53]. When used to control sea lice infestations, IVM can be quantified in low concentrations in marine sediments around fish farms [54]. In water, DT_{50}-values of < 6 [55] and 15.9 h [56] have been reported for IVM in simulated sediment/water systems. This indicates rapid dissipation from aqueous media; presumably binding onto suspended particles and sediment. However, there are no known studies documenting the sorption of macrocyclic lactones in sediments. At the same time, wetlands and sediments are invaluable nurseries for benthic and hyporheic invertebrates as well as emergent aquatic insects (e.g., *Ephemeroptera*, *Plecoptera*, *Trichoptera*) which carry nutrients and biomass to terrestrial habitats [57, 58]. The drivers of global insect decline are under discussion [59] and it is worth investigating to what extent environmental chemicals and pharmaceuticals may contribute. Although sediments can act as both sinks and sources for contaminants and serve vital functions in aquatic food chains, environmental risk assessment in this compartment is fragmentary [34]. Diepens et al. [60] reiterate this current underrepresentation in regulatory frameworks. If risks of antiparasitics or other VMPs are to be assessed, environmental risk assessment begins with meaningful exposure assessment including a substance's fate in all plausible environmental compartments. Thus, we aim to establish comparable sorption data for antiparasitics in soils and sediments which provide a basis for regulatory decisions.

Experimental approach

We investigated the sorption of 4 macrocyclic lactones used as antiparasitic VMPs: the avermectins ABA (also used as pesticide), DOR, IVM, and the milbemycin MOX. Sorbates were used simultaneously in each sorption experiment and could be determined at once within an analytical run. The methodology for sorption studies is standardized in OECD guideline 106 [61] to predict substance partitioning in soils. As a novelty, we also performed sorption experiments with six sediments in addition to 20 investigated soil samples. Sorption of these drugs in sediments has not been reported before. We also present, to our knowledge, first-time data from a batch equilibrium study on the sorption of these VMPs in soils and sediments from the African continent.

This work promotes linear modeling with constrained intercepts to derive comparable sorption coefficients that enable robust regulatory decisions. To assess the general

hydrophobicity of the antiparasitics and validate our sorption results, we derive and review K_{OW} estimates from K_{OC} coefficients.

Materials and methods

Soil and sediment samples

German soil samples (label DE) were provided by the Hessian Agency for Nature Conservation, Environment and Geology (HLNUG). From a pool of samples, 17 were selected for sorption studies. The selection was based on OECD guidance instructions [61]. These samples represent a range of physicochemical properties, soil horizons, textures, sampling depths as well as pasture and crop locations throughout the state of Hesse. Moroccan samples (label MA) were taken in the Gharb Basin region in the northwest of Morocco with a soil auger, collecting the top 20 cm of soil and sediment. Crop residues on soils were omitted since fields were previously cultivated for various cereals. Bed sediments were sampled along Sebou River (Oued Sebou; MA07 to MA09) and Loukkos river (Oued Loukos; MA04–MA06) with MA04 closest to the Atlantic coast at Merja Zerga lagoon. Before sampling, sediments were cleared of debris. Distance to shore or embankment was 1.5–2 m to sample sediments that were continuously underwater. Table 1 shows the physicochemical properties of soil and sediment samples. In contrast to German samples, the Moroccan samples represent a Mediterranean climate. They are characterized by generally higher pH values in the carbonate buffer range, resulting from limestone and marl limestone deposits in the basin [62]. Samples were air-dried and sieved to 2 mm. Water content was determined by drying aliquots at 105 °C.

Materials

ABA and IVM are mixtures of semisynthetic avermectin B_1 derivatives. They contain at least 80% B_{1a} component (C-25 s-butyl group) and less than 20% B_{1b} component (C-25 isopropyl group), while DOR holds a sole cyclohexyl group at C-25. Chemically related, the smaller MOX molecule is a semisynthetic derivative of the milbemycin nemadectin, a fermentation product of *Streptomyces cyanogriseus*, whereas avermectins are derived from *Streptomyces avermitilis* [3, 65]. Structural differences are shown in Fig. 1.

Antiparasitics were purchased as analytical standards (CAS-no.; product-no., supplier; purity) in powder form: ABA (71751-41-2; 31732-100MG, Sigma-Aldrich; 98.6%), DOR (117704-25-3; DRE-C13083000, LGC Standards; 96.0%), IVM (70288-86-7; DRE-CA14488000, LGC Standards; 96.0%), and MOX (113507-06-5; DRE-CA15335000, LGC-Standards; 94.6%). Acetonitrile (ACN) (20060.320) and propan-2-ol (84881.320P), both ≥ 99.9% purity, came from VWR International; Calcium chloride dihydrate (102382) from Merck. Derivatization chemicals (> 99.0% purity) were bought at Sigma-Aldrich: N-methylimidazole (336092), triethylamine (T0886), trifluoroacetic anhydride (106232), and trifluoroacetic acid (302031). Purified water was prepared with a Milli-Q® system. We used a CHROMABOND® solid-phase extraction (SPE) system (MACHEREY–NAGEL), custom handblown 45 mL glass centrifuge vials with a PTFE-coated silicon seal inside the screw cap, 500 mg Strata C18-E SPE cartridges (8B-S001-HCL, Phenomenex), and 0.45 µm PTFE membrane syringe filters (WIC 79145, WICOM).

Sorption experiments

Experiments were conducted according to OECD guideline 106 [61]. We suspended 1 g dried soil or sediment with 30 mL 0.01 mol/L $CaCl_2$ solution in purified water for a 1:30 (w/v) solid/solution ratio. This ratio was elaborated in own preliminary studies and is situated between the ratios of 1:20–:40 (w/v) applied in a comparable study by Rath et al. [23]. Before spiking, solid samples were pre-shaken in the $CaCl_2$ solution for 24 h. Since these antiparasitics represent highly hydrophobic substances, powdered analytical standards were dissolved in ACN to create stock solutions of 4×10^6 µg/L. These solutions were combined in equal proportions for a mixed solution containing 1×10^6 µg/L of each substance. This was diluted into working solutions to simultaneously spike all drugs in a consistent volume of 30 µL ACN for a 0.1% (v/v) solvent concentration [61]. Sorption in soils DE01 to DE06 was not studied for MOX. In the ongoing sorption study series, we created the following test concentrations in the aqueous phase: 100, 200, 300, 400, and 500 µg/L (samples DE07–DE17); 100, 200, 300, 500, and 1000 µg/L (MA01–MA09); 500, 1000, 1500, 2000, and 2500 µg/L (DE01–DE06). After spiking, solutions were shaken for 48 h (sorption equilibrium time) while glass vials

Table 1 Physicochemical properties, origins, and sampling depths of soils and sediments for the sorption experiments. Soils labeled DE were taken in Germany; samples labeled MA originated in Morocco

Label	Site	Depth (cm)	%OC[a]	C/N[b]	pH[c]	CEC[d]	Reference soil group[e]	Texture (% w/w)		
								Sand	Silt	Clay
DE01	Crop	90–120	0.08	3.7	6	19.2	Luvisol (siltic)	2	61.7	36.3
DE02	Crop	0–20	5.9	20.9	7.4	19.8	Regic anthrosol	59	24.7	16.3
DE03	Crop	65–90	0.73	50.2	7.6	23.2	Terric anthrosol (stagnic)	12.2	26	61.9
DE04	Crop	40–100	0.14	5.6	5.5	4.3	Cambisol (loamic)	79.4	16.4	4.2
DE05	Crop	60–90	0.15	4.8	6.3	18.9	Luvisol (siltic)	2.1	63.4	34.5
DE06	Crop	80–120	0.11	2.7	6.4	11.9	Planosol	12.9	54.5	32.7
DE07	Crop	40–60	0.29	5.7	7.4	32.5	Cambisol (clayic)	5.3	33.4	61.2
DE08	Pasture	30–55	1	6.9	6.8	22.4	Vertic cambisol	3.1	49	47.9
DE09	Crop	0–30	1.8	11.3	5.9	9.9	Umbrisol	51.8	36.3	11.9
DE10	Pasture	30–80	0.83	7.5	6	14.7	Gleyic cambisol (siltic)	13.5	62.5	24
DE11	Pasture	0–30	2.72	8.9	5.3	27.7	Vertisol	4.5	65.9	29.5
DE12	Pasture	0–5	3.15	8.9	4.4	19.9	Umbrisol (loamic)	30.8	50.2	19
DE13	Pasture	0–25	3.57	8.9	5	23.9	Stagnic gleyic cambisol	4.4	62.8	32.8
DE14	Pasture	0–5	3.89	9.7	4.6	23.5	Umbrisol (siltic, leptic)	28.9	49.1	22
DE15	Crop	0–15	6.01	17.5	6.9	27.5	Terric anthrosol (stagnic)	53.3	26.1	20.7
DE16	Crop	95–100	0.9	68.2	7.7	21.5	Terric anthrosol (stagnic)	10.6	27	62.5
DE17	Pasture	0–10	4.7	8.9	5.5	32.8	Gleysol	21.1	52.2	26.6
MA01	Crop	0–20	2.09	18.6	7.4	n/d	Vertic cambisol	10.2	49.7	40.1
MA02	Crop	0–20	1.93	16.7	7.6	n/d	Vertisol	4.3	28.1	67.6
MA03	Crop	0–20	1.33	18.2	7.6	n/d	Vertisol	1.7	27.8	70.6
MA04	Sediment	0–20	0.43	–[f]	7.7	n/d	Not applicable	95.7	1.7	2.6
MA05	Sediment	0–20	1.23	12.5	7.7	n/d	Not applicable	2.2	35.3	62.5
MA06	Sediment	0–20	0.42	26.3	7.6	n/d	Not applicable	60.2	18.9	20.9
MA07	Sediment	0–20	1.62	19.7	7.7	n/d	Not applicable	3.1	32.5	64.4
MA08	Sediment	0–20	1.38	30.1	7.5	n/d	Not applicable	17.5	41.4	41.1
MA09	Sediment	0–20	0.62	50.7	7.5	n/d	Not applicable	19.5	53.4	27.1

n/d not determined

[a] Weight percentage of soil/sediment organic carbon, following DIN ISO 10694

[b] Carbon–to–nitrogen ratio

[c] pH measured in a solution of 0.01 mol/L $CaCl_2$; following DIN ISO 10390

[d] Potential cation exchange capacity in cmolc/kg; following DIN ISO 13536

[e] Reference soil groups according to the World Reference Base for Soil Resources [63] were derived using the German Soil Survey Guidelines, 5th ed. (KA5) and field data from HLNUG. Moroccan soils were characterized on-site. Sediment classification [64] is not provided since gravel content was not available

[f] Not available, minimal N content made determination impossible

were wrapped with aluminum foil to prevent possible photodegradation. Controls contained soil/sediment samples with $CaCl_2$ solution or $CaCl_2$ solution spiked with antiparasitics absent of soil/sediment. An experimental duration of 48 h was selected to reach apparent sorption equilibrium between macrocyclic lactone concentrations in soil/sediment and the aqueous phase. This was based on own preliminary kinetic studies and is supported by comparable experiments. [17, 20]. An exemplary desorption assessment was performed after 72 h and is briefly addressed in the discussion. Systems were equilibrated using a horizontal lab shaker (KS-10 Swip, Edmund Bühler GmbH) at 250 rpm. German samples were spiked in duplicates, Moroccan samples in triplicates. All steps were performed under ambient laboratory conditions at 21 ± 1 °C.

Sample processing

Analytical procedures were based on Wohde et al. [56, 66] and adapted as follows: SPE cartridges were conditioned with 10 mL propan-2-ol followed by 10 mL of a 1:3 mixture (v/v) of propan-2-ol and purified water. At 48 h shaking time, samples were centrifuged at 2820*g* for 30 min and 25 mL supernatant were added to a reservoir atop the SPE cartridges along with 8.333 mL propan-2-ol and 25 µL triethylamine. Dried cartridges were eluted with

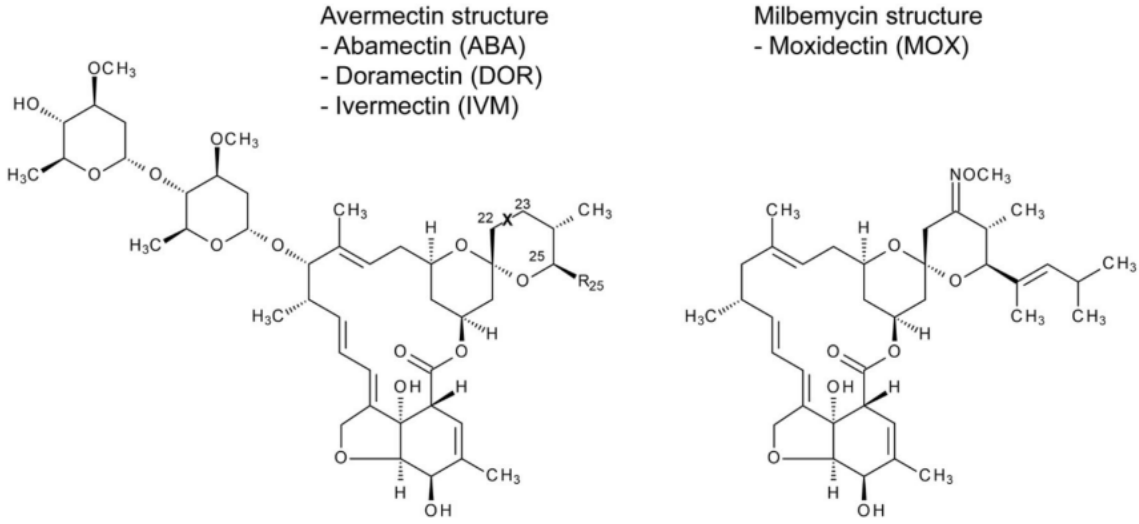


Fig. 1 Chemical structures of the examined antiparasitics. Differences for avermectins (left) are: abamectin (ABA): X = double bond, R_{25} = $CH(CH_3)CH_2CH_3$ and $CH(CH_3)_2$; doramectin (DOR): X = double bond, R_{25} = cyclohexyl group; ivermectin (IVM): X = single bond, R_{25} = $CH(CH_3)CH_2CH_3$ and $CH(CH_3)_2$. The chemically related milbemycin moxidectin (MOX) is shown on the right. Own illustration based on Shoop et al. [3]

10 mL propan-2-ol. Eluates were evaporated to dryness under an N_2 stream at 60 °C. For reconstitution, 1000 µL ACN were added to each vial. Vials were then sonicated for 15 min, horizontally shaken (250 rpm) for 30 min, and again sonicated for 15 min. Between each step, samples were vortexed for 30 s. Subsequently, samples were derivatized and quantified by HPLC-fluorescence detection on an Agilent 1200 HPLC system as elaborated by Wohde et al. [66]. This was applied for all four test substances with 40 µL injection volume and a shorter gradient elution. Mobile phases were A (purified water) and B (ACN); flow 0.3 mL/min; gradient 0–10 min, 88–100% B; 10–11 min, 100% B; 11–20 min 100–88% B. Since a broad range of sample characteristics and expected sorption was covered in the overall study series, we used different linear calibration sets of mixed standard solution with at least seven calibration standards per individual calibration series. All calibration curves displayed a linear response with R^2 > 0.998.

Deriving distribution coefficients

Soil and sediment samples were evaluated alike. Evaluation followed OECD guideline 106 [61]. The distribution coefficient K_D is defined as the ratio of substance concentration in the solid-phase C_s(eq) and the substance concentration in the aqueous-phase C_{aq}(eq) at equilibrium with the equation:

$$K_D = \frac{C_s(eq)}{C_{aq}(eq)} \quad (1)$$

where C_s(eq) is expressed in µg/g, C_{aq}(eq) in µg/mL, and the K_D in mL/g. The measured C_{aq}(eq) was then used to indirectly estimate the remaining amount of substance in the solid phase, delivering C_s(eq). While **Eq. (1)** holds true for a single set of a solid and an aqueous phase, we derived the K_D for each sample by plotting all concentrations and replicates. We obtained the K_D as the slope of a linear regression with the y-intercept constrained. The decision of constraining the y-intercept was deliberate and relied on Chappell et al. [67] who concluded that only if consistency was imposed on a set of linear equations, distribution coefficients could be compared among different soils which is an aim of this work. While different concepts exist to describe distribution with sorption isotherms, such as linear models or nonlinear approaches with the Freundlich and Langmuir equation, they remain of theoretical nature. Linear models assume proportional increase of sorbed amounts with increasing adsorbate concentration in the aqueous phase. They consider no competition of solutes which is a relevant aspect when investigating four substances at once [24]. A constant slope reflects that sorbates have much higher affinity for sorbents than for the aqueous phase. This benefits low and environmentally relevant concentrations and Rao and Jessup [10] suggest the use of linear isotherms if agricultural applications or pathways are considered. Nonlinear sorption isotherms from studies with five test concentrations [61] may appear insufficient to produce a reliable, steady intercept that is not overstated. Especially the lowest concentration step can entail the most uncertainty and could strongly affect

the intercept. Organic carbon (OC) is considered largely responsible for sorptive properties in soils [68]. Thus, the K_D is normalized to this parameter to derive the K_{OC} in mL/g. The K_{OC} can serve as a tool to estimate the mobility of a chemical in soil [69] and is derived with the equation:

$$K_{OC} = \frac{K_D}{f_{OC}} \quad (2)$$

where f_{OC} is the OC fraction of the soil/sediment [70] expressed as weight percentage of soil/sediment OC (%OC). Here, f_{OC} was chosen over %OC to directly plot f_{OC} vs. K_D values and derive the K_{OC} of multiple soils as slope of a linear regression. Both Freundlich and Langmuir models can make determining a tangible K_{OC} impractical. Further, as recommended in OECD guideline 106, we excluded soil samples with < 0.3% OC from K_{OC} calculations for which we selected 13 (12 for MOX) out of 20. Figures 2, 3 are calculated and created using OriginPro 2020b (OriginLab Corporation, Northampton, MA, USA).

Method validation

Limit of detection (LOD) and limit of quantification (LOQ) for the HPLC-method were estimated according to recommendations in guideline Q2(R1) by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [71]. Based on the five lowest calibration standards (2, 5, 10, 50, and 100 µg/L), we used the calibration curve slope (m) and standard deviation (σ) of the response expressed as standard error of the y estimate (derived with the STEYX function in Microsoft Excel 2019). LOD is expressed as 3.3 × σ/m and LOQ as $10 \times \sigma/m$. These results are given in Table 2. Further shown is the total number of replicates from all batch studies (soils and sediments) which were above the LOQ. Control samples did not reveal irregularities in terms of analyte losses or cross-contamination nor relevant sorption to surfaces of laboratory equipment. Pre-empting the results section, the concentration range in which substances were found across all samples reveals a hierarchy in their tendency to remain in the aqueous phase. The trend in lowest C_{aq}(eq) in µg/L in any replicate was ABA (1.2), DOR (0.49), IVM (0.31). Conversely, the order for highest C_{aq}(eq) was IVM (785), DOR (812), ABA (986). MOX conflicts this trend (0.62–247 µg/L), but was not used in soils with low %OC where a high C_{aq}(eq) is suspected.

Table 2 Limit of detection (LOD) and limit of quantification (LOQ) for antiparasitics in sampled aqueous phases of sorption studies using area response of 2, 5, 10, 50, and 100 µg/L calibration steps in $n = 3$ measurements with R^2. Analyte concentration enrichment during sample processing is considered

	Corresponding concentration in the sampled aqueous phase C_{aq}(eq)			Samples above LOQ (%)
	LOD (µg/L)	LOQ (µg/L)	Mean R^2	
ABA	0.53	1.61	0.996	100
DOR	0.56	1.71	0.995	100
IVM	0.55	1.66	0.996	99.0
MOX	0.67	2.02	0.993	99.2

We monitored the stability of fluorescent ABA, DOR, IVM, and MOX derivates for 20 min, 24, 48, and 72 h after derivatization ($n = 6$). After a slight decrease over time, 72 h average fluorescence recovery remained at 86.5, 85.1, 92.7, and 89.3% for ABA, DOR, IVM, and MOX derivates compared to 20 min. Consistently, samples were measured within 24 h after derivatization. Measurements of up to 72 h after derivatization of calibration standards and samples should not impair overall results.

Although the HPLC protocol yields favorable separation, a quality control was performed. Chromatograms of standard solutions containing only a single analyte showed minor fluorescence at retention times other than the main peak. This is presumably attributed to the purity (94.6–98.6%) of purchased standards. IVM and MOX peaks showed no overlap with impurities of other analytes. We found a fluorescence increase for ABA and DOR main peaks of 1.1 and 3.4% and downscaled these accordingly. ABA and IVM sorption results will represent their major (> 96%) B_{1a} component.

For additional method validation, a standard soil (LUFA 2.2) was purchased from LUFA Speyer (loamy sand; 1.61% OC; 0.18% nitrogen; pH 5.6 (0.01 mol/L $CaCl_2$); CEC 8.5 meq/100 g). Therewith, we performed a mass balance determination [61] at 300 µg/L spiked concentration. Liquid phase extraction was performed with the presented SPE method. Soils and vessel walls were extracted two times with 5 mL ACN. The overall recovery of spiked antiparasitics ranged from 86 to 118% for the four substances. Mean recoveries (± SD, $n = 4$) were: ABA 90.8 (4.1), DOR 107 (4.1), IVM 112 (2.1), and MOX 115.9% (1.6). This indicates that there is no relevant degradation of analytes within 48 h of shaking. Test substances can be considered to be stable. Determination with the indirect

method [61] should thus be appropriate. This is in line with previous mass balance and stability reports on the sorption of avermectins [19,20,21]. The same soil and drug concentration were used to compare sorption of all four analytes with sorption when only IVM is added. IVM slope K_D (± SE, n = 4) was 532 (12) with only IVM and 471 (26) mL/g with four analytes. Under these conditions only negligible competition in sorption is indicated when all four substances are spiked at once. Additional information on the method validation is provided in the Additional file 1.

Results and discussion

Sorption in soils

Batch equilibrium studies were evaluated with linear sorption isotherms which served for calculation of K_D values. Plotting soil K_D against f_{OC} resulted in Fig. 2. It shows the K_{OC} as the slope of the linear regression through 13 (12 for MOX) selected soils with the intercept constrained which creates a narrowing confidence corridor. For soils included in this regression, K_D values ranged from 38 to 211 (ABA), 63 to 428 (DOR), 76 to 642 (IVM), and 166 to 3123 mL/g (MOX). This dispersion characterizes the variability of the selected soils. Individual K_D values are listed in the Additional file 1.

The detail area of Fig. 2 shows soils with less than 0.3% OC. The linear regressions with 95% confidence bands of the used dataset fall below the individual K_D values for each substance in this region of low f_{OC}. Recommended in OECD guideline 106, the procedure of removing these soils from K_{OC} calculations is corroborated by Krahe et al. [72] who also showed that below 0.3% soil OC linear model approaches become uncertain. They argue that at low concentrations, the accuracy of OC analyses could be reduced and that other sorption surfaces could become more relevant. It appears reasonable to assume that with little OC available, substances more likely sorbed to other available surfaces like clay, silt or dissolved organic matter, therefore displaying a K_D above the regression. Of the thus five excluded soils, four displayed above average clay or silt concentrations among all 20 soils which could explain their relatively high sorption. Only DE04 with the highest sand content and low cation exchange capacity contradicts this rationale. With the presented parameters, its sorption behavior remains elusive. Both DE15 and DE02 showed relatively low K_D values and contradicted the linear trend. This could be attributed to the fact that both samples originated from soil horizons with only moderately decomposed organic material and DE15 displayed stagnic properties. However, quality and detailed composition of organic material and its influence on the pH would have to be considered. Less decomposed organic material can harbor more hydrophilic groups, indicated by a lower elemental H/O ratio [73]. More available hydrophilic

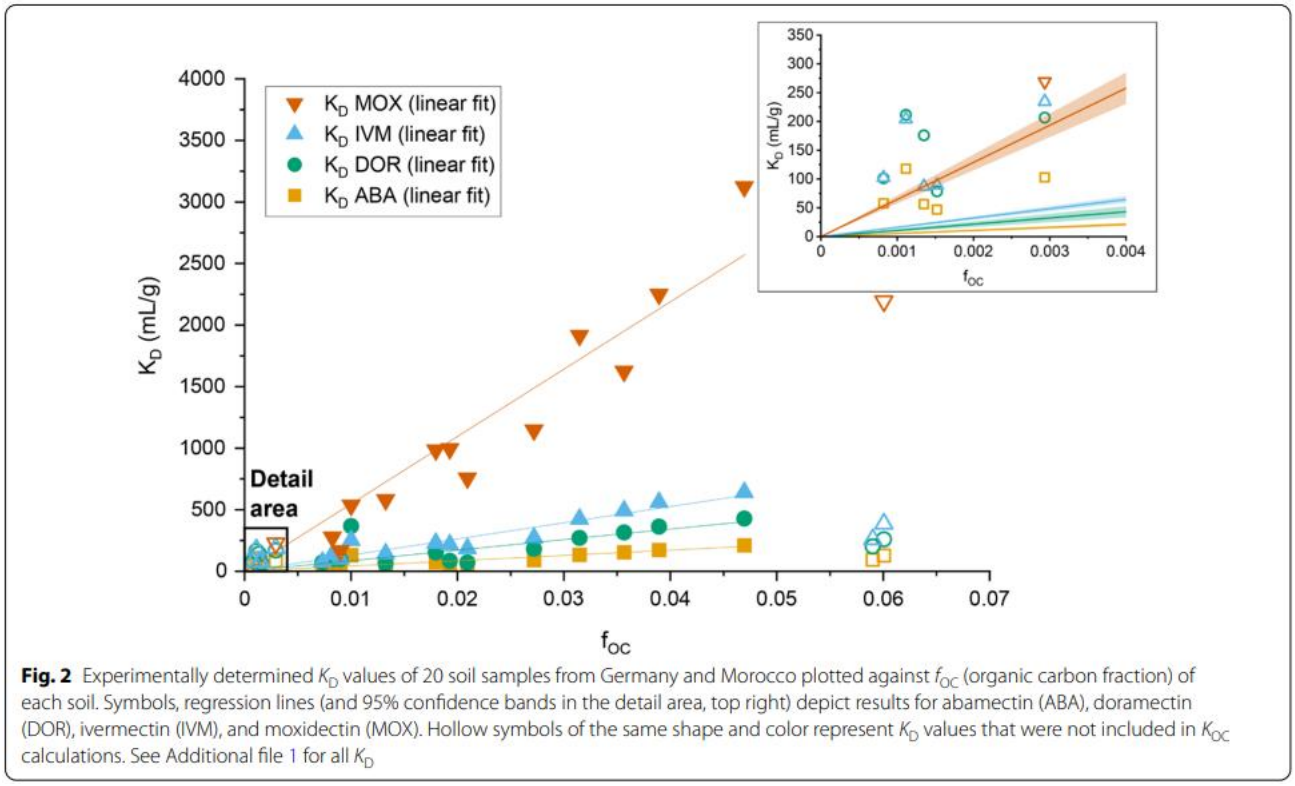


Fig. 2 Experimentally determined K_D values of 20 soil samples from Germany and Morocco plotted against f_{OC} (organic carbon fraction) of each soil. Symbols, regression lines (and 95% confidence bands in the detail area, top right) depict results for abamectin (ABA), doramectin (DOR), ivermectin (IVM), and moxidectin (MOX). Hollow symbols of the same shape and color represent K_D values that were not included in K_{OC} calculations. See Additional file 1 for all K_D

groups can explain lower sorption for hydrophobic substances if OC is the main sorbent. Thus, we further excluded soils DE15 and DE02 with OC contents of 6.0 and 5.9% and in total seven out of 20 soils for the K_{OC} calculation which are shown with hollow symbols. In a meta-analysis on atrazine sorption, Ou et al. [16] concluded that soils with OC > 6% should be considered as outliers.

Next, Table 3 displays derived cumulated K_{OC} values using the previously selected 13 soils. We distinguish between the preferable description as slope of a linear regression through the origin (RTO) and an ordinary least squares (OLS) regression with floating intercept. The table further shows K_{OC} values expressed as the mean and median of individual K_{OC} values from soils considered suitable for the linearized approach. This illustrates the ambiguity that comes with the need to define a single value which quantifies a substance's sorption behavior.

Linearized RTO log K_{OC} were 3.63 (ABA), 3.93 (DOR), 4.12 (IVM), and 4.74 mL/g (MOX). For the OLS model, the log K_{OC} were 3.58, 3.87, 4.13, and 4.82 mL/g, respectively. The OLS y-intercepts amounted to 15.1 (ABA), 32.2 (DOR), − 8.8 (IVM), and − 349.9 mL/g (MOX). This partially reflects the increasing steepness of sorption from ABA < DOR < IVM << MOX. However, the negative y-intercepts for IVM and MOX may also illustrate the shortcomings of an OLS regression with a floating intercept since negative sorption at zero or minimal OC would be implausible.

The R^2 for the RTO K_{OC} were 0.94 (ABA), 0.85 (DOR), 0.97 (IVM), and 0.97 (MOX). However, since a constrained y-intercept skews R^2 calculations it makes it less meaningful and complicates comparison with R^2 obtained from OLS. Instead, the standard error (SE) of both regressions can be an alternative measure [74]. In this regard, the RTO K_{OC} appears to provide a more suitable fit. The R^2 of the OLS K_{OC} were 0.75 (ABA), 0.53 (DOR), 0.91 (IVM), and 0.93 (MOX). This reflects the wide spread of individual K_D values, especially for ABA and DOR. Thus, it is conceivable that sorption of the more hydrophobic IVM and MOX is better explained with the K_{OC} concept than for the slightly less hydrophobic ABA and DOR. This deduction is reiterated by Tolls [11] for hydrophobic VMPs and their soil interactions in general. For the core range of 0.3–4.7% OC in soils, the relation between OC and distribution is well explained for IVM and MOX. This range also broadly represents the %OC found in most European agricultural topsoils [75]. In low OC environments, other surfaces such as clay are more relevant, while especially with a higher %OC, organic matter quality and composition appear to skew the K_D-f_{OC} relation. Lastly, we applied a Box–Cox transformation on all soil K_D values to ensure normal distribution and subjected them to a multiple linear regression with OriginPro 2020b to compare them to soil properties from Table 1. With α = 5%, soil OC demonstrated significant influence on ABA, DOR, and IVM K_D. C/N and pH were significant predictors for ABA and DOR K_D. The complete output is listed in the Additional file 1. While OC is a convenient and established estimator for contaminant sorption in soils, it is plausible that, together with the pH, the detailed composition of organic matter would also predict sorption in soils once a large enough number of samples is studied.

Broader context of soil sorption

Litskas et al. [22] stressed that avermectin sorption in soils determines bioavailability for non-target organisms. They suspected that once incorporated into soil, avermectins could withstand degradation and possibly accumulate if microbial activity was reduced due to unfavorable abiotic conditions or biocides [76]. This could be true for soils where agriculturally used biocides or

Table 3 Summarized K_{OC} data for the selected soils (n = 13 for ABA, DOR, IVM; n = 12 for MOX) showing a linearized and averaged approach to define a cumulated soil K_{OC}. All values in mL/g

Substance	Linearized K_{OC} approach[a]		Averaged K_{OC} approach		
	RTO K_{OC} (SE)	OLS K_{OC} (SE)	Mean (SD)[b]	Median	Range (min–max K_{OC})
ABA	4286 (319)	3769 (651)	4941 (2581)	4343	2653–13,032
DOR	8574 (1025)	7470 (2134)	10,133 (8334)	8866	3423–36,683
IVM	13,139 (611)	13,441 (1288)	13,266 (4137)	12,795	8850–25,109
MOX	54,721 (3136)	66,506 (5666)	47,046 (13,356)	48,555	18,493–66,522

[a] Expressed as slope of a linear regression of K_D vs. f_{OC} (± standard error of the regression slope) with the y-intercept forced through zero (*RTO* linear regression through the origin) or floating (*OLS* ordinary least squares)

[b] Arithmetic mean with standard deviation (SD)

disinfectants are spread with manure, potentially combined with antibiotics, antiparasitics, or other VMPs. Occurrence and transformation of biocides in manure and their fate in soils are only marginally investigated [77, 78]. Moreover, biocide release into the environment could increase due to the SARS-CoV-2 pandemic [79].

For IVM, promising mass drug administrations to livestock to target malaria vectors [80] may increase drug release onto soils. If this approach is complemented with human IVM treatments [7, 81], aquatic pathways in sewage systems could be subject to monitoring and analysis. This makes thorough drug exposure and fate assessments necessary. And it signals the need to include soils from the African continent and other previously neglected regions into sorption studies to provide most-needed One-Health solutions. To realize a safe and sustainable agricultural production, revised herd management strategies may also provide ecological and economic benefits while reducing stress on dung arthropod communities [82]. A sophisticated proposal for post-authorization monitoring of antiparasitics already exists [83] and a deliberate drug use could further address emerging anthelmintic resistances [84].

Lastly, the observed sorption in soils is in line with reported distribution coefficients for ABA of K_D 10–161 mL/g [85] and for IVM of K_D 57–396 mL/g [17]. Rath et al. [19] described IVM sorption K_D between 60 and 1953 mL/g and desorption K_D between 47 and 431 mL/g. Previous ABA K_{OC} ranged from 1495 to 7893 mL/g [28]. For IVM, K_{OC} between 4000 and 25,800 mL/g were documented [17] and for MOX between 18,000 and 41,000 mL/g [30]. However, it is difficult to compare K_D data from linearly modeled sorption experiments with other studies which used Freundlich sorption isotherms to produce a K_F. Although nonlinear models can provide a better fit, they lack comparability, especially when the Freundlich exponent differs significantly from 1. Based on Rath et al. [19] we performed a desorption experiment using the LUFA 2.2 standard soil by replacing the analyzed liquid phase with the same amount of fresh $CaCl_2$ solution and shaking for 72 h. Mean percentual desorption (± SD, n = 6) at a single concentration amounted to: ABA 4.6 (0.3), DOR 3.5 (0.1), IVM 2.9 (0.1), and MOX 2.6 (0.1)%. While only a fragmentary approximation for a full desorption study [61], these percentages compliment the sorption data of the four antiparasitics in soils and indicate mostly irreversible sorption processes.

Sorption in sediments

Compared to soils, sediment K_D showed a range from 21 to 296 (ABA), 35 to 376 (DOR), 53 to 915 (IVM), and 87 to 2326 mL/g (MOX). Less indicative, mean sediment K_D (mL/g) were higher for ABA (106 vs. 98) and IVM (394 vs. 287) but lower for DOR (137 vs. 197) and MOX (861 vs. 1196). The distribution of all sediment K_D results is illustrated in Fig. 3 which again reveals the strongest sorptive behavior by MOX.

