

HOW PESTICIDES USED IN LIVESTOCK FARMING THREATEN BEES

VETERINARY TREATMENTS, BIOCIDAL PRODUCTS & POLLINATING INSECTS

A UNAF REPORT

WITH THE COOPERATION OF BEE LIFE EUROPEAN
BEEKEEPING COORDINATION, CNTESA AND THE FRENCH
FEDERATION OF PROFESSIONAL BEEKEEPERS



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SUMMARY AND REQUESTS FROM BEEKEEPERS' ORGANISATIONS

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At the beginning of winter 2008-2009, beekeepers from Ariège (South of France) reported worrying death rates in their colonies. They observed more than 4000 dead hives and whole apiaries decimated, leading to a strong suspicion of bee poisoning. However, although they practice transhumance in the high mountains, they are located at considerable distances from crops. Therefore, they began suspecting insecticides used to treat neighbouring livestock. Since then, deaths in comparable situations have been reported several times, such as in Aveyron in 2010, or during the winter of 2013-2014 in the Eastern Pyrenees, affecting hundreds of hives.

To better understand these phenomena, the Union Nationale de l'Apiculture Française, member of BeeLife European Beekeeping Coordination, commissioned a report to take stock of the insecticidal substances used in cattle and sheep farms. Its objective was to understand the mechanisms of action of such substances on bees, as well as questioning marketing rules and measuring the risks they pose to beekeeping activity. Results were expected to shed some light on the issue and provide further insights, not only for these particular cases but to consider a possible impact on good practices at European level as well as EU regulation.

NEUROTOXIC INSECTICIDES FOR VETERINARY AND BIOCIDAL USE, SOMETIMES SYSTEMIC, AND ALWAYS HARMFUL TO BEES

Neurotropic insecticides are highly toxic to all arthropods, including non-target species such as bees. In animal husbandry, they are used for several purposes. They are available, on the one hand, as veterinary treatments to treat parasitic infestations and, on the other, as biocidal products to rid vehicles and livestock buildings of insects. They contain active substances that belong to several major families of neurotoxics: macrocyclic lactones, pyrethroids, organophosphates, and others.

In veterinary medicine, pyrethroids and organophosphates are used to treat infestations of external parasites such as scabies and myiasis. Veterinarians apply them through external treatments (baths, showers, earrings, application by pouring the product on the animal's back). On the other hand, Macrocyclic lactones are endectocides, meaning that they act on both internal and external parasites of the animal. These substances are systemic and can be applied by injection, orally or on the animal's back (topical).

Contrarily, insecticidal biocides are not administered directly to animals. They are applied by spraying or nebulising on the surfaces of buildings and vehicles, as well as in livestock's environment. It is mainly the case in the context of imposed controls during outbreaks of regulated, notifiable vector-borne diseases (e.g. bluetongue). Insecticides can also be applied directly to manure and slurry to kill any insect larvae that may develop among it.

A WORRYING LACK OF KNOWLEDGE BY THE PUBLIC AUTHORITIES OF THE PESTICIDES USED AND THE QUANTITIES USED IN LIVESTOCK FARMING

These pesticides are subject to a marketing authorisation scheme (MA), which requires a procedure for assessing the products and particularly the environmental risks they generate. Nevertheless, regulation of biocidal products is in a transitional period: although the active substances they contain have been authorised at European level, the vast majority of products on the French market do not have marketing authorisations. Besides, the market for veterinary antiparasitic drugs and biocidal products is poorly monitored. It is, therefore, challenging to estimate the quantities used within the French and European livestock sectors. Even though conditions may vary from country to country, monitoring around Europe is insufficient to assess the market adequately.

