



## Review

## Eco-toxicological effects of the avermectin family with a focus on abamectin and ivermectin



Shahla Hosseini Bai\*, Steven Ogbourne

GeneCology Research Centre, Faculty of Science, Health, Education and Engineering, University of the Sunshine Coast, Maroochydore DC, QLD 4558, Australia

## H I G H L I G H T S

- Avermectins are highly effective and naturally produced compounds.
- Abamectin is unique natural compound used for crop protection and pharmaceuticals.
- Avermectin may pose eco-toxicity to non-target species but can be alleviated.
- Food contamination may occur but not sufficient to pose health risk.

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## A B S T R A C T

Avermectin family members are categorised as highly effective but toxic natural products that are used as pharmaceuticals in both humans and animals and for crop protection. Abamectin and ivermectin are the two most commonly used compounds from this family with abamectin the only compound to be used for both crop protection and pharmaceutical purposes. Avermectins are produced by the soil dwelling actinomycetes *Streptomyces avermitilis* and despite having complex chemical structures, they are manufactured via synthesis in large scales for commercial use.

Although the extent of the eco-toxicological effects of avermectins is not well documented, reports of eco-toxicity exist. Avermectins have short half-lives and their residues can be eliminated through different food processing methods. However, avermectins can persist in water, sediment, soil and food products and therefore management practices that reduce the potential risks associated with eco-toxicity of these highly toxic compounds need to be further developed. This manuscript provides a critical review of the eco-toxicological risks and the potential for food contamination associated with avermectin use.

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\* Corresponding author.

E-mail address: [shosseini@usc.edu.au](mailto:shosseini@usc.edu.au) (S.H. Bai).

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## 1. Introduction

Avermectins were discovered in 1967 in fermentation broths of an actinomycete culture received from the Kitasato Institute in Japan, following an intensive search designed to find natural products with anthelmintic activity (Lasota and Dybas, 1991). It was subsequently shown that avermectins are produced by the soil dwelling actinomycete, *Streptomyces avermitilis* (Kwon et al., 2010; Hüter, 2011). Avermectins represent a class of macrocyclic lactones with nematocidal, acaricidal and insecticidal activity (Lasota and Dybas, 1991), which are now marketed as agricultural, veterinary and pharmaceutical agents (Geary, 2005; Copping and Duke, 2007; Canga et al., 2008). Avermectins are highly effective against targeted species and have remained popular over the last two decades with sales of ivermectin alone (used in animal health) greater than US\$1 billion per annum during that period (Crump and Omura, 2011).

Avermectin family members include moxidectin, milbemycin oxime, doramectin, selamectin, abamectin, ivermectin and eprinomectin but abamectin and ivermectin are the most commonly used compounds of this family. The chemical structure of avermectins is closely related to 16-membered macrocyclic lactones but avermectins are categorised as neither antibacterial nor antifungal compounds (Campbell, 2012). Avermectins are mainly distinguished from those groups by possessing a bisoleandroxyloxy substituent located at the C<sub>13</sub> (Shoop et al., 1995). Avermectins contain eight structural components including A<sub>1a</sub>, A<sub>1b</sub>, A<sub>2a</sub>, A<sub>2b</sub>, B<sub>1a</sub>, B<sub>1b</sub>, B<sub>2a</sub> and B<sub>2b</sub> (Shoop et al., 1995). Usually a and b compounds are mixed (80%:20% respectively) and therefore the groups are known as A<sub>1</sub>, A<sub>2</sub>, B<sub>1</sub>, B<sub>2</sub>. Differences of each group are summarised in Table 1. Abamectin and ivermectin (Fig. 1; Table 1) are active against helminths and arthropods (Lumaret et al., 2012). Group a and b components belong to sec-butyl and isopropyl homologues respectively, which possess similar toxicological and functional activities and therefore it is unnecessary to separate group a and b components (Horvat et al., 2012).

Avermectins are classified as neurotoxins, which act through the glutamate and/or  $\gamma$ -amino butyric acid (GABA)-gated chloride channel (Duce et al., 1995; Bloomquist, 2003; Hüter, 2011). GABA is a neurotransmitter that functions between nerve and muscle cells (Lasota and Dybas, 1991). In invertebrates, however, the glutamate-gated chloride (GluCl) channels are assumed to be the primary target of avermectins and are vital to the control of invertebrate functions (Pemberton et al., 2001; Wolstenholme, 2012). Although the precise physiological function of the GluCl channels is not well

understood, it is known that in the presence of avermectins, the chloride channel remains open resulting in signal blockage between neuron and muscle due to increased chloride permeability (Lasota and Dybas, 1991; Dent et al., 1997). The exposed parasites are subsequently paralysed resulting in uncoordinated movement (Kwon et al., 2010), starvation and ultimately death due to inhibition of pharyngeal pumping (Geary et al., 1993).

The relevance of the mechanism of action and the side effects of avermectins in mammals is not clear. For example, in mammals, GABA is present in brain cells and hence secured by the blood-brain barrier, which makes this drug relatively safe for vertebrates (Omura, 2008). However, GluCl channels that exist in insects, nematodes and mites, are closely related to the cys-loop channel receptor family, which include the GABA type A receptors found in mammals (Nakao et al., 2015).

Somewhat surprisingly, specific mechanisms for different members of the avermectin family are yet to be identified. However, different avermectins may in fact have similar modes of action with each compound having different pharmacokinetic profiles, which may be influenced by drug formulation, administration route and the target animal species (Borges et al., 2007; Gopal et al., 2004). For example, abamectin successfully treated a strain of *Trichostrongylus colubriformis* in sheep, which had previously shown resistance to ivermectin, with the activity reported to be associated with differences in the structure and pharmacokinetics between the agents (Gopal et al., 2004). Given that little is known about the interaction between avermectins and their receptors, particularly in mammals, it is necessary to further develop our understanding of the mode of action of avermectin family members in both target and non-target species.

Abamectin is the only compound from this family used for both crop protection and pharmaceutical purposes (Shoop et al., 1995). Abamectin also known as Avermectin B<sub>1</sub>, AVM, C-076 and MK-936 with trade names of Avomec, Agri-Mek, Avid, Dynamec, Vertimec and Zephyr (Krieger, 2001; Campbell, 2012), is a mixture of two avermectins (avermectin B<sub>1a</sub> and avermectin B<sub>1b</sub>) initially introduced by Merck Sharp and Dohme Agvet as an insecticide and acaricide, but is now produced by Syngenta (Copping and Duke, 2007).

Avermectins, particularly abamectin and ivermectin, are now extensively used and thus pose potential ecological risks. This manuscript aims to critically review and summarise the potential risks associated with avermectin use (with a focus on abamectin and ivermectin) for non-target species in different ecosystems as well as possible food chain contamination.