Although sediment MA06 had the lowest %OC (0.42), it displayed the highest K_D values for ABA, DOR, and IVM, and the third-highest for MOX among the six sediments. Since it cannot be inferred from the limited sediment sample size if this behavior is an outlier or part of an unknown trend, we removed MA06 from further calculations. However, parameters other than %OC could be more relevant for sorption in MA06. In comparison, MA04 with the highest sand content and similarly low %OC expectedly proved to be least prone for sorption. Because sediments also had a lower average %OC than soils, the resulting log K_{OC} of 4.03 (ABA), 4.13 (DOR), 4.61 (IVM), and 4.97 (MOX) mL/g were higher compared to soils when using an RTO. As was observed in soils, sediment log K_{OC} also ranked MOX >> IVM > DOR > ABA, again reflecting the diverging behavior of MOX, presumably due to structural differences to the avermectins. Higher mean K_{OC} in sediments than in soils were also documented by Chiou and Kile [70]. For a larger sample size, they described that for carbon tetrachloride and 1,2-dichlorobenzene mean sediment K_{OC} were about

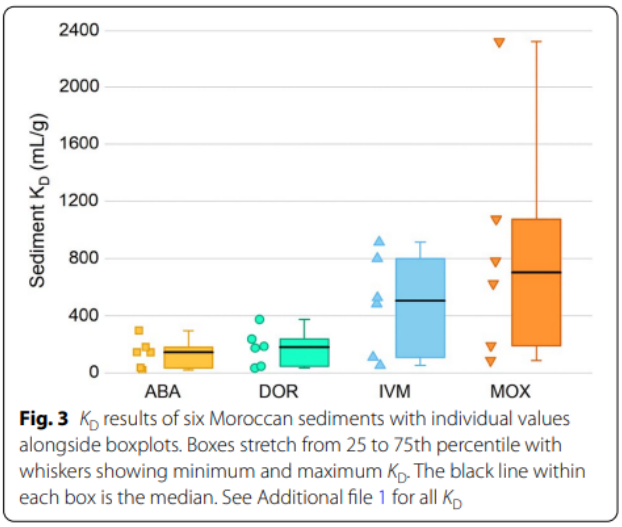


Fig. 3 K_D results of six Moroccan sediments with individual values alongside boxplots. Boxes stretch from 25 to 75th percentile with whiskers showing minimum and maximum K_D. The black line within each box is the median. See Additional file 1 for all K_D

1.7 times higher than soil K_{OC}. Adding to that, we report sediment K_{OC} to soil K_{OC} ratios of 1.8 for ABA, 1.2 for DOR, 2.4 for IVM and 1.4 for MOX when comparing five selected sediments and 13 selected soils. Higher sediment than soil K_{OC} with a factor of about 1.9 was also shown for the antiparasitic drug albendazole by Mutavdžić Pavlović et al. [86]. Chiou and Kile [70] reported that during sedimentation, organic components fractionate and polar components dissolve over time, leaving behind hydrophobic components in the bed sediment.

Change of organic matter composition during sedimentation is known to affect sorption especially for nonionic compounds [73] and could be relevant for the examined antiparasitics. Their strong sorption in sediments is worrisome for inhabitants of these ecosystems, exemplarily shown by chronic effects of IVM on benthic invertebrates [45]. Adverse effects on sediment-dwelling non-target organisms must especially be considered when avermectins are applied in aquaculture [53]; an industry directly burdening aquatic ecosystems with VMPs [9] which may then pass into sediments. Davies et al. [34] expected risks for polychaetes living below or around fish cages and an IVM half-life in marine sediment > 100 days. Prasse et al. [55] reported a comparable timeframe and documented high persistence of IVM in a simulated sediment/water system (DT_{50} = 127 days) driven by strong sorption in the sediment. Mesocosm experiments by Roberts et al. [87] with trout farm effluents showed moderate toxicity to benthic macroinvertebrates and no sensitive taxa were found in the receiving stream. The study, however, was performed unrelated to the use of pharmaceuticals. However, IVM is indicated to be highly persistent in sediments [44] and to possibly accumulate in aquatic organisms [47, 88]. This further encourages thorough, regulated exposure and risk assessments for hyporheic and benthic taxa. Sediment classification [64] and organic matter composition may also be relevant variables to predict K_D data.

Relationship between K_{OC} and K_{OW}

The K_{OC} and K_{OW} of a substance are inextricably linked since both serve the concept that OC and 1-octanol act as hydrophobic counterparts to a chemical [89]. The K_{OW} is also the most frequently used indicator of hydrophobicity of a chemical and an essential parameter in toxicology and environmental sciences [90]. Over time, different concepts were developed to predict the sorption of organic chemicals in soils based on molecular properties. We ventured to predict the log K_{OW} of the studied antiparasitics if the RTO log K_{OC} were the only available variable. For this, we applied well-known concepts [68, 91,92,93] which aim to quantify the relationship between log K_{OC} and log K_{OW} based on log K_{OW} data. These predictions are depicted in Table 4. While it is apparent that conditions and limitations apply to these concepts, our decent set of log K_{OC} data should allow for an estimate of the antiparasitics' hydrophobicity when expressed as log K_{OW}. However, these estimations must not be overstated. A K_{OW} is easier to obtain experimentally than performing complex sorption batch studies. Hence, applying the slow-stirring method from OECD guideline 123 [35] would yield more accurate log K_{OW} data for the studied VMPs. The log K_{OW} of 5.6 (± 0.3) for IVM [13] defined this way could thus validate our own results. Estimates based on Gerstl [91] and Sabljić et al. [92] come closest to this value. This indicates a possible correlation which could also apply to the other three antiparasitics, especially when using log K_{OC} from sediment studies.

The log K_{OW} is a hydrophobicity indicator linked to a molecule itself and it is immaterial whether said molecule would be released into soil, sediment, or other parts of the environment. Thus, an implied distinction between a log K_{OW} based on either soil or sediment sorption

Table 4 Estimations for log K_{OW} of the investigated antiparasitics based on RTO log K_{OC} reported in this work. Compiled K_{OC}–K_{OW} correlations are sorted chronologically

Substance in soils	Estimated log K_{OW} calculated from reported K_{OC}–K_{OW} correlations			
	Karickhoff [68][a]	Gerstl [91][b]	Sabljić et al. [92][c]	Baker [93][d]
ABA	4.02	4.37	4.36	3.92
DOR	4.32	4.81	4.73	4.25
IVM	4.52	5.09	4.96	4.46
MOX	5.14	6.00	5.73	5.15
Substance in sediments				
ABA	4.42	4.96	4.85	4.36
DOR	4.53	5.11	4.98	4.47
IVM	5.01	5.81	5.57	5.00
MOX	5.38	6.34	6.01	5.40

[a] Original equation: $\log K_{oc} = 0.989 * \log K_{ow} - 0.346$ (for hydrophobic chemicals)

[b] Original equation: $\log K_{oc} = 0.679 * \log K_{ow} + 0.663$ (for non-specific chemicals)

[c] Original equation: $\log K_{oc} = 0.81 * \log K_{ow} + 0.10$ (for predominantly hydrophobic chemicals)

[d] Original equation: $\log K_{oc} = 0.903 * \log K_{ow} + 0.094$ (for non-specific chemicals)

coefficients remains theoretical. Still, with the derived log K_{OC} data, all four substances displayed a log K_{OW} > 4 except for ABA in soils if calculated according to Baker [93]. This may indicate that in regulatory terms all drugs could carry a potential for bioaccumulation to occur in the environment [12] with IVM and MOX giving the biggest cause for concern in this regard. Then again, Tolls [11] described that the prediction from log K_{OW} could underestimate the log K_{OC}. A reverse estimate based solely on sorption coefficients could therefore overestimate the log K_{OW}. However, Tolls [11] also concluded that for large hydrophobic molecules such as avermectins log K_{OC} predictions would not deviate to a great extent which bolsters our predictions. The use of these estimations is to provide a general indication of hydrophobicity based on a common dataset of K_{OC} for all four substances.

Although more sophisticated approaches such as quantitative structure-activity relationships can be employed, K_{OC} to K_{OW} correlations can be useful if transparent and verifiable K_{OW} data are not available. Benefits are conceivable since the K_{OW} is also an important parameter for environmental risk assessments. Prichard et al. [15] provided a consistent dataset of K_{OW} estimations and used atomic parameters to calculate the following order of coefficients (log K_{OW}): EPR (4.4), IVM (4.8), ABA (5.3), DOR (5.6), MOX (6.0), and selamectin (6.3). Fittingly, selamectin was also assessed by Römbke et al. [13] with the slow-stirring method to indicate a log K_{OW} of 6.0 (± 0.7). Meanwhile, risk assessments for VMPs rely on robust data. Dissipation of macrocyclic lactone antiparasitics varies depending on climate and field conditions [20, 66, 94] and a harmonized dataset on experimental K_{OW} and their environmental fate properties would be admirable.

A limitation of sorption studies with pharmaceutical compounds is the transferability to the environmental reality. The K_{OC} concept does not account for organic matter composition and may misinterpret substance behavior at particular locations, especially in sediments. If enough data is available, a multiple linear regression with all soil/sediment properties is always advisable. Also, while for IVM low metabolization has been described in animal species [14], human metabolism of IVM could be more pronounced [81]. Transformation products of varying size and polarity could hypothetically demonstrate different sorption behavior in soils and sediments. Investigating the abundance and fate of antiparasitic metabolites after excretion is thus a logical future task. In light of the upcoming European veterinary regulation [Regulation (EU) 2019/6] steadfast assessments will gain in importance [39]. Our estimations of log K_{OW} based on log K_{OC} highlight the possible K_{OW} discrepancies and a precarious aspect of regulatory decision-making: while data may appear insufficient, they may be the only data available.

Conclusions

The investigated antiparasitics show strong sorption to the organic matter of soils and also sediments. Sorption strength in general (as K_D) and normalized to organic carbon (as K_{OC}) is characterized by the order: ABA < DOR < IVM << MOX. Exemplary desorption from soils indicates mostly irreversible sorption processes and follows the same rationale with MOX showing the lowest transfer back into the liquid phase. The applied SPE-HPLC method with fluorescence detection is suitable for reliable quantification of all four analytes at once.

The consequent use of linear modeling with constrained intercepts allows to derive transparent and comparable sorption coefficients and facilitates future referral to our dataset. A variety of K_{OW} estimates urges to re-assess this important regulatory parameter with the appropriate technique. While for IVM and MOX our findings suggest the need to examine potential aquatic or terrestrial bioaccumulation, the medical and economic benefits of all four pharmaceuticals must not be denied. It is thus desirable to elaborate on their environmental fate and also include sediment-dwelling organisms in frameworks for toxicity testing. In perspective, risk mitigation measures for macrocyclic lactones should be improved to make antiparasitics a luminous example for the sustainable use of veterinary pharmaceuticals.

Availability of data and materials

All relevant data and material are included in this published article and its supplementary information (SI). Other data and calculation tools for this research are available upon reasonable request from the authors A. P. Heinrich and R-A. Düring.

Abbreviations

ABA: Abamectin; ACN: Acetonitrile; DOR: Doramectin; EMA: European Medicines Agency; EPR: Eprinomectin; EU: European Union; f_{OC}: Organic carbon fraction of the soil/sediment; HLNUG: Hessian Agency for Nature Conservation, Environment and Geology; IVM: Ivermectin; K_D: Distribution coefficient; K_{OC}: Organic carbon–water partition coefficient; K_{OW}: Octanol–water partition coefficient; LOD: Limit of detection; LOQ: Limit of quantification; MOX: Moxidectin; OC: Organic carbon; OECD: Organisation for Economic Co-operation and Development; OLS: Ordinary least squares regression; %OC: Weight per- centage of soil/sediment organic carbon; RTO: Regression through the origin; SE: Standard error; VMPs: Veterinary medicinal products.

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Disclaimer

The study investigates the sorption of veterinary antiparasitics in soils and sediments for academic purposes. The aim of the article is to provide information on the environmental fate of these pharmaceuticals. The article may not be understood as a regulatory assessment.

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Contributions

APH wrote the first draft of the manuscript. RAD conceived and designed the study. RAD, MW, LB, and APH conceived and designed experiments. TZ and APH performed experiments. APH, TZ, and RAD performed statistical analyses. SJ, YEM, and AD took Moroccan samples and performed additional chemical analyses. All authors read and approved the final manuscript.

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Ethics declarations

Ethics approval and consent to participate

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Consent for publication

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Supplementary Information

Additional file 1

Table S1. Analyte recovery (%) when subjected to the presented SPE procedure compared to directly measured standards. **Table S2.** Output (OriginPro 2020b) of the multiple linear regression with transformed K_D values and soil properties. **Table S3.** Supplemental data for Fig. 2. Individual soil K_D values (mL/g). **Table S4.** Supplemental data for Fig. 3. Individual sediment K_D values (mL/g). **Figure S1.** Chromatogram of standard solution with all 4 analytes (Abamectin, ABA; Doramectin, DOR; Ivermectin, IVM; Moxidectin, MOX). **Figure S2.** Chromatogram of the extracted aqueous soil solution with all 4 analytes (Abamectin, ABA; Doramectin, DOR; Ivermectin, IVM; Moxidectin, MOX).

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5.2 Supporting Information

Additional File 1

Sorption of Selected Antiparasitics in Soils and Sediments

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I – The solutions of the calibration curve were not prepared using the solid phase extraction (SPE) procedure. To address this, we performed an additional experiment with n = 6 replicates each to compare standard solution measured directly and standard solution added to 0.01 mol/L $CaCl_2$ which then underwent identical sample processing as described in the manuscript (including SPE and filtration). These recoveries are listed below in Table S1.

Table S1: Analyte recovery (%) when subjected to the presented SPE procedure compared to directly measured standards.

	Abamectin (%)	Doramectin (%)	Ivermectin (%)	Moxidectin (%)
Mean (n = 6)	96.8	96.1	95.8	93.0
Standard deviation	1.8	1.4	2.1	1.7

II – The output (OriginPro 2020b) of the multiple linear regression (see "Results and Discussion - Sorption in soils") is shown below in table S2. The comparison with soil properties from table 1 in the manuscript is as follows (α = 5 %):

Table S2: Output (OriginPro 2020b) of the multiple linear regression with transformed K_D values and soil properties.

	ABA K_D	DOR K_D	IVM K_D	MOX K_D
n =	20	20	20	14
	Prob>|t|	Prob>|t|	Prob>|t|	Prob>|t|
%OC	0.008	0.013	0.009	0.215
C/N	0.046	0.042	0.114	0.372
pH	0.029	0.021	0.051	0.120
CEC	0.180	0.209	0.315	0.250
Sand	0.709	0.917	0.876	0.252
Silt	0.708	0.918	0.876	0.253
Clay	0.710	0.915	0.875	0.253

III – Characteristic HPLC-fluorescence chromatograms of standard solution with all 4 analytes (Abamectin, ABA; Doramectin, DOR; Ivermectin, IVM; Moxidectin, MOX) and of the extracted aqueous soil solution are depicted in figures S1 and S2.

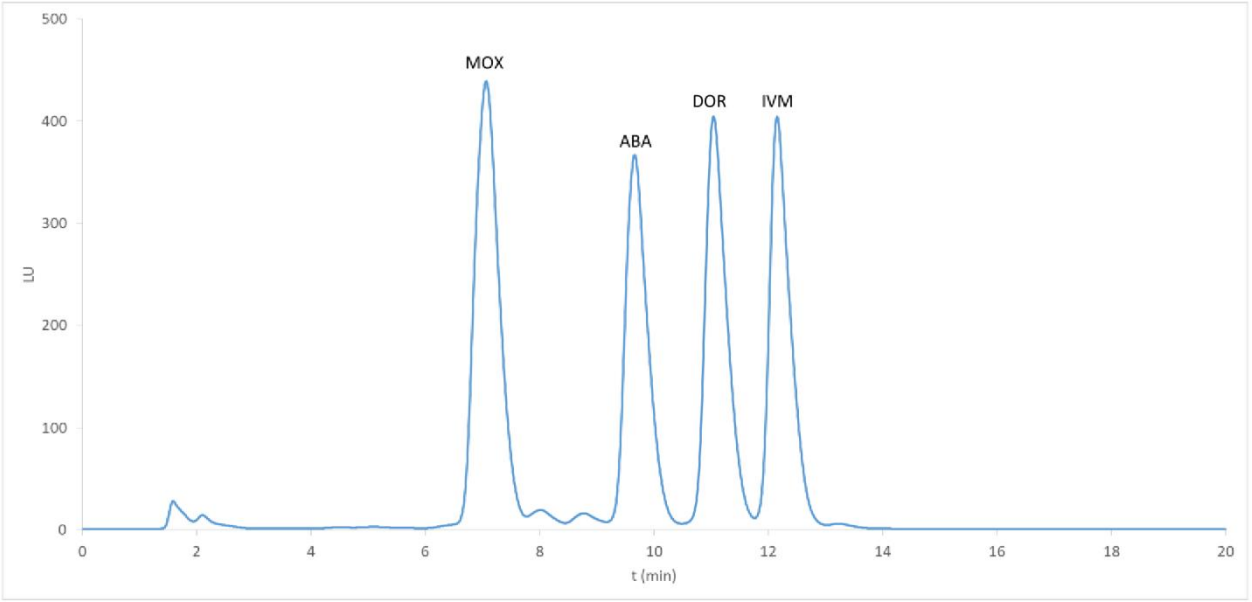

Figure S1: Chromatogram of standard solution with all 4 analytes (Abamectin, ABA; Doramectin, DOR; Ivermectin, IVM; Moxidectin, MOX).

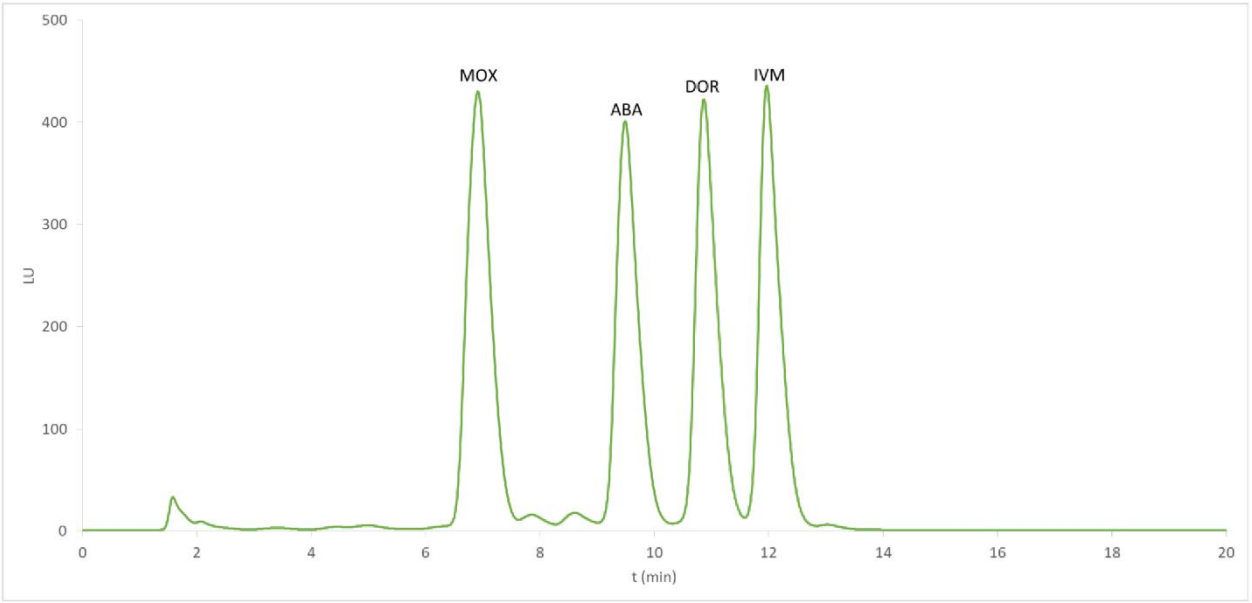

Figure S2: Chromatogram of the extracted aqueous soil solution with all 4 analytes (Abamectin, ABA; Doramectin, DOR; Ivermectin, IVM; Moxidectin, MOX).

IV – Supplemental data for manuscript figures 2 and 3. Individual Soil K_D values (mL/g) for soils (Table S3) and sediments (Table S4).

Table S3: Supplemental data for figure 2. Individual soil K_D values (mL/g).

Soil	f_{OC}[a]	ABA K_D	DOR K_D	IVM K_D	MOX K_D
DE01	0.001	52.6	84.2	81.7	n/d
DE06	0.001	107.3	163.5	176.9	n/d
DE04	0.001	52.5	140.1	75.0	n/d
DE05	0.002	46.9	71.5	79.8	n/d
DE07	0.003	84.3	168.3	188.1	227.6
DE03	0.007	37.8	70.9	76.2	n/d
DE10	0.008	47.9	92.0	136.6	276.5
DE16	0.009	48.7	94.8	101.3	166.3
DE08	0.010	130.5	367.4	251.5	535.8
MA03	0.013	48.5	63.2	143.9	580.1
DE09	0.018	73.8	152.9	230.0	985.1
MA02	0.019	66.8	84.6	216.9	994.5
MA01	0.021	55.5	71.7	185.3	756.0
DE11	0.027	92.2	181.4	271.8	1146.2
DE12	0.031	134.3	270.7	424.2	1915.2
DE13	0.036	154.8	316.1	492.2	1623.6
DE14	0.039	172.8	362.9	561.6	2249.2
DE17	0.047	210.8	427.6	641.5	3123.2
DE02	0.059	93.4	202.0	259.8	n/d
DE15	0.060	127.0	259.2	386.7	2193.7

[a] f_{OC} is the organic carbon fraction of the soil

n/d = not determined

Table S4: Supplemental data for figure 3. Individual sediment KD values (mL/g).

Sediment	f_{OC}[a]	ABA K_D	DOR K_D	IVM K_D	MOX K_D
MA06	0.004	296.1	375.8	915.4	783.2
MA04	0.004	21.5	35.2	52.6	87.2
MA09	0.006	36.3	47.5	109.1	191.8
MA05	0.012	143.8	187.1	482.3	625.4
MA08	0.014	145.4	175.5	526.4	1076.2
MA07	0.016	181.7	237.6	800.7	2325.5

[a] f_{OC} is the organic carbon fraction of the sediment

6 Von der Sorption zur Bioakkumulation: Ivermectin in Boden und Regenwürmern

6.1 Veröffentlichung

Dieses Kapitel wurde in *Chemosphere* (Elsevier) veröffentlicht als:

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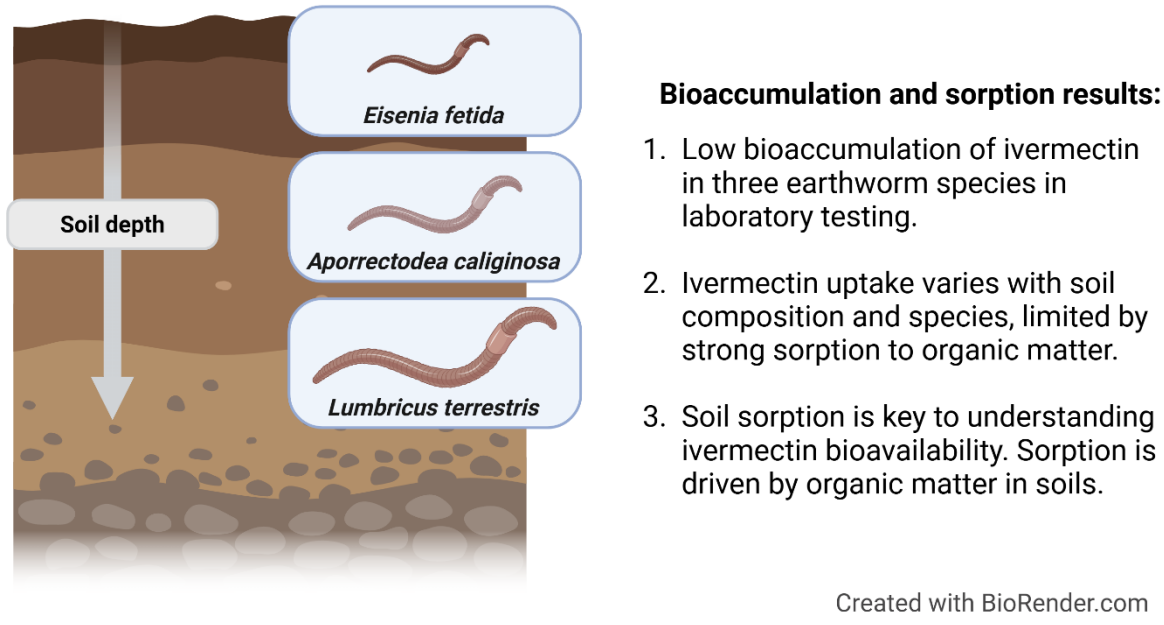
Der Inhalt des Kapitels wurde manuell an das Layout der Dissertation angepasst. Die begutachtete Veröffentlichung in ihrer originalen Form und mit allen Zusatzinformationen ist zu finden unter folgendem **Link zur Zeitschrift**: https://doi.org/10.1016/j.chemosphere.2025.144228

Graphical Abstract



Graphical abstract. Heinrich, A. (2025) https://BioRender.com/e20x740

Abstract

Ivermectin (IVM), a widely used antiparasitic drug in veterinary medicine, has emerged as an environmental contaminant due to its semi-persistence and potentially harmful ecotoxicological impacts on non-target terrestrial fauna. This study investigates the innovative combination of sorption, desorption, and bioaccumulation dynamics of IVM in soil-earthworm systems, focusing on the species *Eisenia fetida*, *Aporrectodea caliginosa*, and *Lumbricus terrestris*. Sorption experiments in artificial soil (AS) and its components (sand, clay, peat) revealed a strong affinity of IVM for organic-rich substrates, reducing bioavailability and bioaccumulation.

Bioaccumulation studies showed that the kinetic bioaccumulation factor BAF_k for IVM in *E. fetida* ranged from 0.505 to 0.727 g soil dw/g earthworm dw, with elimination kinetics best described by a biphasic model, and suggesting minimal net accumulation. *A. caliginosa* and *L. terrestris* showed slightly higher accumulation potential, with accumulation factors exceeding 1 during the uptake phase, although equilibrium was not reached within 21 days. The prolonged accumulation process, combined with a calculated DT_{50} of 142 days in AS, underscores IVM's potential environmental persistence and risk, particularly its ecotoxicological relevance. The results also suggest that strong sorption to organic matter in soils can mitigate bioaccumulation.

Highlights

- Low bioaccumulation of ivermectin in *E. fetida* despite prolonged exposure.
- *A. caliginosa* and *L. terrestris* show moderately higher bioaccumulation potential.
- Bioaccumulation varies with earthworm species and soil composition.
- Ivermectin elimination in *E. fetida* follows biphasic kinetics.
- Strong sorption to organic matter affects ivermectin persistence in artificial soil.

Keywords

Anthelmintics, Avermectins, Bioaccumulation, Hydrophobicity, Oligochaeta, Persistence, Sorption

1. Introduction

The widely used veterinary drug ivermectin (IVM), an endectocide against endo- and ectoparasites, has become a recognized environmental contaminant due to extensive use in targeted livestock parasite control (Liebig et al., 2010; Bair et al., 2017; Mesa et al., 2020). IVM consists of two main components, B_{1a} and B_{1b}, with virtually identical activities (Shoop et al., 1995). For decades, the semi-persistence of IVM and potential adverse effects on terrestrial non-target dung and soil fauna, have raised concerns (Strong, 1992; Liebig et al., 2010; Souza and Guimarães, 2022). IVM residues in soils have also been reported to affect and interact with soil microorganisms (Lagos et al., 2022, 2023). While IVM dissipation varies with environmental conditions, degradation half-lives in soils >100 d have been reported (Dubroca et al., 2003; Krogh et al., 2009), placing IVM in the range of persistence under REACH regulations (Annex XIII) (Regulation (EC) 1907/2006). Given the potential environmental stability and extensive environmental input of IVM, legitimate concerns emerge regarding chronic exposure and bioaccumulation risks (Verdú et al., 2020; Iglesias et al., 2023; Lorente et al., 2023), as investigated in this study.

Importantly, soil sorption and desorption processes influence mobility and bioavailability of veterinary pharmaceuticals, impacting the extent of bioaccumulation in soil organisms including earthworms (Kong et al., 2012; Carter et al., 2016). Notably, physicochemical properties of soils, such as organic carbon content and soil type, strongly influence sorption of IVM (Krogh et al., 2008; Heinrich et al., 2021). As key ecological species in soils, with a thin, permeable cuticle and high soil intake (Edwards, 2022), earthworms are particularly relevant for studying the bioaccumulation of IVM in terrestrial ecosystems (OECD, 2010; ASTM, 2021).

In bioaccumulation screening, the octanol-water partition coefficient (K_{OW}) is a key parameter for bioaccumulation potential, with IVM displaying a log K_{OW} of 5.6 (Römbke et al., 2019). This exceeds the critical log K_{OW} threshold of 4 defined in the environmental impact assessment for veterinary medicinal products (EMA, 2016), indicating general bioaccumulation potential. While current regulatory cut-offs could be too conservative, higher K_{OW} thresholds for bioaccumulation testing of pharmaceuticals have been suggested (Constantine et al., 2024; Gimeno et al., 2024). However, the use of K_{OW} or molecular size as sole indicators for bioaccumulation can be reductive (Arnot et al., 2010), highlighting the importance of comprehensive bioaccumulation assessments, like this work, to accurately evaluate environmental risks associated with veterinary pharmaceuticals.

The objective of this study was to investigate sorption of IVM in artificial soil (AS) substrate (OECD, 2010) and bioaccumulation behavior of IVM using the earthworm species *E. fetida*, *A. caliginosa*, and *L. terrestris*. These species represent different ecological categories: *E. fetida* is epigeic, living in the litter layer of soils; *A. caliginosa* is endogeic, burrowing shallowly within the soil; and *L. terrestris* is anecic, creating deep vertical burrows (Edwards, 2022). This ecological differentiation allows to capture a range of bioaccumulation dynamics. Also, as outlined by Li et al. (2024), bioaccumulation patterns can vary among earthworm species. Although *E. fetida* is most commonly used for toxicity and bioaccumulation testing (ASTM, 2021), integrating species from deeper or mineral soil layers into testing protocols provides a more comprehensive risk assessment (Bart et al., 2018).

Furthermore, we examined desorption of IVM from AS and its individual components (sand, clay, peat) to illustrate its environmental distribution and retention. Since earthworms primarily consume organic matter (Edwards, 2022), this directly influences exposure to hydrophobic soil contaminants like IVM and possible bioaccumulation. We analyzed bioaccumulation kinetics of IVM to detail uptake and elimination dynamics. Our results contribute to a better understanding of the environmental risks associated with IVM in terrestrial systems and to refining risk assessments for veterinary pharmaceuticals.

2. Materials and methods

2.1. Test substrates and test organisms

Artificial soil (AS) was provided by ECT Oekotoxikologie GmbH (Germany). It was adapted from OECD guideline 207 (OECD, 1984) for a composition of 74.77% industrial quartz sand (F36, Quarzwerke Frechen, Germany), 20% kaolin clay (Chinafill 100, Amberger Kaolinwerke,

Germany), 5% peat, and 0.23% $CaCO_3$ for pH adjustment. The AS was used for the bioaccumulation study with *E. fetida*. For sorption/desorption studies, AS and its individual components were air-dried and sieved to 2 mm. The bioaccumulation study with *A. caliginosa* and *L. terrestris* was performed with LUFA 2.2 soil (LUFA Speyer, Germany), a natural loamy sand with a pH of 5.6 (0.01 M $CaCl_2$), water holding capacity of 43.3%, and 1.6% organic carbon (C_{org}). The AS had a pH of 6.9 (0.01 M $CaCl_2$), water holding capacity of 45.3%, and total organic matter was determined through the loss on ignition method following DIN 18128:2002–12. This was then converted to C_{org} using the factor 1.724 by Sabljić (1989). The resulting C_{org} of AS was 3.6 ± 0.1% (mean ± SD, n = 6). The pH of AS components measured in 0.01 M $CaCl_2$ were 5.8 (sand), 6.0 (clay), and 2.5 (peat). LUFA 2.2 soil was selected for *A. caliginosa* and *L. terrestris* based on practical and ecological considerations regarding their natural habitats (Römbke et al., 2005; Edwards, 2022).

E. fetida were obtained from the laboratory culture of ECT Oekotoxikologie GmbH, *A. caliginosa* were provided by Prodigga SAS (France), and *L. terrestris* were sourced from a commercial supplier (Wurmwelten.de, Germany). For *E. fetida*, we assessed the lipid content as described in the Supporting Information. The mean ± SD lipid content (n = 6) of *E. fetida* was calculated to be 6.5 ± 1.2% (dry weight, dw) or 1.4 ± 0.3% (fw), respective to the determined water content of 78.2 ± 0.8%. In the bioaccumulation experiment, adult individuals with a fully developed clitellum were used, with fresh weights ranging from 250–600 mg (*E. fetida*), 500–870 mg (*A. caliginosa*), and 3400–8600 mg (*L. terrestris*) per individual. While *E. fetida* were cultivated in coniferous bark humus (Plantop, Germany), both *A. caliginosa* and *L. terrestris* were kept and acclimatized in LUFA 2.2 soil at 21 ± 1 °C. Weekly, substrate moisture content was checked and readjusted, and appropriate feed was provided: ground oatmeal for *E. fetida*, and dried horse manure for *A. caliginosa* and *L. terrestris*.

2.2. Chemicals and materials

The sorption/desorption study investigated IVM, purchased as analytical standard (LGC-Standards). Additionally, for the IVM bioaccumulation study, doramectin (LGC-Standards) was used as internal recovery standard during analysis. Chemical product details are listed in the Supporting Information. Test containers for the bioaccumulation study were 250 mL borosilicate glass beakers for *E. fetida*, and 1 L glass Weck jars for *A. caliginosa* and *L. terrestris*, each covered with plastic mesh. For solid-phase extraction (SPE), CHROMABOND® equipment (MACHEREY–NAGEL, Germany) and 6 mL, 500 mg Strata C18-E cartridges (8B–S001-HCL, Phenomenex, Germany) were used. Vessels for sorption/desorption were custom 45 mL glass vials with a PTFE-coated silicon seal. Other materials included a Beta 1–8 LSCplus freeze dryer (Martin Christ Gefriertrocknungsanlagen GmbH, Germany), a tissue grinder pestle (WD-1366, neoLab Migge GmbH, Germany), 0.45 µm PTFE membrane syringe filters (6272817, LLG Labware, Germany), and purified water from a Merck Milli-Q® system.

2.3. Preparation of substrates

Air-dried substrates were hydrated with deionized water to achieve a water content of 22.7% in AS and 23% in LUFA 2.2 standard soil, each related to the dw. For AS, the mixture was initially produced with 10% (w/w) less sand, as this was later used for spiking. Both substrates were then stored at 7 °C for 48 h for moisture equilibration. For spiking, IVM was dissolved in acetonitrile (ACN) and added to 10% of substrate mass. For AS, this was 10% of remaining sand, and for LUFA 2.2, 10% of dry soil. After complete evaporation of ACN, the additional 10% of substrate were mixed with the previously hydrated 90%. Deionized water was added to readjust the total water content, and the mixtures were equilibrated at 21 ± 1 °C for 96 h (OECD, 2010). The spiked IVM test concentration was 0.5 mg/kg dw in both substrates, chosen to approximate 1% of the LC_{50} for *E. fetida* (OECD, 2010; Wang et al., 2012). This approach aimed to avoid IVM-induced mortality while ensuring sufficient concentrations for quantitative assessment.

2.4. Bioaccumulation experiments and sampling

The bioaccumulation experiments were conducted in a climate chamber at 21 ± 1 °C, 69.8 ± 7% relative air humidity, and a 16/8 (h) day/night cycle with an illuminance of 400–800 lx. Sampling during the uptake phase is detailed in Table 1. At the end of the uptake phase, *E. fetida* were transferred to uncontaminated AS for the elimination phase (21 d): Beakers were emptied, organisms were

Table 1
Experimental setup overview. For all species, each sampling day featured n = 3 individual containers. Substrate mass and earthworms per container were adjusted along recommendations in OECD guideline 317 on soil-to-worm ratio. Water content was 22.7% in the AS substrate and 23% in the LUFA 2.2 soil with weekly readjustment. Containers were randomly positioned in the climate chamber.