BEEES EXPOSED TO POTENTIALLY HARMFUL DOSES OF THESE MOLECULES THROUGH CONTAMINATION OF WATER AND LIVESTOCK EXCREMENTS

These insecticides can be released into the environment through several pathways and spread depending on both their physicochemical properties and the environmental characteristics. Many veterinary antiparasitic drugs, partially metabolised in the body of treated animals, are excreted in faeces and urine, sometimes for long periods of time. Multiple studies have shown that these discharges pose ecotoxicity problems for coprophagous wildlife, such as dung beetles. Moreover, flows

generated by external pest control operations and biocidal treatments, if poorly managed, release these substances into the external environment. Once they reach the exterior, some very persistent insecticidal substances may persist for a long time before they degrade. The mentioned environmental contamination is likely to cause exposure to honeybees, who need large quantities of water. Water-bearing foragers seek water within a radius of several hundred metres, favouring sources which are rich in mineral salts. Such is the case for livestock excreta and water contaminated by discharges from livestock operations. Also, contaminated excrements can eventually degrade, generating insecticide-laden dust, which can be accumulated and deposited within the flowers that bees collect. Similarly, the fate of these excreta raise questions about the contamination of the soil and even the plants that grow there as well as regarding the pollen and nectar from flowers.

A PROBLEM IGNORED BY THE EVALUATION OF THESE PRODUCTS

Considering the toxicity of neurotropic insecticides to bees is necessary, mainly since the amounts excreted by a single animal treated with pyrethroids or macrocyclic lactones are sufficient to decimate colonies. However, the environmental risk assessment which antecedes the marketing authorisation of these products does not take this issue into account. The potential exposure - and therefore the ecotoxic risk - incurred by bees when using insecticides in livestock farming is never quantified.



OUR REQUESTS

BASED ON THIS REPORT AND TAKING INTO ACCOUNT THE TOXICITY OF THE SUBSTANCES USED AS WELL AS THE RISK OF EXPOSURE OF BEES WHICH CANNOT BE IGNORED, THE NATIONAL UNION OF FRENCH BEEKEEPING (UNAF), THE FRENCH FEDERATION OF PROFESSIONAL BEEKEEPERS (FFAP) AND BEE LIFE ADDRESS SEVERAL REQUESTS TO THE PUBLIC AUTHORITIES:

• We call for real consideration to be given to the risks associated with the toxicity of veterinary and biocidal products used in animal husbandry on pollinating insects and in particular on honeybees. Ecotoxicity issues for pollinating insects must be better integrated into the environmental risk assessment before obtaining marketing authorisations for veterinary medicinal products and biocidal products. Besides, marketing authorisation dossiers submitted by manufacturers should include methods for detecting insecticidal substances in the matrices associated with bees (honey, bees, beeswax, pollen), just as seen in dossiers of plant protection products. In doing so, the detection of these substances during monitoring plans and in case of suspected bee colony poisoning would be facilitated.

• It is essential to strengthen current knowledge on the factors of exposure of bees to insecticides used in animal husbandry. It can be achieved by developing studies under real conditions but also through appropriate laboratory risk assessments. Strengthening knowledge also requires a better understanding of the workers' watering/feeding processes on potentially contaminated sources that must be accurately characterised (contamination rate, availability, metabolites, and others.). Also, specific epidemiological studies should be conducted to estimate the extent of damage caused to bee colonies when these livestock insecticides are identified in their environment.

• Concerning vector control, UNAF, FFAP and BeeLife are calling for the revision of Directive 2000/75/EC, which imposes systematic treatments on livestock farms, insofar as they have proved ineffective and pose an ecotoxic risk to non-target organisms. The directive was drafted intending to eradicating Bluetongue, which is no longer on the agenda in many areas.

• Additionally, it is essential to ensure better public knowledge about the market for veterinary pesticides and insecticidal biocidal products. Considering the pollution that these products cause or may cause, particularly in watercourses, this issue is as much a public health issue as it is an environmental risk. For the same reason, it does not seem appropriate for farmers to be exempted from certification on biocides use on the grounds that their use of biocidal products would not expose «uninformed populations». Because of the risks of contamination associated with specific treatment devices, such as insecticide baths, consideration should be given to establishing better precautions for the use of veterinary antiparasitic drugs. It could even be performed jointly with more continuous monitoring of the proper implementation of these conditions of use.