## 2. Degradation and persistence

Avermectin derivatives are generally classified as *cis-trans* isomers that are not always less active than the parental molecule (Fisher, 1990). For example, two spotted spider mites were exposed to different avermectin (AVM) derivatives (e.g. AVM B1-8,9-Oxide; 10,11-dihydro AVM B1; 10,11,22,23-tetrahydro AVM B1 and 10-fluoro-10,11-dihydro AVM B1), some of which resulted in 100% mortality at concentrations comparable to the parent compounds (~0.5 ppm) (Fisher, 1990). However, photo-degradation in soil produces a mixture of  $\alpha$ -hydroxy-compounds and the corresponding ring-opened aldehyde, which in the case of abamectin are

**Table 1**  
Structural differences among avermectin family members (Shoop et al., 1995).

A-components	Methoxy group at the 5-position
B-components	Hydroxy group at the 5-position
1-components	Double bond between the 22- and 23-position
2-components	Single bond with a hydroxy group at the 23-position
a-components	Secondary butyl side chain at the 25-position
b-components	Isopropyl substituent at the 25-position

Abamectin: 80% avermectin B<sub>1a</sub> (22,23-dihydroavermectin B<sub>1a</sub>: C<sub>48</sub>H<sub>72</sub>O<sub>14</sub>) and 20% avermectin B<sub>1b</sub> (22,23-dihydroavermectin B<sub>1b</sub>: C<sub>47</sub>H<sub>70</sub>O<sub>14</sub>).  
Ivermectin: 80% 22,23-dihydroavermectin B<sub>1a</sub>: C<sub>48</sub>H<sub>74</sub>O<sub>14</sub> and 20% 22,23-dihydroavermectin B<sub>1b</sub>: C<sub>47</sub>H<sub>72</sub>O<sub>14</sub>, 80:20.

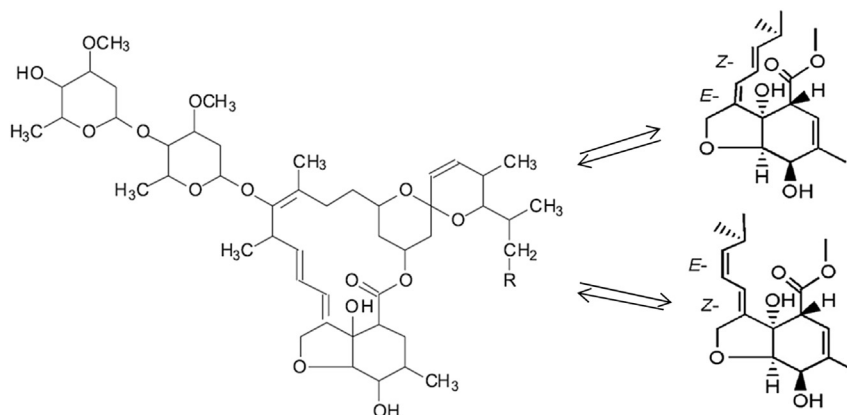


Fig. 1. Structure of avermectin (B<sub>1a</sub>: R = CH<sub>3</sub> and B<sub>1b</sub>: R = H) adapted from Kolberg et al. (2009) and photo-isomerisation under UV light adapted from Horvat et al. (2012).

both less toxic than the parent molecule (Wislocki et al., 1989; Bull et al., 1984).

The main pathway of degradation for avermectin family members in the presence of light is photo-degradation (Halley et al., 1993; Demchak and Dybas, 1997). Both abamectin and ivermectin can be rapidly degraded when exposed to light, on plant surfaces, in soil, dung and water (Halley et al., 1993). Photodegradation occurs at specific wavelengths below the UV-B range (Escalada et al., 2008). In the absence of UV-light these compounds can also undergo degradation by reactive oxygen species (ROS) pathways (Escalada et al., 2008). Recently, it was shown that avermectin B<sub>1a</sub> can produce different products through different degradation pathways including re-arrangement forming 8,9-Z-isomer, hydroxylation forming 8a-hydroxy-avermectin B<sub>1a</sub>, oxidation forming 8a-oxo-avermectin B<sub>1a</sub>, demethylation forming 3''-O-desmethyl-avermectin B<sub>1a</sub> and photolytic cleavage forming an acetic acid derivative (European Food Safety Authority, 2010). More recently, biodegradation of abamectin by the soil bacterium ZJB-14120 (*Stenotrophomonas maltophilia*) and GB-01 (*Burkholderia* sp.) has been reported (Ali et al., 2010; 2012; Wang et al., 2015). This can be a particularly important degradation pathway for abamectin that has been immobilised by binding to organic matter, clay and minerals in soil.

The degradation products of abamectin may differ in soil, water and plants depending on environmental conditions (Escalada et al., 2008; European Food Safety Authority, 2010). For example, under laboratory conditions in soil, the degradation products of avermectin B<sub>1a</sub> was reported to be 8a-hydroxyavermectin B<sub>1a</sub> and the corresponding ring-opened aldehyde (Wislocki et al., 1989; Bull et al., 1984). Whereas in liquids, at 300 nm UV light, the diene functional group of abamectin was transformed to 14,15-Z and 16,17-Z in less than 1 h (Fig. 1) (Horvat et al., 2012). In plants, avermectin B<sub>1a</sub> is dissipated very quickly producing several different compounds, however, only 8,9-Z-isomer ( $\delta$ -8,9 isomer) of avermectin B<sub>1a</sub> is considered to be of major toxicological significance (European Food Safety Authority, 2010). The residue detected when ivermectin was bound to sediment included ivermectin monosaccharide and ivermectin aglycone (Prasse et al., 2009).

Half-lives of members of the avermectin family can vary between 0.5 and 23 days in different substrates including soil, faeces and plant surfaces (Table 2). Whilst the half-life of avermectins in water can be short (within hours; Table 2), if the compound is adsorbed to sediment, the half-life may be quite long (up to 100 d; Table 2). Moye et al. (1987) reported a long half-life for avermectin in soil (Table 2) but the detection rates were relatively low and the rate of application was up to 50% higher than manufacturers'

recommendations and application occurred three times. As a result, Moye et al. (1987) concluded that soil residue detection and half-lives under farming conditions are likely to be lower than that reported in their research. Bull et al. (1984) found that avermectin B<sub>1a</sub> persistence in soil was dose dependent (Table 2), which likely explains the high half-life reported by Moye et al. (1987). Erzen et al. (2005) detected abamectin and doramectin up to 70 days after sheep treatments in soil, soil-faeces and faeces but the concentration of abamectin after day 6 was low ( $<1.4 \mu\text{g kg}^{-1}$  dry soil) in dry soil. Such prolonged doramectin detection was subsequently related to dry conditions and therefore those authors concluded that weather conditions are one of the key driving factors involved in avermectin degradation (Erzen et al., 2005). The half-life of avermectin family members seems to vary significantly under different field conditions. Therefore, there is a need to undertake research in different landscapes and under different climatic conditions and to complete meta-analyses of existing data to better understand the persistence of avermectin family members in the environment.