Species	Substrate	Substrate per container (g dw)	Earthworms per container	Soil and earthworm sampling during uptake phase (d)
E. fetida	Artificial Soil	150	3	0, 1, 2, 4, 7, 10, 14, 17, 21
A. caliginosa	LUFA 2.2	450	3	0, 14, 17, 21
L. terrestris	LUFA 2.2	500	1	0, 14, 17, 21

removed, rinsed with deionized water, gently dried, and transferred without prior gut clearance time into beakers with moistened, IVM-free AS. Organisms of each replicate were reweighed as a group before transfer to determine biomass changes. Newly prepared test containers were again randomized and returned into the climate chamber. For feeding, 1.2 mg ground oatmeal per g (dw) substrate were provided weekly per container. Soil and earthworm sampling for *E. fetida* during elimination was at 6 h and 1, 2, 4, 7, 10, 14, 17, and 21 d after transfer, with n = 3 replicates each. For *A. caliginosa* and *L. terrestris*, soil and earthworm sampling were conducted in the uptake phase at three timepoints, as larger test containers limited the number of feasible replicates. The experimental design represented the most practical balance to allow for a broad yet detailed assessment across all three species with a focus on the earthworm *E. fetida*.

Soil samples were taken from each container, adjusted to 50% water content, and fortified with the internal recovery standard doramectin before extraction with room-temperature ACN. Earthworm samples consisted of pooled organisms from each container. Earthworms were placed on moist filter paper to purge their guts overnight (OECD, 2010) before freeze-drying, fortification with doramectin, and extraction with cooled ACN (−32 °C). Details of the extraction procedures are provided in the Supporting Information. Weighed sample quantities (dw, mean ± SD) for soil (n = 107), *E. fetida* (n = 63), *A. caliginosa* (n = 15), and *L. terrestris* (n = 15) were 3.87 ± 0.05, 0.27 ± 0.04, 0.32 ± 0.15, and 1.13 ± 0.36 g, respectively. Control soil and earthworm samples were taken at days 0 and 21 of each phase.

2.5. Bioaccumulation kinetics

Hypothetical concentration decreases during the uptake phase can be described in the form of a decaying exponential function (OECD, 2010):

$$C_s(t) = C_0 * e^{-k_0 t} \quad (1)$$

where C_s is the IVM concentration in soil (ng/g dw), k_0 is the degradation constant (d^{-1}), C_0 is the initial IVM concentration in soil (ng/g dw), and t is the time (d). To estimate DT_{50} (time until 50 % of the substance has dissipated) of IVM in AS, k_0 can be used:

$$DT_{50} = \frac{\ln(2)}{k_0} \quad (2)$$

A first-order kinetic equation (OECD, 2010) is used to generally describe IVM uptake in *E. fetida*:

$$C_a(t) = \left(\frac{k_s}{k_e}\right) * C_s * (1 - e^{-k_e t}) \quad (3)$$

where C_a is the IVM concentration in earthworms (ng/g dw), k_s is the uptake rate constant into tissue (g soil dw/g earthworm dw d^{-1}), and k_e is the elimination rate constant (d^{-1}). To estimate k_e, we analyzed data from the elimination phase of *E. fetida* using a one-compartment model (OECD, 2010):

$$C_a(t) = C_{a,0} * e^{-k_e t} \quad (4)$$

where $C_{a,0}$ is the initial concentration of IVM in earthworms. Subsequently, we used **Eq. 3** to solve for k_s. Final values of k_s and k_e can be used to derive the kinetic bioaccumulation factor (BAF_k) for *E. fetida* under the premise that no steady state was reached after 21 d of exposure (OECD, 2010):

$$BAF_k = \frac{k_s}{k_e} \quad (5)$$

Here, the BAF_k can be expressed as g soil dw/g earthworm dw, though in some cases it may be reported as dimensionless, depending on the units used for k_s and k_e.

Elimination profiles of hydrophobic substances in earthworms can also exhibit biphasic patterns, characterized by a rapid initial phase and a slower terminal phase (Belfroid and Sijm, 1998). To capture this, a two-compartment model was applied, accounting for both fast and slow elimination processes (Bruns et al., 2002):

$$C_a(t) = C_A * e^{-k_a t} + C_B * e^{-k_b t} \quad (6)$$

where C_A and C_B are the two compartments (ng/g dw), and k_a and k_b are the respective elimination rate constants (d^{-1}). The sum of compartments C_A and C_B represents the total concentration of IVM in the organism at equilibrium. The equation remains applicable even if equilibrium is not achieved, reflecting the influences of both compartments at any given time. For our data, the overall k_e used for calculating the BAF_k, was obtained as the weighted mean of k_a and k_b from the two-compartment model, based on their respective contributions. Finally, the biota-soil accumulation factor was derived (OECD, 2010):

$$BSAF = BAFk * \frac{f_{OC}}{f_{lip}} \quad (7)$$

where $BSAF$ is the biota-soil accumulation factor, adjusted for C_{org} and lipid content, f_{OC} is the organic carbon fraction of the substrate (dw), and f_{lip} is the fraction of earthworm lipid (dw).

In addition to the first-order kinetic model **(Eq. 3)**, a Michaelis-Menten model was applied to account for the observed variability in uptake concentrations of IVM in *E. fetida*. The equation, typically used to describe enzyme kinetics (Dowd and Riggs, 1965), was interpreted to fit the uptake data as follows:

$$C_a(t) = \frac{V_{max} * t}{K_m + t} \quad (8)$$

where V_{max} would represent the maximum uptake rate of IVM into earthworms, and K_m is the half-saturation constant, with the uptake rate constant k_s approximated by the ratio V_{max}/K_m.

When necessary, the standard error (SE) of a result was computed by adapting the general propagation of uncertainty formula (Taylor, 1997), accounting for the contributions of multiple independent variables, with the following equation:

$$SE_{Result} = Result * \sqrt{\sum_{i=1}^{n} \left(\frac{SE_{Pi}}{P_i}\right)^2} \quad (9)$$

where P_i represents each contributing parameter. This method was used to account for relative parameter uncertainties when the SE was not available from the software. In other instances, the standard deviation (SD) is provided.

2.6. Sorption and desorption studies

We followed OECD guideline 106 (OECD, 2000) and the reported protocol (Heinrich et al., 2021). Separate tests were conducted for the prepared AS mixture and its individual components (sand, clay, peat). For each series, 1 g of air-dried material was suspended with 30 mL 0.01 mol/L $CaCl_2$ in purified water (Milli-Q®), maintaining a 1:30 (w/v) solid/solution ratio. Suspensions were pre-shaken in $CaCl_2$ solution for 24 h using a horizontal lab shaker (KS 15 B, Edmund Bühler GmbH) at 250 rpm. An IVM stock solution (1×10^6 µg/L) was prepared in ACN and diluted with ACN into working solutions to achieve these test concentrations in the aqueous phase: 100, 200, 300, 400, and 500 µg/L. The 30 µL working solution added to each vessel corresponded to 0.1% (v/v) solvent to avoid cosolvent effects (OECD, 2000). Spiked samples were wrapped in aluminum foil and shaken for 48 h at 250 rpm to reach equilibrium. All steps were conducted at ambient temperature, maintained at 21 ± 1 °C.

After shaking, samples were centrifuged at 2820*g* for 30 min. SPE cartridges were preconditioned with 10 mL propan-2-ol, then 10 mL of a 1:3 (v/v) propan-2-ol/purified water mixture. Subsequently, 25 mL of supernatant from AS, sand, and clay samples, and 20 mL from peat samples, were taken for SPE. In a reservoir fixed to the cartridges, supernatants were fortified with 25 µL triethylamine and 8.333 mL propan-2-ol (AS, sand, clay), or with 20 µL triethylamine and 6.666 mL propan-2-ol (peat). Subsequent elution with propan-2-ol, reconstitution in ACN, derivatization, and quantification by high-performance liquid chromatography (HPLC) with fluorescence detection (FLD) followed the reported procedure (Heinrich et al., 2021).

For desorption from AS components, fresh $CaCl_2$ solution (25 mL for AS, sand, clay; 20 mL for peat) was added to each glass vessel immediately after the supernatant had been removed. Samples were then shaken for 72 h at 250 rpm. We extracted 25 mL (20 mL for peat) of supernatant for HPLC-FLD as referenced above to quantify IVM in the aqueous phase and deduct the amount desorbed from the solid phase. Sorption of AS was performed with six replicates, and sorption/desorption of

individual AS components with two replicates, per test concentration.

2.7. Sorption and desorption parameters

The K_D and K_{OC} distribution coefficients and desorption parameters were calculated based on OECD guideline 106 (OECD, 2000). The K_D, defined as ratio between the substance concentration in the solid phase ($C_s^{ads}(eq)$) and its concentration in the aqueous phase ($C_{aq}^{ads}(eq)$), at equilibrium **(Eq. 10)**, was obtained by plotting these values. The K_D is expressed as mL/g. A linear regression through all concentrations and the origin, outlined by Chappell et al. (2020), , was used to derive K_D as slope of this regression. For K_{OC} calculation, which normalizes K_D to the C_{org} content, we used the f_{OC}. The K_{OC} (mL/g) was calculated by dividing K_D by f_{OC}.

For nonlinear regression, the Freundlich sorption coefficient K_F ($\mu g^{1-1/n} \cdot (mL)^{1/n} \cdot g^{-1}$) was derived from the nonlinear regression using the Freundlich adsorption equation **(Eq. 11)**:

$$K_D = \frac{C_s^{ads}(eq)}{C_{aq}^{ads}(eq)} \quad (10)$$

$$C_s^{ads}(eq) = K_F * C_{aq}^{ads}(eq)^{1/n} \quad (11)$$

Desorption at a timepoint (t_i) is quantified as the percentage of the desorbed mass of the test substance ($m_{aq}^{des}(t_i)$) released under the test conditions, related to the previously adsorbed mass of the test substance at adsorption equilibrium ($m_s^{ads}(eq)$) (OECD, 2000):

$$Desorption\ (t_i) = \frac{m_{aq}^{des}(t_i)}{m_s^{ads}(eq)} * 100\ (\%) \quad (12)$$

For individual AS components, we determined a desorption K_D (K_D^{des}), defined as ratio between the substance concentration remaining in the solid phase ($C_s^{ads}(eq)$) and the desorbed substance concentration in the aqueous phase ($C_{aq}^{des}(eq)$) at desorption equilibrium (OECD, 2000):

$$K_D^{des} = \frac{C_s^{ads}(eq)}{C_{aq}^{des}(eq)} \quad (13)$$

We determined K_D^{des} as slope of a linear regression through the origin, based on the relationship between $C_{aq}^{des}(eq)$ and $C_s^{ads}(eq)$.

2.8. Analytical procedure

Quantification of IVM and doramectin in soil and earthworm samples and for sorption/desorption experiments was adopted from reported methods (Wohde et al., 2016; Heinrich et al., 2021). The protocol is detailed in the Supporting Information. Briefly, after ultrasound-assisted extraction and following centrifugation (soil and earthworm) or after SPE (sorption/desorption), samples or aliquots thereof were evaporated, reconstituted in ACN, and filtered. For quantification, we used HPLC-FLD after derivatization, performed on an Agilent 1200 HPLC system with gradient elution (ACN and purified water) on a C18 column (3 µm, 2.1 × 150 mm). FLD wavelengths were 364 nm for excitation and 463 nm for emission. Extraction recoveries (mean ± SD) of the internal standard doramectin were 104.3 ± 12.2% (n = 107) in soil, 75.8 ± 14.2% (n = 63) in *E. fetida*, 88.5 ± 31.2% (n = 15) in *A. caliginosa*, and 54.1 ± 30.5% (n = 15) in *L. terrestris* samples. IVM concentrations were not corrected for internal standard recovery. Calibration curves consisted of concentrations of 0.5, 1, 5, 10, 25, 50, 100, 500, 1000, and 2000 µg/L, plotted linearly through the origin.

Limit of detection (LOD) and limit of quantification (LOQ) for IVM were estimated using 15 blank samples (ACN). LOD was defined as three times the standard deviation plus mean of blanks; LOQ was calculated as ten times the standard deviation plus mean of blanks (adapted from DIN 38402–60:2013–12). Sample-specific LOD and LOQ were estimated for varying sample masses and extraction protocols. LOD for soil, *E. fetida*, *A. caliginosa*, and *L. terrestris* samples were 0.02, 0.16, 0.14, and 0.10 µg/kg dw, respectively. Corresponding LOQ were 0.05, 0.32, 0.28, and 0.21 µg/kg dw. Notably, all control samples (soils, earthworms, and for sorption/desorption) were consistently free of detectable IVM, i.e., below the LOD.

2.9. Data analysis

Statistical analyses and graphical representations were conducted using OriginPro 2024 with additional analyses in Microsoft Excel 365 v. 2412. Normality of data distributions was confirmed using Shapiro-Wilk test; homogeneity of variances was tested using Levene's test. A one-way ANOVA was applied to compare means between groups, followed by Tukey's HSD post-hoc test when significant differences were detected. To compare

bioaccumulation factors between species, a Kruskal-Wallis test was applied. Post-hoc pairwise comparisons were conducted using Dunn's test. A significance level of $p < 0.05$ was used for all tests. HPLC data analysis was conducted with Agilent ChemStation for LC 3D systems Rev. B.04.01.

3. Results and discussion

3.1. Bioaccumulation experiment

The decrease in IVM concentration during the uptake phase, seen in Fig. 1a, was 3.1% from day 0 to 21, and 12% from day 1 to 21. Homogeneous variances (Levene test, $p = 0.052$) and ANOVA revealed significant differences ($p = 0.047$) in mean concentrations between days 0, 1, and 21. However, Tukey's HSD post-hoc test suggested only significant differences ($p = 0.047$) between the means of days 1 and 21. The nonlinear regression (exponential decay function **Eq. 1**) was performed to hypothesize IVM degradation over a longer period ($t > 21$ d) and yielded a low R^2 of 0.42, a C_0 of 0.41 ng/g dw, and k_0 was 0.00487 d^{-1}. Using k_0, an IVM DT_{50} was calculated **(Eq. 2)** to be 142 d in AS, indicating slow dissipation. Generally, DT_{50} for IVM in soils vary considerably due to environmental conditions, and DT_{50} have previously been reported in a wide range: 10-16 d (Oliveira Ferreira et al., 2019), 16–458 d (Krogh et al., 2009), 19–66 d (Lagos et al., 2022), and around 240 d (Dubroca et al., 2003). For calculations, C_s was managed as mean of the raw soil concentrations from day 0–21, therefore 0.3974 mg/kg dw. This corresponds to 79% of the nominal concentration. Lower C_{soil} values directly after spiking than on the following two sampling days indicate that IVM might need more than 96 h to establish equilibrium between pore-water and soil phase. This is referenced by OECD guideline 317 (OECD, 2010) and Alexander (1995), and is critical for poorly water-soluble substances like IVM.

In Fig. 1b, mean ± SD values for the accumulation factors (C_{worm}/C_{soil}) increased from 0.21 ± 0.08 on day 1 to 0.62 ± 0.2 on day 21. The underlying mean IVM concentrations in *E. fetida* (C_{worm}) near the end of the uptake phase revealed deviations from the overall mean concentration (0.183 ng/g dw) during days 14–21. Here, a Levene test confirmed the homogeneity of variances ($p = 0.307$), and ANOVA indicated no significant differences between the means of days 14, 17, and 21 ($p = 0.382$). Mean C_{worm} were 0.159, 0.156, and 0.233 ng/g dw for days 14, 17, and 21, respectively. Corresponding deviations were −13.1, −14.6, and +27.7%. Since the deviation on day 21 exceeds 20%, criteria for a steady state (OECD, 2010) were not fully met. Uptake and elimination data are displayed in Fig. 2 and the corresponding bioaccumulation parameters are listed in Table 2.

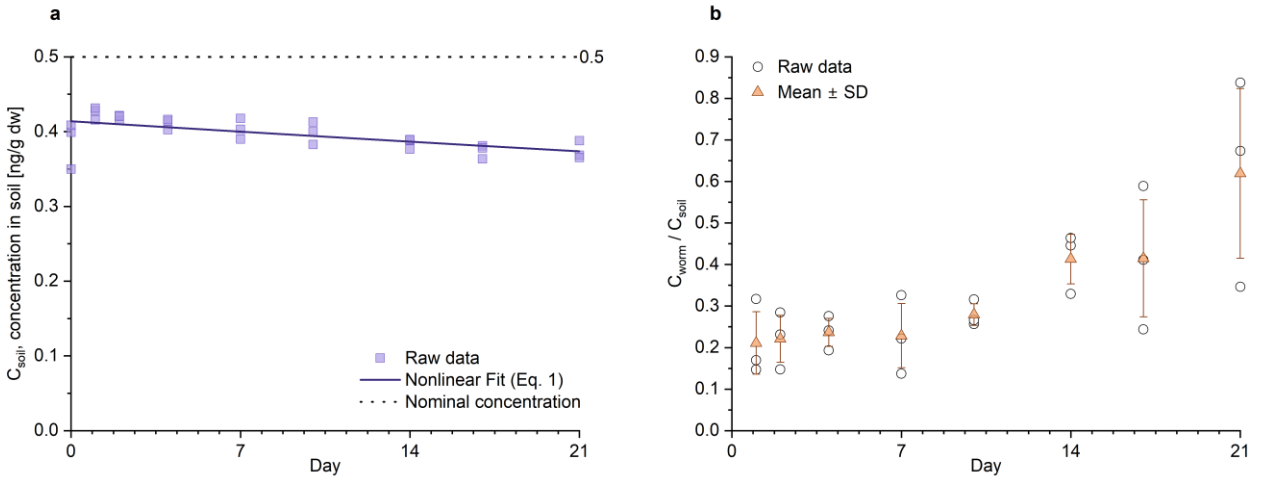


Fig. 1. a, Decrease of ivermectin concentration in the artificial soil substrate (C_{soil}) during the uptake phase of the *E. fetida* bioaccumulation study. The dotted line shows the spiked, nominal concentration (0.5 ng/g dw). The mean concentrations relate to 77% (day 0) and 85% (day 1) of the nominal. **b**, Uptake of ivermectin in *E. fetida* shown as the accumulation factor (ratio of C_{worm}/C_{soil}), providing a direct measure of ivermectin enrichment in earthworm tissue relative to its concentration in soil at the sampled timepoints.

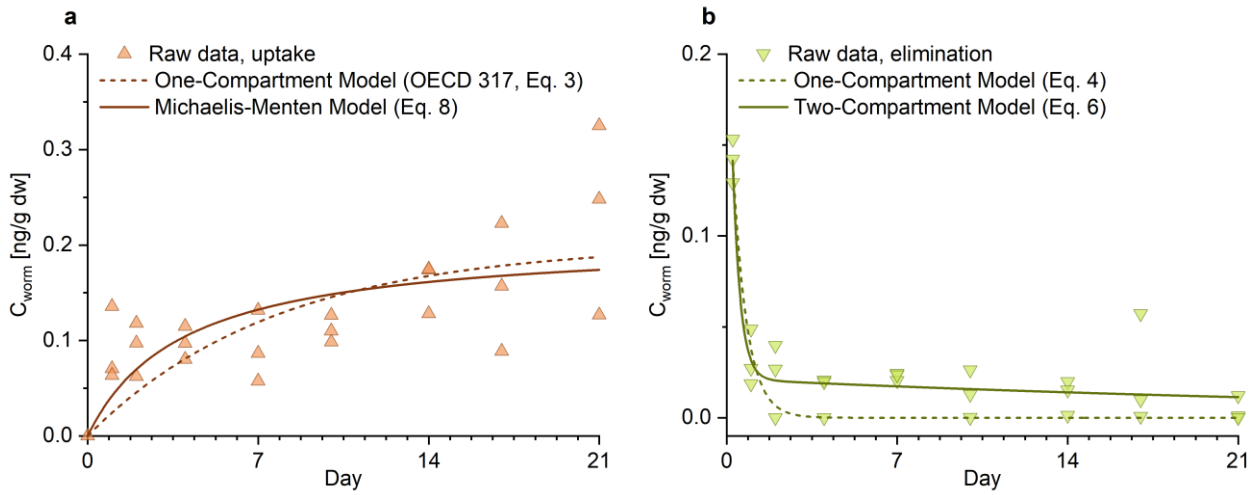


Fig. 2. Uptake (**a**) and elimination (**b**) kinetics of Ivermectin in *E. fetida* over 21 days each, with data points representing measured concentrations (C_{worm}) in earthworms. Uptake fits are modeled using a one-compartment model and a Michaelis-Menten model. Elimination fits are modeled using a one- and a two-compartment model. **b**, The y-axis begins at −0.01.

For *E. fetida*, the absence of a steady state at the end of the uptake phase indicates ongoing IVM accumulation, suggesting prolonged exposure risk beyond 21 d. The BAFk ± SE was calculated as ratio of the derived uptake rate constant and the elimination rate constant and ranged from 0.505 ± 0.301 to 0.727 ± 1.401 g soil dw/g earthworm dw. These values indicate minor accumulation of IVM in *E. fetida*. While OECD guideline 317 (OECD, 2010) does not specify a threshold, a $BAF_k < 1$ can be considered low risk for bioaccumulation, indicating lower substance concentration in earthworm tissue than in the surrounding soil matrix (Proc et al., 2021). However, the implied ongoing bioaccumulation in *E. fetida* beyond 21 d and the DT_{50} of 142 d in AS indicate that IVM remains bioavailable for extended periods. Adjusted for lipid and C_{org} content, the $BSAF$ ± SE ranged from 0.280 ± 0.168 to 0.403 ± 0.776.

Table 2
Bioaccumulation parameters of ivermectin in *E. fetida* in artificial soil substrate, shown as uptake rate constants (k_s (g soil dw/g earthworm dw d^{-1})) and elimination rate constants (k_e (d^{-1})). Compartments C_A and C_B (ng/g dw), and elimination rate constants k_a, k_b (d^{-1}) describe the two-compartment elimination. Kinetic bioaccumulation factors (BAF_k (g soil dw/g earthworm dw)) were determined by dividing k_s by k_e. Values are presented with standard errors of the estimation (±SE).

Phase	Model	R^2	Parameter	Value (± SE)	BAF_k (± SE)
Uptake	One-compartment model (Eq. 3)	0.33	k_s	0.065 (0.021)	0.505 (0.301)
			k_e	0.129 (0.064)	
	Michaelis-Menten model (Eq. 8)	0.38	V_{max}	0.207 (0.039)	n/a
			K_m	3.926 (2.430)	
			$\approx k_s$	0.053 (0.034)	
Elimination	One-compartment model (Eq. 4)	0.79	k_s	0.948 (0.249)	0.546 (0.188)
			k_e	1.737 (0.385)	
			$C_{a,0}$	0.217 (0.031)	
	Two-compartment model (Eq. 6)	0.89	k_s	2.155 (3.025)	0.727 (1.401)
			k_e	2.964 (3.909)	
			C_A	0.268 (0.084)	
			k_a	3.198 (1.339)	
			C_B	0.021 (0.008)	
			k_b	0.030 (0.035)	

For the uptake phase, The Michaelis-Menten model **(Eq. 8)** provided a better fit compared to the one-compartment model, capturing non-linearities and potential saturation in early accumulation. While its application is unconventional, it highlights the complexity and non-linearity of the uptake. In the fitting of the elimination data of *E. fetida*, the high SE of k_e from the two-compartment elimination model is due to uncertainties in k_a and k_b, reducing precision in the weighted mean k_e. Notably, residual IVM levels were still detectable in some earthworm samples at the end of the elimination phase.

Compared to *E. fetida*, the raw accumulation factors, expressed as C_{worm}/C_{soil}, are higher for *A. caliginosa* and *L. terrestris* at the available timepoints (Table 3).

Accumulation factors (C_{worm}/C_{soil}) differed significantly among the three species (Kruskal-Wallis test, $p < 0.001$). Dunn's post-hoc test indicated that *A. caliginosa* and *L. terrestris* had significantly higher accumulation factors than *E. fetida* ($p < 0.05$), while no significant difference was observed between *A. caliginosa* and *L. terrestris* ($p > 0.05$).

Table 3
Accumulation factors of *A. caliginosa* and *L. terrestris*. n = 3 replicates per sampling day.

Species	Day	C_{worm}/C_{soil}		Steady state at the end of uptake phase, related to C_{worm} vs. time (d)
		Raw data	Mean ± SD	
A. caliginosa	14	1.01, 0.74, 1.04	0.9 ± 0.14	No; day 14 deviation from mean is −25.0% and day 17 deviation from mean is +23.4%.
	17	2.29, 1.35, 1.21	1.6 ± 0.48	
	21	1.14, 2.30, 1.35	1.6 ± 0.50	
L. terrestris	14	0.44, 0.79, 0.71	0.6 ± 0.15	No; day 21 deviation from mean is −22.0%.
	17	0.22, 0.82, 1.46	0.8 ± 0.50	
	21	0.25, 1.02, 1.80	1.0 ± 0.63	

These differences may reflect species-specific variations in uptake and elimination dynamics, possibly resulting from anatomical or physiological distinctions, such as larger body size or differing metabolic rates. For *A. caliginosa* and *L. terrestris*, the different soil (LUFA 2.2) used as substrate, or its lower C_{org} can also influence the bioavailability of IVM. Importantly, soil type and C_{org} significantly affect uptake kinetics of organic pollutants in earthworms (Lanno et al., 2004; Carter et al., 2016; Šmídová et al., 2021). A systematic assessment of species- and soil-specific effects would be needed to fully disentangle these factors. However, maintaining multiple species in a uniform substrate poses methodological challenges and may not accurately reflect natural conditions.

In agricultural soils, IVM residues have been detected in the top 0–5 cm beneath dung from IVM-treated cattle (Römbke et al., 2010; Wohde et al., 2016) while a leaching experiment demonstrated vertical migration of IVM in soil down to 18 cm depth (Rath et al., 2016). This suggests that exposure could vary depending on earthworm burrowing depth and feeding strategy. While *E. fetida* primarily inhabits and feeds within surface organic layers, *A. caliginosa* and *L. terrestris* burrow deeper into soil and may encounter residues beyond the topsoil. Nonetheless, the importance of species-specific behavior versus soil depth distribution in real-world agricultural scenarios deserves further and systematic investigation.

In a bioconcentration study with *E. fetida*, *A. caliginosa*, and *L. terrestris*, Li et al. (2024) investigated how lipid content and specific surface area (SSA) influence bioaccumulation. They found that higher lipid content and greater SSA can lead to increased bioconcentration of hydrophobic compounds. Specifically, *E. fetida* exhibited greater pesticide accumulation compared to *A. caliginosa* and *L. terrestris* which had a lower lipid content. However, our results diverge from this trend. Although *E. fetida* could be expected to show higher IVM accumulation due to its previously reported high lipid content (19.4% dw, by Li et al. (2024)), our *E. fetida* individuals had a lower lipid content (6.5% dw) and lower accumulation factors. Notably, other reported lipid contents for *E. fetida* are 11.4% dw (Wang et al., 2014) and 12.95% dw (Bruns et al., 2002), highlighting the variability in lipid content and its relevance for bioaccumulation studies.

In comparison, Iglesias et al. (2023) conducted a similar bioaccumulation study with *E. fetida* and IVM, reporting their results in wet weight concentrations and without stating the lipid content. Moreover, the study was not conducted in soil but dung as substrate. Despite methodological differences, the trends in IVM accumulation align broadly with our findings. Sun et al. (2005) previously demonstrated bioaccumulation and elimination patterns of the closely related substance avermectin B_{1a} (abamectin) in *E. fetida*, highlighting rapid uptake and elimination. Our study advances this knowledge by focusing on IVM and its interactions with soil components, while also providing insights into accumulation behavior of IVM in the earthworms *A. caliginosa* and *L. terrestris*.

Finally, our results highlight the importance of species-specific and environmental factors, such as soil composition in bioaccumulation research for hydrophobic compounds.

3.2. Validity criteria

Extraction recoveries varied among earthworm species, with particularly low recovery for *L. terrestris*. Despite this, IVM concentrations were not corrected for doramectin recovery rates. Nonetheless, correcting these values would increase the overall concentrations in earthworms and imply a higher bioaccumulation potential. Thus, actual accumulation factors may be underestimated. In theory, corrected values could exceed 1, especially as equilibrium is approached, indicating a greater risk of IVM bioaccumulation.

Mortality criteria (mortality during each phase should not exceed 10% (OECD, 2010)) were partially met. For *E. fetida*, only 1.1% of individuals (n = 189) died during both phases of the bioaccumulation experiment. No mortality was observed for *L. terrestris* (n = 17) but 19.6% of *A. caliginosa* (n = 51) died during the uptake phase. Biomass changes for pooled *E. fetida* samples were as follows: In the IVM treatment, biomass decreased by 5.5% during uptake and increased by 2.2% during elimination. In untreated control vessels, earthworms lost 3.7%, and gained 1% mass, respectively. These changes remained below the 20% limit required in OECD guideline 317 (OECD, 2010).

3.3. Sorption experiment

Results of the sorption experiment are illustrated in Fig. 3. Sorption characteristics of IVM in AS and its individual components reveal that IVM binds most strongly to peat while sorption to sand was negligible. Normalized to C_{org}, sorption of IVM in mixed AS (K_D 180 mL/g) results in a K_{OC} of 5002 mL/g (corresponding to log K_{OC} 3.7). This aligns with IVM sorption coefficients reported in natural soils (Krogh et al., 2008; Rath et al., 2016; Heinrich et al., 2021). Considering nonlinear sorption behavior, the K_F for AS was calculated as 79.9 $\mu g^{1-1/n} \cdot (mL)^{1/n} \cdot g^{-1}$, with n = 1.62, consistent with typical Freundlich isotherms (OECD, 2000).

The decrease in sorption affinity at higher aqueous concentrations observed in AS can partly be attributed to clay saturation effects, typical for monolayer adsorption processes. This behavior resembles Langmuir-type sorption (Sparks, 2003), where binding sites become progressively occupied, reducing further sorption efficiency. With clay accounting for 20% of AS, this contributes to the gradual decline in the K_D value for AS.

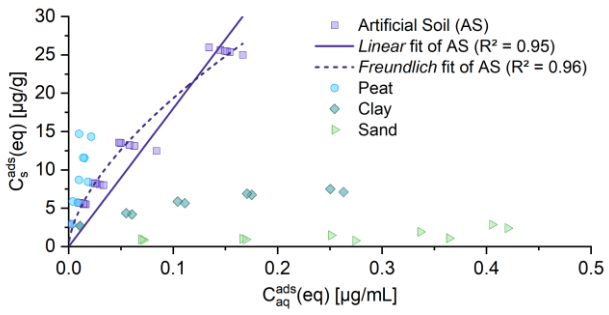


Fig. 3. Sorption of ivermectin in artificial soil (AS), sand, clay, and peat, including fits for AS.

The strong sorption to peat demonstrates the influence of organic matter in retaining IVM. However, dissolved organic matter from peat may artificially increase the aqueous phase IVM concentration in batch experiments, contributing to underestimated sorption for peat. Given that earthworms, including *E. fetida*, are inclined to feed on organic matter (Edwards, 2022), the high sorption observed for peat suggests that IVM is likely retained in soil organic matter, thereby reducing its bioavailability for earthworms (Alexander, 1995). This may account for the low accumulation observed in *E. fetida*. Our desorption studies consolidate this, demonstrating that IVM desorbs least effectively from peat and most readily from sand. The desorption percentage **(Eq. (12)** as mean ± SD ranks: peat (0.7 ± 0.6), clay (20.2 ± 9.2), and sand (72.1 ± 18.8). This suggests that IVM sorption to peat is irreversible, consistent with OECD criteria (OECD, 2000), while clay shows partial reversibility, and sand exhibits nearly reversible sorption. Respective K_D^{des} **(Eq. (13)** are 1450.5 (peat), 35.8 (clay), and 3.5 mL/g (sand). This highlights the retentive capacity of organic substrates, which can trap hydrophobic compounds like IVM and mitigate their release into the environment (Alexander, 1995; Rath et al., 2016).

The lower C_{org} content in LUFA 2.2 likely resulted in lower IVM retention, leading to higher bioavailability and moderately greater uptake in earthworms. Consequently, the strong affinity of IVM for peat not only reduces its bioavailability but can limit bioaccumulation in soil-dwelling organisms. This underscores how interactions with soil organic matter shape IVM's environmental fate and effects on biota. Tracing IVM through these matrices reveals how organic substrates retain hydrophobic compounds, potentially mitigating bioaccumulation risks for earthworms.

3.4. Physiological adaptations of earthworms and molecular properties affecting bioaccumulation

While soil interactions influence IVM distribution and availability, physiological responses of earthworms help manage exposure to xenobiotics like IVM. One of the primary defense mechanisms in organisms are efflux pumps, which actively transport toxic substances out of cells (Epel et al., 2008). For *E. fetida* and *Eisenia andrei*, the presence of efflux pumps, P-glycoprotein, has been

confirmed: In *E. fetida*, P-glycoprotein activity was identified as a defense mechanism (Bošnjak et al., 2014), while in *E. andrei*, efflux activity was demonstrated through modulation by verapamil and dexamethasone (Hackenberger et al., 2012). Notably, variable enzymatic responses to xenobiotics by *L. terrestris* and *E. fetida* reflect diverse detoxification capacities (Henson-Ramsey et al., 2011). Carboxylesterase activity, representing a key enzyme for pesticide detoxification, was also documented in the gut content of *L. terrestris* (Sanchez-Hernandez et al., 2009). High carboxylesterase activity has further been described for *A. caliginosa* and linked to the detoxification of pesticides (Sanchez-Hernandez et al., 2014). These mechanisms could limit IVM bioaccumulation in earthworms, facilitating elimination over accumulation.

Limited bioaccumulation of IVM could also be attributed to its molecular size, with molecular masses of 875.1 g/mol (B_{1a}) and 861.1 g/mol (B_{1b}) for the components in IVM mixtures. Such larger molecules face challenges in permeating biological membranes, affecting uptake and bioaccumulation: As outlined by Arnot et al. (2010), the concept of a molecular size cutoff suggests that beyond certain dimensions, typically defined by effective cross-sectional diameter or maximum diameter, the ability of a substance to bioaccumulate diminishes. However, the validity of strict molecular size cutoffs is debated; while larger molecules often show reduced bioaccumulation due to lower bioavailability or slower diffusion rates, they can still accumulate, yet less efficiently. This underscores the complexity of bioaccumulation processes, which are governed not only by molecular size but also by hydrophobicity and environmental conditions (Arnot et al., 2010; Garg and Smith, 2014; Gimeno et al., 2024). We conclude that the molecular properties of IVM and the biological defenses of earthworms collectively contribute to limited bioavailability and accumulation in the investigated earthworm species.

4. Conclusion

The study demonstrated that BAF_k for IVM ranged from 0.505 to 0.727 g soil dw/g earthworm dw in *E. fetida*. Elimination of IVM from the organisms was best described with a biphasic kinetic, characterized by a rapid initial phase and a slower terminal phase. Here, the fast elimination and low BAF_k implied that no net accumulation occurred. For *A. caliginosa* and *L. terrestris*, results suggested accumulation during the uptake phase with potential accumulation factors greater than 1. However, none of the earthworm species reached optimal equilibrium (steady state) after 21 d, further indicating a slow IVM accumulation process. The calculated DT_{50} of IVM in AS was 142 d. Strong sorption of IVM in the organic fraction of the test substrate further reflects that bioavailability is notably affected by organic matter in soils which might therefore reduce bioaccumulation of IVM in *E. fetida*. Systematic assessments are needed to evaluate risks of veterinary pharmaceuticals for terrestrial environments and to support regulatory decisions.