• Increasing awareness of veterinary doctors should accompany these measures. Veterinary doctors should be increasingly aware of the environmental consequences of prescribed treatments. Such awareness should be developed during their training and education. Veterinarians must relay ecotoxicity issues to farmers. Such awareness could be based, in France, on good practices recommended by the environmental, parasitological and beekeeping commissions of the Société Nationale des Groupements Techniques Vétérinaires, whose compliance should be generalised. At European level, it could be based upon other national or EU authorities.

• Following the example of the approaches encouraged in plant cultivation sectors, the development of alternatives to the most toxic insecticides in veterinary pest management should be promoted.

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GLOSSARY

ADA	Association for Beekeeping Development (in French Association De Développement de l'Apiculture)	GL	Guidelines (Lignes Directrices)
AFSSA	Former French Food Safety Agency (in French, Agence Française de Sécurité Sanitaire de l'Alimentation)	HL	Half Life: sufficient period for half dose Degradation
AFSSET	Former French Agency for Environment and Occupational Health Safety (in French, Agence Française de Sécurité Sanitaire de l'Environnement et du Travail)	INRA	French National Institute for Agricultural Research (in French, Institut National de la Recherche Agronomique)
AIEMV	French Interprofessional Association for the Study of Veterinary Drugs (in French Association Interprofessionnelle Pour L'étude Du Médicament Vétérinaire)	ITSAP	French Technical and Scientific Institute for Bee and Pollination (in French, Institut Technique et Scientifique de l'Abeille et de la Pollinisation)
ANMV	French Veterinary Drugs Agency (in French Agence Nationale Du Médicament Vétérinaire)	K_d	Absorption-Desorption Coefficient
ANSES	Agence Nationale de Sécurité Sanitaire de L'alimentation, de L'environnement et du Travail	K_{oc}	Organic Carbon/Water Sharing Coefficient
BAPESA	Epidemiological Exploration of the Non-Intentional Effects of Biocidal and Antiparasitic Products Used in Animal Production on the Health of Bee Colonies	LC50	Lethal Concentration 50: concentration needed to kill 50% of the exposed individuals
BT	Blue Tongue	LC50	Lethal Dose 50: sufficient dose to kill 50% of the individuals exposed
BTV	Bluetongue Virus	MA	Marketing Authorisation
CS3D	Chambre Syndicale de Désinfection, de Désinsectisation et de Dératissage	OECD	Organisation for Economic Co-operation and Development
CMS	Concerned Member State	ONEMA	French Office for Water and Aquatic Environments (in French, Office National de l'Eau et des Milieux Aquatiques)
CVMP	Committee for Medicinal Products for Veterinary Use	PEC	Predicted Environmental Concentration
DDPP	Departmental Directorates for the Protection of Populations (in French, Direction Départementale de la Protection des Populations)	PNEC	Predicted Non Effect Concentration
DGAL	General Department of Food, within the French ministry of Agriculture (in French Direction Générale de l'Alimentation)	RMS	Reference Member State
DL50	Lethal Concentration 50 : Concentration Needed to Kill 50% of the Exposed Individuals	SIMMBAD	French Computerized Biocide Placing on the Market System: Authorizations and Declarations (in French, Système Informatique de Mise sur le Marché des Biocides : Autorisations et Déclarations)
ECHA	European Chemicals Agency	SIMV	French Union of the Industry of Veterinary and Reactive Medicines (in French Syndicat de l'Industrie du Médicament et réactif Vétérinaires)
EMA	European Medicines Agency	SNGTV	French National Society of Veterinary Technical Groups (in French, Société Nationale des Groupements Techniques Vétérinaires)
EU	European Union	SPC	Summary of Product Characteristics
GDS	French Health Defense Group (in French, Groupe-ment de Défense Sanitaire)	TP3	Biocides Type 3 - Disinfectants for Veterinary Hygiene
		TP18	Biocides Type 18 - Insecticides
		VICH	Veterinary International Conference on Harmonisation