### 3. Crop protection

To date, abamectin (and its derivative emamectin benzoate) remains the sole member of the avermectin family to be used in crop protection and is categorised as highly toxic with acute oral and dermal toxicity of category I and II respectively (US Environmental Protection Agency, 2004) with low LD<sub>50</sub> concentrations for different groups of organisms (Table 3). However, the popularity of abamectin is growing due to its effective pest control for crops, in particular of devastating mites (Table 4). For the purpose of crop protection, abamectin is available as a concentrate emulsion, emulsifiable concentrate (EC) and baits to control mites, leaf miners, suckers, beetles and fire ants (Copping and Duke, 2007) in a vast array of crops including tree fruits, nuts, annual crops (e.g. rice and cotton), herbs and vegetables (Table 4).

#### 3.1. Ecotoxicological risks of abamectin in crop protection

Abamectin may become a source of concern for non-targeted beneficial insects and mites as well as evolving resistance in pests, when used in crop protection. Bees have a very low contact and oral LD<sub>50</sub> (0.002 & 0.009  $\mu\text{g bee}^{-1}$ , respectively; Wislocki et al., 1989) and given their potential exposure via contact with sprayed foliage and foraging in contaminated flowers, might be at particular risk of acute toxicity. However, exposure to treated plants 24 h following application of abamectin did not pose any toxicity on

**Table 2**  
Examples of avermectin family member persistence in different substrates.

Substrate	Rate	Half life	References
Faeces	Abamectin 0.2 mg kg <sup>-1</sup> bw <sup>a</sup>	23 d	Kolar et al. (2006)
Faeces	Doramectin 0.2 mg kg <sup>-1</sup> bw <sup>a</sup>	22 d	Kolar et al. (2006)
Faeces	Abamectin 0.2 mg kg <sup>-1</sup> bw <sup>a</sup>	30 d	Eržen et al. (2005)
Faeces	Doramectin 0.2 mg kg <sup>-1</sup> bw <sup>a</sup>	18 d	Eržen et al. (2005)
Soil	Abamectin Not provided	2.7 d	Liu et al. (2011)
Soil	AvermectinB <sub>1a</sub> 0.1 ppm	14 d	Bull et al. (1984)
Soil	AvermectinB <sub>1a</sub> 1 ppm	28 d	Bull et al. (1984)
Soil	AvermectinB <sub>1a</sub> 50 ppm	56 d	Bull et al. (1984)
Soil	<sup>14</sup> C-AvermectinB <sub>1a</sub> 0.025–0.030 ai.acre: three applications (25–50% higher than maximum recommended rates)	102–132 d	Moye et al. (1987)
Soil-faeces mixture	Abamectin 0.2 mg kg <sup>-1</sup> bw <sup>a</sup>	23 d	Eržen et al. (2005)
Soil-faeces mixture	Ivermectin Not provided	7–14 d	Halley et al. (1993)
Soil-faeces mixture	Doramectin 0.2 mg kg <sup>-1</sup> bw <sup>a</sup>	27 d	Eržen et al. (2005)
Water (Paddy water)	Abamectin Not provided	Up to 4.5 d	Liu et al. (2011)
Water	Not provided	0.5 d	Wislocki et al. (1989)
Water	Ivermectin 1 µg in 300 mL water	6 h	Prasse et al. (2009)
Water/sediment system	Ivermectin 1 µg in 300 mL water	127 d	Prasse et al. (2009)
Sediment	Ivermectin 0.1, 0.2, 0.4, 0.8 and 1.6 mg kg <sup>-1</sup>	Over 100 d	Davies et al. (1998)
Plant	Abamectin Not provided	5 h	Matsuura et al. (2011)
Plant – Surface application on cotton leaf	AvermectinB <sub>1a</sub> 100 µg leaf <sup>-1</sup>	<24 h	Bull et al. (1984)
Plant – Cotton (oil, lint and seed)	Abamectin 0.8, 14.5, 18.5, 22.5, 29.0 g a.i ha <sup>-1</sup> 1.9 EC	Not detected post-harvest	Jasmine et al. (2011)
Milk	Abamectin 0.2 mg kg <sup>-1</sup> bw <sup>a</sup>	1.9–3.8 d	Cerkvenik-Flajs et al. (2007)
Milk	Ivermectin 0.2 mg kg <sup>-1</sup> bw	1.90–2.46 d	Imperiale et al. (2004)
Milk	Ivermectin		
Egg	Ivermectin 0.4 mg kg <sup>-1</sup> for 5 days	1.73 d (only detected in yolk)	Moreno et al. (2015)
Liver of broiler chickens	Ivermectin 2 µg g <sup>-1</sup> of diet for 5 weeks	No residue found	Miller (1990)
Liver and breast of squabs	Ivermectin 3.3 µg mL <sup>-1</sup> of drinking water in parents pigeons for 3 days	Detected for 1 week	Bennett and Cheng (2012)

<sup>a</sup> Single subcutaneous dose; a.i stands for active ingredient.

**Table 3**  
Toxicity of abamectin and ivermectin in different groups of non-target species.

Non-target species	LD <sub>50</sub> or LC <sub>50</sub>	Relative toxicity	References
<i>Abamectin</i>			
Rat	Oral: 10 mg kg <sup>-1</sup>	Very toxic	Commercial labels
Rabbit	Dermal >2000 mg kg <sup>-1</sup>	Slightly toxic	Commercial labels
Quail	>2000 mg kg <sup>-1</sup>	Non toxic	Commercial labels
Honey bees	>0.009 µg bee <sup>-1</sup>	Highly toxic	Commercial labels
Trout (96 h)	>0.004 mg L <sup>-1</sup>	Very highly toxic	Commercial labels
Earthworm (14 d)	33 mg kg <sup>-1</sup>	Moderately toxic	Lewis et al. (2015)
Duck	<77 mg kg <sup>-1</sup>	Highly toxic	Lewis et al. (2015)
Daphnia (48 h)	0.0001 mg L <sup>-1</sup>	Highly toxic	Lewis et al. (2015)
Midge (28 d)	0.000081 mg L <sup>-1</sup>	Highly toxic	Lewis et al. (2015)
Duckweed (7 d)	3.9 mg L <sup>-1</sup>	Moderately toxic	Lewis et al. (2015)
<i>Ivermectin</i>			
Rat	Oral: 50 mg kg <sup>-1</sup>	Moderately toxic	Commercial labels
Rat	Dermal: >660 mg kg <sup>-1</sup>	Slightly toxic	Commercial labels
Mouse	Oral: 29.5 mg kg <sup>-1</sup>	Moderately toxic	MSDS
Rabbit	Dermal: 406 mg kg <sup>-1</sup>	Slightly toxic	Commercial labels
Dog	Oral: 80 mg kg <sup>-1</sup>	Moderately toxic	Commercial labels

bees (Wislocki et al., 1989; Lumaret et al., 2012) and for two main reasons, it is possible that high exposure to bees may not be of concern; (a) it is very unlikely that the inside of flowers receive significant amounts of pesticide and (b) abamectin has a short half-life (<24 h) on the plant surface (Table 2). Despite this, it is not recommended to apply abamectin when plants are flowering (European Food Safety Authority, 2008).