CRediT authorship contribution statement

Andre Patrick Heinrich: Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Johannes Junck:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **Rolf-Alexander Düring:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Funding acquisition, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used OpenAI's ChatGPT in order to improve clarity and language in certain sections of the text. After employing this tool, the authors thoroughly reviewed and edited the content to ensure accuracy and completeness. The authors take full responsibility for the content of the publication.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chemosphere.2025.144228

Data availability

Data will be made available on request.

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6.2 Supporting Information

Supporting Information

From soil sorption to bioaccumulation: Tracing the endectocide ivermectin in soil and earthworms

I. Table of contents

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II. Chemicals used for the experiments

Table S 1 | Chemicals used for ivermectin extraction, derivatization, and quantification.

Substance	CAS-no.	Supplier	Product-no.	Purity (%)
Ivermectin	70288-86-7	LGC-Standards	DRE-CA14488000	94.4
Doramectin	117704-25-3	LGC-Standards	DRE-C13083000	95.0
Acetonitrile	75-05-8	VWR International	20060.320	≥ 99.9
Propan-2-ol	67-63-0	VWR International	20880.320	≥ 99.8
N-methylimidazole	616-47-7	Sigma-Aldrich	336092	> 99.0
Triethylamine	121-44-8	Sigma-Aldrich	T0886	> 99.0
Trifluoroacetic anhydride	407-25-0	Sigma-Aldrich	106232	> 99.0
Trifluoroacetic acid	76-05-1	Sigma-Aldrich	302031	> 99.0
Calcium chloride dihydrate	10035-04-8	Sigma-Aldrich	1.02382	> 99.0

III. Lipid content determination

To standardize the bioaccumulation results, a preliminary determination of the lipid content of the test organisms was conducted. This was carried out using six plastic containers (thermoplastic trays) filled with untreated artificial soil (AS), each housing 12 individuals of *E. fetida* for a duration of six weeks. The preparation of AS followed the procedure described in the main text. The water content was initially set at 22.7%, monitored weekly, and adjusted if necessary. The test organisms were fed weekly with 1.2 mg of ground oatmeal per g AS (dry weight). After six weeks, the organisms were removed, washed with deionized water, gently dried with filter paper, and transferred to Petri dishes for 24 hours to clear their gut contents. Fresh weight was then measured by weighing the organisms into 50 mL polypropylene vials. The organisms were subsequently euthanized by freezing at -32 °C, followed by freeze-drying for 72 hours to determine the dry weight. The freeze-dried samples were stored at -32 °C until further analysis.

The lipid determination then followed the Weibull-Stoldt method. The procedure employed for lipid determination follows an internal protocol established by a collaborating lab: Six replicates of the freeze-dried *E. fetida* samples were ground using a mortar, with approximately 1 g of freeze-dried sample material weighed into 400 mL glass beakers. The beakers were pre-cleaned with acetone to prevent contamination, and gloves were worn throughout the process. Each sample was mixed with 150 mL of 4 M hydrochloric acid and heated on a magnetic stirrer at 100 °C and 500 rpm for 30 minutes. The samples were then filtered using paper filters, with continuous addition of 100 mL boiling water to aid the filtration process. The filters containing the sample material were dried in an oven at 105 °C for 2.5 hours and then stored overnight in a desiccator with a nitrogen atmosphere.

The following day, the beakers were weighed to a constant mass, and the mass of extracted lipids was determined by the difference between the empty weight of the beakers before extraction and their weight after extraction. The percentage lipid content of each sample was calculated based on the dry and fresh weight of the samples. The mean lipid content across all samples was then determined.

IV. Details of the extraction and quantification procedure

Sample quantities as fresh weight (fw) for soil or by number of earthworms (freeze-dried and ground with a tissue-grinder) were weighed into polypropylene vials and extracted with acetonitrile. Table S 2 details the procedure, where (✓) indicates that this step was performed for all sample types.

Table S 2 | Details of the extraction procedure for ivermectin and doramectin.

Step	Soil	*E. fetida*	*A. caliginosa*	*L. terrestris*
Volume of polypropylene vial (mL)	50	15	15	50
Sample quantity	5 g (fw)	3 earthworms	3 earthworms	1 earthworm
Target water content (%) (add purified water)	50	80	80	80
Rehydrate for 24 h at room temperature	✓	✓	✓	✓
Add internal recovery standard	✓	✓	✓	✓
Add acetonitrile (mL)	25	10	10	25
Shake 5 s by hand	✓	✓	✓	✓
Ultrasonic bath (40 W/L) for 15 min	✓	✓	✓	✓
Horizontal shaker for 30 min at 350 rpm	✓	✓	✓	✓
Ultrasonic bath (40 W/L) for 15 min	✓	✓	✓	✓
Centrifugation for 30 min at 2820*g*	✓	✓	✓	✓
Transfer supernatant with glass pipette (mL)	10	8	8	10
Evaporate under N_2 in 60 °C water bath	✓	✓	✓	✓
Add 1000 µL acetonitrile for reconstitution	✓	✓	✓	✓
Vortex mixer for 30 s	✓	✓	✓	✓
Ultrasonic bath (40 W/L) for 15 min	✓	✓	✓	✓
Vortex mixer for 30 s	✓	✓	✓	✓
Horizontal shaker for 30 min at 350 rpm	✓	✓	✓	✓
Vortex mixer for 30 s	✓	✓	✓	✓
Ultrasonic bath (40 W/L) for 15 min	✓	✓	✓	✓
Vortex mixer for 30 s	✓	✓	✓	✓
Filter through 0.45 µm PTFE syringe filter	✓	✓	✓	✓

After filtration through a 0.45 µm PTFE syringe filter, 700 µL of reconstituted, filtered sample were transferred into an amber glass 2 mL HPLC-vial (WIC 41160, WICOM Germany GmbH). Then, reagents for derivatization of ivermectin and doramectin (internal recovery standard) were added in the following order and quantity: 100 µL N-methylimidazole:acetonitrile (1:1, v/v); 50 µL triethylamine; 100 µL trifluoroacetic anhydride:acetonitrile (1:1, v/v); 50 µL trifluoroacetic acid. After each reagent, HPLC vials were closed, shaken for 5 s, and left to rest for 3 min before adding the next reagent. After the last reagent, HPLC vials were closed and heated in a lab oven for 30 min at 60 °C. The cooled vials were then added into the HPLC tray for quantification. Chemicals for all steps are detailed in Table S 1.

Quantification was performed on an Agilent 1200 HPLC system with gradient elution on a C18 column (3 µm, 2.1 × 150 mm, Acclaim™ Polar Advantage II, Thermo Scientific). The HPLC injection volume was 40 µL. Mobile phases for the gradient elution were A (purified Milli-Q® water) and B (acetonitrile); flow 0.3 mL/min; gradient 0 to 10 min, 88 to 100 % B; 10 to 11 min, 100 % B; 11 to 20 min 100 to 88 % B. Wavelengths of the fluorescence detector were 364 nm for excitation and 463 nm for emission. The calibration curves consisted of concentrations of 0.5, 1, 5, 10, 25, 50, 100, 500, 1000, and 2000 µg/L, plotted linearly through the origin.

As stated in the main text, extraction recoveries (mean ± SD) of the internal standard were 104.3 ± 12.2% (n=107) in soil, 75.8 ± 14.2% (n=63) in *E. fetida*, 88.5 ± 31.2% (n=15) in *A. caliginosa*, and 54.1 ± 30.5% (n=15) in *L. terrestris* samples. Ivermectin concentrations were not corrected for internal standard recovery. For soil samples, 100 µL of a 20000 µg/L doramectin solution (in acetonitrile) was spiked into each sample prior to extraction. For earthworm samples, 50 µL of the same solution was added. Recovery rates were calculated as percentage of detected doramectin relative to the amount initially spiked. By not correcting with doramectin recovery rates, the protocol aims for a conservative assessment of bioaccumulation potential, prioritizing methodological robustness and data comparability across all sample types. For adapted applications, the protocol could further be improved by optimizing the solvent or extraction temperature to enhance efficiency across different matrices. Additionally, adjusting for lipid content and exploring alternative solvent mixtures or extraction systems may improve recoveries, particularly for species with complex tissue structures.

7 Eine ökotoxikologische Sicht auf Malariavektorkontrolle mit Ivermectin-behandelten Nutztieren

7.1 Veröffentlichung

Dieses Kapitel wurde in *Nature Sustainability* (Springer Nature) veröffentlicht als:

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Der Inhalt des Kapitels wurde manuell an das Layout der Dissertation angepasst. Die begutachtete Veröffentlichung in ihrer originalen Form und mit allen Zusatzinformationen ist zu finden unter folgendem **Link zur Zeitschrift:** https://doi.org/10.1038/s41893-024-01332-8

Abstract

Malaria remains an enduring challenge in sub-Saharan Africa, affecting public health and development. Control measures can include the use of insecticides that target adult Anopheles mosquitoes transmitting the malaria-causing Plasmodium parasite. Such mosquitoes can also bite livestock, allowing vector populations to be maintained at levels that enable parasite transmission. Thus, one way to control the spread of malaria includes the use of endectocide-treated livestock which renders the blood of cattle toxic to such mosquito populations. Here we present an ecotoxicological perspective on malaria vector control, using cattle treated with the endectocide ivermectin to target zoophagic and opportunistic Anopheles coluzzii mosquitoes. Our study employs an innovative, long-acting injectable ivermectin formulation with over 6 months of sustained mosquitocidal activity. Robust vector population modelling underscores its promising field effectiveness. Environmental implications (soil sorption and dissipation) of excreted ivermectin and potential ecotoxicological risks to non-target dung organisms in West Africa are discussed, in addition to actionable, locally inspired risk mitigation measures to protect sub-Saharan soils and agroecosystems from chemical pollution. We highlight how ecotoxicology and environmental chemistry improve livestock-based vector control with ivermectin for effective and more sustainable malaria management.

In 1962, Rachel Carson's 'Silent Spring' revealed the ecological costs of DDT, an insecticide that had previously revolutionized agriculture and malaria control[1,2,3]. Carson's revelations marked a pivotal moment in environmentalism, highlighting the necessary balance between immediate benefits and potential long-term ecological implications. This awakening paved the way for the holistic strategy called 'One Health'—an interdisciplinary, multisectoral approach that 'aims to sustainably balance and optimize the health of people, animals and ecosystems'[4]. However, some One Health engagements sidelined environmental aspects[4,5,6]. Our study intends to integrate environmental health considerations into malaria control efforts using ivermectin-treated cattle.

In 2022, 249 million malaria cases were reported, primarily in sub-Saharan Africa, where malaria impairs public health and development[7]. Combating malaria includes early diagnosis of the causative *Plasmodium* parasites, antimalarial drugs and control of *Anopheles* mosquitoes, the malaria vectors[7,8]. Control measures widely rely on insecticides targeting adult mosquitoes since modest reductions in survival may substantially lower parasite transmission[9]. Central control tools are long-lasting insecticidal nets (LLINs) and indoor residual spraying[10].

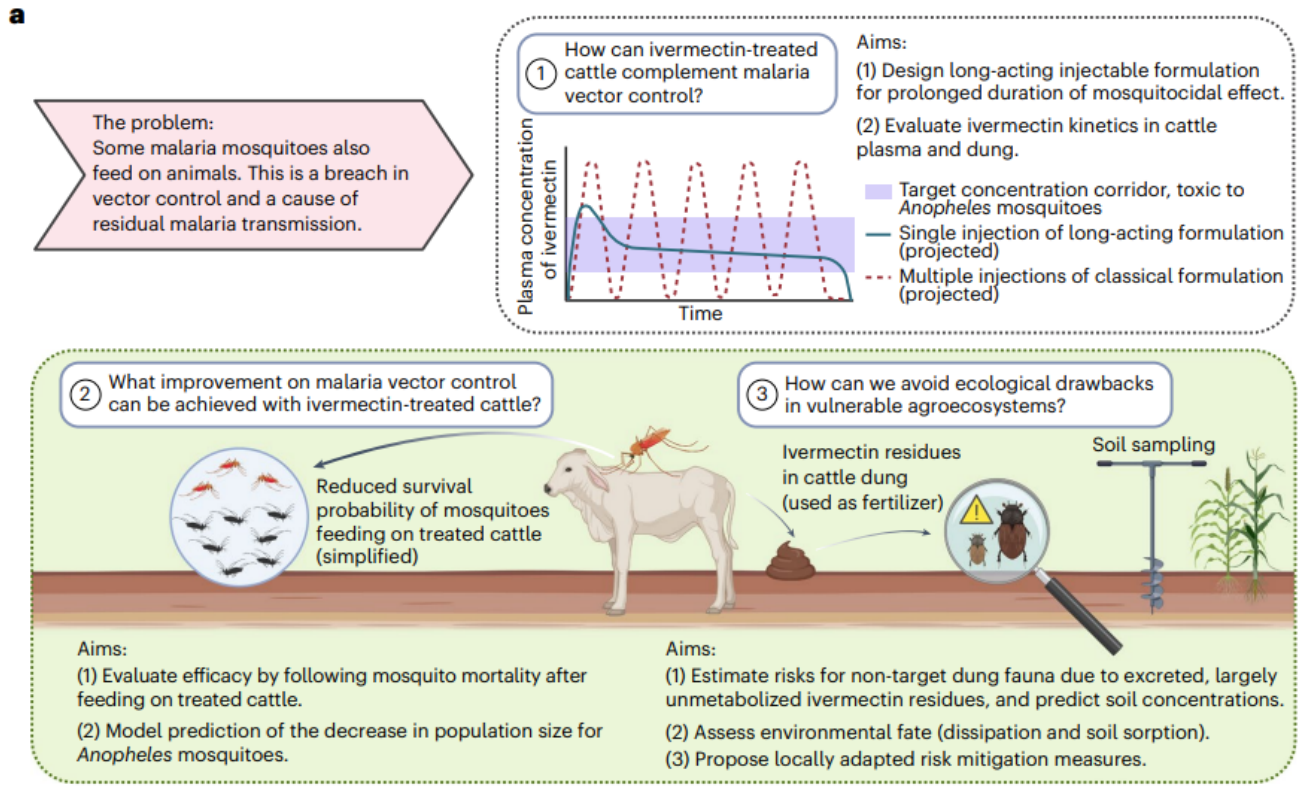
Persistently high incidences are partly explained by *Anopheles* mosquitoes adapting to environmental changes and extensively used insecticides[3,7,11]. Some mosquitoes show increased survival against insecticide contact (physiological resistance[12]) or avoid contact by biting humans who are not protected by LLINs (behavioural resistance[13]). Mosquitoes also exhibit behavioural resistance by biting animals instead of humans, maintaining vector populations at levels enabling parasite transmission[14]. This largely neglected gap in current control measures motivates this study.

Using the endectocide ivermectin, we aimed to render cattle blood toxic to behaviourally resistant malaria mosquitoes of opportunistic or zoophagic feeding habits (Fig. 1a). With endectocide-treated livestock (ETL), vectors are exposed to mosquitocidal drugs in animal blood, and ivermectin is considered suitable for ETL[15,16,17,18]. It is safe and effective in treating parasites in animals (and humans) and improves animal health while boosting livestock productivity[15,19,20]. From a One Health perspective, ETL already links human and veterinary health. However, animals excrete ivermectin mainly unmetabolized in faeces[21]. These residues can enter agroecosystems and harm dung and soil organisms[22,23,24,25]. After injection, most commercialized veterinary ivermectin formulations reach peak plasma levels within days, with limited terminal half-life[21]. These formulations provide mosquitocidal protection for approximately 2 weeks, fostering the popularity of long-acting formulations to fully cover malaria transmission seasons[16,26,27]. However, long-acting endectocide formulations can also prolong release via cattle dung, with longer-lasting risks to non-target fauna[28].

We investigated cattle and *Anopheles coluzzii* mosquitoes from Burkina Faso and compared a commercialized injectable ivermectin veterinary formulation and a long-acting depot formulation, repurposed to control vectors for at least 6 months. First, we characterized pharmacokinetic profiles in cattle plasma and dung. Second, we assessed mosquitocidal efficacy through direct skin-feeding assays on cattle (Fig. 1b). Modelling approaches were used to predict field effectiveness. Third, considering environmental risks, we monitored ivermectin dissipation in dung and performed soil sorption studies with soils from Burkina Faso. We related measured dung concentrations to published ecotoxicological observations on dung organisms and propose risk mitigation measures.

While ivermectin-based strategies promise notable advantages in malaria vector control and potential benefits against other arthropod-borne zoonotic diseases, these must be balanced with environmental implications. Considering these dual perspectives, we promote a holistic view of ivermectin administration to sustainably harness its potential.

Empowered by an extensive dataset, our vector population model underscores the transformative potential of ivermectin-treated cattle and long-acting ivermectin formulations. By bridging cutting-edge vector control with ecotoxicological insight, our research aligns with a comprehensive vision that encompasses animal health, community well-being and ecosystem preservation, reflecting the integrated, unifying approach[4] necessary for sustainable development.



b

1x IVM-BEPO injection[a] — 7 cattle received 1x 2.4 mg kg^{-1} bw

6x IVOMEC-D injections[b] — 7 cattle received 6x 0.4 mg kg^{-1} bw

Day after injection (DAI)	–18[c]	2	7	14	21	28	45	75	89	106	120	137	150	160	167	174	181	190	197	204	211
Mosquito feeding assays[d]	X	X	X	X	X	X	X	X	X	X	X	–	X	X	X	X	X	X	X	X	X
Plasma sampling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dung sampling	X	X	X	X	X	X	X	X	–	X	–	X	–	X	X	X	–	–	–	X	X
Storage of dung samples	–	X	X	–	–	–	–	–	–	–	–	–	–	–	–	X	–	–	–	X	–

[a] IVM-BEPO injection at DAI 0 (study start) based on initial and projected body weight (bw); this is the novel, long-acting product

[b] IVOMEC-D injections monthly at DAI 0, 31, 61, 92, 123, 153 based on current bw; this is the commercially available product

[c] Control assays and samples from 18 days before the (first) injection

[d] Daily mosquito survival was assessed for 30 days post feeding

Dash (–) indicates no samples were taken or processed that day

Results

Ivermectin pharmacokinetics in cattle plasma and dung

Mean ivermectin concentrations in cattle plasma and dung are shown in Fig. 2. After a single injection with the commercial IVOMEC-D formulation (not long-acting), ivermectin was detected in plasma and dung for up to 28 days (Fig. 2a,b). In plasma from the long-acting IVM-BEPO-treated cattle, ivermectin levels exceeded the limit of quantification for at least 211 days, our study duration (Fig. 2c). All control samples before and during treatment were free of detectable ivermectin. Peak mean ± s.d. concentrations for IVOMEC-D cattle were 122 ± 35 ng ml^{-1} in plasma (DAI (day after injection) 7 after the sixth injection, 160 days after study start) and 1,927 ± 912 ng g^{-1} dry weight (dw) in dung on DAI 2 after the first injection. After treatment with the long-acting formulation, maximum mean plasma concentration in the first month was documented on DAI 7 (22.9 ± 8.9 ng ml^{-1}) and, overall, on DAI 204 (32.7 ± 6.2 ng ml^{-1}). The highest mean concentrations in dung throughout the study were measured on DAI 7 (530 ± 327 ng g^{-1} dw) after depot injection. The C_{max}/dose index for plasma and dung is considerably lower for IVM-BEPO since the injected dose was six times higher compared with IVOMEC-D. Individual data points, sample sizes and pharmacokinetic parameters for ivermectin in cattle plasma and dung are summarized in Supplementary Tables 1–3.

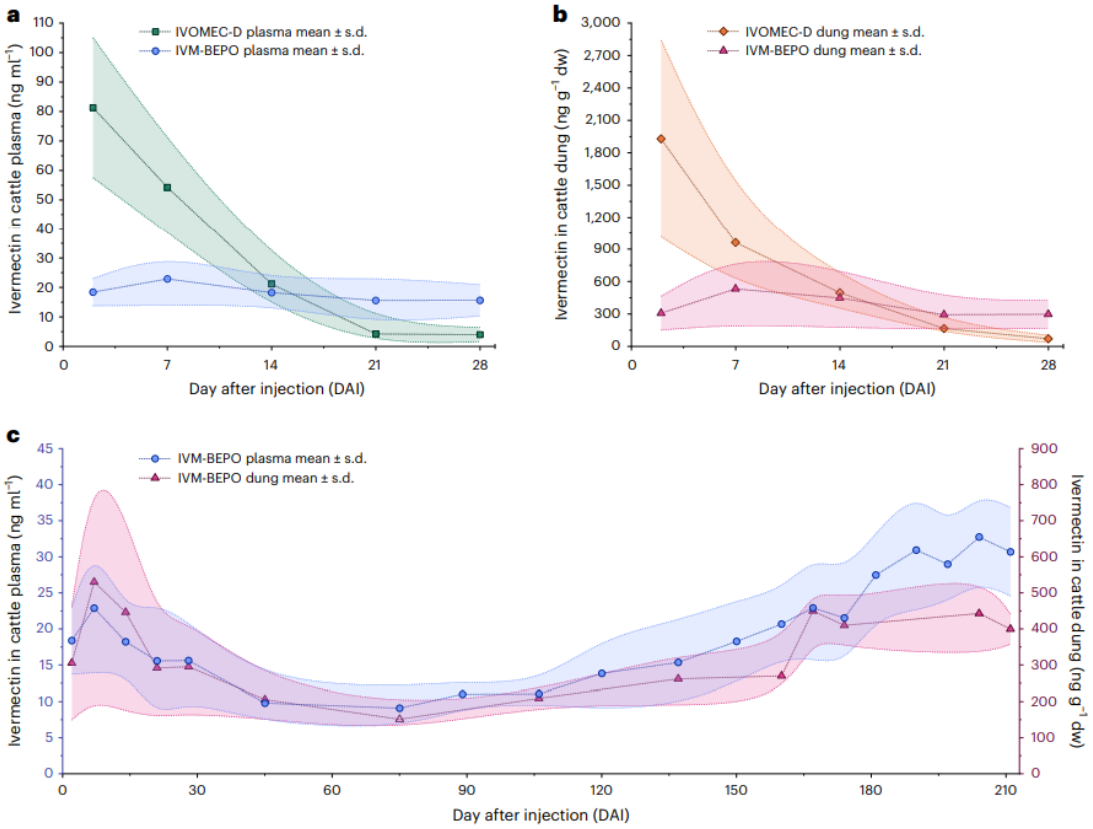


Fig. 2 | Pharmacokinetic profiles of ivermectin in cattle plasma and dung. **a**,**b**, Arithmetic mean ± s.d. ivermectin concentrations over 2–28 days in cattle plasma (**a**) and cattle dung (**b**) after one subcutaneous injection of a commercial (0.4 mg kg^{-1}, IVOMEC-D) or a long-acting (2.4 mg kg^{-1}, IVM-BEPO) ivermectin formulation. On DAI 21 and 28, several IVOMEC-D concentrations were below the limit of quantification in plasma (Supplementary Table 1). **c**, Continuation of IVM-BEPO arithmetic mean ± s.d. ivermectin concentrations over 2–211 DAI in cattle plasma and dung. All points display quantifiable concentrations. **a**–**c**, Error bar areas show the smoothed (B-spline) s.d. of 4–8 measured samples from 2–4 treated cattle. The *y* axes in **c** use different scales.

Mosquitocidal activity

Overall, 26,637 adult female mosquitoes were allowed to blood-feed on cattle in different experimental arms, 94% of which successfully fed, without differences between arms (Wald $X^2 = 1.70$, $P = 0.42$; Supplementary Fig. 1). For survival measurements, we followed 5,384, 4,852 and 5,400 females blood-fed on control, IVOMEC-D and IVM-BEPO cattle, respectively. Mosquitoes fed on IVM-BEPO cattle always had higher mortality probabilities than control mosquitoes (all hazard ratios >1; $P < 0.001$; Supplementary Table 4). IVOMEC-D-fed mosquitoes repeatedly showed similar mortality probabilities to the control (hazard ratio not significantly different from 1 on DAI 120, 204, 211). Mosquitoes fed on IVM-BEPO-treated cattle rarely survived beyond 10 days (Fig. 3a), the median extrinsic developmental period for *Plasmodium falciparum* in field mosquitoes[29]. With this treatment, only mosquitoes that ingested *Plasmodium* before ivermectin exposure could become infectious, transmitting parasites during only 1–3 gonotrophic cycles. However, monthly IVOMEC-D treatments often resulted in mosquito survival over 10 days, failing to block transmission. Ivermectin concentrations killing 50% of mosquitoes after 10 days were equal between formulations (IVOMEC-D LC_{50} ± s.e.: 7.5 ± 0.7 ng ml^{-1}; IVM-BEPO LC_{50}: 8.3 ± 0.3 ng ml^{-1}; *t*-test comparison between formulations: $t = -1.17$, $P = 0.23$). Unlike IVOMEC-D, the depot formulation reached this level over 211 days (Fig. 2c, Supplementary Table 5 and Supplementary Fig. 2). The 10-day LC_{90} differed significantly, with lower concentrations needed to cause 90% mortality with the depot (IVOMEC-D LC_{90}: 31.8 ± 2.8 ng ml^{-1}; IVM-BEPO LC_{90}: 19.2 ± 0.6 ng ml^{-1}; $t = 4.20$, $P < 0.001$).

Our vector population simulation model demonstrates that using ivermectin-treated cattle, combined with bed nets, reduces mosquito populations by 25 to over 90% (Fig. 3b,c; refined modelling scenarios in Supplementary Fig. M1). Model outputs predict increased effectiveness for both formulations when cattle outnumber humans as the host population and when vectors prefer animals. Treatments primarily affect infectious mosquitoes aged 10 days old or older since feeding likelihood on treated cattle and dying increases with age. The long-acting depot consistently reduces epidemiologically relevant vectors by

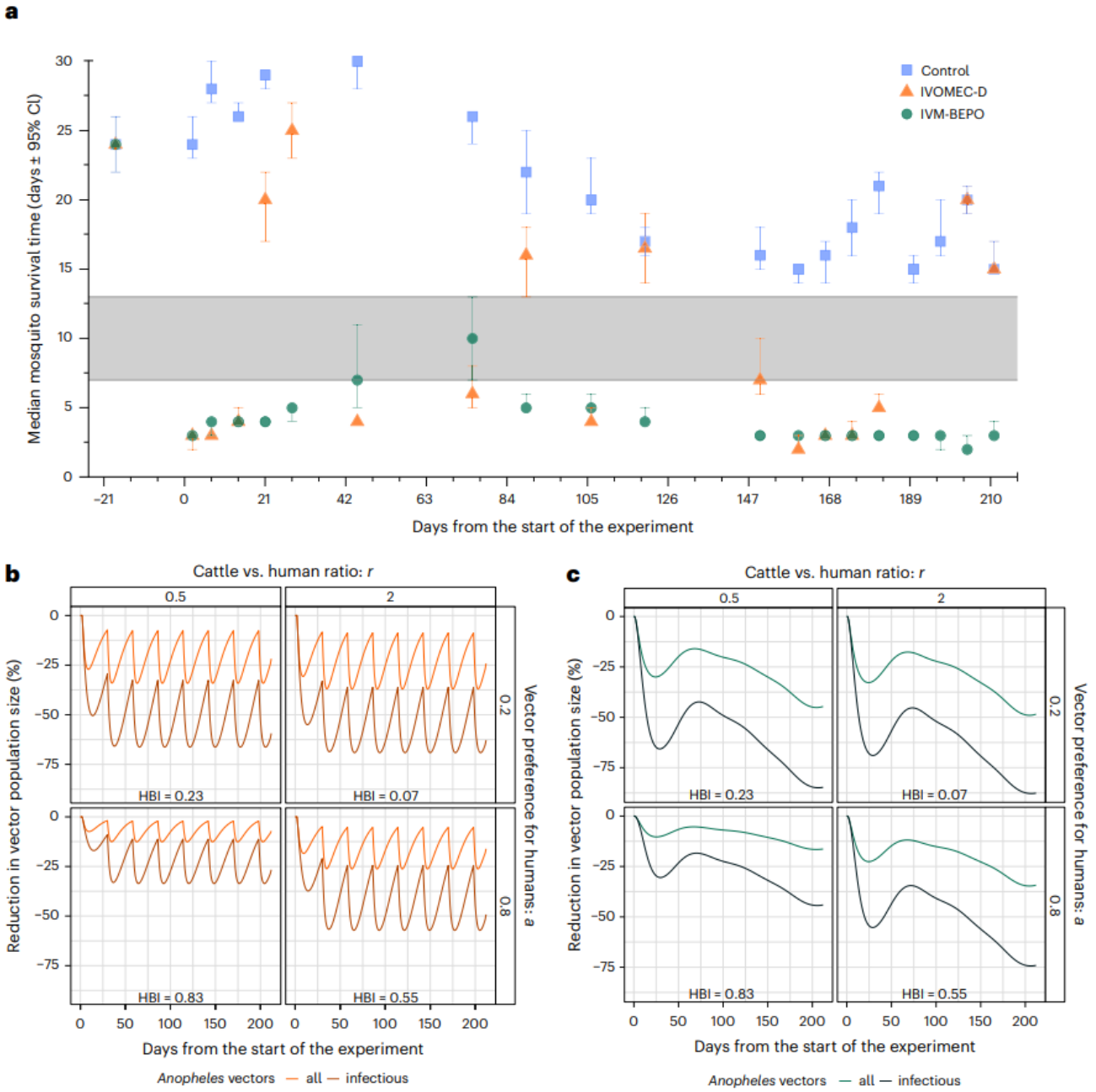


Fig. 3 | Efficacy endpoints of the ivermectin treatments measured experimentally through mosquito survival and simulated in silico using a population model. a, Median survival times ± 95% CI of mosquitoes after feeding on cattle (total n = 5,384, 4,852 and 5,400 female mosquitoes, blood-fed on control, IVOMEC-D and IVM-BEPO cattle, respectively; mean ± s.d. mosquitoes per respective sampling date: 269 ± 21.7, 269 ± 19.4, 270 ± 20.7). The shaded area represents median survival times mosquitoes should reach after feeding to become infectious. *Plasmodium* extrinsic incubation period is considered 10 days, gonotrophic cycle 3 days[29]. Survival time range encompasses two scenarios where mosquitoes feed on treated cattle 3 days before or after an infectious blood meal[27]. Because of high survival of control mosquitoes at 21 and 45 days after the experiment started, reliable upper confidence intervals could not be computed. **b**,**c**, Model prediction of IVOMEC-D (**b**; the model simulates up to 8 injections) and IVM-BEPO (**c**) formulation relative effects on mosquito field population densities after mass treatment of cattle. Treatments were simulated as in this study: 0.4 mg kg^{-1} bw monthly (**b**) or on a single dose of 2.4 mg kg^{-1} bw (**c**). Different parameters were given arbitrary values to simulate treatment efficacy in different scenarios: r = cattle versus human ratio; a = vector preference for humans as measured in choice test experiments; LLIN coverage = 0.5; HBI = calculated index representing the number of mosquitoes that have taken a blood meal on humans considering all other parameters. HBI values are for an LLIN coverage index of 0.5. Refined modelling scenarios are shown in the Supplementary Information Modelling chapter.

over 50% for at least 6 months and peaks at 95% reduction. Multiple injections with IVOMEC-D are less effective, with vector populations cyclically increasing after peaks of 5–72% reduction.

Mosquito toxicity and ecotoxicological effects

Figure 4a shows ivermectin correlation in cattle plasma and dung after one injection of the depot formulation. Calculated 10-day LC_{50} and LC_{90} for *A. coluzzii* translate to predicted ivermectin concentrations in cattle dung ranging from 138–319 ng g^{-1} dw. The mean ± s.d. excreted

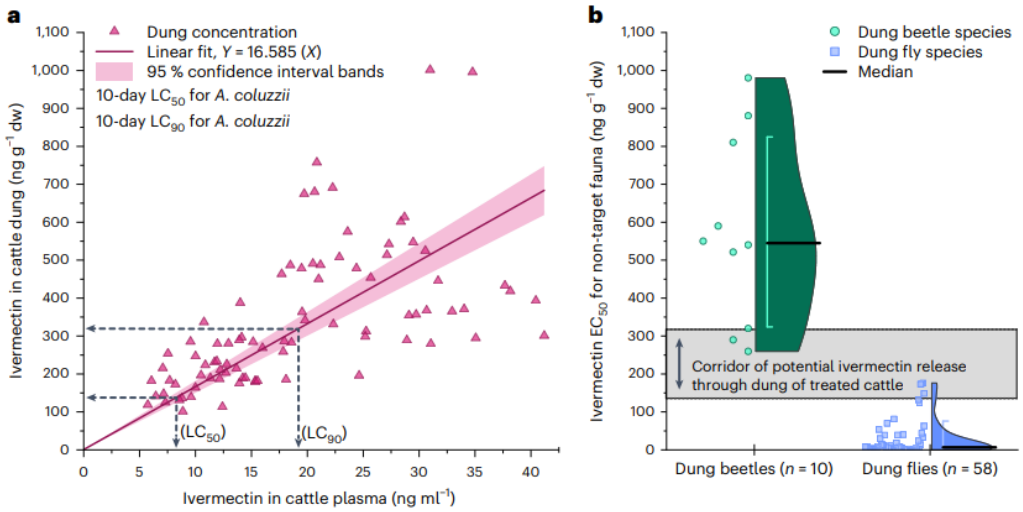


Fig. 4 | Connection of ivermectin in cattle plasma and cattle dung and impact on non-target dung fauna. a, Simple linear regression ($Y = 16.585X$) through the origin ($R^2 = 0.83$), with 95% CI bands demonstrating the correlation between ivermectin concentrations in cattle dung (ng g^{-1} dw) versus cattle plasma (ng ml^{-1}) for the long-acting IVM-BEPO formulation (data from 2–211 days after injection where both plasma and dung data are available). Dashed anchor lines indicate predicted concentrations in dung for previously determined 10-day LC_{50} and LC_{90} for *A. coluzzii*. **b**, Half-violin plots of aggregated EC_{50} data from ecotoxicological single-species testing with dung beetles (mortality and reproduction) and dung flies (mortality); *n* = number of findings from reviewed literature. The EC_{50} dataset is detailed in Supplementary Table 6 and refers to the dry weight concentration in dung. Dotted lines and the shaded area are extended from the LC_{50} and LC_{90} values in **a** and illustrate a corridor of potential ivermectin release through dung of treated cattle. Whiskers in the kernel density plot show the standard deviation around the median (black line). All dung concentration measurements and EC_{50} are reported on a dry weight basis to facilitate accurate comparisons across studies.

concentration, however, was higher at 337 ± 185 ng g^{-1} dw (*n* = 86), corresponding to a mean plasma concentration of 19.1 ± 9.2 ng ml^{-1}, regardless of time. These concentrations were descriptively compared to ecotoxicological half maximal effective concentration (EC_{50}) data from standard tests (for example, refs. [30,31]) with non-target dung beetles and flies (Fig. 4b and Supplementary Table 6). For a comparable formulation with similar release pattern under large-scale field conditions, predicted ivermectin concentrations in dung could exceed EC_{50} values for most tested dung flies. For flies and beetles, only EC_{50} data were compared, meaning that statistically, even lower concentrations could endanger a proportion of coprophagic arthropod communities[32]. Effectively, Fig. 4b serves as preliminary risk estimation for dung fauna based on laboratory data.