INTRODUCTION

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At the beginning of winter 2008-2009, beekeepers from Ariège (South of France) reported worrying death rates in their colonies. They observed more than 4000 dead hives and whole apiaries decimated, leading to a strong suspicion of bee poisoning. However, these beekeepers, whose hives are located in mountain areas or who practice transhumance in high mountains, are located at considerable distances from agricultural crops. But, these apiaries were located in the vicinity of sheep and cattle farms, which use insecticide treatments in the context of compulsory vector disease control, which was the case in Ariège in 2008[1]. [1].

Indeed, some insecticidal substances are used in livestock production, either for animal pest control or for hygienic treatment of premises and equipment. Often administered to target a specific category of arthropods, these substances with non-specific modes of action are likely to affect non-target animals. Also, like plant protection products, these insecticides can be released into the environment and harm pollinating insects.

Although this issue had been neglected for long, it seems to be increasingly taken into account. So evidences the implementation of a French official survey including relating to neighbouring farms, potential sources of food poisoning (foraging, water sources) or passive (hives exposed to dust) carried out in the event of acute mass mortality of bees (French ministry of Agriculture Technical instruction DGAL/SASPP/2018-444). Thus, if analyses reveal that colonies have been exposed to certain antiparasitic agents and toxic biocides used in animal husbandry (such as macrocyclic lactones - avermectins family - or pyrethroids), then an investigation should be carried out within the nearest farms [2]. Taking into account this potential source of poisoning reveals an acknowledgement by the French authorities of the ecotoxic risks associated with the use of pesticides/biocides/veterinary medicines on livestock farms.

Besides, the French Technical and Scientific Institute of Beekeeping and Pollination (IT-SAP) - Institut de l'Abeille - initiated a prospective epidemiological study to address this issue in 2015. Such is the BAPESA study (Epidemiological investigation of the unintended effects of biocidal and antiparasitic products used in animal husbandry on the health of bee colonies, in French)[3]. Having mobilised various partners from the beekeeping world (ADAs), breeders (GDS France), veterinarians (SNGTV), research (INRA, ANSES), and government services (DDPP, DGAL), it will soon present its results. After two seasons of data collection on a couple of livestock areas previously affected by bee mortality, this study aims to provide additional information on the previously established link between animal husbandry practices and colony poisoning.

Pending further scientific knowledge and data, our present report aims to provide an overview of the diversity of insecticide products used in livestock farming and the conditions under which they are applied. An attempt can then be made to identify the ecotoxic risks associated with these uses, given the toxicity of these products to bees and other pollinators. Finally, gaps in the environmental assessment procedures for these products are identified.



A

B_{1a}

ACTIVE INGREDIENTS AND FORMULATIONS

B_{1b}

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1. VETERINARY ANTIPARASITIC TREATMENTS

A - A PRACTICE THAT HAS BEEN TRANSFORMED BY SUCCESSIVE DISCOVERIES OF NEW ACTIVE INGREDIENTS

The pharmaceutical and plant protection industry is constantly exploring new molecules in order to meet operators' requirements, particularly in terms of efficacy. This is to maintain a lead in the race against parasitic resistance, which pharmaceutical products themselves generate by selection.

Therefore, veterinary pest control has seen a long progression, marked by the successive discoveries of several families of insecticides. With a new compound marketed every five years, the increasing efficacy of the active ingredients - improved by at least 50% with each discovery - has led to a reduction in the doses administered [4]. We saw a succession of organochlorines, organophosphates, pyrethroids. However, it was ivermectin, introduced in 1981 in veterinary medicine, that truly revolutionised antiparasitic treatments as the first molecule representing the macrocyclic lactone family, and more specifically avermectins. Used as endectocides - to eliminate both internal and external parasites - the latter have radically transformed practices thanks to their remarkable effectiveness.