Abamectin is also highly toxic to beneficial mites. For example, *Phytoseius plumifer* was exposed to abamectin at rates 10-fold lower than recommended field rates (i.e. 0.0018 µg cm<sup>-2</sup>), which resulted in 100% mortality within the first 24 h (Noii et al., 2008). The toxicity of abamectin for *P. plumifer* was also reported by Hamed

et al. (2011) and Nadimi et al. (2009). However, there are also studies that show that abamectin was not toxic for *Phytoseiulus persimilis* (Malezieux et al., 1992; Cote et al., 2002). It is difficult to verify such contradictory results but there are reports that show abamectin is also found to be highly toxic for other beneficial predators (Youn et al., 2003; Li et al., 2006; Biondi et al., 2012; Pakyari and Enkegaard, 2015) and therefore can potentially affect longer term crop health by causing an imbalance in predator and pest population ratios. Nonetheless, despite being highly toxic for beneficial invertebrates (Table 5), rapid dissipation on crops minimises the threat for beneficial invertebrates (Table 2).

Evolving pest resistance against abamectin is another eco-

**Table 4**

Withholding periods for abamectin (trees, herbs &amp; vegetables) and ivermectin (milk &amp; meat) as shown in commercial labels.

Crop/product	Withholding period	Time restriction for grazing or entry to orchard	Targeted pests
<i>Trees</i>			
Apples	14 d	14 d	<i>Tetranychus urticae</i> ; <i>Panonychus ulmi</i> ; <i>Typhlocyba pomaria</i>
Pears	28 d	14 d	<i>T. urticae</i> ; <i>Panonychus ulmi</i> ; yellow mite; pear rust mite; pear psylla
Avocados	14 d	14 d	<i>Oligonychus perseae</i> ; <i>Scirtothrips perseae</i>
Citrus	7 d	Do not graze in treated orchard	<i>Tegolophus australis</i> ; <i>Phyllocoptera oleivora</i> ; <i>Polyhagotarsonemus latus</i> ; <i>Phyllocnistis citrella</i> ; <i>Scirtothrips citri</i>
Stone fruits	21 d	Do not graze in treated orchard	<i>T. urticae</i> ; Pacific spider mites; <i>P. ulmi</i>
Nuts	21 d	Do not graze in treated orchard	<i>T. urticae</i> , <i>P. ulmi</i> ; Pacific spider mites; strawberry spider mite
Grapes	28 d	REI: 12 h –4 d	<i>T. urticae</i> ; Pacific spider mites; variegated leafhoppers; western grape leafhoppers; willamette spider mite
<i>Animal products</i>			
Milk	28 d		Gastrointestinal Roundworms ( <i>Ostertagia ostertagi</i> , <i>Haemonchus placei</i> <i>Trichostrongylus axei</i> , <i>Trichostrongylus colubriformis</i> , <i>Cooperia oncophora</i> , <i>Cooperia punctate</i> , <i>Cooperia eriasurnabada</i> , <i>Strongyloides papillosus</i> , <i>Oesophagostomum radiatum</i> , <i>Oesophagostomum venulosum</i> , <i>Trichuris spp.</i> , <i>Nematodirus spp.</i> ), Eyeworm ( <i>Thelazia spp.</i> ), Lungworms ( <i>Dictyocaulus viviparus</i> ), Cattle Grubs ( <i>Hypoderma bovis</i> , <i>Hypoderma lineatum</i> ), Mites ( <i>Chorioptes bovis</i> , <i>Sarcoptes scabiei</i> var. <i>bovis</i> ), Lice ( <i>Linognathus vituli</i> , <i>Haematopinus eurysternus</i> , <i>Damalinia bovis</i> , <i>Solenopotes capillatus</i> ), Horn Flies ( <i>Haematobia irritans</i> ) Gastrointestinal roundworms ( <i>Haemonchus contortus</i> , <i>Ostertagia circumcincta</i> , <i>Trichostrongylus colubriformis</i> ), Lungworm ( <i>Dictyocaulus filarial</i> , Itchmite ( <i>Psorergates ovis</i> ), Nasal bot ( <i>Oestrus ovis</i> ), Buffalo Fly ( <i>Haematobia irritans exigua</i> ), Tick ( <i>Boophilus microplus</i> )
Meat (beef)	28 d (injectable) 42 –48 d (pour on)		
Meat (lamb)	10 d (drench)		
Meat (deer)	35 d (pour on)		
<i>Herbs and vegetables</i>			
Celeriac	7 d	–	<i>T. urticae</i>
Tuberous vegetables	14 d	–	Colorado potato beetles; liriomyza leafminers; potato psyllids; spider mites
Onion and bulb	30 d	–	Liriomyza leafminers; thrips
Cucurbit	7 d	–	<i>T. urticae</i> ; leafminers
Tomato	3 d	3 d	<i>T. urticae</i> ; <i>Aculops hyocopersici</i> ; <i>Liriomyza</i> spp.
Dry beans	7 d	–	<i>T. urticae</i> ; Liriomyza leafminers
Fruiting vegetables	7 d	7 d	Broad mites, colorado potato beetles; liriomyza leafminers; potato psyllids; spider mites; <i>Thrips palmi</i> ; tomato psyllids; tomato russet mites
Hops excluding California <sup>a</sup>	4 d	4 d	<i>T. urticae</i>
Leafy vegetables	14 d	–	Carmine mite; liriomyza leafminers; two spotted mite
Mints	30 d	–	<i>T. urticae</i>
Herbs	14 d (chive: 7 d)	Do not graze in treated orchard	<i>T. urticae</i> , liriomyza leafminers
<i>Other groups</i>			
Strawberries	3 d	–	<i>T. urticae</i> ; aphids; carmine mites; strawberry spider mites; thrips
Ornaments	DO NOT cut or graze for stock food	–	<i>T. urticae</i>
Cotton	20 d	20 d	<i>T. urticae</i> ; <i>Tetranychus cinnabarinus</i> ; <i>Helicoverpa punctigera</i>

REI: Restricted entry intervals.

<sup>a</sup> In some labels withholding period is recommend to be 28 days.

toxicological concern, which may result in increased usage. For example, abamectin is considered to be the most effective acaricide to control two devastating mites, *Tetranychus urticae* and *Panonychus ulmi*, in different cropping systems (Nauen et al., 2001). However, Sato et al. (2005) reported a moderate resistance in *T. urticae* populations collected from strawberry farms subjected to abamectin application for the past ten years with at least 6 applications in the last six years. There are also reports of abamectin resistance in other pests including leaf-miners and the diamond-back moth (Siqueira et al., 2001; Ferguson, 2004; Pu et al., 2010). Interestingly, it has been shown that the abamectin resistance is not stable (Sato et al. 2005; Nicastro et al., 2010). Sato et al. (2005) showed that the abamectin resistance in *T. urticae* decreased from 75% to 15% within six month of cessation of abamectin application. Therefore, abamectin should not be applied every year, instead treatment gaps of several generations should be implemented such that any evolved resistance disappears from the population (Pu et al., 2010).