Environmental fate of ivermectin

Figure 5a presents the particle size distribution and organic carbon (C_{org}) content of 30 agricultural soils from three Burkina Faso villages. Since sorption studies[33] were performed with fine soil (<2 mm), boxplots display the proportion of fine soil, considering high coarse-soil contents in many samples. Individual fine-soil analysis[34] revealed mostly loams, sandy loams and silt loams in the study region. The K_D sorption coefficients for six selected soils ranged from 55–123 ml g^{-1}, averaging 84.5 ml g^{-1}. Normalized to soil C_{org}, the K_{OC} sorption coefficients varied from 6,630–10,870 ml g^{-1} (Supplementary Table 7). Sorption correlated significantly ($P < 0.05$) with C_{org} and pH value ($r = 0.86$ each) (Fig. 5b). Regarding dung storage for studying ivermectin dissipation (Fig. 5c), results were categorized into external and internal storage. Significant differences ($P < 0.01$) in ivermectin concentrations were observed in samples stored under internal laboratory conditions. Figure 5d displays mean ivermectin dissipation in internally stored samples. First-order kinetics describe the dissipation in stored dung. Including the day 0 concentration (normalized to unity), the fit through days 0, 30, 60 and 90 resulted in a degradation constant $k_1 = 0.00145$ (adj. $R^2 = 0.059$), 50% dissipation time (DT_{50}) = 478 and DT_{90} = 1,588 days. With only days 30, 60 and 90, this fit yielded $k_1 = 0.00381$ (adj. $R^2 = 0.968$), DT_{50} = 182 and DT_{90} = 604 days in dung.

Discussion

Initially, we posed three questions (Fig. 1a) to also guide future ETL endeavours:

(1) How can ivermectin-treated cattle complement malaria vector control? (2) What improvement on malaria vector control can be achieved with ivermectin-treated cattle? (3) How can we avoid ecological drawbacks in vulnerable agroecosystems?

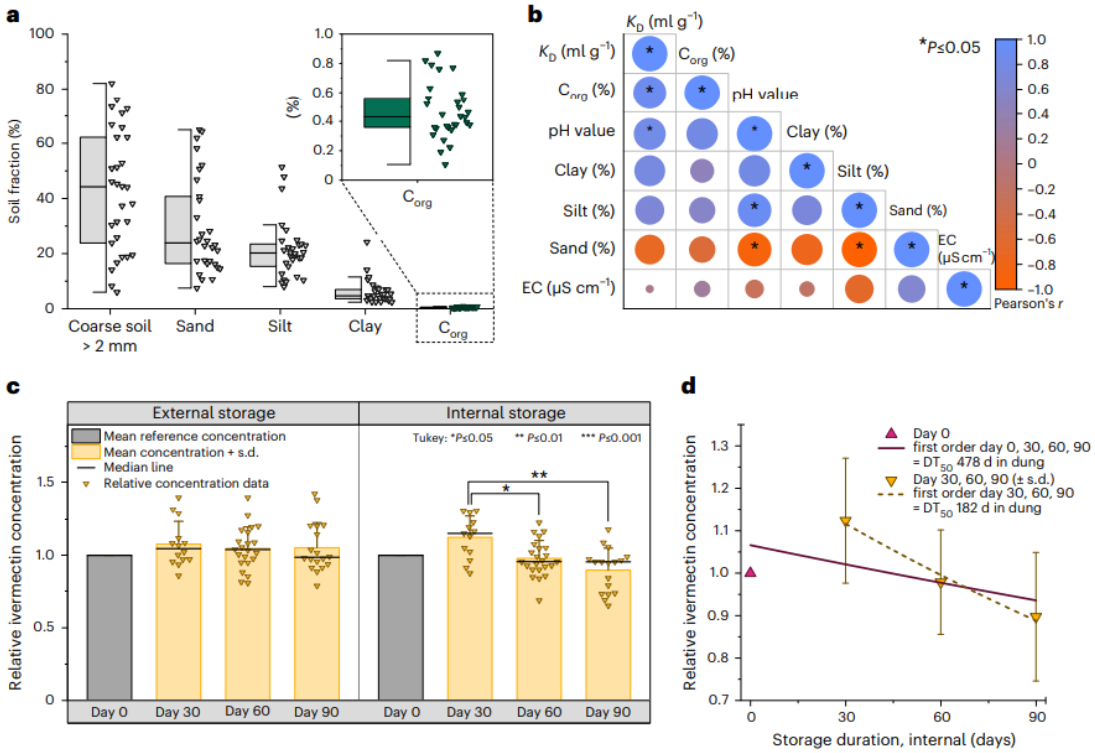


Fig. 5 | Soil properties, sorption correlation and degradation of ivermectin in stored dung samples. a, Particle size distribution and organic carbon (C_{org}) in topsoils ($n = 30$). Sand, silt, clay and C_{org} percentages are normalized to 100% to complement the coarse-soil fraction. Shown fine-soil distributions do not describe soil texture. The black line in boxes is the median, with boxes stretching from the 25th to the 75th percentile. Whiskers display the upper and lower inner fences. See Supplementary Table 12 for village-specific details. **b**, Correlation (Pearson's r) between linear K_D sorption coefficients and soil properties ($n = 6$ selected soils). Circle sizes represent absolute values of the correlation coefficient; $^*P \leq 0.05$. EC, electrical conductivity. **c**, Relative ivermectin IVM-BEPO concentrations in stored dung ($n = 13$–23) related to storage time under external (semi-field) and internal (insectary) conditions. Concentrations in stored dung are from timepoints DAI 2, 7, 75, 174 and 204 to cover the study duration. Respective day 0 concentrations are normalized to unity for comparison (two-sided Tukey pairwise mean comparison, with specific comparisons revealing: 30 days versus 60 days ($P = 0.02$), and 30 days versus 90 days ($P = 0.0002$)); storage concentrations followed a normal distribution ($P < 0.05$). **d**, Modelled dissipation in stored dung (internal conditions) following simple first-order kinetics, with x axis from −3 to 93 and y axis abridged. DT_{50} and DT_{90} show the predicted time (days) for 50% and 90%, respectively, of the initial ivermectin concentration to dissipate. Day 0 concentration normalized to unity. Days 30, 60 and 90 show mean ± s.d. of $n = 13$, 23 and 17 stored dung samples, respectively.

Efficacy of a single-depot injection versus repeated injections

Considering our proof-of-concept[26], we adjusted the ivermectin formulation and statistical design. The long-acting formulation sustains ivermectin release over at least 6 months. Although the release pattern and dose need adjustment to refine the release period, the potential long-term efficacy meets WHO criteria for malaria transmission control with endectocides[35]. The slow release of ivermectin from the subcutaneous depot leads to a rate of absorption in blood lower than the rate of elimination from the body. The lipophilicity of ivermectin causes high volumes of distribution in animals and accumulation in target tissues, acting as secondary drug reservoir[21]. Hence, concentrations of ivermectin and metabolites in subcutaneous fat tissue may remain high in IVM-BEPO-treated cattle, enhancing effectiveness.

The zoophagic proportion in mosquito populations, relevant for residual *Plasmodium* transmission[11], can increase with widespread LLIN use[36]. In southwestern Burkina Faso, populations of the major vector *A. coluzzii* show opportunistic blood-feeding behaviour, with over 50% feeding on alternative animal hosts, while their innate feeding preference remains toward humans[36]. Our approach with ivermectin-treated cattle addresses these zoophagic vector compartments of malaria transmission, which are not yet considered in conventional anthropocentric malaria control programmes[35]. The long-acting ivermectin formulation mitigates logistical and cost challenges of repeated injections, offering a stronger barrier against malaria transmission by preventing vector population resurgence between treatments. While zooprophylaxis against malaria is a complex concept, leaning towards zoopotentiation depending on transmission context[37], our approach capitalizes on existing cattle, rendering their blood toxic to opportunistic and zoophagic mosquitoes while improving cattle health and milk production[20].

ETL impact on vector populations could be greater than modelled since ivermectin is also toxic to traits influencing fitness other than survival[38]. Moreover, opportunistic vectors failing to feed on net-protected humans and seeking alternative hosts are not addressed in our model. Overall, effectiveness depends on the human blood index (HBI), indicating the proportion of mosquito populations feeding on humans. Blood feeding tendencies should therefore be characterized before ETL field deployment, especially since livestock other than cattle could represent alternative hosts. Effectiveness also relies on local livestock density and the treated herd fraction.

Moreover, ETL evaluation should consider veterinary benefits through parasite control and incorporate realistic animal populations into models, including gestating and lactating females, and animals for consumption (meat and milk[39]). Following Joint FAO/WHO Expert Committee on Food Additives[40] guidelines and involving animal owners is essential.

Ecotoxicological considerations

Ivermectin's capacity to control vectors holds promise for mitigating malaria and improving animal health and productivity[15,18]. However, vigilance is required concerning potential environmental consequences. Comprehensive research spanning over 30 years has consistently flagged non-target effects of ivermectin and other avermectins on dung and soil biota[22,23,24,25,41].

In a preliminary assessment via literature review, plasma concentrations lethal to 50–90% of mosquitoes (Fig. 4) could produce excreted ivermectin levels harmful to most dung insects. However, it is important to recognize limitations of laboratory data and seek validation in field scenarios. Notably, a landscape-field study[25] confirmed ivermectin effects on non-target fauna and emphasized the importance of spatio-temporal realism in environmental assessments. For the related endectocide eprinomectin, cattle treated with a long-acting injectable formulation excreted residues for over 25 weeks, suppressing dung-breeding insects and reducing insect diversity[28]. While much current literature centres on temperate and Mediterranean species, a clear knowledge gap persists concerning West Africa, and few studies assess impacts on (sub-)tropical entomofauna, indicating an urgent research objective.

The use of veterinary ivermectin reportedly carries adverse implications for dung fauna biodiversity and ecosystem functioning[42,43,44]. Given these potential ecotoxicological impacts, the precautionary principle becomes a guiding factor to proactively address and mitigate risks to biodiversity and ecosystem health in West African agroecosystems. This is especially imperative considering the scarcity of research on the ecological impacts of long-acting injectable ivermectin formulations.

Environmental fate of ivermectin and exposure assessment

Our K_D and K_{OC} soil sorption coefficients, the first for Burkina Faso, align with previous reports[22,45]. Strong, mostly irreversible ivermectin sorption[45], emphasizes reduced mobility and availability. However, sorption tests are conducted with fine soil[33], potentially overestimating sorption in tropical soils with abundant coarse soil and limited surface area.

Ivermectin is moderately persistent, and dissipation in soil and manure increases under warm, aerobic and humid conditions[46,47]. In soils, comparable models projected DT_{50} of 16–67 days at 20 °C and 89–105 days at 6 °C (ref. [47]) and from 10–16 days[48]. In soil–manure mixtures, DT_{50} ranges from 7–240 days[47]. These authors concluded that sorption influences dissipation and even under aerobic conditions, ivermectin dissipation in soils is relatively slow[47]. Our dissipation results in cattle dung indicate persistence under these conditions. Storage during dry seasons may lead to reduced dissipation and could preserve ivermectin until the next cultivation period when dung is utilized as fertilizer. Increasing ivermectin concentrations in dung after 30 days (Fig. 5c) presumably show relative enrichments because readily degradable organic matter decomposes while ivermectin remains. In soils, ivermectin dissipation fluctuates with climatic conditions[46,47,48], and its behaviour under sub-Saharan climates remains ambiguous. In West African soils, weaker sorption and higher temperatures might accelerate dissipation. However, data on ivermectin's environmental fate under ETL scenarios, especially within soil–dung mixtures during seasonal rainfall, are lacking. Consequently, managing ivermectin residues should also account for climatic conditions, encompassing Sahelian, Sudanian and Guinean zones.

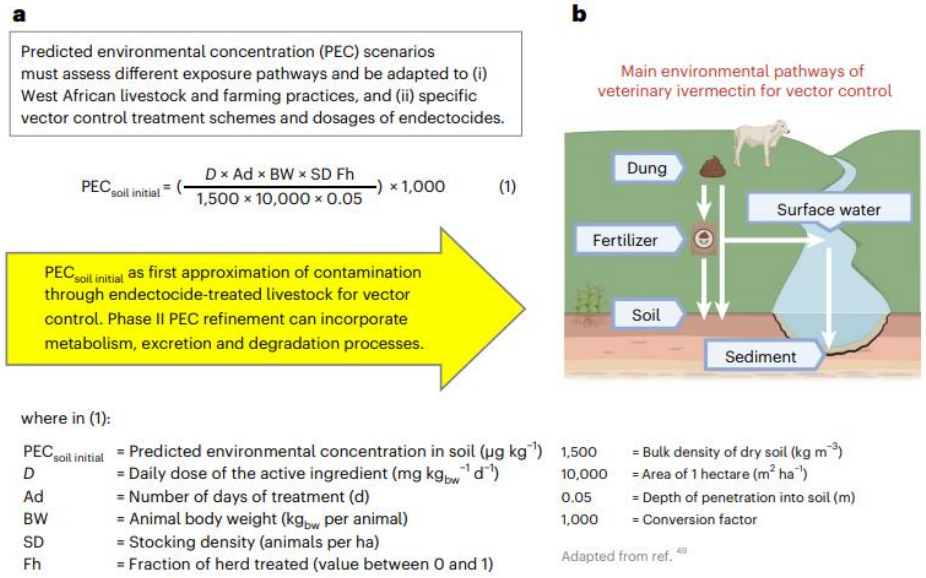


Fig. 6 | Exposure assessment as the initial step of environmental risk assessment for endectocide-based approaches to control opportunistic and zoophagic malaria vectors. a, Equation (1) for $PEC_{soil\ initial}$ is based on ref. 49. Exemplary parameters for a 211-day pasture scenario: $D = 0.0019$, Ad = 211, BW = 160, SD = 9.5, Fh = 1. Phase I screens products and includes initial PEC estimations, while Phase II conducts detailed assessments using refined data, field studies and modelling. Fh, the treated herd fraction, is notably relevant for refugia[51] incorporation to manage resistance in vectors and parasites. **b**, Exposure assessment of endectocides used for vector control, such as ivermectin, must consider various pathways, including direct excretion or dung use as fertilizer for potential drug residue transfer into agricultural soils. Soil contamination is also conceivable on adjacent unmanaged soils. Contamination of surface water and sediment can occur through run-off, erosion or direct excretion, potentially exposing aquatic fauna and larval vectors to ivermectin. Figure 6b was created with BioRender.com.

In the European Union, environmental risk assessment during veterinary pharmaceutical registration involves estimating a predicted environmental concentration (PEC)[32,49]. This process utilizes a toolbox spanning Phase I and Phase II assessments. An initial step in ecotoxicological oversight of ETL should establish PECs in dung, soils, dung–soil mixtures, surface waters and sediments (Fig. 6). Here, dung fauna exposure was estimated using measured ivermectin concentrations in dung (Fig. 4b).

To transfer exposure from dung to soil, an exemplary $PEC_{soil\ initial}$ was calculated at 4.86 μg kg^{-1} for the long-acting formulation dosed at 2.4 mg kg^{-1}. This compares to reported PECs for pasture grazing[22]. However, estimating and refining soil PECs varies with livestock treatment and data availability[22,49], making assessments challenging without defined treatment scenarios. The longer release of long-acting formulations is especially critical. Since dung is a valuable agricultural resource in many malaria endemic zones where breeding and agricultural practices are integrated, responsible dung management remains imperative.

Environmental risk mitigation

Ecotoxicological guidance for ivermectin-based vector control should encompass exposure assessment, effect assessment, risk assessment and risk mitigation measures (RMMs). Integrating these tools with vector control measures can yield synergies and improve cost effectiveness. Should ivermectin contaminate puddles or surface waters, minor degradation is anticipated, but more likely rapid dissipation and sorption into the sediment[22,45]. Ivermectin degradation through photolysis[22] in dung patties or soils is limited to upper layers. In our external storage experiment, samples were shielded from sunlight (Extended Data Fig. 1c). However, given common agricultural practices of incorporating dung into soils, substantial sunlight exposure for excreted drugs is unlikely.

For veterinary pharmaceuticals, RMMs to reduce environmental risks for non-target fauna are already conceptualized[32,50]. Importantly, RMMs synergize with measures to reduce resistance in livestock parasites and facilitate sustainable parasite control. Reducing ivermectin distribution with RMMs also limits contact for adult and larval vectors, mitigating resistance selection pressure. Modifying previous recommendations[50], RMMs for ETL

should respect local conditions and could be guided by these principles:

(1) Prevent drug entry into surface waters.

(2) Corral treated animals whenever possible.

(3) Leave fractions of the herd periodically untreated to create refugia[51]. This allows safe consumption (meat and milk) and reduces resistance pressure and non-target fauna risks.

(4) Implement measures of animal performance and routine diagnostics for early detection of ivermectin-resistant parasites, aligning livestock health and vector control goals while minimizing drug use and environmental exposure.

(5) Capitalize on existing agro-pastoral systems of dung collection and store dung under conditions that promote drug degradation.

(6) Avoid repeated application of dung with drug residues as fertilizer if long-term effects on non-target fauna are unknown.

In our study region of Burkina Faso, manure storage pits called 'fosses fumières' are common (Extended Data Fig. 1a). Pits are excavated near settlements and filled with dung, crop residues and kitchen waste during dry seasons. They are later emptied and the mixture is spread as fertilizer in the following cultivation period. We encourage exploring composting conditions in these pits for potential ivermectin degradation. However, ivermectin residues and their associated toxicity may not completely dissipate during storage[52]. Adapting RMMs designed for temperate climates and pasture scenarios while respecting agricultural practices in West Africa remains fundamental. This also requires training opportunities for herders and veterinarians.

Side effects on plants

Regarding potential effects of ivermectin on crops, limited research exploring phytotoxicity is available for real-world environments. Some reports[24,53] considered that via livestock, ivermectin may affect plants. Since this concern is mostly undiscussed for West Africa, caution is appropriate. For Burkina Faso, potential effects on local varieties of corn, sorghum, cotton or millet (Extended Data Fig. 2b) should be investigated under field scenarios with tropical soils.

Potential ivermectin-induced mosquito resistance

Human and animal intakes can alter volatile plume signatures, influencing *Anopheles* vector host recognition[54]. With ETL, changed animal odour may affect host attractiveness or repellency, raising ethical concerns about redirecting opportunistic mosquitoes toward humans. Although ETL targets adult female mosquitoes, resistance to lethal ivermectin concentrations in populations may develop through selection pressures. These arise from adult females ingesting ivermectin during blood feeding and larvae exposure to ivermectin-contaminated dung in surface waters. Large-scale ETL deployments should also incorporate phenotypic diagnostic tools for on-field mosquito resistance monitoring[55].

Notably, our approach inherently incorporates refugia: not treating entire herds creates a refuge for susceptible parasites, aligning with known strategies for mitigating anthelmintic resistance[51]. This fortifies the efficacy and sustainability of ETL solutions.

Towards sustainability in vector control

The One Health Joint Plan of Action (2022–2026) by FAO, UNEP, WHO and WOAH consolidates that 'health of the environment is a critical foundation for the health and well-being of humans, animals and plants'[4]. Aligned with a modern, non-anthropocentric view of human health, this emphasizes the need for ecological equity[56]. Therefore, vector control approaches based on endectocides must equally consider socio-economic realities, as well as human, animal and environmental health dimensions.

Ecotoxicological guidance addresses environmental impacts of ETL and underscores the importance of biodiversity, soil health and sustainable resource management. Integrating traditional organic waste management (for example, fosses fumières) with scientific advancements could optimize composting and drug degradation. This engages communities and strengthens nutrient cycles and soil resilience against erosion and climate change. Protecting non-target fauna and enhancing soil carbon balances can mitigate risks to biodiversity and ecosystem services. Echoing Rachel Carson's sentiments in 'Silent Spring' on health risks of insecticides, '…prevention is the imperative need'[1] is a notion equally applicable to environmental health.

We demonstrate that long-acting ivermectin formulations for cattle can transform malaria vector control. This strategy meets WHO efficacy criteria, remarkably improves animal health and potentially extends control over other arthropod-borne zoonotic diseases.

Our unique multidisciplinary approach, embedding comprehensive modelling, an innovative formulation and ecotoxicological insights promises a new aspect of sustainable vector control. Before widespread implementation, potential ecotoxicological risks associated with ivermectin residues in dung demand careful consideration. We recommend: (1) studying ivermectin degradation in manure pits; (2) characterizing the entomofauna of West African agroecosystems; and (3) initiating ecotoxicological routines in West Africa to identify potential ecological consequences.

In addition, we propose actionable, bottom-up and region-specific risk mitigation strategies. If endectocide-treated cattle become routine in vector control, interdisciplinary research, generational knowledge and ecotoxicological insights must converge to create locally adapted, environmentally mindful solutions. Bridging the research–policy gap is essential to establishing necessary regulatory frameworks to translate research into sustainable action.

Methods

Layout of the study design

We randomly assigned 24 male cattle into three study arms: 8 were treated with monthly injections of a commercial IVOMEC-D ivermectin formulation, 8 received the long-acting IVM-BEPO ivermectin formulation and 8 had no ivermectin treatment (control). An animal from each arm was put aside as spare animal (data from 7 cattle per arm were then further collected). Doses were based on cattle body weight (bw) on injection day: 0.4 mg kg^{-1} bw for monthly IVOMEC-D injections and 2.4 mg kg^{-1} bw for a single IVM-BEPO injection at study start. These doses were doubled on the basis of our previous data[26,27] to increase efficacy and remanence. Injections were administered by veterinary technicians. Study duration was 34 weeks (Fig. 1). We sampled cattle blood plasma and dung to determine ivermectin pharmacokinetics and performed skin-feeding assays on cattle to assess mosquito mortality as a proxy for formulation efficacy. Selected dung samples were stored to determine ivermectin degradation. Soils from southwestern Burkina Faso were sampled to assess ivermectin sorption.

Ivermectin formulations, dosage and injections

The long-acting injectable formulation was built on BEPO technology[57], an injectable in situ-forming depot technology based on biodegradable copolymers. Following subcutaneous injection, the block copolymers precipitate upon contact with body fluids, thereby entrapping the therapeutic molecule within the formed polymeric solid matrix (the depot). The depot progressively bioresorbs while delivering the active pharmaceutical ingredient with the desired pharmacokinetics. The same technology has been used to assess the macro- and microfilaricidal efficacy of a 12-month ivermectin formulation prototype against *Onchocerca ochengi* and as a proof-of-concept, tested against *A. coluzzii*[27].

The IVM-BEPO formulation was selected from a preliminary study[27] and composed of 45% (w/w) copolymer comprising a tri-block PLA_{97}-PEG_{45}-PLA_{97} and a di-block $mPEG_{45}$-PLA_{130}, 5% (w/w) ivermectin and 50% (w/w) dimethyl sulfoxide (DMSO). The formulation was designed to release ivermectin for at least 6 months. Before preparation, the tri- and di-block copolymers of the formulation were preliminarily dissolved overnight in DMSO (Procipient, Gaylord Chemical) at room temperature and under continuous stirring. Then, ivermectin (Fagron) was added to the polymer solution until complete dissolution. The formulation was sterile filtered using 0.2 µm filters (Minisart SRP 15, Sartorius) and then administered to cattle according to their bw (2.4 mg of ivermectin kg^{-1} bw, that is, 48 mg of formulation kg^{-1} bw) with a hypodermic syringe capped with a 16-gauge needle. Volumes were adjusted to the weight each cattle was expected to reach 3 months after the injection (mid experimental time) to consider potential dilution of the product due to animal growth. Expected weight gains were calculated from weighing performed before treatments in January and April 2019 (Supplementary Table 8). A 25% increase in 3 months was estimated for cattle below 130 kg, 15% for cattle weighing 130–170 kg and 10% for the heaviest cattle (>170 kg). Weights and corresponding volumes of the long-acting formulation injected per cattle and per treatment were calculated accordingly (Supplementary Table 9). The long-acting formulation was imported into Burkina Faso under clearance provided by the 'Direction Générale des Services Vétérinaires' of Burkina Faso (Visa from the 'Direction de la

Santé Publique Vétérinaire et de la Législation' issued 11 January 2019).

The IVOMEC-D injectable veterinary formulation was used at a dose of 0.4 mg kg^{-1} bw and injected each month subcutaneously (Fig. 1b) using a hypodermic syringe capped with an 18-gauge needle. Cattle were weighed before each treatment to adjust injection volumes (Supplementary Table 10). Remaining cattle from the experiment were weighed each month as well. Weight gain of all cattle was examined to ensure their well-being and to identify potential treatment effects (generalized linear modelling; Supplementary Fig. 3). For both formulations, the ivermectin dose was selected on the basis of experiences from our previous studies[26,27].

Ethics oversight

The study received approval from the CIRDES ethics committee under letter no. 15/CE-CIRDES/16-10-2018.

Cattle care, blood and dung sampling

All cattle were crossbred Soudaneese Fulani Zebu × Baoulé Taurine and were kept at the Centre International de Recherche-Développement sur l'Elevage en zone Subhumide (CIRDES) in Bobo-Dioulasso, Burkina Faso. One month before the experiment started, animals were moved into a net-protected stable and received a veterinary examination and prophylactic treatment with diminazene aceturate (Berenil2000, 3.5 mg kg^{-1} bw) against trypanosomiasis and albendazole (one bolus Benzal 2,500 mg per animal) against gastrointestinal parasites. The latter was chosen over ivermectin to avoid cross-contamination in later sampling. At the beginning of the study, mean cattle age was 3 years and mean weight was 122 kg (cattle were weighed monthly). Stable openings were closed by fine-meshed filtering tissue to protect cattle from insects and outside animals. Cattle were checked daily by cowherds for signs of parasite infestation or disease symptoms and before each mosquito blood-feeding experiment by veterinary engineers (engineers checked for clinical signs of aphthae, cough, nasal discharge, slime, anaemia, recumbent position, anorexia, diarrhoea, fever, scabies). There was no incidence of any symptoms during the whole experiment. Unfortunately, an animal from the IVM-BEPO group died following an accident with a stable box barrier that fell on its head at night. This happened 3 months after treatment. The animal was replaced by the spared animal from the same treatment.

According to local recommendations[59], cattle were fed twice daily with rice straw and cotton cake (5 kg and 1 kg in total per animal, respectively). Water and a mineral complement block were offered ad libitum. Blood samples were collected from the jugular vein with 5 ml heparin tubes at the timepoints given in Fig. 1b. Plasma was immediately collected after sample centrifugation at 1,500 *g* for 15 min, and stored at −20 °C until further processing. Dung samples were collected directly from the cattle rectum or on freshly deposited dung synchronously with plasma. We constituted samples (30 g each) for ivermectin dosage on fresh dung and on dung after storage. For IVM-BEPO dung samples, fresh dung was distributed in plastic vials in two groups and according to the intended storage duration (30, 60 or 90 days). One group was inside the insectary (to mimic steady, fresh and humid conditions) and the other outdoors (exposed to dry season conditions). Plastic vials were covered with a piece of bed net (Extended Data Fig. 1c). Environmental conditions in the insectary were measured daily and were 26 ± 2 °C and 75 ± 5% relative humidity. For external storage, daily and nightly temperatures during the respective storage periods are given in Supplementary Table 11 (from ref. [60]). Mean outdoor temperatures ranged from 32.1–39.6 °C during the day and from 17.9–22.8 °C at night. After fresh sampling or storage, dung samples were kept at −20 °C for a minimum of 24 h, freeze dried for 24 h, ground for 15 min using a mortar and pestle, disposed into labelled plastic bags and stored at −20 °C before chemical analysis.

Mosquito protocol

An *A. coluzzii* mosquito colony was established between February and March 2019 in the insectary of CIRDES in collaboration with the Institut de Recherche en Sciences de la Santé. Wild blood-fed females were collected in dwellings of the Kou Valley, 50 km northwest of Bobo-Dioulasso in southwestern Burkina Faso. Mosquito breeding and direct skin-feeding assays on cattle (Extended Data Fig. 2a,b) followed a previously reported procedure[26], except that mosquitoes received a 10% glucose feeding solution instead of 5%. Exposure took place in 20 instances, including one pre-treatment to test for potential cattle confounding effects on mosquito survival (Fig. 1b). All 24 cattle were included in this pre-treatment study. Overall survival was assessed in 15,637 fully engorged females that were followed from days 1–30 post feeding. The targeted number of females per cattle and time point was 40, distributed in lots of 10 in 4 white cardboard cages (V = 200 cm^3) covered with an untreated mosquito net fixed using a rubber band. Each day, the number of dead females was counted and surviving females at the end of the experiment were also counted. Mosquito survival

analysis data, sample sizes and the R code are available on GitHub at

https://github.com/angeliqueporciani/ANIVERMATE.

Soil sampling and characterization

Soil samples were taken in Tuy Province, southwestern Burkina Faso, in the villages of Sébédougou, Waly and Kari (Extended Data Fig. 2a). We aimed to sample a representative variety of Burkinabé arable soils under comparable climatic conditions. At each village, we sampled ten fields currently used for regional crops. On each field, five disturbed soil samples were taken with an auger at 0–15 cm depth and mixed for a composite sample. Soil properties were derived from field notes and harmonized into WRB soil classification[61]. Laboratory analyses were performed for soil pH value (0.01 M $CaCl_2$), electrical conductivity, coarse-soil fraction, particle size distribution and C:N ratio. Carbonate content was estimated following the semi-quantitative preparation step of EN ISO 10693:2014, which indicated no inorganic carbon present. Thus, C_{total} from C:N measurements with a UNICUBE trace CN elemental analyser was used as a substitute for organic carbon (C_{org}). A complete characterization of sampled locations and soils is given in Supplementary Tables 12 and 13. Furthermore, six soil profiles were described in the sampled locations and brief descriptions are provided in Supplementary Figs. 4–9. Soil samples were transported under clearance provided by the RP Gießen, Pflanzenschutzdienst, Germany (issued 26 September 2019) and the Direction de la protection des végétaux et du contrôle des végétaux alimentaires et des Pesticides, Burkina Faso (issued 5 November 2019).

Environmental studies

To address the environmental fate of ivermectin after excretion, we conducted soil sorption studies and monitored ivermectin degradation in stored dung samples over 90 days. Sorption experiments and derivation of linear distribution coefficients K_D and K_{OC} were based on ref. [33] and published methods[45,46]. Correlation (Pearson's r) between linear K_D sorption coefficients and soil properties was described with the OriginPro 2022 application Correlation Plot (v.1.31). Storage of dung samples was conducted in Burkina Faso under external, semi-field conditions and internal, laboratory storage (see above). These samples were eventually analysed for ivermectin after 30, 60 and 90 days of storage, and concentrations were compared (two-sided Tukey pairwise mean comparison, in OriginPro, v.2022 (64 bit)) to each other and their respective day-zero concentration. Concentrations in stored dung were normally distributed (Shapiro–Wilk, $\alpha = 0.05$, all $P > 0.05$). Next, we applied simple first-order kinetics to approximate future ivermectin concentration changes in stored dung, using the results from the internal storage experiment. Underlying methods are elaborated upon in ref. [47]. The resulting degradation constant, or rate constant, k_1, was used to estimate ivermectin dissipation over time. The time to reach 50% of the initial concentration is expressed as $DT_{50} = \ln 2/k_1$, while the corresponding DT_{90} equals $\ln 10/k_1$ (ref. [47]). OriginPro v.2022 (64 bit) was used to create Figs. 2a–c, 3a, 4a–b and 5a–d.

Chemical ivermectin analysis

Extraction and quantification of ivermectin were based on existing techniques[46,62] and harmonized for plasma and dung samples in this study. For quantitative determination, we used high-performance liquid chromatography (HPLC) with fluorescence detection after derivatization. The complete protocols are listed in Supplementary Table 15 and the accompanying supplemental text. In essence, samples (thawed plasma, freeze-dried dung) were fortified with an internal surrogate standard (doramectin) and extracted with acetonitrile. After ultrasound-assisted extraction and then centrifugation at 3,865*g*, an aliquot of each supernatant was evaporated, reconstituted in acetonitrile and filtered. For HPLC fluorescence detection, ivermectin was derivatized with *N*-methylimidazole/acetonitrile (1:1 v/v), triethylamine, trifluoroacetic anhydride/acetonitrile (1:1 v/v) and trifluoroacetic acid according to reported procedure[46]. Samples were quantified on an Agilent 1200 HPLC system with gradient elution (acetonitrile and purified water) on a reverse-phase, C18 column. Fluorescence detector wavelengths were 364 nm for excitation and 463 nm for emission. Extraction recoveries (mean ± s.d.) of the surrogate doramectin were 106.5 ± 21% in plasma and 103.2 ± 19.7% in dung samples. Each plasma or dung sample was divided into two technical replicates that were extracted and measured individually. Analytical limits of detection (LOD) and quantification (LOQ) were calculated as described in ref. [45]: LOD = 1.47 ng ml^{-1} in plasma, 5.05 ng g^{-1} dw in dung; LOQ = 4.47 ng ml^{-1} in plasma and 15.31 ng g^{-1} dw in dung. Measured concentrations <LOQ were replaced with half the LOQ for further calculations. Data analysis was performed with ChemStation for LC 3D systems Rev. B.04.01 [481] and Microsoft Excel for Office 365.

Statistical analysis, mosquito survival and modelling

All statistical analyses and modelling were performed using R v.4.0.1 (18 May 2021, platform x86_64-apple-darwin17.0 (64 bit), ref. [63]). The data and the R code are available in the referred repository, and the general methodology is described in the Supplementary Information Modelling chapter.

Pharmacokinetic parameters for plasma and dung concentration (maximum concentration (C_{max}; peak plasma level), time to reach maximum concentration (T_{max}), apparent elimination half-life (half-life; time for plasma concentration to be reduced by 50%), and area under the curve (AUC; total drug exposure over time)) were estimated with noncompartmental analysis using the package PKNCA (v.0.9.5, ref. [64]). For the commercial formulation, parameters were estimated using data from the first 28 days, whereas for the long-acting formulation, data until 211 days after injection were used.

Our study was designed to detect hazard ratios from 1.5 and upwards, with a power of 0.9 and a type I error rate of 0.05. The sample size needed to detect this size effect was 171 individuals, which we obtained by exposing at least 40 mosquitoes on each of the 7 cattle of each arm (at least 280 mosquitoes per arm). In comparison, a sample size of 16 mosquitoes is needed to detect a hazard ratio of 4, which meets WHO criteria[35] (hazard ratio ≥ 4) of endectocide products for malaria transmission control.

Kaplan–Meier survival curves and a Cox proportional hazards mixed model with cattle as a random effect were used to investigate mosquito survival differences between cattle clustered by experimental arm. Median survival times with 95% confidence intervals (CI) were plotted. Hazard ratios with associated *P* values were estimated before treatment and at each time point where mosquitoes were exposed for direct skin-feeding assays during the treatment efficacy follow-up (Supplementary Table 4).

We further explored the efficacy of the two formulations by considering the probability that a mosquito ingesting a blood meal containing ivermectin dies before becoming infected with *P. falciparum* sporozoites. The dose effect of ivermectin concentration on mosquito survival probability until a given day post ingestion of blood from treated animals (7, 10 or 13 days) was assessed using a multivariate log-logistic regression model with four input parameters. The lethal ivermectin concentrations inducing 7, 10 and 13-day cumulative LC_{50} and LC_{90} mosquito mortalities were estimated for each scenario and each treatment (Supplementary Table 5).