As a result, ivermectin became the first veterinary drug sold in the world in 1996 [5]. Since then, it has also achieved considerable success in human medicine, particularly against onchocerciasis, a disease that causes eye and skin damage in developing countries[6]. Its first-line use against human scabies is also tending to become more widespread in response to the increase in this disease, even in developed countries.

Today, organophosphates are less used. They are reaching the end of their commercial life cycle, and their use is facing resistance problems from the organisms they target, insects and mites. Nevertheless, depending on the sectors and pathologies, the substitution of these obsolete drugs by new generation products is only partial [7][8][9]. Treatments with avermectins, systemic endectocides, involve a long waiting time before the animal is slaughtered or milked. Indeed, the persistence of the substance in the treated animal's body temporarily renders its products unfit for consumption. It is therefore important not to neglect the continued use of «old» insecticides. Finally, an insecticide can simply be made obsolete by prohibiting its use. Such is the case of Fipronil, an insecticidal substance whose veterinary use on livestock is now banned, and whose presence in egg-based food products caused a health scandal in 2017.

Ivermectin became the first veterinary drug sold in the world in 1996.

It is also important not to completely exclude from the reflection certain anthelmintic products (flukicide, strongylicides...) because they are very widely used in the bovine, ovine and caprine sectors. However, since the substances they contain (benzimidazoles, clorsulon, etc.) are not considered insecticides, little ecotoxicity data on bees exist for them. It is important to note that these substances provide a more targeted, less ecotoxic and less persistent alternative than some endectocides, such as macrocyclic lactones [10].

B - AUTHORIZATION PROCESS FOR ACTIVE INGREDIENTS AND FORMULATIONS

Veterinary medicinal products are subject to a marketing authorisation system (MA), granted after an assessment of the benefits and risks associated with the use of the product. For instance, in France, there are several possible procedures for obtaining such a marketing authorisation for veterinary medicinal products [11][12].

The first procedure is national. It engages the ANSES, which is responsible for carrying out a scientific and regulatory assessment based on the dossier submitted by the veterinary pharmaceutical industry. The assessment refers to the pharmaceutical and chemical qualities of the product, its toxicity and efficacy, to weigh its benefits against the risks it implies. The 210-day procedure includes a dialogue phase with the pharmaceutical group. The decision by ANSES is then published in the Official Journal, while the public evaluation report and the summary of product characteristics (SPC) are made

available on the ANSES website.

The SPC stipulates the appropriate conditions for the use of the products, such as target animal species, allowed application methods and withdrawal periods. Thus, the SPCs of all authorised veterinary medicinal products are made available by the Agence Nationale

du Médicament Vétérinaire (ANMV), the French authority competent for the assessment and management of the risks concerning the veterinary medicinal products included in ANSES [13].

The other three procedures involve the European Union (EU). Thus, the centralised procedure aims to establish a marketing authorisation valid in all EU Member States. Within the European Medicines Agency (EMA), it is managed by the Committee for Medicinal Products for Veterinary Use (in French CVMP), which issues a scientific opinion, then presented as a proposal to the European Commission. The MA may be issued after a vote by the Member States.

The mutual recognition procedure makes it possible to extend a national MA already granted in one Member State - the «Reference Member State» (RMS) - to other States - the «Concerned Member States» (CMS). To do this, they must evaluate the authorisation from the evaluation report carried out by the RMS, before issuing their national marketing authorisation. If a disagreement arises between RMS and CMS, a pre-arbitration procedure led by a Coordination Committee is set up. If this system proves insufficient, the case is referred to the authority of the EMA and its CVMP for arbitration. Finally, the decentralised procedure is similar to the mutual recognition procedure, except that the MA is potentially issued simultaneously in the RMS and CMS.