It is now well established that abamectin is highly toxic for non-target predatory insects and mites and may cause some degree of

resistance in targeted pests. Therefore, in frequently used situations, the efficiency of the pesticide and the number of predatory insects may reduce, which over the long term may result in more severe pest outbreaks with inevitable devastating consequences. Fortunately, and due mainly to the short half-life of abamectin, the introduction of basic management practices can minimise exposure of non-target insects and mitigate environmental eco-toxicity risks. For example, integrated pest management to reduce repeated application, decrease the time of exposure of the non-target species and minimise the risk of pest resistance can be introduced and programs to educate the public about these practices can be implemented.

#### 4. Pharmaceutical and veterinary uses

Avermectins have also become valuable therapeutics since the 1980s, being used to treat parasites in both animals and humans (Geary, 2005; Canga et al., 2008) and have been labled as ‘wonder drugs’ (Geary, 2005; Omura, 2008). Avermectins were initially developed to control onchocerciasis in humans but were then

**Table 5**No observed effect concentrations (NOECs/LOEC), EC<sub>50</sub> or LC<sub>50</sub> of avermectins for non-target species in different mediums.

Exposure	Target group	Compound	NOEC/LOEC (mg kg <sup>-1</sup> bw) of exposure <sup>b</sup>	Duration	EC <sub>50</sub>	LC <sub>50</sub> (mg.kg <sup>-1</sup> dry wt)	Measured variable/response	References
<i>Soil</i>								
0–150 mg kg <sup>-1</sup>	<i>Folsomia candida</i>	Abamectin	1.5	28 d	13 mg kg <sup>-1</sup>	67	–	Kolar et al. (2008)
0–150 mg kg <sup>-1</sup>	<i>Enchytraeus crypticus</i>	Abamectin	8	28 d	3 mg kg <sup>-1</sup>	111	–	Kolar et al. (2008)
0–150 mg kg <sup>-1</sup>	<i>Eisenia andrei</i>	Abamectin	9.8	28 d	–	18	–	Kolar et al. (2008)
0–150 mg kg <sup>-1</sup>	<i>Eisenia andrei</i>	Dormactin	8.4	28 d	–	228	Weight loss of surviving earthworms	Kolar et al. (2008)
0–5 mg kg <sup>-1</sup>	<i>Eisenia fetids</i>	Abamectin	0.25	28 d	0.46 mg kg <sup>-1</sup> drywt	–	Biomass	Jensen et al. (2007)
0–5 mg kg <sup>-1</sup>	<i>Eisenia fetids</i>	Abamectin	–	28 d	1.03 mg kg <sup>-1</sup> drywt	–	Reproduction	Jensen et al. (2007)
0–5 mg kg <sup>-1</sup>	<i>Eisenia fetids</i>	Abamectin	0.25	28 d	0.43 mg kg <sup>-1</sup> drywt	–	Hatching	Jensen et al. (2007)
6–50 mg kg <sup>-1</sup>	<i>Eisenia fetida</i>	Avermectin	–	14 d	–	17.6	–	Sun et al. (2005)
0.5–2.5 mg kg <sup>-1</sup>	<i>Folsomia fimetaria</i>	Abamectin	0.5	21 d	0.48 mg kg <sup>-1</sup>	–	Survival	Diao et al. (2007)
0.5–2.5 mg kg <sup>-1</sup>	<i>Folsomia candida</i>	Abamectin	>2.5	21 d	>2.50 mg kg <sup>-1</sup>	–	Survival	Diao et al. (2007)
0–500 mg kg <sup>-1</sup>	<i>Enchytraeus cryptalis</i>	Abamectin	50	21 d	78.2 mg kg <sup>-1</sup>	–	Survival	Diao et al. (2007)
0.5–5 mg kg <sup>-1</sup>	<i>Eisenia fetida</i>	Abamectin	5	10 weeks	>5.0 mg kg <sup>-1</sup>	–	Survival	Diao et al. (2007)
0.5–2.5 mg kg <sup>-1</sup>	<i>Folsomia fimetaria</i>	Abamectin	<0.25	21 d	0.05 mg kg <sup>-1</sup>	–	Reproduction	Diao et al. (2007)
0.5–2.5 mg kg <sup>-1</sup>	<i>Folsomia candida</i>	Abamectin	0.25	21 d	0.19 mg kg <sup>-1</sup>	–	Reproduction	Diao et al. (2007)
0–500 mg kg <sup>-1</sup>	<i>Enchytraeus cryptalis</i>	Abamectin	10	21 d	12.7 mg kg <sup>-1</sup>	–	Reproduction	Diao et al. (2007)
0.5–5 mg kg <sup>-1</sup>	<i>Eisenia fetida</i>	Abamectin	<0.25	10 weeks	0.06 mg kg <sup>-1</sup>	–	Reproduction	Diao et al. (2007)
0–7 mg kg <sup>-1</sup>	<i>Eisenia andrei</i>	Abamectin	0.85	–	3.91 mg kg <sup>-1</sup>	–	–	Nunes and Espíndola (2012)
<i>Faeces</i>								
0.2 mg kg <sup>-1</sup> bw (subcutaneous)	<i>Folsomia candida</i>	Abamectin	0.81	7 d	1.4 mg kg <sup>-1</sup>	1	–	Kolar et al. (2008)
0.2 mg kg <sup>-1</sup> bw (subcutaneous)	<i>Enchytraeus crypticus</i>	Abamectin	0.81	7 d	0.94 mg kg <sup>-1</sup>	1.1	–	Kolar et al. (2008)
0.2 mg kg <sup>-1</sup> bw (subcutaneous)	<i>Eisenia andrei</i>	Abamectin	>1.4	7 d	>1.4 mg kg <sup>-1</sup>	>1.4	–	Kolar et al. (2008)
0.2 mg kg <sup>-1</sup> bw (subcutaneous)	<i>Euoniticellus fulvus</i> (dung beetle)	Ivermectin	–	–	–	–	Delayed development	Lumaret et al. (1993)
Pour-on (cattle) 500 µg kg <sup>-1</sup> bw	<i>Liatongus minutus</i> (dung beetle)	Ivermectin	–	–	–	–	Delayed development- Reduced egg-adult survival in the first 14 days	Iwasa et al. (2005)
Pour-on (cattle) 500 µg kg <sup>-1</sup> bw	<i>Aphodius constans</i> (dung beetle)	Ivermectin	–	–	–	590 µg kg <sup>-1</sup> dung	–	Lumaret et al. (2007)
Injectable (cattle) 200 µg kg <sup>-1</sup> .bw	<i>Coleoptera</i> spp.	Ivermectin	–	–	–	–	No effect on richness of species	Kryger et al. (2005)
<i>Crop protection</i>								
	Bees	Abamectin	–	24 h	–	0.002 µg bee <sup>-1</sup>	Survival	Wislocki et al. (1989)
	Bumblebee	Abamectin	–	72 h:Oral	–	0.07 µg bumblebee <sup>-1</sup>	Survival	Marletto et al. (2003)
	Bumblebee	Abamectin	–	72 h: Topical contact	–	0.14 µg bumblebee <sup>-1</sup>	Survival	Marletto et al. (2003)
10% of the recommended farm application	<i>Phytoseius plumifer</i>	Abamectin	–	24 h	–	–	Survival	Noii et al. (2008)
<i>Water</i>								
	<i>Lumbriculus variegatus</i>	Ivermectin	–	72 h	–	560 nM	–	Ding et al. (2001)
	<i>Daphnia magna</i>	Abamectin	0.0047 µg L <sup>-1</sup>	21 d	0.25 µg L <sup>-1</sup>	–	–	Tisler and Erzen (2006)
	Zebrafish	Abamectin	–	96 h	50.4 µg.L <sup>-1</sup>	–	–	Tisler and Erzen (2006)