A modelling approach was developed to predict, in the field, the efficiency of ivermectin formulations in decreasing vector populations that transmit *P. falciparum*, with emphasis on ivermectin efficiency against infectious vectors. Efficiency was predicted under different field contexts relative to the proportion of cattle in a human–cattle host population, the long-lasting insecticide-impregnated net usage by human hosts (LLIN use proportion) and the intrinsic vector feeding preference (as measured experimentally using a dual-choice olfactometer). Four mathematical models were combined: (1) a generalized additive model and a one-compartment pharmacokinetic model describing the ivermectin cattle plasma concentration dynamics; (2) a Cox proportional hazards model to describe how this dynamic impacts mosquito survival; (3) a deterministic mosquito *P. falciparum* transmission model (the susceptible-exposed-infectious malaria transmission model from ref. [65]), modified to take into account 2 host species (cattle and human) and 2 vector control interventions (the use of LLINs to protect humans and the injection of ivermectin formulations into cattle hosts); and (4) a vector behaviour model to take into account the mosquito intrinsic feeding preference and the probability of dying when encountering an LLIN. These models were all fed using parameters from the present study and parameters taken from the literature. The model descriptions, equations and parameters with the corresponding values used to feed the models are given and detailed in the Supplementary Information Modelling chapter.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The data and methods supporting the article are available in the Supplementary Information. All data are also available upon reasonable request. Relevant raw data for Figs. 2–5 are listed in Excel files and provided as source data files. References for EC_{50} data from ecotoxicological standard tests (Fig. 4b) are provided in Supplementary Table 6. Outdoor temperature data were sourced online from NASA LP DAAC (MYD11A1 MODIS/Aqua Land Surface Temperature/Emissivity Daily L3 Global 1 km SIN Grid V006). Statistical analyses and modeling for Fig. 3 were performed using R v.4.0.1. Data (incl. mosquito survival analysis data and sample sizes) are available

in the ANIVERMATE repository on GitHub at https://github.com/angeliqueporciani/ANIVERMATE, and additional methodology is described in the Supplementary Information. Source data are provided with this paper.

Code availability

The relevant R codes are available via GitHub at https://github.com/angeliqueporciani/ANIVERMATE.

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A.P.H., S.H.P., C.R., M.-S.M., A.-L.C., R.K.D., J.R., R.-A.D. and K.M. conceptualized the study and experiments. A.P.H., S.H.P., A.P., C.R., A.-L.C., N.M., R.K.D., R.-A.D. and K.M. developed the methodology. A.P.H., S.H.P., L.Z., A.S. and M.-S.M. were involved in the investigation. A.P.H., S.H.P., A.P., A.S. and N.M. conducted formal analysis. A.P. and N.M. managed the software. A.P.H., S.H.P., A.P. and L.Z. curated data. C.R., A.-L.C., R.K.D., R.-A.D. and K.M. provided resources. A.P.H., A.P. and K.M. performed visualization. A.P.H., S.H.P., A.P. and J.R. performed validation. R.K.D., R.-A.D. and K.M. administered the project. R.-A.D. and K.M. jointly supervised and conceived the project and acquired the funding. A.P.H. and K.M. wrote the original draft. All authors wrote, reviewed and edited the paper.

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Ethics declarations

Competing interests

The patent related to the long-acting depot formulation used in this study has the number WO2012/090070 and belongs to Medincell S.A., Jacou, France. C.R. is still an employee and shareholder of Medincell S.A. M.-S.M. and A.-L.C. are former employees and still shareholders of Medincell S.A. All authors and contributors currently or formerly employed at Medincell S.A. did not influence or contribute to sample collection, data collection, sample analysis, data analysis, evaluation, risk assessment, decision to publish, or conclusions presented in this paper. The other authors declare no competing interests.

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Extended data

Extended Data Fig. 1

a, Photographed example of a fosse fumière (a manure pit) in Burkina Faso containing cattle dung. The fosse fumière is generally dug in the field near a homestead. The dimensions are approximately 3 m on each side and 1.2 m depth. It is filled mainly during the dry season with animal dung, crop residues, and other kitchen waste. The pit is emptied before the beginning of the cultivation period to spread the dung-mixture on fields. **b**, Arrangement for keeping cattle during the mosquito blood meal (skin-feeding assay). The mosquitoes are contained in small plastic bowls attached to the animal flank. **c**, Outdoor storage of cattle dung samples. The dung was kept in plastic bottles covered with mosquito net fabric and placed in a shaded area outside the stable. **a–c**, Photo credit: Hermann Sié Pooda. Panel (b) shows Saïdou Boly, who gave formal consent for his image to be published.

Extended Data Fig. 2

a, The Centre International de Recherche-Développement sur l'Elevage en zone Subhumide (CIRDES) and Institut de Recherche en Sciences de la Santé (IRSS) are located in Bobo-Dioulasso. Soil samples were taken east of Bobo-Dioulasso in three villages in the region of Koumbia. The experimental mosquito colony was established from wild mosquitoes caught northwest of Bobo-Dioulasso in dwellings of the Kou Valley. **b**, Top commodities production in Burkina Faso in 2021, modified plot after FAO raw data (n.e.c. = not elsewhere classified).

Source data

Source Data Fig. 2

Ivermectin concentrations in plasma and dung of treated cattle. Arithmetic mean ± s.d. for both formulations in plasma and dung over 28 d. Continuation of IVM-BEPO arithmetic mean ± s.d. ivermectin concentrations over 211 d in cattle plasma and dung.

Source Data Fig. 3

Median survival times ± 95% CI of mosquitoes after feeding on cattle. Sample sizes of mosquitoes in the blood-feeding assays.

Source Data Fig. 4

Ivermectin concentrations in cattle dung versus cattle plasma for the long-acting IVM-BEPO formulation (data from 2–211 days after injection where both plasma and dung data are available). EC_{50} data from ecotoxicological single-species testing with dung beetles (mortality and reproduction) and dung flies (mortality).

Source Data Fig. 5

Particle size distribution and organic carbon (C_{org}) in topsoils. Linear sorption coefficients and input variables for correlation between sorption and soil properties. Relative ivermectin concentrations in stored dung under external and internal conditions for 30, 60 and 90 days of storage, for selected timepoints. Arithmetic mean ± s.d. relative concentrations for internal storage.

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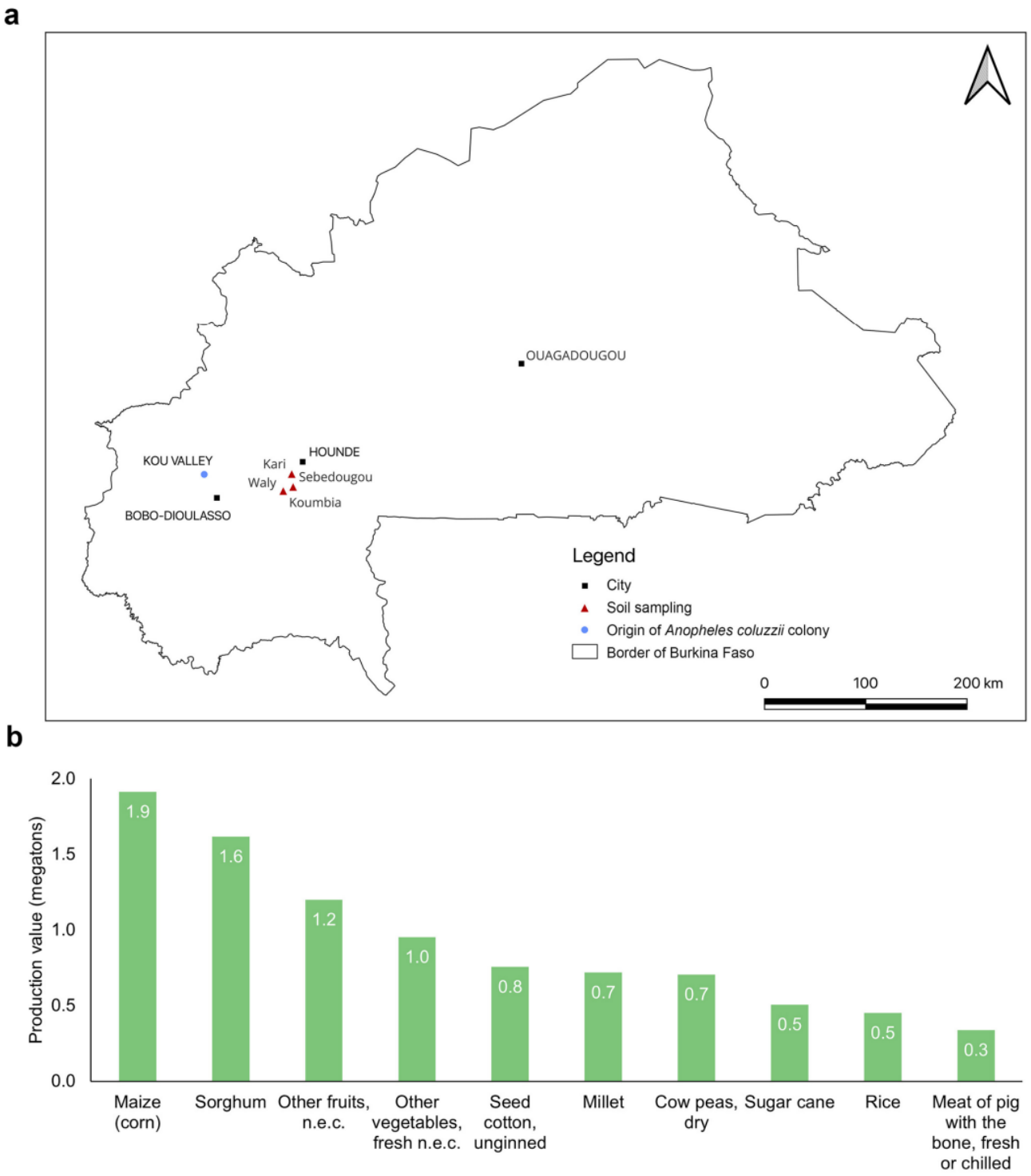
Extended Data Fig. 1

Extended Data Fig. 1 | Additional photography to illustrate manure pits for composting in Burkina Faso, mosquito skin-feeding assays, and external storage of dung samples. a, Photographed example of a fosse fumière (a manure pit) in Burkina Faso containing cattle dung. The fosse fumière is generally dug in the field near a homestead. The dimensions are approximately 3 m on each side and 1.2 m depth. It is filled mainly during the dry season with animal dung, crop residues, and other kitchen waste. The pit is emptied before the beginning of the cultivation period to spread the dung-mixture on fields. **b**, Arrangement for keeping cattle during the mosquito blood meal (skin-feeding assay). The mosquitoes are contained in small plastic bowls attached to the animal flank. **c**, Outdoor storage of cattle dung samples. The dung was kept in plastic bottles covered with mosquito net fabric and placed in a shaded area outside the stable. **a**–**c**, Photo credit: Hermann Sié Pooda. Panel (b) shows Saïdou Boly, who gave formal consent for his image to be published.

Extended Data Fig. 2



Extended Data Fig. 2 | Geographic overview, map of Burkina Faso, and agricultural production. a, The Centre International de Recherche-Développement sur l'Elevage en zone Subhumide (CIRDES) and Institut de Recherche en Sciences de la Santé (IRSS) are located in Bobo-Dioulasso. Soil samples were taken east of Bobo-Dioulasso in three villages in the region of Koumbia. The experimental mosquito colony was established from wild mosquitoes caught northwest of Bobo-Dioulasso in dwellings of the Kou Valley. b, Top commodities production in Burkina Faso in 2021, modified plot after FAO raw data (n.e.c. = not elsewhere classified).

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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No software was used for data collection.
Data analysis	R, version 4.0.1 (2021-05-18, platform x86_64-apple-darwin17.0 (64-bit)), including the package PKNCA (version 0.9.5); OriginPro, version 2022 (64-bit) SR1, including the application Correlation Plot (v1.31); ChemStation for LC 3D systems Rev. B.04.01 [481]; Microsoft Excel for Office 365. The R Code is available at https://github.com/angeliqueporciani/ANIVERMATE

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- A description of any restrictions on data availability
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The data supporting the article are available in the Supplementary Information. All data are also available upon reasonable request. Relevant raw data for Figs. 2–5 are listed in Excel files and provided as source or supplementary data files. Source data are provided with this paper. Figures 1 and 6b were created with BioRender

(BioRender.com). References for EC50 data from ecotoxicological standard tests (figure 4b) are provided in Supplementary Table 6. Outdoor temperature data were sourced online from NASA LP DAAC (MYD11A1 MODIS/Aqua Land Surface Temperature/Emissivity Daily L3 Global 1km SIN Grid V006). Statistical analyses and modeling for figure 3 were performed using R, version 4.0.1.; Data (incl. mosquito survival analysis data and sample sizes) are available in the ANIVERMATE repository, and additional methodology is described in the Supplementary Information file. Link to the GitHub repository: https://github.com/angeliqueporciani/ANIVERMATE

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	not applicable
Population characteristics	not applicable
Recruitment	not applicable
Ethics oversight	not applicable

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

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☐ Life sciences ☐ Behavioural & social sciences ☒ Ecological, evolutionary & environmental sciences

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Ecological, evolutionary & environmental sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	This study was designed to measure the efficacy and environmental risks of a One Health vector control approach using ivermectin against malaria mosquitoes. The study had three experimental arms (control, commercial ivermectin formulation, novel long-acting ivermectin formulation) with seven cattle per arm. We also considered environmental side-effects of ivermectin treatment and risk assessment. Mosquito survival data were transferred into a malaria transmission model to predict efficacy of the approach under field contexts.
Research sample	Ivermectin efficacy was tested on Anopheles coluzzii mosquitoes. The mosquito colony was established from mosquitoes caught in the wild in the study region. This species is opportunistic and feeds on animals and humans and is a major malaria vector in the region. Cattle crossbreed Soudaneese Fulani Zebu x Baoulé Taurine was selected because it represents the major breed in this same region of Burkina Faso. Soil samples were collected in the same area and represent a variety of Burkinabé agricultural soils.
Sampling strategy	Seven cattle per experimental arm plus reserve cattle (as hosts for the sampled mosquitoes) were the maximum holding capacity of the research stable, allowing to take into account potential cattle effects. The resulting number of mosquito data (40 mosquitoes per cattle and time point) were considered from previous study experience to be a sufficient sample size for this descriptive study to assess ivermectin efficacy. The resulting sampling scheme for pharmacokinetic data represented a feasible scope for the chemical analysis with our established methods. The number of soil samples was selected from previous experience and relied on approval of farmers to allow sampling on their fields.
Data collection	Plasma, dung, and mosquito samples were collected and processed by Lamidi Zéla and Sié Hermann Pooda with assistance from the CIRDES technical team. Soil samples were taken and processed by Daniel Frank Kaiser with assistance from Sié Hermann Pooda and Andre Patrick Heinrich. Chemical analysis of ivermectin was performed by Andre Patrick Heinrich and Alexandra Schinzel, assisted by technical staff and students.
Timing and spatial scale	Plasma, dung, and mosquito samples were collected from April-December 2019 for up to 21 instances. Soil samples from 30 fields were collected in late October 2019 in three villages, located around 80 km from Bobo-Dioulasso where the cattle were kept. Villages were clustered in a radius of approximately 20 km. Chemical analysis was performed starting in March 2020.
Data exclusions	No data were excluded from the presented analyses.
Reproducibility	Mosquito samples for each time point represent clusters of 4x10 mosquitoes per cattle. Each plasma or dung sample was divided into two technical replicates which were extracted and measured individually. All experimental procedures were based on established, tested protocols. All details on procedures in the manuscript and Supplemental information will allow to reproduce the experiments. We did not attempt to repeat the experiment.
Randomization	Cattle were randomly assigned to the experimental arms and to a place in the stable using a random number generator in MS Excel. Seven cattle per experimental arm were used for efficacy data and considered as random in the statistical modeling. Mosquitoes exposed to cattle were for every exposure time point subsamples from different mosquito breeding cages which were mixed to

	increase variability. The location of exposure cages (four cages, containing ten mosquitoes each per cattle) in the insectary for mortality follow-up was random. Chemical analysis of ivermectin in dung and plasma was partially randomized in groups of 10-20 consecutive samples per analysis at once.
Blinding	Blinding was not considered necessary for the scope for this study.

Did the study involve field work? ☒ Yes ☐ No

Field work, collection and transport

Field conditions	Thirty fields, clustered in different groups, were sampled in three villages in southwestern Burkina Faso in late October 2019. Average outdoor temperatures are provided in Supplementary Table 11.
Location	Coordinates of all sampled fields are provided in the Supplementary Information (Methods and Data) file and on a map in the main manuscript.
Access & import/export	The fields for the soil sampling campaign were pre-selected by local agricultural technicians who informed field owners about the process. Final choice depended on the permission of farmers who volunteered to allow sampling on their fields. Soil sample material from Burkina Faso was imported to Germany under clearance provided by the RP Gießen, Pflanzenschutzdienst under Directive 2008/61/EC, issued in document no. 2019/539925, endorsed by the Direction de la Protection des Végétaux et du Conditionnement (DPVC), Burkina Faso.
Disturbance	Field owners were informed about the intended soil sampling on their fields which was only undertaken with their approval.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☐	☒ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals	Cattle were of crossbreed Soudaneese Fulani Zebu x Baoulé Taurine and were kept in a net-protected stable at the Centre International de Recherche-Développement sur l'Elevage en zone Subhumide (CIRDES), in Bobo-Dioulasso, Burkina Faso. At the beginning of the study, average cattle age was 3 years, and average cattle weight was 122 kg. Information on veterinary care are provided in the manuscript, and data on cattle weight gain in the Supplementary Data file.
Wild animals	For the established Anopheles coluzzii mosquito colony, wild blood-fed females were collected in dwellings of the Kou Valley, 50 km northwest of Bobo-Dioulasso in southwestern Burkina Faso (decimal degrees 11.387222, -4.411667), between February and March 2019. At the start of the experiments, mosquitoes were 2 months old. The colony was kept in the insectary of CIRDES in collaboration with the Institute de Recherche en Sciences de la Santé (IRSS).
Reporting on sex	Cattle involved in the study were all male from the same crossbreed. This was done to avoid sex-confounding effects on mosquito survival and ivermectin pharmacokinetics, and to avoid accidental treatment of gestating cattle.
Field-collected samples	Cattle plasma and dung samples were collected in the stable as described in the main manuscript.
Ethics oversight	The study received approval from the CIRDES ethical committee under letter N°15/CE-CIRDES/16-10-2018.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

7.1 Supporting Information

An Ecotoxicological View on Malaria Vector Control with Ivermectin-treated Cattle

Supplementary Information

Chapter: Methods and Data, 23 pages

Chapter: Modeling, 8 pages

Chapter: Methods and Data

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II. Ivermectin concentrations, quantified with HPLC-fluorescence detection (raw data)

A. Classical formulation: IVOMEC-D®

Supplementary Table 1 | Ivermectin concentrations in plasma (ng/mL) and dung (ng/g dw) of cattle treated with the classical (IVOMEC-D®) ivermectin formulation, multiple injections[a]. Raw data for cattle B09, B11, B14, and B15, counted from the day of the 1st injection (DAI, day after injection).

Plasma	DAI	2	7	14	21	28	45	75	89	106	120	137	150	160	167						
Cattle ID	B09	94.4	33.4	20.6	2.2	2.2	23.2	9.6	2.2	20.6	-	-	2.2	81.7	40.9						
		-	41.3	26.4	2.2	< LOD	31.3	9.8	2.2	18.0	-	-	2.2	86.7	5.6						
	B11	103.0	71.1	14.7	2.2	< LOD	-	49.5	2.2	-	-	-	8.1	171.1	64.8						
		-	73.6	15.9	2.2	< LOD	-	47.3	2.2	-	-	-	7.8	149.2	-						
	B14	79.0	44.3	14.2	2.2	2.2	-	19.7	2.2	-	-	-	9.8	114.9	50.9						
		-	41.9	12.6	2.2	2.2	-	22.8	2.2	-	-	-	11.7	127.0	44.4						
	B15	48.9	66.7	29.0	10.3	6.8	-	10.3	< LOD	-	-	-	< LOD	-	-						
		-	61.9	35.6	9.9	6.4	-	9.8	< LOD	-	-	-	< LOD	-	-						
Dung	**DAI**	**2**	**7**	**14**	**21**	**28**	**45**	**75**	**89**	**106**	**120**	**137**	**150**	**160**	**167**	**174**	**181**	**190**	**197**	**204**	**211**
Cattle ID	B09	2012.2	720.2	521.5	134.1	60.6	386.6	229.9	-	321.6	-	268.2	-	1006.0	632.8	-	-	-	-	7.7	41.3
		2024.6	808.3	528.4	144.4	40.4	373.2	175.8	-	322.1	-	262.7	-	983.9	629.6	-	-	-	-	18.8	59.7
	B11	1769.0	1003.1	310.8	103.4	39.1	335.0	504.8	-	574.4	-	-	-	1844.2	-	-	-	-	-	7.7	17.5
		1735.6	997.4	318.4	101.5	38.1	390.9	538.8	-	589.5	-	-	-	1747.0	-	-	-	-	-	7.7	51.7
	B14	3267.1	527.2	493.3	180.7	86.3	763.9	400.1	-	722.1	-	-	-	-	-	266.7	-	-	-	18.5	50.5
		3061.9	582.2	440.6	170.2	55.6	727.2	409.9	-	743.3	-	-	-	-	-	268.5	-	-	-	19.7	31.5
	B15	805.7	1485.8	675.1	234.7	117.7	344.2	178.6	-	321.0	-	117.9	-	1035.4	-	253.8	-	-	-	-	23.9
		742.6	1559.9	667.0	242.5	112.7	322.5	172.5	-	295.2	-	110.2	-	944.2	-	267.8	-	-	-	7.7	18.9

[a] IVOMEC-D® injections were administered monthly at days 0, 31, 61, 92, 123, 153 from the start of the experiment; as described in Supplementary Table 10.

Measured concentrations below the limit of quantification (LOQ) were replaced with half the LOQ and are marked as underlined.

Dash (-) indicates no samples were taken or processed that day.

< LOD describes concentrations below the limit of detection.

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B. Long-acting depot formulation: IVM-BEPO®

Supplementary Table 2 | Ivermectin concentrations in plasma (ng/mL) and dung (ng/g dw) of cattle treated with the depot (IVM-BEPO®) ivermectin formulation, single injection[a]. Raw data for cattle B08, B19, B20, and B23, counted from the day of the depot injection (DAI, day after injection).

Plasma	DAI	2	7	14	21	28	45	75	89	106	120	137	150	160	167	174	181	190	197	204	211
Cattle ID	B08	16.7	18.6	18.1	31.1	17.9	13.9	8.6	11.0	12.7	6.5	16.6	15.1	15.3	17.3	13.1	22.8	22.5	29.8	41.2	30.7
		-	18.0	15.4	15.2	16.0	14.2	8.9	12.3	12.2	12.7	12.9	13.8	15.6	16.9	14.5	18.6	27.7	25.4	35.1	33.0
	B19	13.7	11.7	-	7.3	10.0	7.2	14.5	13.6	12.8	19.6	23.0	23.8	28.9	31.4	-	32.9	42.3	34.0	34.0	38.2
		-	11.9	10.5	5.7	9.6	8.8	12.4	12.9	10.9	21.7	10.6	27.0	25.2	30.7	29.7	36.3	41.8	37.6	40.4	37.7
	B20	24.6	31.0	22.3	13.0	12.0	7.1	6.1	8.7	10.4	14.7	10.8	21.1	22.3	14.0	21.0	25.4	33.0	23.7	27.3	19.5
			34.8	20.7	14.1	13.9	7.5	6.5	10.0	9.3	14.5	25.3	-	19.8	-	19.5	32.2	25.8	27.6	23.6	29.1
	B23	18.5	28.7	20.9	17.7	21.2	10.0	7.7	9.2	10.0	10.3	11.3	13.5	17.5	27.1	28.7	26.5	-	24.7	30.6	31.7
		-	28.4	19.7	20.5	24.4	9.6	8.2	10.4	10.1	10.9	12.2	13.6	20.7	22.9	24.1	25.3	23.4	-	29.5	25.7
Dung	**DAI**	**2**	**7**	**14**	**21**	**28**	**45**	**75**	**89**	**106**	**120**	**137**	**150**	**160**	**167**	**174**	**181**	**190**	**197**	**204**	**211**
Cattle ID	B08	-	282.1	185.0	278.6	258.0	174.7	130.5	-	202.4	-	-	-	181.0	-	-	-	-	-	300.2	366.6
		222.0	285.9	178.6	283.9	268.0	188.5	100.6	-	186.1	-	-	-	180.9	-	-	-	-	-	293.8	364.4
	B19	214.0	230.5	208.6	124.7	163.3	146.9	188.8	-	224.6	-	-	-	288.3	-	355.9	-	-	-	370.5	417.6
		189.9	233.0	195.8	118.0	138.2	135.6	112.7	-	222.9	-	-	-	298.0	-	355.9	-	-	-	392.4	432.4
	B20	195.0	1001.0	690.3	279.9	278.7	214.6	181.2	-	-	-	335.9	-	330.4	387.0	449.3	-	-	-	541.6	362.6
		526.6	994.9	679.3	295.7	288.7	253.1	140.6	-	-	-	311.8	-	340.5	392.1	477.5	-	-	-	574.3	354.2
	B23	486.1	613.0	756.8	462.6	486.8	246.2	182.1	-	-	-	188.5	-	-	513.1	-	-	-	-	523.9	444.6
		-	600.6	674.1	490.1	478.1	284.6	171.8	-	-	-	209.9	-	-	507.2	-	-	-	-	546.8	453.1

[a] IVM-BEPO® injection administered as described in Supplementary Table 9.

Dash (-) indicates no samples were taken or processed that day.

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III. Pharmacokinetics and cattle treatments for survival assays

A. Pharmacokinetic parameters and hazard ratios

Supplementary Table 3 | Ivermectin pharmacokinetic parameters in plasma and dung of cattle treated using IVOMEC-D® or IVM-BEPO® formulations. For IVOMEC-D®, the parameters were calculated for a single injection (i.e., 28 days). Parameters were obtained using the PKNCA R Package.

PK parameters	Value	Treatment	
		IVOMEC-D®	IVM-BEPO®
Cattle plasma			
Cmax (ng/ml)	Geometric Mean	83.8	35.5
	CV	21.1	15.1
Tmax (days)	Median	2	197
	Range	2-7d	7-204
half.life (days)	Arithmetic mean	4.29	NA
	SD	1.41	NA
$AUC_{0\text{-tlast}}$ (ng days/mL)	Geometric Mean	760	3510
	CV	17.5	8.8
Indicator of quality	Cmax mean/Dose	209.5	14.8
	IQ+/-SD	205.2; 211.3	14.3; 15.3
Cattle dung			
Cmax (ng/ml)	Geometric Mean	2030	533
	CV	32.5	60.4
Tmax (days)	Median	2	109
	Range	2;7	07;204
half.life (days)	Arithmetic mean	4.81	NA
	SD	0.624	NA
$AUC_{0\text{-tlast}}$ (ng days/mL)	Geometric Mean	16200	54500
	CV	9.78	27.7
Indicator of quality	Cmax mean/Dose	5075	222.1
	IQ+/-SD	5071; 5078	221.4; 222.8

For IVOMEC-D®, the parameters are calculated for the first 28 days.

R Package used for pharmacokinetic parameter calculations

Denney W, Duvvuri S, Buckeridge C (2015). "Simple, Automatic Noncompartmental Analysis: The PKNCA R Package." Journal of Pharmacokinetics and Pharmacodynamics, *42*(1), 11-107,S65. ISSN 1573-8744, doi: 10.1007/s10928-015-9432-2 (URL: https://doi.org/10.1007/s10928-015-9432-2), R package version 0.9.5, <URL: https://github.com/billdenney/pknca>.

Supplementary Table 4 | Hazard ratios estimated from cox proportional hazards mixed model exploring the effect of ivermectin cattle treatments using IVOMEC-D® and IVM-BEPO® formulations on mosquito survival. Cattle clustered by experimental arms were considered as random effect.

Comparison against the control	DAI	Hazard Ratio	asymp.LCL	asymp.UCL	z.ratio	p-value
IVOMEC-D	0	1.028	0.686	1.54	0.16	0.986
IVM-BEPO	0	1.016	0.678	1.524	0.095	0.995
IVOMEC-D	2	47.52	23.367	96.641	12.748	< 0.0001
IVM-BEPO	2	17.074	8.638	33.748	9.761	< 0.0001
IVOMEC-D	7	28.46	17.129	47.286	15.457	< 0.0001
IVM-BEPO	7	12.848	7.853	21.02	12.156	< 0.0001
IVOMEC-D	14	4.401	1.979	9.785	4.346	< 0.0001
IVM-BEPO	14	7.669	3.441	17.094	5.957	< 0.0001
IVOMEC-D	21	2.164	1.249	3.75	3.29	0.003
IVM-BEPO	21	9.095	5.252	15.751	9.422	< 0.0001
IVOMEC-D	28	1.785	1.038	3.068	2.505	0.033
IVM-BEPO	28	7.394	4.316	12.669	8.708	< 0.0001
IVOMEC-D	45	9.237	6.033	14.141	12.234	< 0.0001
IVM-BEPO	45	3.926	2.583	5.967	7.657	< 0.0001
IVOMEC-D	75	3.539	1.989	6.295	5.141	< 0.0001
IVM-BEPO	75	2.827	1.593	5.019	4.245	< 0.0001
IVOMEC-D	89	1.496	1.05	2.131	2.664	0.021
IVM-BEPO	89	2.993	2.127	4.212	7.525	< 0.0001
IVOMEC-D	106	4.216	2.58	6.892	6.864	< 0.0001
IVM-BEPO	106	3.086	1.869	5.095	5.269	< 0.0001
IVOMEC-D	120	0.914	0.489	1.708	-0.338	0.939
IVM-BEPO	120	2.841	1.521	5.305	3.918	< 0.0001
IVOMEC-D	150	2.596	1.187	5.678	2.857	0.012
IVM-BEPO	150	8.94	4.071	19.63	6.527	< 0.0001
IVOMEC-D	160	34.527	19.189	62.125	14.131	< 0.0001
IVM-BEPO	160	9.44	5.433	16.403	9.523	< 0.0001
IVOMEC-D	167	17.353	8.99	33.495	10.17	< 0.0001
IVM-BEPO	167	10.534	5.522	20.095	8.544	< 0.0001
IVOMEC-D	174	6.931	3.427	14.016	6.443	< 0.0001
IVM-BEPO	174	12.085	5.939	24.592	8.221	< 0.0001
IVOMEC-D	181	3.607	1.557	8.356	3.579	0.001
IVM-BEPO	181	9.174	3.937	21.38	6.14	< 0.0001
IVM-BEPO	190	7.536	4.074	13.941	6.436	< 0.0001
IVM-BEPO	197	32.076	11.903	86.44	6.857	< 0.0001
IVOMEC-D	204	1.316	0.382	4.54	0.52	0.861
IVM-BEPO	204	18.576	5.318	64.885	5.475	< 0.0001
IVOMEC-D	211	1.025	0.33	3.188	0.052	0.999
IVM-BEPO	211	10.546	3.356	33.145	4.821	< 0.0001

B. Blood feeding rate

The effect of the ivermectin treatments on the proportion of mosquitoes that took blood meals during direct skin feeding experiments has been explored using a generalized linear mixed model (glmm) with a binomial distribution of the error and days from the start of the experiment and cattle as random intercept.

$$Y_{ij} \sim Bin(1, p_{ij})$$

$$logit(p_{ijde}) = \beta_0 + \beta_1 \cdot Treatment_{ij} + a_d + b_e$$

with $a_d \sim N(0, \sigma_a^2)$ and $b_e \sim N(0, \sigma_b^2)$

P_{ij} is the probability of mosquito individual i on treatment j is blood fed. $Treatment_{ij}$ is the formulation to which the individual has been exposed. a_d correspond to random intercept for days from the start of the experiment and b_e correspond to random intercept for cattle individual.

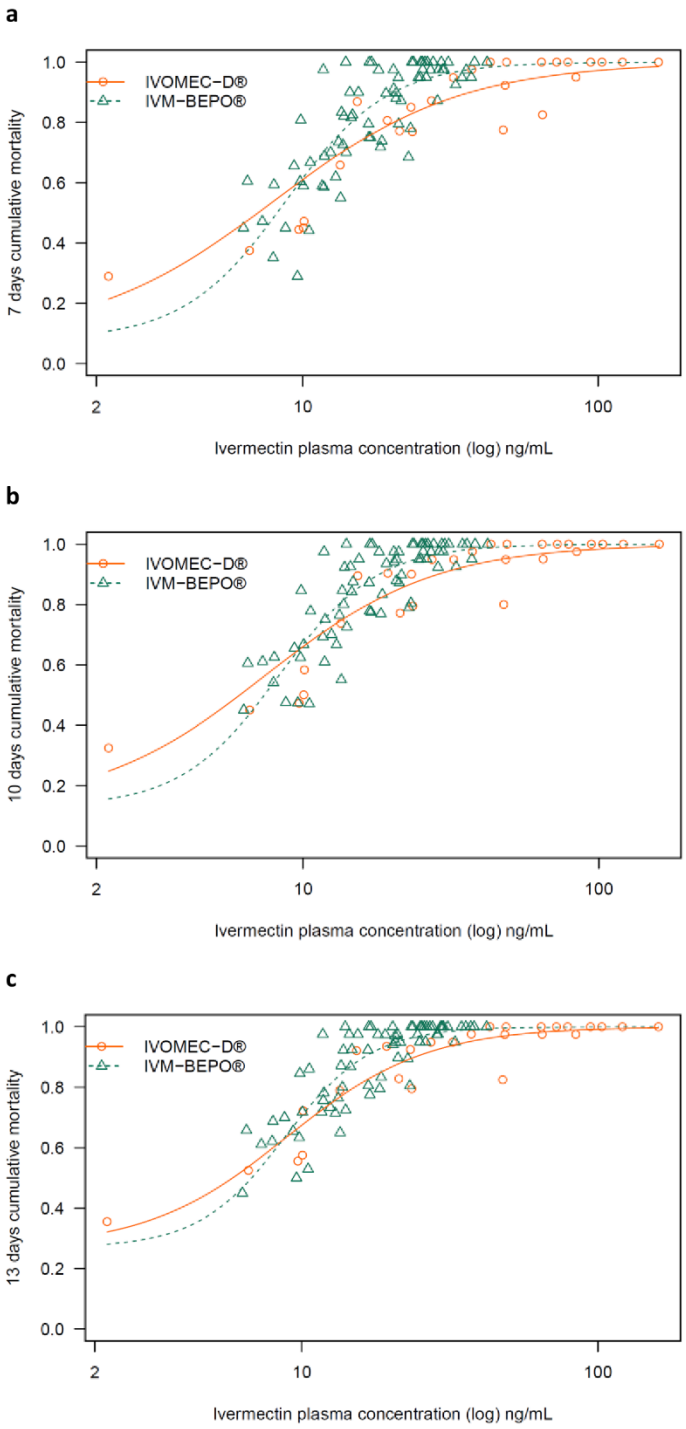
Supplementary Figure 1 | Generalized linear mixed model characterizing the blood feeding rate in function of ivermectin treatments.

C. Estimated effective concentrations to block transmission

Effective transmission blocking concentrations were here considered as the ivermectin plasma levels lethal to mosquitoes before they could transmit *Plasmodium falciparum* parasites. Based on simple scenarios where ivermectin blood meal is taken from cattle before, the same day, or after the infectious one, 7, 10 and 13-days cumulative mosquito mortalities, respectively, were plotted against ivermectin concentrations (Supplementary Figure 2). Data were considered as binomial (i.e., dead (1) or not dead (0) before t=n days after ivermectin blood feeding). Dose-effect of ivermectin concentration on mosquitoes' survival until a given day post treatment was assessed using a 4 parameters dose-response log-logistic regression for different times of mortality during a follow-up of 30 days (7, 10 or 13 days). The 10-day scenario (i.e., both ivermectin and infectious blood meals are taken the same day) would imply in nature that mixed blood meals taken sequentially from cattle and human occurred, which is frequently reported (refs. [1,2]). This scenario has been considered because it offers comparison with the existing literature on projected human mass ivermectin administrations, where ivermectin induced mosquito death post blood feeding is set at maximum 10 days, the median extrinsic incubation period (EIP). From the log-logistic model, we determined the ivermectin plasma concentrations in the blood meal taken from treated cattle that kill 50 % and 90 % (LC_{50} and LC_{90}) of the mosquitoes before the EIP of the parasite is completed (Supplementary Table 5).