C - AUTHORIZED DRUGS AND SOME OF THEIR ECOTOXIC CHARACTERISTICS

In France, the ANMV makes available to everyone all the SPCs of authorized veterinary drugs [13]. As of 8/02/2018, there are:

> 20 insecticide/acaricide drugs for livestock. They are formulated with 8 different substances (amitraz, cypermethrin, deltamethrin, dicyclanil, dimpylate, fenvalerate, flumethrin, phoxime). Most SPCs for these drugs mention toxicity to aquatic organisms and coprophagous insects. Some cypermethrin, deltamethrin, flumethrin and phoxim-based drugs also report RCP toxicity to bees..

> 81 endectocidal drugs for livestock. They are formulated based on macrocyclic lactones (ivermectin, doramectin, éprinomectin, moxidectin), sometimes combined with anthelmintic substances (clorsulone, closantel, praziquantel, triclabendazole). The SPCs of these products indicate toxicity to aquatic organisms. Some, including the majority of eprinomectin and doramectin products, also mention toxicity to coprophages. It is questionable why this is not indicated in the RCPs of all macrocyclic lactone drugs.

Besides, many antiparasitic products for veterinary use have an anthelmintic action: they aim to eliminate nematodes (e.g. Strongylida), trematodes (e.g. flukes) or cestodes (e.g. tapeworms) which very commonly infest farm animals. These treatments will not be discussed further here because they are not designed to target insects. However, some of these drugs are still toxic to aquatic organisms and/or coprophagous insects (e.g. closantel, in its RCP [13]; dichlorvos and albendazole [14]). Therefore, it suggests that the toxicity of these products to bees and other pollinating insects cannot be ruled out. Further studies on the ecotoxicity of molecules from the families of salicylanilides and benzimidazoles would, consequently, be desirable, in a broader context. There are 75 anthelmintic drugs for livestock. They are formulated with albendazole, closantel, febantel, fenbendazole, levamisole, netobimine, nitroxinil, oxfendazole, oxclozanide, piperazine, praziquantel, pyrantel and triclabendazole.



1 - VETERINARY ANTIPARASITIC TREATMENTS

D - MAIN FAMILIES OF SUBSTANCES AND THEIR MODES OF ACTION

Particular attention will be paid here to neurotoxic insecticidal substances, which represent the most significant part of the options for insecticide control and possess the highest toxicities. The focus will be on macrocyclic lactones (mainly ivermectin), pyrethroids (mainly deltamethrin and cypermethrin), organophosphates (phoxime and dimpylate), and amitraz. These substances were chosen because of their toxicity and widespread use in the cattle and sheep husbandry. Thus, the focus will be on these large-scale sectors, which mobilise insecticide treatments likely to cause exposure of ecosystems.

> **Macrocyclic lactone.** Including avermectins and milbemycins, they are among the most toxic insecticides. Initially produced by bacteria of the genus *Streptomyces*, they act at the synapses by stimulating the opening of the GABA-dependent chloride channels. The first avermectin, ivermectin, revolutionised pest control in both humans and animals. Its powerful endectocidal action - which eliminates both internal and external parasites - is indeed highly effective in many diseases [15]. Also widely used, moxidectin is at least as effective, if not more [16] [17], while doramectin, widely used on cattle, is the most ecotoxic [18]. However, in livestock farming, their use requires long waiting times before the animal or its products are safe for consumption. Other macrocyclic lactones may be an alternative to less severe constraints, such as eprinomectin, which has no withdrawal time for dairy cows [10][13].

With acute toxicity resulting in an average LD50 of 0.04 µg/bee, the macrocyclic lactone family is one of the most toxic to bees (geometric mean [20]).