(continued on next page)

Table 5 (continued)

Exposure	Target group	Compound	NOEC/LOEC (mg kg <sup>-1</sup> bw)	Duration of exposure <sup>b</sup>	EC <sub>50</sub>	LC <sub>50</sub> (mg.kg <sup>-1</sup> dry wt)	Measured variable/response	References
Dissolved state	<i>Daphnia similis</i>	Abamectin	—	48 h	5.1 ng.L <sup>-1</sup>	—	—	Novelli et al. (2012)
	<i>Danio rerio</i>	Abamectin	—	48 h	33 µg.L <sup>-1</sup>	—	—	Novelli et al. (2012)
	<i>Chironomus xanthus</i>	Abamectin	—	96 h	2.67 µg.L <sup>-1</sup>	—	—	Novelli et al. (2012)
	<i>Salmo salar</i>	Ivermectin	—	96 h	—	3 µg kg <sup>-1</sup>	—	Kilmartin et al. (1997)
Injection	<i>Salmo salar</i>	Ivermectin	—	96 h	—	500 µg kg <sup>-1</sup>	—	Kilmartin et al. (1997)
Sediments	Trout	Abamectin	—	58 h	4 µg L <sup>-1a</sup>	—	—	Jenčić et al. (2006)
	<i>Corophium lövutator</i>	Ivermectin	0.05 mg kg <sup>-1</sup>	10 d	—	0.18 mg kg <sup>-1</sup>	Survival	Davies et al. (1998)
	<i>Asterias rubens</i>	Ivermectin	5 mg kg <sup>-1</sup>	10 d	—	23.6 mg kg <sup>-1</sup>	Survival	Davies et al. (1998)

<sup>a</sup> LD75.<sup>b</sup> To estimate EC50 or LD50.

extended to control a vast array of human parasites (Ottesen and Campbell, 1994; Geary, 2005; Canga et al., 2008). Economic damage of animal parasites can also be very significant, which makes effective drugs like those in the avermectin family extremely popular (Cringoli et al., 2009). As a result, they are now used to control onchocerciasis, lymphatic filariasis, strongiloidiasis, scabies, head lice, ancylostomiasis, anterobiasis, trichuriasis and sea lice (Davies and Rodger, 2000; Canga et al., 2008; Patra, 2010). Recently, there are also clinical trials to examine the wider potential uses of this group of drugs to combat infectious diseases including malaria, dengue fever and demodicidosis (<https://clinicaltrials.gov/ct2/home>). In the case of malaria, the results seems promising but additional investigations are required to ensure safety (Chaccour et al., 2013).

#### 4.1. Eco-toxicological risks of avermectins in pharmaceutical and veterinary use

##### 4.1.1. Soil organisms

Avermectins are potentially toxic to soil invertebrates but the majority of data that highlights this is derived from in vitro experiments under controlled conditions or from contact to the faeces of cattle treated with avermectins (Kolar et al., 2006, 2008; Jensen et al., 2007). Soil nematodes, earthworms, protozoa and collembola are usually used as bio-indicators to investigate land use management practices in soil (King and Hutchinson, 2007) and some of these groups have been used to examine abamectin toxicity in different studies with many reporting a dose dependent responses following exposure (Jensen et al., 2007; Kolar et al., 2008). For example, sub-lethal doses were used in a trial to investigate abamectin toxicity in the earthworm (*Eisenia fetida*) and toxicity was observed at 0.25 mg kg<sup>-1</sup>. Furthermore, no offspring were produced when abamectin levels exceeded 5 mg kg<sup>-1</sup> and cocoon hatching was significantly decreased when *E. fetida* exposure rates were higher than 1.5 mg kg<sup>-1</sup> (Jensen et al., 2007). Changes in reproduction due to abamectin exposure have also been reported for other soil species (Diao et al., 2007; Jensen et al., 2007; Kolar et al., 2008). However, other studies have shown no negative effects on earthworm reproduction (Kolar et al., 2008) or egg hatch of *Deraeocoris brevis* following abamectin exposure (Kim et al., 2006).

Soil and faeces contamination following treatment of cattle with avermectin family members may affect both soil and dung dwellers

(Sun et al., 2005; Kolar et al., 2008; Jochmann and Blanckenhorn, 2016). However, the effects of avermectin residues in faeces on soil dwellers depends on (a) residue concentration, (b) administration route, (c) time after treatment and (d) cattle density in the pasture (Borges et al., 2007; Kolar et al., 2008; Liebig et al., 2010; Lumaret et al., 2012). Additionally, some species may have the potential to tolerate relatively high exposures to avermectin family members without being significantly affected. Supporting this, it was previously shown that when earthworms were exposed, nearly 95% of the avermectin residues were eliminated within 24 h following cessation of feeding with avermectin residues (Sun et al., 2005).

Based on the available literature, soil contamination with avermectin family members may be a source of concern for some but not all species (Jochmann and Blanckenhorn, 2016). Whilst, the Environmental Risk Assessment (ERA) of Pharmaceuticals did not consider ivermectin to be a source of concern for dung dwellers (Liebig et al., 2010), Liebig et al. (2010) suggested that the ERA guidance may not be applicable in high intensity situations and the estimate of predicted environmental concentrations (PECs) for ivermectin in soil was potentially too low. Hence, it seems appropriate to apply risk mitigation measures when ivermectin is used in high intensity reared animal farms. These could include not treating the cattle in the same pasture every season, prevent spreading manure of treated animals, limit access of the treated cattle to surface water and improve disposal and sewage treatment techniques (Liebig et al., 2014). There are very few comprehensive toxicity studies using other avermectin compounds on non-targeted species, which presents a major gap in knowledge.