Supplementary Table 5 | Estimated lethal concentrations (ng/mL) killing 50 % and 90 % of the mosquitoes before they become infectious following a blood meal taken on a *Plasmodium falciparum* infected human 3 days before, the same day, or 3 days after a blood meal on an ivermectin treated cattle using IVOMEC-D® and IVM-BEPO®. Only LC_{90} values are significantly different between both formulations (likelihood ratio test, p<0.001 in all instances).

Ivermectin formulation	Cumulative mortalities	LC_{50} values ± SE	LC_{90} values ± SE
IVOMEC-D®	7-days	8.00 ± 0.66	39.59 ± 3.67
	10-days	7.46 ± 0.66	31.76 ± 2.81
	13-days	8.88 ± 0.83	43.69 ± 4.98
IVM-BEPO®	7-days	8.78 ± 0.29	21.08 ± 0.67
	10-days	8.31 ± 0.30	19.22 ± 0.59
	13-days	8.77 ± 0.31	23.44 ± 0.98



Supplementary Figure 2 | Estimation of the dose-response relationship between ivermectin plasma concentrations and mosquito cumulative mortalities when calves are injected with IVOMEC-D® or IVM-BEPO® formulations. a-c, Lines are the estimated relationships following the log-logistic regression while circles and triangles represent means of experimental data. Ivermectin induced mortality is explored according to three scenarios that would decrease the parasites' transmission: **a**, the mosquito dies within 7 days after an Ivermectin blood meal (Ivermectin blood meal is taken 3 days after the infectious one); **b**, the mosquito dies within 10 days after the ivermectin blood meal (Ivermectin blood meal is taken the same day as the infectious one); **c**, the mosquito dies before 13 days after an ivermectin blood meal (Ivermectin is taken 3 days before the infectious one).

IV. Ecotoxicological assessment and environmental fate

A. Ecotoxicity of ivermectin

Supplementary Table 6 | Half maximal effective concentration (EC_{50}) data from ecotoxicological standard tests with dung beetles and dung flies for ivermectin toxicity testing. Concentration in dry weight (dw) dung.

Dung beetles					
Genus	**Species**	**EC_{50} (ng/g dw)**	**Endpoint**	**Reference**	**Note**
Aphodius	*fimetarius*	540	Larval mortality	3	
Aphodius	*constans*	880	Larval mortality	3	
Aphodius	*constans*	980	Larval mortality	3	
Euoniticellus	*intermedius*	521	Larval mortality	4	a
Aphodius	*constans*	590	Larval mortality	5	
Aphodius	*constans*	550	Larval mortality	6	b, c
Aphodius	*constans*	260	Larval mortality	6	c, d
Aphodius	*constans*	290	Reproduction (21 d)	6	c
Aphodius	*constans*	810	Larval mortality	5	b, c
Aphodius	*constans*	320	Reproduction (21 d)	5	c
Dung flies					
Genus	**Species**	**EC_{50} (ng/g dw)**	**Endpoint**	**Reference**	**Note**
Scathophaga	*stercoraria*	148.97	Larva-to-adult mortality	7	
Scathophaga	*suilla*	63.04	Larva-to-adult mortality	7	
Musca	*autumnalis*	33.14	Larva-to-adult mortality	7	
Musca	*domestica*	176.19	Larva-to-adult mortality	7	
Archisepsis	*armata*	44.20	Larva-to-adult mortality	8	
Archisepsis	*diversiformis*	13.70	Larva-to-adult mortality	8	
Dicranosepsis	*emiliae*	1.72	Larva-to-adult mortality	8	
Microsepsis	*armillata*	175.21	Larva-to-adult mortality	8	
Microsepsis	*mitis*	173.30	Larva-to-adult mortality	8	
Meroplius	*fukuhari*	24.31	Larva-to-adult mortality	8	
Saltella	*sphondylii*	1.42	Larva-to-adult mortality	8	
Sepsis	*cynipsea*	4.35	Larva-to-adult mortality	8	
Sepsis	*cynipsea*	2.59	Larva-to-adult mortality	8	
Sepsis	*cynipsea*	3.50	Larva-to-adult mortality	8	
Sepsis	*cynipsea*	0.57	Larva-to-adult mortality	8	
Sepsis	*cynipsea*	1.16	Larva-to-adult mortality	8	
Sepsis	*cynipsea*	1.42	Larva-to-adult mortality	8	
Sepsis	*cynipsea*	2.02	Larva-to-adult mortality	8	
Sepsis	*cynipsea*	2.23	Larva-to-adult mortality	8	
Sepsis	*dissimilis*	0.76	Larva-to-adult mortality	8	
Sepsis	*duplicata*	0.64	Larva-to-adult mortality	8	
Sepsis	*flavimana*	0.34	Larva-to-adult mortality	8	
Sepsis	*fulgens*	40.51	Larva-to-adult mortality	8	
Sepsis	*fulgens*	6.32	Larva-to-adult mortality	8	
Sepsis	*fulgens*	6.43	Larva-to-adult mortality	8	
Sepsis	*fulgens*	9.02	Larva-to-adult mortality	8	
Sepsis	*fulgens*	8.62	Larva-to-adult mortality	8	
Sepsis	*fulgens*	39.68	Larva-to-adult mortality	8	
Sepsis	*fulgens*	18.43	Larva-to-adult mortality	8	
Sepsis	*lateralis*	5.73	Larva-to-adult mortality	8	
Sepsis	*latiforceps*	81.53	Larva-to-adult mortality	8	
Sepsis	*neocynipsea*	1.65	Larva-to-adult mortality	8	
Sepsis	*neocynipsea*	1.64	Larva-to-adult mortality	8	
Sepsis	*neocynipsea*	11.21	Larva-to-adult mortality	8	
Sepsis	*neocynipsea*	5.23	Larva-to-adult mortality	8	

(Table continued) Half maximal effective concentration (EC_{50}) data from ecotoxicological standard tests with dung beetles and dung flies for ivermectin toxicity testing. Concentration in dry weight (dw) dung.

Dung flies					
Genus	**Species**	**EC_{50} (ng/g dw)**	**Endpoint**	**Reference**	**Note**
Sepsis	*neocynipsea*	4.93	Larva-to-adult mortality	[8]	
Sepsis	*orthocnemis*	70.48	Larva-to-adult mortality	[8]	
Sepsis	*orthocnemis*	7.77	Larva-to-adult mortality	[8]	
Sepsis	*orthocnemis*	39.12	Larva-to-adult mortality	[8]	
Sepsis	*punctum*	11.83	Larva-to-adult mortality	[8]	
Sepsis	*punctum*	124.18	Larva-to-adult mortality	[8]	
Sepsis	*punctum*	14.17	Larva-to-adult mortality	[8]	
Sepsis	*punctum*	14.22	Larva-to-adult mortality	[8]	
Sepsis	*punctum*	132.22	Larva-to-adult mortality	[8]	
Sepsis	*punctum*	30.25	Larva-to-adult mortality	[8]	
Sepsis	*punctum*	54.48	Larva-to-adult mortality	[8]	
Sepsis	*secunda*	9.50	Larva-to-adult mortality	[8]	
Sepsis	*thoracica*	4.57	Larva-to-adult mortality	[8]	
Sepsis	*thoracica*	1.39	Larva-to-adult mortality	[8]	
Sepsis	*thoracica*	0.63	Larva-to-adult mortality	[8]	
Sepsis	*thoracica*	2.50	Larva-to-adult mortality	[8]	
Sepsis	*thoracica*	2.22	Larva-to-adult mortality	[8]	
Sepsis	*thoracica*	3.98	Larva-to-adult mortality	[8]	
Sepsis	*thoracica*	2.55	Larva-to-adult mortality	[8]	
Sepsis	*violacea*	3.26	Larva-to-adult mortality	[8]	
Sepsis	*violacea*	9.39	Larva-to-adult mortality	[8]	
Sepsis	*violacea*	6.33	Larva-to-adult mortality	[8]	
Themira	*minor*	8.95	Larva-to-adult mortality	[8]	

[a] Calculated from reported effect value of 85.5 µg ivermectin/kg dung fresh weight and 83.6 % moisture.

[b] Larvae test according to OECD Guidance Document on the Determination of the Toxicity of a Test Chemical to Dung Beetles. Draft. Organisation for Economic Co-Operation and Development. 2010. Paris, France.

[c] Associated data; performed with the referenced work in cooperation with the German Environment Agency[9]

[d] Elongated larvae test (ca. 70 d)

B. Sorption of ivermectin

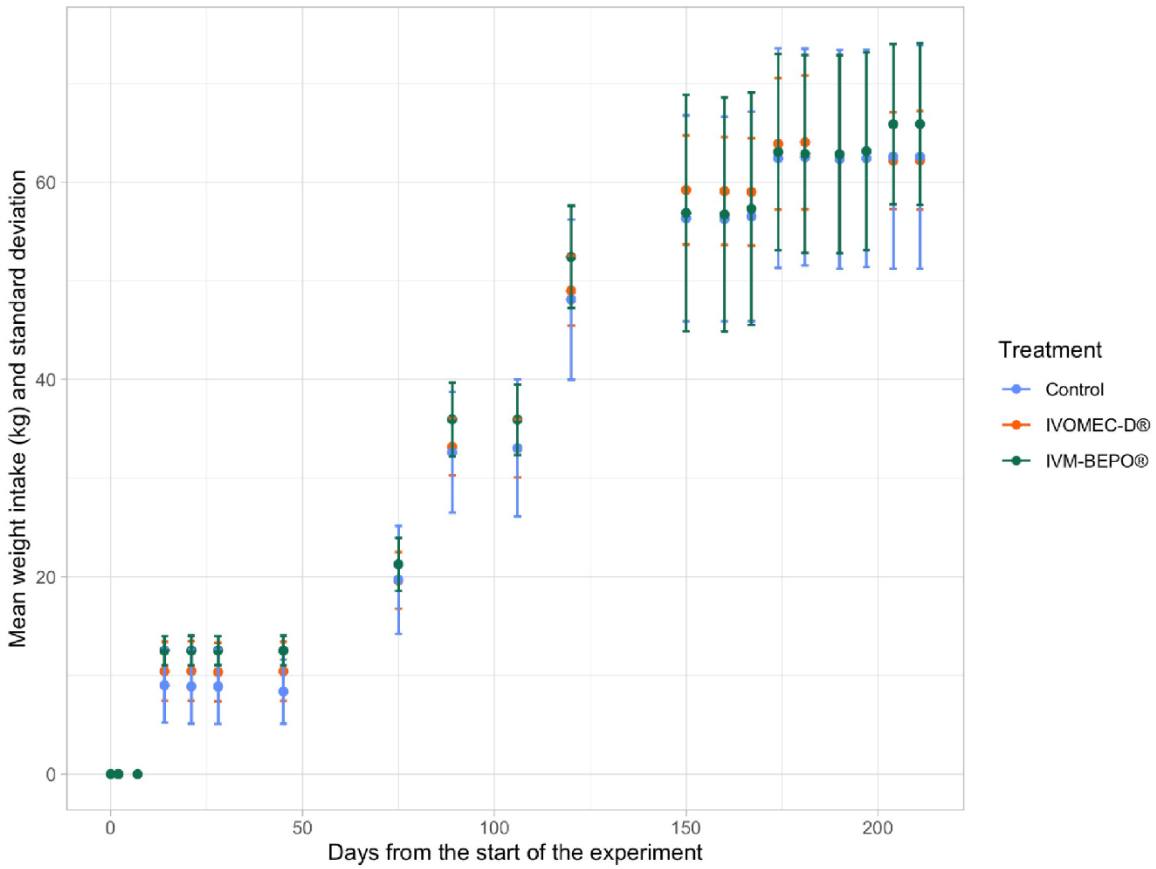
Supplementary Table 7 | Linear sorption coefficients and input variables for correlation between sorption and soil properties (n = 6 selected soils).

				pH value[a]					
Soil_ID	**K_D (mL/g)**	**K_{OC} (mL/g)**	**C_{org} (%)**	**measured**	**delogarithmized**	**Clay (%)**	**Silt (%)**	**Sand (%)**	**EC (µS/cm)**
SF5	91.46	10162	0.90	5.65	450817	9.79	43.98	46.23	41.1
SM3	69.19	7603	0.91	5.72	527230	9.45	39.32	51.22	43.1
WF2	55.01	6628	0.83	5.50	318420	8.32	24.20	67.49	50.7
WM4	53.49	7327	0.73	5.31	205589	6.57	14.25	79.19	50.8
KF4	122.86	10873	1.13	5.78	598412	12.37	36.91	50.72	50.5
KM4	115.07	8338	1.38	5.78	597035	8.79	37.99	53.23	50.4

[a] The correlation was performed with the delogarithmized pH values.

V. Cattle treatments for survival assays

A. Cattle weight gain



Supplementary Figure 3 | Mean weight gain in kg (± SD) in function of the time elapsed since the start of the experiment for cattle clustered by experimental arms (n = 7 animals per arm).

The cattle weight intake was compared between experimental arms using a generalized linear mixed model with a gaussian distribution of the error and cattle individual as random intercept.

The selected model is described by the following equation:

Supplementary Equation 1

$$Y_{ij} = \beta_0 + \beta_1 \cdot Treatment_{ij} + \beta_2 \cdot Days_{ij} + b_{0i} + \epsilon_{ij}$$
$$\text{with } \epsilon_{ij} \sim N(0, \sigma_\epsilon^2) \text{ and } b_{0i} \sim N(0, \sigma_b^2)$$

Supplementary Table 8 | Cattle weights measured with three months intervals, weight ranges attribution and calculated weight estimates at mid experiment for IVM-BEPO® treatment planning.

Cattle ID	Initial weight (kg) (29.01.2019)	Weight (kg) (30.04.2019)	Weight gain in 3 months (kg)	% weight ratio after 3 months	% increase range attributed	Mid experiment weight estimates (kg) (30.07.2019)	planned treatments
B1	104.4	125.4	21	120.11	25	156.75	IVM-BEPO®
B2	118.6	111.8	-6.8	94.27	25	139.75	IVM-BEPO®
B3	104.6	117.0	12.4	111.85	25	146.25	Ivomec-D®
B4	147.4	164.0	16.6	111.26	15	188.60	Control
B5	191.2	176.4	-14.8	92.26	10	194.04	Control
B6	95	110.8	15.8	116.63	25	138.50	Control
B7	118	134.2	16.2	113.73	25	167.75	Control
B8	113.6	113.4	-0.2	99.82	25	141.75	IVM-BEPO®
B9	120.8	127.2	6.4	105.30	25	159.00	Ivomec-D®
B10	131.2	152.8	21.6	116.46	15	175.72	IVM-BEPO®
B11	115	119.8	4.8	104.17	25	149.75	Ivomec-D®
B12	134	139.2	5.2	103.88	15	160.08	Ivomec-D®
B13	104.02	115.8	11.78	111.32	25	144.75	Control
B14	132.2	143.4	11.2	108.47	25	179.25	Ivomec-D®
B15	127	134.2	7.2	105.67	25	167.75	Ivomec-D®
B16	130.8	147.6	16.8	112.84	15	169.74	Control
B17	137.8	128.2	-9.6	93.03	15	147.43	Ivomec-D®
B18	123	143.4	20.4	116.59	25	179.25	Control
B19	106.6	112.0	5.4	105.07	25	140.00	IVM-BEPO®
B20	110	127.8	17.8	116.18	25	159.75	IVM-BEPO®
B21	110.4	117.4	7	106.34	25	146.75	Ivomec-D®
B22	101	107.2	6.2	106.14	25	134.00	Control
B23	139.6	148.4	8.8	106.30	15	170.66	IVM-BEPO®
B24	106.4	119.6	13.2	112.41	25	149.50	IVM-BEPO®

B. Injected ivermectin doses

Supplementary Table 9 | Cattle weight estimates and corresponding injected weight values for the ivermectin treatment using the IVM-BEPO® formulation.

Cattle ID	Mid experiment cattle weight estimates (kg)	Weight of the injected IVM-BEPO® (mg)	Corresponding volume of the injected IVM-BEPO® (mL)
B1	156.75	7013.90	6136.39
B2	139.75	6253.22	5470.88
B8	141.75	6342.71	5549.18
B10	175.72	8546.44	7477.20
B19	140.00	6264.41	5480.67
B20	159.75	7148.14	6253.84
B23	170.66	8300.34	7261.89
B24	149.50	6689.49	5852.57

Supplementary Table 10 | Cattle weight measured each month before the ivermectin treatment using the Ivomec-D® formulation. The injected dose is 0.4 mg/kg every month. Injected volume of the formulation is proportional to the weight (2 mL injected per 50 kg of weight, according to the manufacturer's recommendations).

Cattle ID	Cattle weight (kg) measured each month before Ivomec-D® injection					
	1st month	2nd month	3rd month	4th month	5th month	6th month
B3	117	124.6	137.2	147.4	173.2	174.6
B9	127.2	139.8	148.6	162.4	188.2	191.2
B11	119.8	126.2	134.4	147.4	171.8	173.2
B12	139.2	150.4	162.8	175.2	209.4	215.2
B14	143.4	152.8	164.8	178.4	204.4	207.4
B15	134.2	143.6	153.4	166.6	192.2	202.4
B17	128.2	137.2	136.4	136.6	161.2	158.4
B21	117.4	133.4	134.2	153	172.4	182.4

VI. Environmental conditions and characterization of soil samples

A. Outdoor temperatures during dung sample storage

Outdoor temperatures are online data obtained from a weather station nearby the Centre International de Recherche-Développement sur l'Elevage en zone Subhumide (CIRDES) in Bobo-Dioulasso, Burkina Faso; data provided by NASA LP DAAC (ref.[10]).

Supplementary Table 11 | Mean daily and nightly outdoor temperatures in Bobo-Dioulasso during the respective storage periods of externally stored cattle dung.

Dung_ID	DAI[a]	Date of fresh dung collection	Mean outdoor temperatures (°C) in the corresponding timeframe		
			during 30-day storage	during 60-day storage	during 90-day storage
L1_dung	2	08.05.2019	-	Day: Mean = 38.20; Min = 33.47; Max= 43.89	Day: Mean = 38.02; Min = 33.47; Max= 43.89
			-	Night: Mean = 22.8; Min = 17.20; Max = 27.73	Night: Mean = 22.14; Min = 17.20; Max = 27.73
L2_dung	7	13.05.2019	Day: Mean = 37.12; Min = 33.47; Max= 39.83	Day: Mean = 39.18; Min = 34.11; Max= 43.89	Day: Mean = 38.60; Min = 34.11; Max= 43.89
			Night: Mean = 21.17; Min = 17.20; Max = 26.74	Night: Mean = 22.54; Min = 17.69; Max = 27.45	Night: Mean = 21.88; Min = 17.69; Max = 27.45
L7_dung	75	20.07.2019	-	Day: Mean = 32.13; Min = 27.22; Max= 37.32	Day: Mean = 32.66; Min = 27.22; Max= 38.68
			-	Night: Mean = 20.94; Min = 17.84; Max = 23.59	Night: Mean = 22.19; Min = 19.38; Max = 24.88
L14_dung	174	27.10.2019	Day: Mean = 38.04; Min = 30.67; Max= 42.39	Day: Mean = 39.55; Min = 34.92; Max= 43.61	Day: Mean = 37.83; Min = 27.84; Max= 43.61
			Night: Mean = 21.47; Min = 16.08; Max = 24.33	Night: Mean = 18.58; Min = 15.11; Max = 23.19	Night: Mean = 18.90; Min = 10.83; Max = 24.33
L18_dung	204	26.11.2019	Day: Mean = 39.50; Min = 34.92; Max= 43.61	Day: Mean = 37.82; Min =27.84; Max= 43.61	-
			Night: Mean = 18.66; Min = 15.11; Max = 23.19	Night: Mean = 17.92; Min = 10.83; Max = 23.19	-

[a] DAI refers to Day After Injection of the long-acting IVM-BEPO® as described in the main manuscript.

Dash (-) indicates no samples were taken or processed that day.

B. Laboratory methodology and soil characteristics

For sampled soils, pH values in 0.01 M $CaCl_2$ were measured according to EN 15933:2012 (*European Committee for Standardization: EN15933 - Sludge, treated biowaste and soil – Determination of pH; German version: EN 15933:2012*) with m:v ratios of 7.5 g soil in 25 mL solution.

Carbonate content was estimated in the field following the semi-quantitative preparation step of EN ISO 10693:2014 (*European Committee for Standardization: Soil quality – Determination of carbonate content – Volumetric method, German version: EN ISO 10693:2014*). For this, a few drops of 37 % hydrochloric acid (CAS 7647-01-0) were added to about 1 g of soil. No reaction was detected in all samples. Supplementary Table 12 displays pH values that were also used for correlation with the K_D sorption coefficients.

Determination of electrical conductivity (EC) of soil samples was based on ISO 11265:1994 + ISO 11265:1994/Cor.1 : 1996 (*ISO: Soil quality – Determination of the specific electrical conductivity, German version: ISO 11265:1994 + ISO 11265:1994/Cor.1 1996).*

Particle size distribution was determined based on ISO 11277:1998 + ISO 11277:1988/ Cor.1:2002 (*ISO (2002): Soil quality – Determination of particle size distribution in mineral soil material – Method by sieving and sedimentation: ISO 11277:1998 + ISO 11277:1988/Cor.1:2002*). Here, 10 g soil were weighted into an 800 mL glass beaker. Approximately 200 mL deionized water were added. Destruction of organic substance was initiated by addition of 25 mL 30 % hydrogen peroxide (CAS 7722-84-1).

For analysis of total carbon and nitrogen content, an aliquot of 14 to 87 mg of ground up sample material was measured with a UNICUBE trace CN elemental analyser (Elementar Analysensysteme GmbH, Germany). The total carbon content was subtracted by the inorganic carbon content, thereby indirectly deriving the organic carbon content (shown therefore only as C (%) in Supplementary Table 12).

Supplementary Table 12 | Soil properties of sampled fields. Soils from fields chosen for the sorption study are highlighted in bold and light grey.

Sample site				Depth	pH value	EC	Coarse soil	Fine soil | < 2 mm | particle size distribution (rounded)										C:N ratio		
								sand	silt	clay	gS	mS	fS	gU	mU	fU	T	C	N	C:N
Village	Fertilizer	Soil_ID	Crop	(cm)	0.01M $CaCl_2$	(µS/cm)	> 2 mm fraction	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	ratio
Sébédougou	organic/fumier	SF1	corn	0-15	6.21	61.2	0.67	52	38	9	18	10	25	27	8	3	9	1.09	0.10	10.4
Sébédougou	organic/fumier	SF2	cotton	0-15	5.90	47.9	0.46	46	46	9	14	9	22	36	7	2	9	0.68	0.08	9.0
Sébédougou	organic/fumier	SF3	cotton	0-15	6.28	53.0	0.73	47	39	14	11	10	26	26	8	4	14	0.84	0.09	9.1
Sébédougou	organic/fumier	SF4	cotton	0-15	5.69	38.8	0.76	44	39	17	17	12	16	19	14	6	17	0.44	0.06	7.9
Sébédougou	**organic/fumier**	**SF5**	**cotton**	**0-15**	**5.65**	**41.1**	**0.62**	**46**	**44**	**10**	**11**	**10**	**26**	**31**	**10**	**3**	**10**	**0.90**	**0.07**	**13.9**

(Table continued) Soil properties of sampled fields. Soils from fields chosen for the sorption study are highlighted in bold and light grey.

Sample site				Depth	pH	EC	Coarse soil	Fine soil | < 2 mm | particle size distribution (rounded)										C:N ratio		
								sand	silt	clay	gS	mS	fS	gU	mU	fU	T	C	N	C:N
Village	Fertilizer	Soil_ID	Crop	(cm)	0.01M $CaCl_2$	(µS/cm)	> 2 mm fraction	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	ratio
Sébédougou	anorg./nothing	SM1	cotton	0-15	5.06	38.2	0.66	48	45	7	13	11	24	30	11	4	7	0.79	0.06	13.9
Sébédougou	anorg./nothing	SM2	cotton	0-15	5.19	52.3	0.30	25	63	12	3	4	18	50	10	2	12	1.11	0.08	13.2
Sébédougou	**anorg./nothing**	**SM3**	**cotton**	**0-15**	**5.72**	**43.1**	**0.51**	**50**	**40**	**9**	**10**	**13**	**27**	**27**	**1**	**12**	**9**	**0.91**	**0.07**	**12.8**
Sébédougou	anorg./nothing	SM4	cotton	0-15	5.25	41.9	0.45	50	39	12	18	11	20	27	8	4	12	0.69	0.06	11.9
Sébédougou	anorg./nothing	SM5	corn	0-15	5.04	42.5	0.82	42	45	14	17	11	14	30	11	4	14	1.07	0.07	14.4
Waly	organic/fumier	WF1	corn	0-15	4.93	39.6	0.14	39	33	28	8	21	9	16	13	5	28	0.44	0.04	11.6
Waly	**organic/fumier**	**WF2**	**corn**	**0-15**	**5.50**	**50.7**	**0.08**	**67**	**24**	**8**	**19**	**36**	**13**	**14**	**7**	**3**	**8**	**0.83**	**0.06**	**13.8**
Waly	organic/fumier	WF3	cotton	0-15	5.41	55.1	0.17	70	24	6	18	35	17	17	6	2	6	0.64	0.05	13.0
Waly	organic/fumier	WF4	cotton	0-15	5.80	49.5	0.06	69	23	8	17	34	18	15	6	2	8	0.93	0.07	12.5
Waly	organic/fumier	WF5	cotton	0-15	5.77	44.3	0.32	68	26	6	16	34	18	18	6	2	6	0.73	0.06	11.7
Waly	anorg./nothing	WM1	cotton	0-15	5.35	40.8	0.37	65	31	4	14	32	19	23	6	2	4	0.56	0.05	12.2
Waly	anorg./nothing	WM2	cowpea	0-15	5.23	44.5	0.24	67	26	7	17	32	18	17	6	3	7	0.57	0.05	12.4
Waly	anorg./nothing	WM3	cotton	0-15	4.52	38.0	0.32	58	36	6	15	27	16	28	7	2	6	0.53	0.04	12.8
Waly	**anorg./nothing**	**WM4**	**corn**	**0-15**	**5.31**	**50.8**	**0.19**	**79**	**14**	**7**	**36**	**28**	**15**	**9**	**4**	**2**	**7**	**0.73**	**0.06**	**12.7**
Waly	anorg./nothing	WM5	soy	0-15	5.22	51.4	0.26	70	25	5	25	30	16	18	6	1	5	0.42	0.04	11.9
Kari	organic/fumier	KF1	corn	0-15	5.43	53.4	0.19	28	63	9	3	4	21	49	12	3	9	0.68	0.06	11.5
Kari	organic/fumier	KF2	cotton	0-15	6.18	51.8	0.38	40	37	23	12	9	18	22	10	5	23	1.28	0.10	13.3
Kari	organic/fumier	KF3	cotton	0-15	6.66	68.4	0.62	28	62	10	9	7	12	44	13	4	10	1.14	0.09	12.6
Kari	**organic/fumier**	**KF4**	**cotton**	**0-15**	**5.78**	**50.5**	**0.44**	**51**	**37**	**12**	**14**	**15**	**21**	**18**	**10**	**9**	**12**	**1.13**	**0.11**	**9.9**
Kari	organic/fumier	KF5	corn	0-15	5.92	49.6	0.71	56	34	10	26	14	16	23	7	4	10	1.35	0.10	13.4
Kari	anorg./nothing	KM1	corn	0-15	6.12	55.8	0.44	27	54	19	5	5	16	35	14	5	19	1.00	0.07	13.7
Kari	anorg./nothing	KM2	corn	0-15	5.72	44.2	0.51	46	47	7	15	11	19	33	11	4	7	0.95	0.07	12.9
Kari	anorg./nothing	KM3	cotton	0-15	5.41	49.7	0.53	49	39	12	18	13	18	22	10	6	12	1.11	0.09	12.9
Kari	**anorg./nothing**	**KM4**	**cotton**	**0-15**	**5.78**	**50.4**	**0.73**	**53**	**38**	**9**	**25**	**12**	**16**	**27**	**8**	**3**	**9**	**1.38**	**0.11**	**13.0**
Kari	anorg./nothing	KM5	cotton	0-15	4.90	44.7	0.19	26	59	14	5	4	17	45	11	3	14	1.02	0.07	13.9

Supplementary Table 13 | Fertilizer types used on sampled fields and GPS-coordinates. Soils from fields chosen for the sorption study are highlighted in bold and light grey.

Sample site			Origin of manure or organic fertilizer applied in 2019[a]	Location[b]		Elevation
Village	Fertilizer	Soil_ID		Latitude	Longitude	(m a.s.l.)
Sébédougou	organic/fumier	SF1	cattle	11.25626	-3.611683	322
Sébédougou	organic/fumier	SF2	cattle	11.26033	-3.598493	300
Sébédougou	organic/fumier	SF3	cattle & sheep	11.27462	-3.63948	316
Sébédougou	organic/fumier	SF4	cattle	11.27936	-3.636616	314
Sébédougou	**organic/fumier**	**SF5**	**cattle**	**11.26854**	**-3.647866**	**333**
Sébédougou	anorg./nothing	SM1	-	11.25045	-3.608582	323
Sébédougou	anorg./nothing	SM2	-	11.25485	-3.599221	302
Sébédougou	**anorg./nothing**	**SM3**	**-**	**11.25775**	**-3.617965**	**335**
Sébédougou	anorg./nothing	SM4	-	11.26702	-3.630448	322
Sébédougou	anorg./nothing	SM5	-	11.27482	-3.648085	322
Waly	organic/fumier	WF1	cattle	11.21012	-3.707705	297
Waly	**organic/fumier**	**WF2**	**cattle**	**11.20718**	**-3.710422**	**301**
Waly	organic/fumier	WF3	cattle	11.20084	-3.710714	301
Waly	organic/fumier	WF4	cattle	11.19789	-3.710981	301
Waly	organic/fumier	WF5	cattle	11.19335	-3.711064	299
Waly	anorg./nothing	WM1	-	11.17978	-3.714767	280
Waly	anorg./nothing	WM2	-	11.18832	-3.710555	288
Waly	anorg./nothing	WM3	-	11.18902	-3.712498	283
Waly	**anorg./nothing**	**WM4**	**-**	**11.19147**	**-3.708281**	**289**
Waly	anorg./nothing	WM5	-	11.21813	-3.720314	293
Kari	organic/fumier	KF1	cattle	11.37689	-3.597652	325
Kari	organic/fumier	KF2	cattle	11.37545	-3.597742	319
Kari	organic/fumier	KF3	cattle	11.33847	-3.638355	311
Kari	**organic/fumier**	**KF4**	**cattle**	**11.34313**	**-3.633998**	**307**
Kari	organic/fumier	KF5	cattle & compost	11.32684	-3.645747	311
Kari	anorg./nothing	KM1	-	11.31432	-3.645813	337
Kari	anorg./nothing	KM2	-	11.31492	-3.646008	335
Kari	anorg./nothing	KM3	-	11.35887	-3.610465	338
Kari	**anorg./nothing**	**KM4**	**-**	**11.35901**	**-3.609922**	**335**
Kari	anorg./nothing	KM5	-	11.37092	-3.602486	322

[a] As described by field owners; soil samples were taken in 2019.

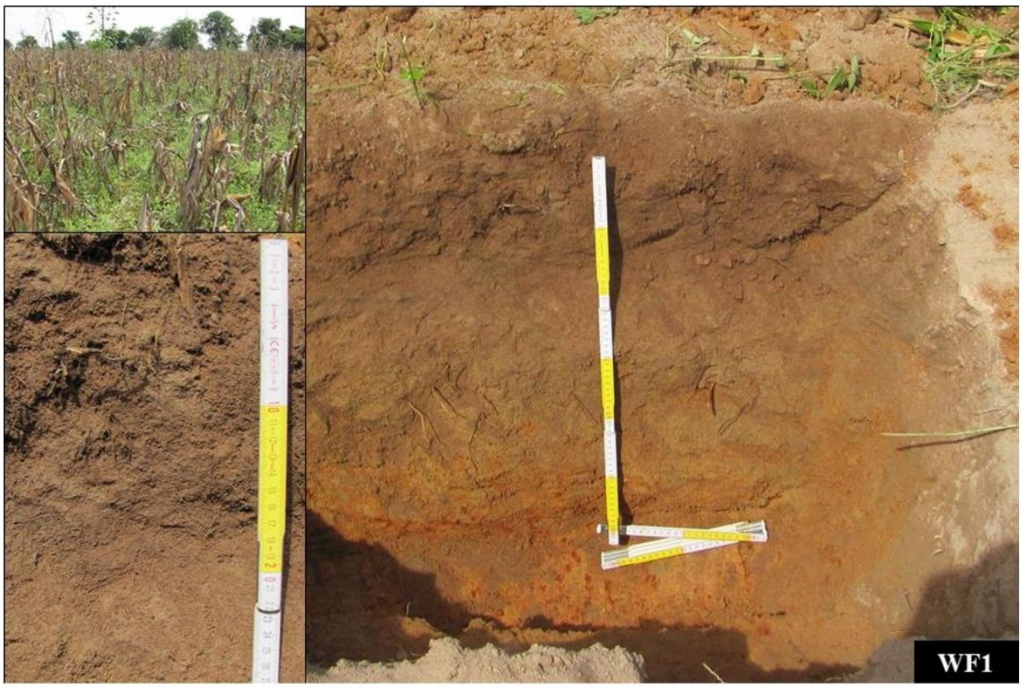
[b] First sampling point per field is given as approximation; all field auger samples are comprised of five subsamples.

Dash (-) indicates no manure or organic fertilizer were applied.

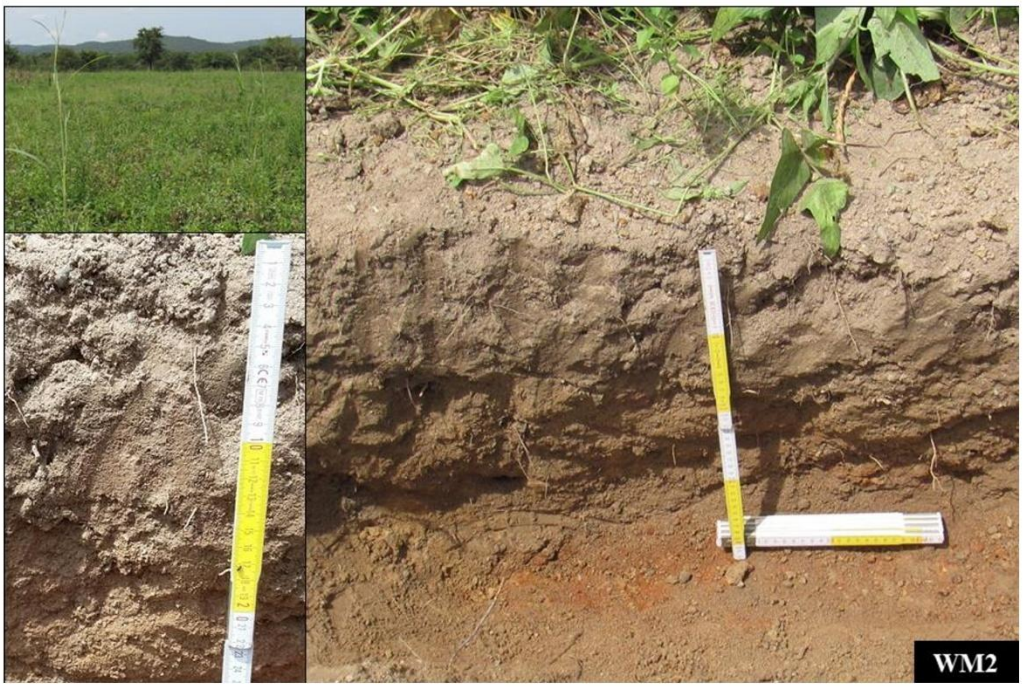
In the investigated area in south-western Burkina, six soil profiles were additionally described and classified. Soil descriptions, illustrations, and captions in Supplementary Figure 4 to Supplementary Figure 9 were provided by Daniel Frank Kaiser, Justus Liebig University Giessen, Germany.