Ivermectin:

55 formulations identified (cattle, sheep, horses, pigs)

Moxidectin:

12 formulations identified (cattle, sheep, horses)

Eprinomectin:

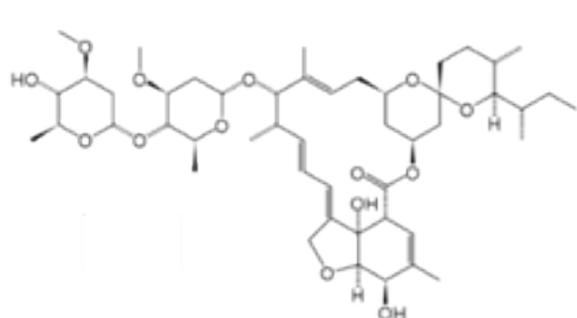
10 formulations identified (cattle, sheep, goats)

Doramectin:

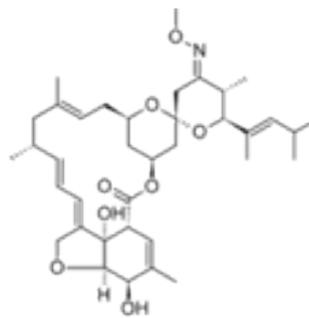
7 formulations identified (cattle, sheep, pigs)

> **Pyrethroids.** Derived from the synthesis of compounds initially isolated from certain chrysanthemums, they are also essential insecticides. They have a range of toxicity on bees comparable to those of avermectins [20]. These molecules impede the closure of sodium channels located on nerve cell membranes, causing the loss of the nerve signal [21]. Among these active ingredients, deltamethrin and cypermethrin are widely used, and have well-documented toxicity values and are essential for insecticide control in livestock [10].

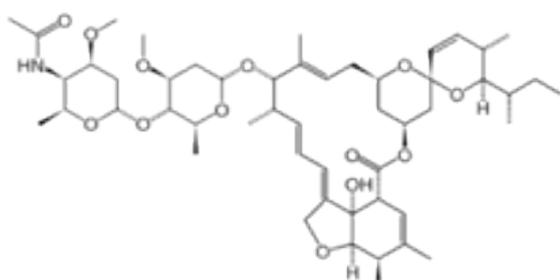
With acute LD50s around the average value of 0.4 µg/bee, this is also one of the most toxic families [20]. It should be noted that some molecules, such as deltamethrin (LD50 of 1.5 ng/bee [22]), have much lower LD50s [20].



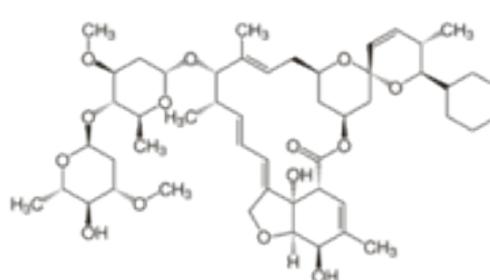
Ivermectin B₁₂



Moxidectin

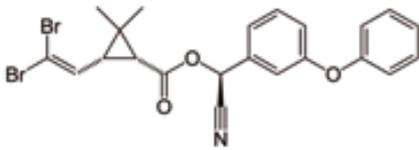


Eprinomectin

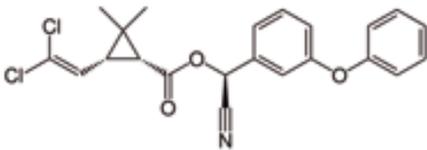


Doramectin

Figure 1 : Semi-developed formulas of the main molecules of the macrocyclic lactone family used in animal husbandry [19].