##### 4.1.2. Aquatic organisms

Water contamination can occur from both runoff following crop protection or from pharmaceutical drugs used for aquatic farming. Avermectins are not likely to be detected in high concentrations in water due to their relatively short half-lives (Table 2). However, avermectin residues in water have not been well documented and therefore this assumption must be viewed with caution, particularly when they have been classified as 'H410' very toxic to aquatic life with long lasting effects. For example, reports that show abamectin and ivermectin are highly toxic for some aquatic species due to the fact that avermectins can pass the blood–brain barrier in some aquatic species (Høy et al., 1990; Novelli et al., 2012, 2016).

Thus, if water is contaminated through run-off and/or accidental introduction, abamectin becomes a major source of concern for some aquatic species (Table 5). For example, abamectin (Vertimec® 18EC) was applied at the recommended rate of 0.75 mL L<sup>-1</sup>, after which samples of runoff water were collected to investigate toxicity for aquatic species (Braun et al., 2012). The EC<sub>50</sub> (48 h) for *Daphnia similis* was found to be at 7-fold dilutions of the runoff samples (Braun et al., 2012), which contained abamectin residues at 5.54 µg L<sup>-1</sup> (Braun et al., 2012); 20 times less than the concentration used by Xu et al. (2005) to study abamectin toxicity in rosy barbs where reported no major cytotoxicity of abamectin for rosy barb. As a general premise, water-management conservation technologies, careful handling and reduced number of applications may need to be implemented to prevent contaminated runoff entering aquatic systems (Novelli et al., 2012). However, in the absence of comprehensive investigations, the extent of abamectin residues in waters remains unclear.

Avermectin family members, particularly ivermectin, are approved for use as treatments in fish farming. However, this is not the case in all countries, and due to ivermectins' highly effective control of sea lice, it is known to be used in some countries without the manufacturers recommendation (Omura, 2008). The safety margin of ivermectin between targeted and non-targeted species is very small and thus residues in fish faeces and unconsumed food pellets can become a source of concern for aquatic species (Davies and Rodger, 2000). However, Davies and Rodger (2000) argue that accumulation in farmed fish is highly unlikely as avermectins strongly bind to soil and sediment organic matter (Davies and Rodger, 2000). Interestingly, this may highlight potential toxicological issues for soil and sediment dwellers rather than fish in aquatic systems (Davies et al., 1998; Omura, 2008). Consequently, implementation of practices to mitigate the risks of avermectins in fish farming is extremely important. Approval of avermectins currently used without the manufacturers recommendation would ensure safety margins are established and documented, likely resulting in more judicious use; in high risk farms, the number of applications and/or the applied doses may require reduction; and strict environmental quality standards need to be implemented (Haya et al., 2005). The majority of studies investigating the toxicity of ivermectin for aquatic species are based on acute toxicity and investigation to explore the chronic effects of ivermectin on aquatic species remains a major gap of knowledge (Liebig et al., 2010).

## 5. Humans and higher order animals

Other than a large report on abamectin provided by the European Food Safety Authority (2015), there is limited documentation available to indicate whether avermectin family members are of significant eco-toxicological concern for humans or higher order animals. However, acute poisoning in humans seems unlikely following the report of a patient consuming five times the reported lethal dose of abamectin (51 mg kg<sup>-1</sup>) who had a full recovery following immediate treatment (Aminiahadashti et al., 2014). Chronic and sub-chronic toxicity at low exposures may be of more concern, however there are no robust studies available and as a result the magnitude of potential toxicity for humans or higher order animals is poorly understood (Martens and Perry, 2013). Based on studies conducted primarily in the rat and the dog, the European Food and Safety Authority (2008) concluded that with regards to general toxicology, abamectin is almost completely absorbed in the gastrointestinal tract following IV or oral administration (bioavailability ~86%) and is subsequently distributed throughout all major tissues and organs before being rapidly eliminated from the body in the faeces. Abamectin is very toxic if inhaled or swallowed and therefore the classification of 'T+, R48/25 Toxic, danger of

serious damage to health by prolonged exposure if swallowed' was recommended (European Food Safety Authority, 2008).

The data that demonstrate cytotoxicity, genotoxicity and reproductive toxicity are not particularly robust and the majority of conclusions are based on in vitro trials (Molinari et al., 2010; European Food Safety Authority, 2008). The European Food Safety Authority (2015) concluded that abamectin has no carcinogenic potential, however we identified two studies reporting potential negative reproductive effects from abamectin exposure when used in crop protection (Celik-Ozenci et al., 2011, 2012). Decreased sperm quality and/or motility was reported in humans or rats following exposure to abamectin (Celik-Ozenci et al., 2011, 2012). In one study, male rats were fed by oral gavage at 1 mg kg<sup>-1</sup> day<sup>-1</sup> and 4 mg kg<sup>-1</sup> day<sup>-1</sup> for 1 and 6 weeks, respectively, giving 4 treatment groups in total (Celik-Ozenci et al., 2011). Whilst no signs of toxicity were observed, sperm motility, sperm number and increased seminiferous tubule damage in each of the four treatment groups was reported (Celik-Ozenci et al., 2011). Plasma abamectin concentrations were reported at between 5.12 and 77.14 ng mL<sup>-1</sup> in the four treatment groups (Celik-Ozenci et al., 2011). In the second study, decreased sperm quality was observed in farmers who applied abamectin up to 5 times for five consecutive years without using appropriate protective equipment (Celik-Ozenci et al., 2012). Although specific rates of exposure were difficult to quantify, the average plasma abamectin concentration in exposed farm-workers was ~1.3 ng mL<sup>-1</sup> (Celik-Ozenci et al., 2012).

The European Food Safety Authority report that the reproductive NOAELs for rats and rabbits are 1.6 and 1.0 mg kg<sup>-1</sup> bw day<sup>-1</sup>, respectively and that rats did not show any maternal abnormality at exposure rates of 0.4 mg kg<sup>-1</sup> bw day<sup>-1</sup> (European Food Safety Authority, 2008). Furthermore, studies that looked at two generations of rats failed to show any maternal toxicity (European Food Safety Authority, 2008). Abamectin is however, classified as 'H360 possible damage to fertility and to the unborn child' following the observation of several malformations (e.g. cleft palate, changed sex ratio, omphalocele, clubbed fore-feet, delayed ossification and increased number of foetuses with lumbar rib and lumbar count) in rat and rabbit teratogenicity studies (European Food Safety Authority, 2008).