Supplementary Figure 4 | Soil Profile on field SF1. Petroplinthic Umbric Plinthosol (loamic).

Supplementary Figure 5 | Soil profile on field SM1. Petroplinthic Plinthosol (Loamic).



Supplementary Figure 6 | Soil profile on field WF1. Acrisol (Arenic); (under the premise that lowest visible horizon qualifies as an argic horizon. Otherwise: Arenosol).



Supplementary Figure 7 | Soil profile on field WM2. Leptic Regosol (Arenic).

Supplementary Figure 8 | Soil profile on field KF1. Gleysol.

Supplementary Figure 9 | Soil profile on field KM2. Regosol (Loamic).

VII. Chemical analysis

Supplementary Table 14 | Chemicals used for ivermectin extraction, derivatization, and quantification.

Substance	CAS-no.	Supplier (brand)	Product-no.	Purity (%)
Ivermectin	70288-86-7	LGC-Standards	DRE-CA14488000	96.0
Doramectin	117704-25-3	LGC-Standards	DRE-C13083000	96.0
Acetonitrile	75-05-8	VWR International	20060.320	≥ 99.9
N-methylimidazole	616-47-7	Sigma-Aldrich	336092	> 99.0
Triethylamine	121-44-8	Sigma-Aldrich	T0886	> 99.0
Trifluoroacetic anhydride	407-25-0	Sigma-Aldrich	106232	> 99.0
Trifluoroacetic acid	76-05-1	Sigma-Aldrich	302031	> 99.0
Calcium chloride dihydrate	10035-04-8	Supelco	1.02382	> 99.0
Ethyl acetate	141-78-6	Honeywell Chemicals	31063	> 99.0

A. Ivermectin sample preparation protocol

Supplementary Table 15 | Stepwise protocols for ivermectin extraction from cattle plasma, cattle dung, and soil samples, and quantification with HPLC-fluorescence detection. Chemicals used refer to the list in Supplementary Table 14.

Extraction	**Cattle plasma**	**Cattle dung**
Polypropylene vial	15 mL	50 mL
Sample quantity	1000 µL, thawed	450 mg, freeze-dried
Target water content (add purified water)	n/a	85 %
Rehydrate for 24 h at room temperature	n/a	●
Internal standard doramectin	25 µL	100 µL
Add acetonitrile	3 mL	25 mL
Shake 5 s by hand	●	●
Ultrasonic bath (40 W/L)	30 min	15 min
Vortex mixer	30 s	n/a
Horizontal shaker for 30 min at 350 rpm	●	●
Vortex mixer	30 s	n/a
Ultrasonic bath (40 W/L)	30 min	15 min
Vortex mixer	30 s	n/a
Centrifugation for 30 min	●	●
Transfer supernatant with glass pipette	3 mL	10 mL
Evaporation under N_2 in a 60 °C water bath	●	●
Reconstitution	**Cattle plasma**	**Cattle dung**
Add acetonitrile	600 µL	1000 µL
Vortex mixer for 30 s	●	●
Ultrasonic bath (40 W/L)	30 min	15 min
Vortex mixer for 30 s	●	●
Horizontal shaker for 30 min at 350 rpm	●	●
Vortex mixer for 30 s	●	●
Ultrasonic bath (40 W/L)	30 min	15 min
Vortex mixer for 30 s	●	●
Filter through 0.45 µm syringe filter (polytetrafluoroethylene)	●	●
Transfer into amber glass 2 mL HPLC-vial	300 µL	700 µL
Derivatization	**Cattle plasma**	**Cattle dung**
After each reagent, close vial, shake 5 s, wait 3 min	●	●
N-methylimidazole:acetonitrile (1:1, v/v)	43 µL	100 µL
Triethylamine	21 µL	50 µL
Trifluoroacetic anhydride:acetonitrile (1:1, v/v)	43 µL	100 µL
Trifluoroacetic acid	21 µL	50 µL
Heat HPLC-Vials in oven for 30 min at 60 °C	●	●
Let HPLC-Vials cool for 20 min at room temperature	●	●

n/a = this step was not performed or not applicable

● = this step was performed

B. HPLC protocol

HPLC injection volume was 40 µL on an Agilent 1200 HPLC system. Mobile phases for the gradient elution were A (purified Milli-Q® water) and B (acetonitrile); flow 0.3 mL/min; gradient 0 to 10 min, 88 to 100 % B; 10 to 11 min, 100 % B; 11 to 20 min 100 to 88 % B. Stationary phase was a reverse-phase, 150 mm, C18, 3 µm column (Acclaim™ PolarAdvantage II, Thermo Fisher Scientific) and the HPLC oven temperature was 30 °C. The fluorescence detector was set at 364 nm for excitation and 463 nm for emission. Retention times for the peaks of interest were around 11.0 min for doramectin and 12.1 min for ivermectin.

C. Sorption study protocol

All experimental steps were performed under ambient laboratory conditions at 21 ± 1 °C. A stock solution was prepared at 1.5×10^6 µg/L by dissolving 15 mg ivermectin in 10 mL acetonitrile. From this, working solutions for the sorption study and the calibration series were diluted in acetonitrile. The calibration series was 1, 2, 5, 10, 50, 100, 500, 2500, 5000, and 10000 µg/L. Solutions were stored at -32 °C and kept at ambient temperature for at least 15 min before use. For the sorption series, final ivermectin concentrations in relation to the soil phase were 0.45, 1.5, 3, 22.5, and 45 µg/g to cover two orders of magnitude (as recommended in OECD test guideline 106, ref. [11]).

A 0.01 mol/L $CaCl_2$ solution, prepared in purified Milli-Q® water, served as aqueous phase. For each soil and replicate, 1000 ± 1 mg soil were suspended with 30 ± 0.3 mL $CaCl_2$ solution in custom 45 mL glass centrifuge vials with a polytetrafluoroethylene-coated silicon seal inside the screw cap. This was done in triplicates.

Closed glass vials were manually shaken for 10 s, wrapped in aluminum foil, fixed to an orbital innova® platform shaker (New Brunswick Scientific, USA), and pre-shaken at 120 rpm for 24 h. This speed was enough to keep the soil in suspension. Vials were removed from the shaker, reopened and 30 µL working solution were added with a 10-100 µL positive-displacement pipette. Controls and blanks underwent the same routine except for spiking. Processing order of all samples was randomized. Closed vials were again manually shaken for 10 s, fixed to the shaker, and agitated at 120 rpm for 48 h (sorption equilibrium time). Shaking times of 24 and 48 h were supported by comparable sorption studies.[12,13] Vials were recovered from the shaker and centrifuged at 880 *g* for 30 min in a Rotanta 460 R benchtop centrifuge (Andreas Hettich GmbH & Co. KG, Germany).

Sample processing followed the previously described technique[12] with a liquid-liquid extraction (LLE) step which was based on the reported procedure[13]. For the LLE, 25 mL supernatant from a centrifuged sample were transferred into a second 45 mL glass vial, and 5 mL ethyl acetate were added to the vial. The mixture was vortexed for 30 s and put to rest upright for 10 min to let the phases separate. Then, much as possible of the upper, ethyl acetate, phase was quickly transferred with a disposable borosilicate glass Pasteur pipette into a pre-weighted 15 mL polypropylene centrifuge vial. This extraction step was repeated once with the addition of another 5 mL ethyl acetate followed by the described procedure. The recovered solvent within the 15 mL vials was eventually weighed. With the solvent's density at the ambient temperature, the transferred volume was calculated. The solvent was then evaporated under a gentle stream of nitrogen, with vials in a water bath at 60 °C. After evaporation, vials were frozen and stored at -32 °C.

Subsequent reconstitution and derivatization of soil sorption samples were performed identically to the procedure described for cattle dung samples in Supplementary Table 15. Ivermectin was quantified using the HPLC-fluorescence detection protocol as described above.

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An Ecotoxicological View on Malaria Vector Control with Ivermectin-treated Cattle

Supplementary Information

Chapter: Modeling

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I. Content (Modeling) **1**

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II. Dynamic of ivermectin in cattle blood

For the IVM-BEPO® formulation, the ivermectin concentration in the plasma of the treated cattle was fitted to the number of days post injection using a Generalized Additive Model (GAM) with automatic choice of smoothing parameters. We used the "gam" function of the "mgcv" package (1) in "R" (2). The GAM model was then used to predict the mean concentration of ivermectin in bovine plasma from 1 to 211 days post-injection. For IVOMEC-D®, the dynamic of ivermectin plasma concentrations for a multi-administration scheme (once a month) was simulated with a 1 compartmental infusion absorption model with 5 injections times (linpk package, Benjamin Rich (2022). linpk: Generate Concentration-Time Profiles from Linear PK Systems. R package version 1.1.2).

III. Effect of ivermectin on Anopheles mortality:

We assume that a vector biting on a given day after host ivermectin injection, using either formulation (and treatment scheme), will experience an increased risk of death and, moreover, it will die at a new constant mortality rate governed by the amount of ivermectin in the cattle blood at the time the blood meal was taken (see above). A Cox proportional hazards survival model was used to describe how this concentration of ivermectin affects mortality. The relationship between the log of the concentration of ivermectin ingested by the mosquito and its mortality was modeled using a second-order polynomial function. The hazard from the survival model was converted into a mortality rate by multiplying the baseline mortality rate ($\mu_{v0} = 0.1$) by the relevant hazard for mosquitoes biting on each day post host ivermectin injection. We used the "coxph" function of the "survival" package (3) in "R" for this task.

IV. Malaria transmission model

A. Susceptible-Exposed-Infectious (SEI) model of *P. falciparum* transmission

The model described by Slater *et al.* (2014) (4) was modified to account for two types of host (cattle and human) and for the effect on vector mortality of two interventions (ivermectin in cattle and LLINs in humans).

State variables and parameters of the model are described in Supplementary Table M 1.

We defined the time that ivermectin is injected to cattle as s. The length of time that ivermectin has a mosquitocidal effect is denoted l and is taken as the number of days where the mortality rate is greater than the baseline mortality rate ($\mu_{v0} = 0.1$). We then define an 'on-off' switch to determine whether ivermectin is having an effect on the vector population or not.

Each day a proportion of mosquito blood meal is taken on cattle (*1-HBI*) of which a proportion (based on the ivermectin coverage rate C_{ivm}) will contain ivermectin. These vectors then move to a new compartment where they will have a higher mortality rate based on the amount of time after ivermectin injection where the bloodmeal was taken. Once vectors moved to the new compartment on the specified day, they will have that mortality rate for the rest of their lifespan. The mortality rate for vector biting on day i post ivermectin injection is denoted μ_v^{di} and is given by the vector mortality model (*i.e.,* the cox model). The mortality rate of all non- ivermectin blood fed mosquitoes equals the baseline mortality rate μ_{v0}.

Each day a proportion of susceptible mosquitoes take a blood meal on humans (*HBI*). A proportion of these vectors will move to the infected compartment based on the *P. falciparum* prevalence (P_{pf}) in

the human population and on an infectiousness probability (*k*). Infected vectors will move to the infectious compartment after *n* days (duration of the extrinsic incubation period of *P. falciparum*).

Among the vectors that take a blood meal on humans, a proportion μ_h will die due to the presence of LLINs.

Supplementary Table M 1 | State variables and parameters of the Susceptible-Exposed-Infectious (SEI) model of *P. falciparum* transmission.

State variables and parameters	Definition	Value
S_v	Susceptible vectors that have not taken a bloodmeal containing ivermectin	-
E_v	Exposed vectors that have not taken a bloodmeal containing ivermectin	-
I_v	Infectious vectors that have not taken a bloodmeal containing ivermectin	-
S_v^{di}	Susceptible vectors that took a bloodmeal containing ivermectin on day i post-injection	-
E_v^{di}	Exposed vectors that took a bloodmeal containing ivermectin on day i post- injection	-
I_v^{di}	Infectious vectors that took a bloodmeal containing ivermectin on day i post-injection	-
P_{pf}	Plasmodium falciparum prevalence in the human population	0.5
k	Infectiousness: probability that a vector become infectious while taking a blood meal on an infectious host	0.1
g	Duration of the gonotrophic cycle	2
BR	Biting rate: rate at which a vector takes a blood meal (in $days^{-1}$)	1/g
n	Duration of P. falciparum extrinsic incubation	11
s	Day of ivermectin injection	50
l	Duration of ivermectin efficacy (in days)	250
E	New vector births per day	300
μ_{v0}	Baseline daily mortality (The mortality rate of all non- ivermectin ingested mosquitoes)	0.1
μ_v^{di}	Daily mortality rate for vector biting on day i post ivermectin injection	Cox model
μ_h	Probability of death due to the LLINs (pre- and post-bite mortality) while searching for a blood meal.	Vector behavior model eq. (2)
HBI	Human Blood Index: Proportion of blood meals taken from humans	Vector behavior model eq. (3)
C_{ivm}	Proportion of cattle treated with ivermectin	0 or 1
p_{ivm}	Probability that a fed vector took its bloodmeal from an ivermectin treated cattle	(1 - HBI) x C_{ivm}
p_{inf}	Probability that a fed vector becomes infected (i.e., moves to the exposed compartment)	k x P_{pf} x HBI

Using the following function to move mosquitoes to a new compartment:

$$\delta(t,\tau,d) = \begin{cases} 1 & \text{if } \tau \le t \le \tau + d \\ 0 & \text{otherwise.} \end{cases} \qquad (1)$$

The following equations are used to describe the system:

Susceptible, no ivermectin

$$\frac{dS_v}{dt} = E - \mu_{v0} S_v - BR \cdot S_v(\mu_h + (1-\mu_h)(P_{inf} + P_{\mathrm{IVM}} \cdot \delta(t,s,l)))$$

Susceptible, ivermectin (for i = 1,…,l)

$$\frac{dS_v^{di}}{dt} = \delta(t,s,l) \cdot (1-\mu_h) \cdot P_{\mathrm{IVM}} \cdot BR \cdot S_v - S_v^{di}((1-\mu_h) \cdot BR \cdot P_{inf} - \mu_v^{di} - BR \cdot \mu_h)$$

Exposed, no ivermectin

$$\frac{dE_v}{dt} = (1-\mu_h) \cdot P_{inf} \cdot BR \cdot S_v - E_v(1/n - \mu_{v0} - \delta(t,s,l) \cdot (1-\mu_h) \cdot P_{\mathrm{IVM}} \cdot BR - BR \cdot \mu_h)$$

Exposed, ivermectin (for i = 1,… ,l)

$$\frac{dE_v^{di}}{dt} = \delta(t,s,l) \cdot (1-\mu_h) \cdot P_{\mathrm{IVM}} \cdot BR \cdot E_v + (1-\mu_h) \cdot BR \cdot P_{inf} \cdot S_v^{di} - E_v^{di}(1/n - \mu_v^{di} - BR \cdot \mu_h)$$

Infectious, no ivermectin

$$\frac{dI_v}{dt} = 1/n \cdot E_v - I_v(\mu_{v0} - \delta(t,s,l) \cdot (1-\mu_h) \cdot P_{\mathrm{IVM}} \cdot BR - BR \cdot \mu_h)$$

Infectious, ivermectin (for i = 1,…,l)

$$\frac{dI_v^{di}}{dt} = \delta(t,s,l) \cdot (1-\mu_h) \cdot P_{\mathrm{IVM}} \cdot BR \cdot I_v + 1/n \cdot E_v^{di} - I_v^{di}(\mu_v^{di} - BR \cdot \mu_h)$$

B. Vector behavior model

A vector behavior model was developed to feed the SEI model of *P. falciparum* transmission with variable values of (i) probability that a bloodmeal taken on cattle (1 - *HBI*) and (ii) probability of death due to the LLINs μ_h (for vectors in search of a bloodmeal) under various scenario:

- varied cattle:human ratio in the host population (i.e., twice more cattle, equal number of human and cattle, or twice more humans),

- varied levels of LLIN coverage in the human host population (20, 50 or 80 %) and,

- varied host preference phenotype (human *vs.* cattle) in the *Anopheles* population as measured in dual choice olfactometer experiments.

We assume that the probability at which a vector chooses a host species (human or cattle) is independent on the origin of a previous blood meal and that LLIN have no remote effect (i.e., no deterrence). We assume as well that mosquitoes host preferences are fixed. Parameters of the vector behavior model are described in Supplementary Table M 2.

In addition to **Fig. 3b–c** from the main manuscript, the **Supplementary Figure M 1** on page 7 shows refined calculations of our modeling approach.

Supplementary Table M 2 | Parameters used in the vector behavior model.

Parameter	Definition	Value	Source
C_h	Net coverage: proportion of the human population that uses LLINs	Variable (0.2; 0.5; 0.8)	-
$r_{C:H}$	Cattle:human ratio	Variable (0.5; 1; 2)	-
a	Preference for human (against cattle) as it would be measured in a dual choice olfactometer	Variable (0.2; 0.5; 0.8)	-
P_{ii}	Proportion of exposure to bite during which LLIN is in use	0.9	(5,6)
$\mu_{h.u}$	Death probability when entering an experimental hut (EH) with unprotected host	0.0485	
$\mu_{h.p}$	Death probability when entering an experimental hut (EH) with a LLIN protected host	0.4438	(7), data for Permanet2 in the Kou Valley area.
f_{hu}	Successful feeding probability when surviving in a hut with an unprotected human	0.7859	
f_{hp}	Successful feeding probability when surviving in a hut with a protected human	0.1076	

Calculation of the probability of death due to the LLINs (for a vector looking for a blood meal)

We assume that a malaria vector can take a blood meal either on human or on cattle. Human are considered either protected (if they use LLINs) or unprotected. The probability for a vector that an encountered human is protected by a LLIN equals the proportion of human P_p that are protected by a LLIN. Giving the LLIN coverage (C_h) in the human population and the proportion of exposure to bite during which LLIN is in use (P_{ii}), we calculated P_p as follows:

$$P_p = C_h \cdot P_{ii} \qquad (2)$$

The use of LLINs in the human population increases the probability of mortality for vectors searching for human hosts. From experimental huts trials (EHT) data, we calculated μ_{hp}, the probability of death for a vector entering a hut with a human protected by a LLIN, and μ_{hu}, the probability of death for one entering a hut with an unprotected human (i.e., the control hut). In order to obtain the probability μ_{hLLLIN} of death due to the insecticide on the LLIN for a vector entering a hut with a LLIN protected human, we applied Abbott's correction to μ_{hp} as follows:

$$\mu_{hLLLIN} = \frac{(\mu_{hp} - \mu_{hu})}{(1 - \mu_{hu})}$$

μ_h <- ph.p * pref.h * μ_hLLLIN

Knowing the proportion of hosts P_p that is protected by a LLIN (equation (1)), we can deduce the probability of death due to the LLIN (μ_h) for a mosquito willing to take a blood meal on humans as follows:

$$\mu_h = P_p \cdot a \cdot \mu_{hLLLIN} \cdot A_h \qquad (3)$$

Calculation of the probability that a vector feeds on cattle

Each day, the proportion of fed vectors having taken a blood meal on humans is the realized Human blood index (*HBI*). It can be expressed as:

$$HBI = \frac{F_h}{(F_h + F_c)} \quad (4)$$

With F_h, the probability that, on one night, a vector successfully feeds on human and F_c, the probability that a vector successfully feeds on cattle.

F_h and F_c are the product of, for each host, its relative availability in the community (A), the probability of successful feeding (f) when encountering this host and the preference (a) of the vector population for this host:

$$F_h = A_h \cdot f_h \cdot a \quad (5)$$

$$F_c = A_c \cdot f_c \cdot (1 - a) \quad (6)$$

The preference (a) for human hosts is defined as the intrinsic preference (i.e., phenotypic) of the vector population, i.e., the proportion of a sample of the vector population that would choose the human host in a dual-choice (human vs. cattle odor) olfactometer.

Relative availability of each host can be expressed as the proportion it represents in the total host population. Giving a defined ratio of cattle per human ($r_{C:H}$) in a community and the proportion P_p (equation (1)) of human that are protected by a LLIN, we can calculate:

The proportion A_h of hosts that are humans:

$$A_h = 1/(1 + r_{C:H}) \quad (7)$$

The proportion A_p of hosts that are protected human:

$$A_p = A_h \cdot P_p \quad (8)$$

The proportion A_u of hosts that are unprotected human:

$$A_u = A_h \cdot (1 - P_p) \quad (9)$$

And the proportion A_c of hosts that are cattle:

$$A_c = 1 - A_h \quad (10)$$

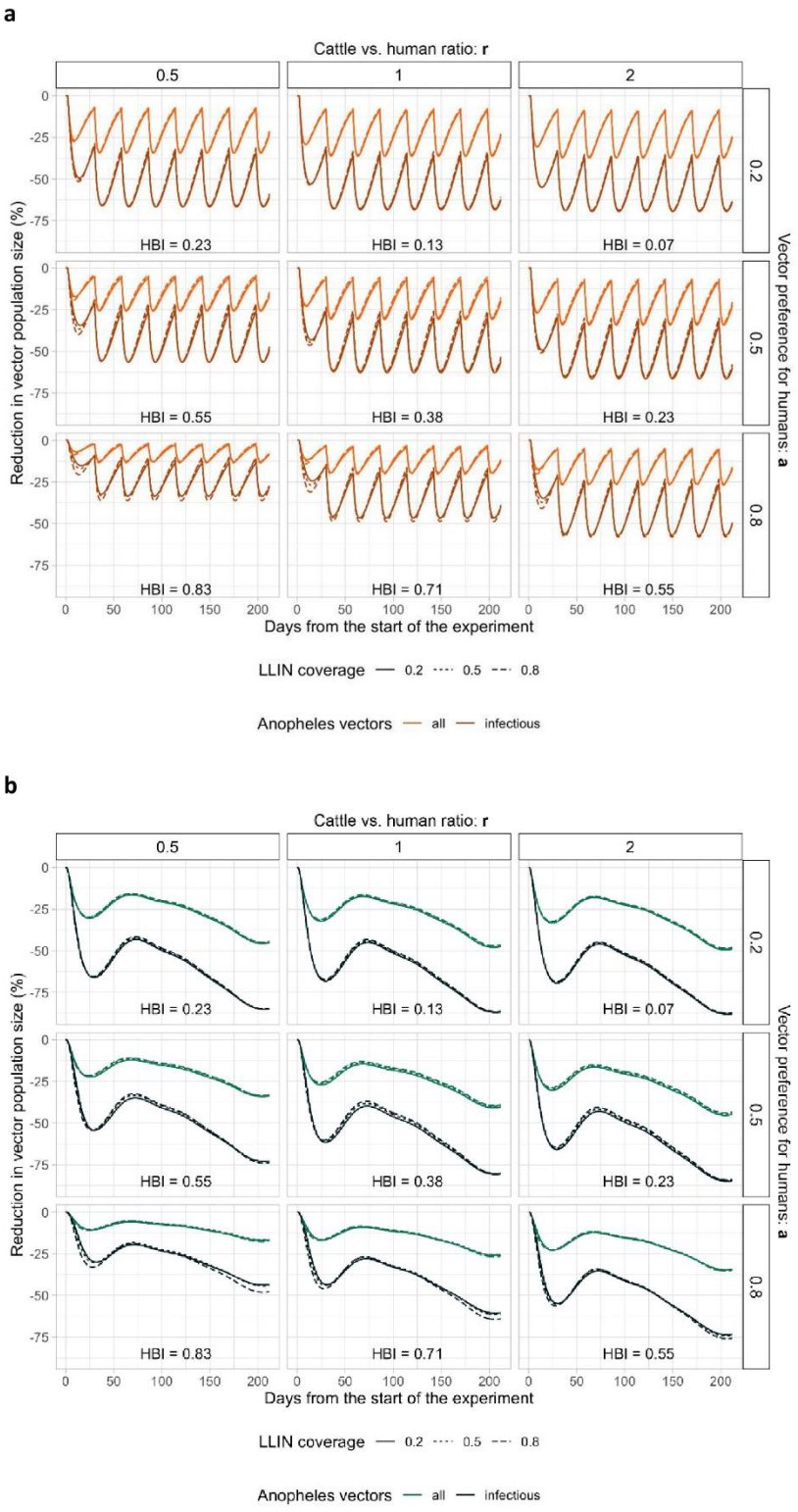
Successful feeding probabilities when surviving in a hut with a protected (f_{hp}) or unprotected human (f_{hu}) were deduced from EHT data by dividing the number of alive blood fed vectors collected in the huts by the sum of alive mosquitoes in the hut (for both treated and control huts, respectively). Successful feeding probability when encountering cattle was considered equal to the one of unprotected human. We therefore can calculate F_h and F_c as follows:

$$F_h = (A_p \cdot f_{hp} + A_u \cdot f_{hu}) \cdot a \quad (11)$$

$$F_c = A_c \cdot f_{hu} \cdot (1 - a) \quad (12)$$

F_h and F_c can then be used to calculate *HBI* for solving equation (4).

The probability that a fed vector took its blood meal on a calf is equal to *1 – HBI*.



Supplementary Figure M 1 | Vector population modeling for efficacy prediction of IVOMEC-D® (a, the model simulates up to 8 injections) and IVM-BEPO®(b, single injection). Intermediary outputs. The same model as in the main manuscript was used, and the same figure legend as for Fig. 3b–c applies. Outputs from additional, intermediary scenarios are given using the following values for the different model parameters: cattle to human ratio of 1, vector preference of 0.5, and LLIN coverage of 0.2 and 0.8.

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Anhang

Liste der begutachteten Veröffentlichungen

Um den Eigenanteil an den der Dissertation zugrundeliegenden Veröffentlichungen zu definieren, wird die CRediT Taxonomie entsprechend der deutschen Übersetzung verwendet. Während des Promotionszeitraums wurden drei Arbeiten als Erstautor veröffentlicht.

1) Nieman, C.C., Floate, K.D., Düring, R.-A., Heinrich, A.P., Young, D.K., Schaefer, D.M., 2018. **Eprinomectin from a sustained release formulation adversely affected dung breeding insects**. *PLOS ONE* 13 (8), e0201074. doi:10.1371/journal.pone.0201074.

Beitrag: Untersuchung | Methodik | Validierung | Visualisierung | Schreiben – Überprüfung und Überarbeitung

2) Heinrich, A.P., Zöltzer, T., Böhm, L., Wohde, M., Jaddoudi, S., El Maataoui, Y., Dahchour, A., Düring, R.-A., 2021. **Sorption of selected antiparasitics in soils and sediments**. *Environmental Sciences Europe* 33 (1), 77. doi:10.1186/s12302-021-00513-y.

Beitrag: Untersuchung | Formale Analyse | Visualisierung | Validierung | Schreiben – Originalentwurf

3) Laber, L., Jandowsky, A., Frölich, K., Heinrich, A.P., Düring, R.-A., Donath, T.W., Eichberg, C., 2023. **Dose-dependent in vivo effects of formulated moxidectin on seedling emergence of temperate grassland species**. *Science of the Total Environment* 905, 167152. doi:10.1016/j.scitotenv.2023.167152.

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Beitrag: Konzeptualisierung | Formale Analyse | Untersuchung | Methodik | Validierung | Visualisierung | Schreiben – Originalentwurf | Geteilte Erstautorenschaft mit Pooda, S.H.

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Beitrag: Untersuchung | Formale Analyse | Schreiben – Überprüfung und Überarbeitung

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Beitrag: Konzeptualisierung | Formale Analyse | Untersuchung | Methodik | Validierung | Visualisierung | Schreiben – Originalentwurf

Liste der Konferenzbeiträge als Erstautor

Heinrich, A, Düring, R-A. **Dringend gesucht: Die SETAC-Expertise für umweltfreundliche „One Health" Lösungen mit Antiparasitika**. Vortrag. SETAC GLB Jahrestagung 2024. Gießen.

Heinrich, A, Kruckenfellner, L, Ebke, P, Düring, R-A. **Antiparasitika im Fokus – Eprinomectin und sein Schicksal im Gewässer**. Poster. SETAC GLB Jahrestagung 2024. Gießen.

Heinrich, A, Pooda, HS, Roberge, C, Düring, R-A, Mouline, K. **From Science to Practice: Ecotoxicological Insights in Malaria Vector Control in Burkina Faso**. Poster. SETAC Europe Annual Meeting 2024, Sevilla, Spanien.

Heinrich, A, Pooda, HS, Roberge, C, Düring, R-A, Mouline, K. **A One Health Solution to Control Residual Malaria Transmission: The Not So Hidden Added Value of Ecotoxicology and Environmental Chemistry**. Poster. SETAC Europe Annual Meeting 2023, Dublin, Irland.

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Hintergrundtabellen

Tabelle A 1 | Detailübersicht der verwendeten Chemikalien.

Stoff	CAS-Nr.	Lieferant	Artikel-Nr.	Reinheit (%)
Ivermectin	70288-86-7	LGC-Standards	DRE-CA14488000	94,4
Doramectin	117704-25-3	LGC-Standards	DRE-C13083000	95,0
Abamectin	71751-41-2	Sigma-Aldrich	31732	98,6
Moxidectin	113507-06-5	LGC-Standards	DRE-CA15335000	94,6
Acetonitril	75-05-8	VWR International	20060.320	≥ 99,9
Propan-2-ol	67-63-0	VWR International	20880.320	≥ 99,8
N-Methylimidazol	616-47-7	Sigma-Aldrich	336092	> 99,0
Triethylamin	121-44-8	Sigma-Aldrich	T0886	> 99,0
Trifluoressigsäureanhydrid	407-25-0	Sigma-Aldrich	106232	> 99,0
Trifluoressigsäure	76-05-1	Sigma-Aldrich	302031	> 99,0
Calciumchlorid-Dihydrat	10035-04-8	Sigma-Aldrich	1.02382	> 99,0

Tabelle A 2 | Volumina der verwendeten Chemikalien für Sorptions-, Desorptions- und Extraktionsprotokolle.

Sorptions-Desorptions-Versuche	Probenmenge	Zugabe $CaCl_2$ (0,01 mol/L) (mL)	Aliquot (mL)	Derivatisiertes Volumen (µL)	Reagenzienzugabe (µL) [a]			
					NMI	TEA	TFAA	TFA
Sorption	1 g (dw)	30	25/20 [b]	700	100	50	100	50
Desorption	keine neue Einwaage	25/20 [b]	25/20 [b]	700	100	50	100	50
Probentyp zur Extraktion	**Probenmenge**	**Zugabe Acetonitril (mL)**	**Aliquot (mL)**	**Derivatisiertes Volumen (µL)**	**Reagenzienzugabe (µL) [a]**			
					NMI	TEA	TFAA	TFA
Boden	5 g (fw)	25	10	700	100	50	100	50
E. fetida	3 Würmer	10	8	700	100	50	100	50
A. caliginosa	3 Würmer	10	8	700	100	50	100	50
L. terrestris	1 Wurm	25	10	700	100	50	100	50
Rinderdung	450 mg (dw)	25	10	700	100	50	100	50
Rinderplasma	1000 µL	3	3	300	43	21	43	21

[a] Zugabe der Reagenzien zur Derivatisierung: NMI = N-Methylimidazol/Acetonitril (1:1, v/v);
TEA = Triethylamin; TFAA = Trifluoressigsäureanhydrid/Acetonitril (1:1, v/v); TFA = Trifluoressigsäure
[b] jeweils 25 mL für Böden, Sedimente, Artificial Soil, Ton, Sand sowie 20 mL für Torf

Tabelle A 3 | Einzelwerte zu Datenbankabfragen der berechneten log K_{OW}-Werte.

Datenbank/Seite	ChemSpider	PubChem	VCCLAB	ChEMBL	ChEMBL	EPI Suite	ADMETlab
Parameter/Version	ACD/LogP	XLogP3-AA	ALOGPS 2.1	CX LogP	AlogP	KOWWIN v1.68	logP
Substanz							
Eprinomectin B_{1a}	6.22	3.80	4.14	5.56	5.52	4.93	5.15
Eprinomectin B_{1b}	5.69	3.50	3.90	5.51	5.13	4.44	4.79
Avermectin B_{1a}	6.50	3.80	4.22	5.85	5.38	4.39	5.13
Avermectin B_{1b}	5.97	3.50	3.91	5.40	4.99	3.90	4.76
Doramectin	7.16	4.50	4.31	6.27	5.91	5.26	6.06
Ivermectin B_{1a}	6.61	4.10	4.37	5.83	5.60	4.61	5.07
Ivermectin B_{1b}	6.08	3.80	4.04	5.38	5.21	4.11	4.71
Selamectin	6.83	5.40	5.09	6.21	6.07	4.92	6.12
Milbemycin A4 Oxime	6.75	4.70	5.60	n/a	n/a	4.51	4.94
Milbemycin A3 Oxime	6.21	4.10	5.23	n/a	n/a	4.02	4.61
Moxidectin	8.43	4.30	5.30	5.67	5.73	6.70	5.36

Quellen: Chemspider (ChemSpider, 2024); PubChem (PubChem, 2024); VCCLAB (Tetko et al., 2005); ChEMBL (ChEMBL, 2024b, 2024a; Zdrazil et al., 2024); EPI SUITE (EPI Suite, 2024); ADMETlab (Fu et al., 2024)
n/a = kein Wert verfügbar

Eidesstattliche Erklärung

Erklärung gemäß § 17 (2) der Promotionsordnung des Fachbereichs 09 vom 07.07.2004 in der Fassung des 2. Änderungsbeschlusses vom 19.05.2019

Ich erkläre: Ich habe die vorgelegte Dissertation selbständig und ohne unerlaubte fremde Hilfe und nur mit den Hilfen angefertigt, die ich in der Dissertation angegeben habe. Alle Textstellen, die wörtlich oder sinngemäß aus veröffentlichten Schriften entnommen sind, und alle Angaben, die auf mündlichen Auskünften beruhen, sind als solche kenntlich gemacht. Bei den von mir durchgeführten und in der Dissertation erwähnten Untersuchungen habe ich die Grundsätze guter wissenschaftlicher Praxis, wie sie in der „Satzung der Justus-Liebig-Universität Gießen zur Sicherung guter wissenschaftlicher Praxis“ niedergelegt sind, eingehalten.

Andre Patrick Heinrich

Ergänzende Erklärung

Während der Vorbereitung dieser Arbeit wurde ChatGPT von OpenAI verwendet, um die Klarheit und Sprache in bestimmten Abschnitten des Textes zu verbessern. Während und nach dem Einsatz dieses Werkzeugs wurde der Inhalt gründlich überprüft und persönlich bearbeitet, um Genauigkeit und Vollständigkeit zu gewährleisten. Der Verfasser übernimmt die volle Verantwortung für den Inhalt der Arbeit.

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Abb. 4 wurde erstellt aus eigenen Aufnahmen (A. Heinrich).

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