## 6. Food contamination

Residues of avermectin family members used in veterinary pharmaceuticals to control parasites have been found in animal products such as meat and milk. The maximum residue limit (MRL) of abamectin and ivermectin for milk in cattle is 0.005 mg kg<sup>-1</sup> and 0.01 mg kg<sup>-1</sup>, respectively (CODEX, 2001, 2015). The half-life of abamectin and ivermectin varies between 2 and 4 days in milk (Imperiale et al., 2004; Cerkenik-Flajs et al. 2007). However, abamectin and ivermectin have been detected in milk up to 23 days and 21 days post treatment following oral and subcutaneous treatment (Imperiale et al., 2004; Cerkenik-Flajs et al. 2007). Therefore, it has been suggested to avoid using milk and its products within 30 days post cattle treatment (Cerkenik-Flajs et al. 2007). European regulation bans the presence of veterinary medicines in milk used for human consumption (EEC, 1990). However, a withholding period has not been established for all food following ivermectin or abamectin exposure. As described previously for abamectin, it is important that these products gain approval, such that best practice in their use can be adopted, according to appropriate labelling guidelines, including withholding periods (Bennett and Cheng, 2012; Moreno et al., 2015).

Food processing can reduce avermectin residues in food, however the degree to which this occurs varies under certain conditions. For example, under low thermal conditions when milk was

heated at 65 °C for 30 min or at 75 °C for 15 s, ivermectin levels did not decrease due to the fact that avermectins are lipophilic drugs (Imperiale et al., 2009). However, in another study, through processing milk to make cheese that is ripened for up to 60 days, ivermectin residues were below detection levels between days 5 and 25 (Cerkvenik et al., 2004). In a survey of 1060 beef samples in Europe, less than 3% of samples showed detectable residues of different veterinary drugs, and all were under acceptable European MRLs (Cooper et al., 2012). Residues in meat can be reduced up to an additional 50% by frying or boiling (Slanina et al., 1989). Hence, it is unlikely that residues in processed meat and aged cheese will pose any concern for humans with current levels of avermectin family use. However, completion of additional research in this area, especially as avermectin use increases as is predicted, would seem wise to ensure this is the case.

The acceptable MRL for abamectin in fruit and vegetables is 0.01–0.02 mg kg<sup>-1</sup> (FAO/WHO, 1997). However, there are very few studies that have assessed whether abamectin residue limits in different foods are met, irrespective of whether abamectin was used as an acaricide or a veterinary treatment (Palmer et al., 1997; Cerkvenik-Flajs et al. 2007; Kamel et al., 2007). The European Food Safety Authority investigated the residue toxicity of abamectin in several crops including peach, apricot, cucurbits, Chinese cabbage and celery and have proposed increases in MRL of up to 0.05 mg kg<sup>-1</sup> in some cases (European Food Safety Authority, 2010, 2015). However, they concluded that the residues detected will not result in consumer exposure to toxicological reference limits and were unlikely to pose a public health concern (European Food Safety Authority, 2010, 2015). Commercial labels for abamectin products propose withholding periods of between 3 and 20 days in different crops (Table 3) and given the reported short half-life for abamectin on plant surfaces (Table 2), these withholding periods seem sufficient to prevent food contamination. Furthermore, research indicates that abamectin does not significantly penetrate through fruit and vegetables from the plant surface (European Food Safety Authority, 2010). Consequently, rinsing and peeling can remove up to 50% and 80%, respectively of the residues on the fruit surfaces (European Food Safety Authority, 2010).

The acceptable daily intake (ADI) of abamectin based on short term studies in dogs is 0.0025 mg kg<sup>-1</sup> bw day<sup>-1</sup> (European Food Safety Authority, 2008). And whilst the current general consensus is that abamectin residue levels in foods are not of toxicological concern, there are very few reported studies that provide rigorous data to support this. In fact, there are reports of abamectin residues being detected in fruit, vegetables and processed food at levels that are high enough such that the ADI could be breached. For example, Kamel et al. (2007) reported initial residue levels in dates of 0.09 mg kg<sup>-1</sup> with about 60% of the residue dissipated by day 7 and 90% by day 14. Considering that the withholding period for dates is 10 days and at this time point, abamectin residues would most likely be higher than the accepted MRL of 0.01–0.02 mg kg<sup>-1</sup> for fruit (FAO/WHO, 1997). Despite this, it is unlikely that the consumption of dates would lead to an adult meeting the ADI under most circumstances. However, it is important to note that in some countries in the Middle East, dates are consumed, on average, 10 times more than other countries and therefore, it is possible that abamectin residues in dates could be of concern (Kamel et al., 2007). However, those authors did not examine the effect of rinsing the samples before residue examination, which as discussed previously, can eliminate up to 50% of abamectin residues (European Food Safety Authority, 2010).

We know that the half-life of abamectin on crops can be short (Table 2) and up to 50% of residue can be eliminated by rinsing, and therefore this pesticide seems unlikely to pose a risk of food contamination given current usage. Despite this, Nougadère et al.

(2011) argued that abamectin should be categorized as a substrate of concern that requires monitoring in food, because there is insufficient data available to dismiss with certainty the possible risks of abamectin residues in crops.

## 7. Conclusion

Avermectins are successful natural products that can be synthesised for commercial supply and are used as pesticides, veterinary therapeutics and pharmaceutical drugs. They have significant potential to be utilised for additional purposes in crop and animal protection as well as in the health sector. Despite being highly toxic, the half-life of avermectins in most cases is relatively short and rates of application are very low, which consequently minimises their eco-toxicological potential. However, when used in crop protection, there are reports of eco-toxicity for non-target species, with insects generally and bees in particular being at the highest risk. There are also a few reports of evolving resistance to avermectins in target species when used for crop and livestock protection and therapeutic purposes. Therefore, it would seem prudent to implement integrated management when using avermectins to reduce repeated applications or treatments, decrease the time of exposure of non-target species and minimise the risk of pest and disease resistance. The volume of literature that is available with regards to avermectin eco-toxicity is very limited. As a result, there remains a significant gap in our understanding of avermectin eco-toxicology, which needs to be urgently addressed.

In terms of food contamination, the available information suggests that avermectin residues are unlikely to be at concentrations high enough to pose a significant health risk to humans, which is primarily due to the relatively short half-life and reduction of residues during food processing. However, there is a distinct lack of comprehensive food residue analysis and given the highly toxic nature of avermectins, additional research is urgently required to be certain of the potential toxicological significance of food contamination by avermectin family members.

Avermectins are highly effective and their use, both in terms of volume and range of applications, is likely to grow. However, due to a lack of available data in the literature, this review was unable to conclude to what degree avermectins are a source of concern to our environment. This major gap of knowledge needs to be addressed before the eco-toxicological risks of this family can be thoroughly understood and minimised through implementation of best management practices. Most importantly, guidelines outlining how to undertake residue analysis need to be developed and mechanisms of action in both targeted and non-targeted species need to be more thoroughly understood. Several measures to mitigate eco-toxicity while using these products were proposed in this review, however they are inevitably general in nature without access to additional residue, safety, toxicity and mechanistic data.

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