Deltaméthrin



Cyperméthrin

Figure 2 : Formules semi-développées des principales molécules de la famille des pyréthrinoïdes utilisées en élevage [19]

Deltamethrin: 9 formulations identifiées (cattle, sheep)

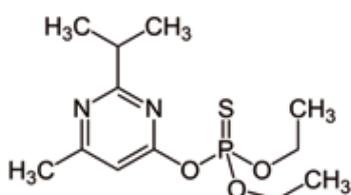
Cypermethrin: 3 formulations identifiées (cattle, sheep)

> **Organophosphates.** Although in the process of becoming obsolete, they continue to be regularly used external antiparasitic agents [9]. These compounds, such as dimpylate (or diazinon) or phoximia, inhibit acetylcholine esterase, leading to an abnormal accumulation of acetylcholine in cholinergic synapses - causing paralysis[23]. In general, less toxic than macrocyclic lactones and pyrethroids, these substances still have LD50s for bees around 0.6 µg/bee [20].

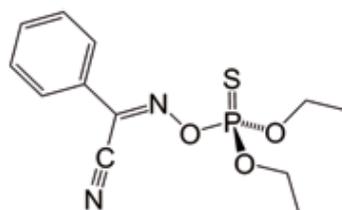
Dimpylate : 1 formulation identifiée (Cattle, goats, dogs, sheep, pigs) (DIMPYGAL® - Qalian)

Phoxime : 3 formulations identifiées (Cattle, sheep, goats, horses, pigs, laying hens)

> **Neonicotinoids.** Other neurotoxic insecticides directly target acetylcholine nicotinic receptors at these same synapses. These are neonicotinoids. Their harmfulness to bees is no longer to be demonstrated (geometric mean LD50: 0.13 µg/bee [20]). However, their use as veterinary treatments is not allowed on livestock. In animal husbandry, neonicotinoids are therefore restricted to use as biocidal substances



Dimpylate

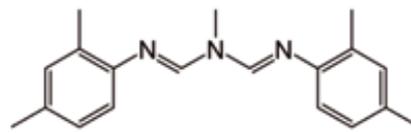


Phoxime

Figure 3 : Semi-developed formulas of the main molecules of the organophosphate family used in animal husbandry [19]

> **L' Amitraze** A formamidine, is an octopaminergic receptor inhibitor[20]. Less toxic to bees than the substances previously listed (LD50: 50 µg/bee [20]), this neurotoxin is still of particular importance because it is used as an acaricide band inside the hives to control the parasite of *Varroa destructor* bees. This use plays on a delicate balance that takes advantage of the substance's difference in toxicity to the mite and bees - a balance that may be disrupted if the bee's environment includes other pesticides that can act synergistically.

Amitraze : 1 formulation outside the beekeeping environment (Cattle, goats, sheep, pigs) (TAKTIC® - Intervet).



Amitraze

Figure 4 : Semi-developed formula of the Amitraz[19]

2 - SURFACE BIOCIDES

A - DISTINCTION WITH VETERINARY DRUGS AND TYPOLOGY

The function of biocidal products is to eliminate undesirable or harmful organisms. They are often confused with certain plant protection or veterinary products, with which they may share the same active substances. However, they differ in their use [24][8]. Thus, they are mainly used to treat the surfaces of premises, equipment, tools, vehicles, etc. In the context of animal husbandry, where the biocidal product is applied directly to the animal, its use must be in accordance with general hygiene practices without therapeutic claims. Otherwise, the product falls within the scope of veterinary medicinal products.

There is a typology of biocidal products, depending on their use and the organisms they target [25]. Among them, two types of products can be associated with the problem of insecticide control in livestock farming.

> TP18: arthropod control products

These are mainly insecticides applied in and around livestock facilities. Among the TP18s are insecticidal substances used in veterinary drugs. However, no TP18 biocide is intended to be applied directly to livestock. These products come in the form of toxic granulated insect baits, fluids to be sprayed or brushed on surfaces (e. g. Figure 5), or larvicides (granules or liquids) to be applied to manure and slurry [25].

Considering the toxicity - especially to bees - of the insecticidal substances they contain, such as pyrethroids or neonicotinoids, it is the TP18 biocides that seem to be of the greatest concern from an ecotoxic point of view.



Figure 5 : Biocidal treatment of an empty barn by thermonebulisation. The insecticide solution is sprayed in fine droplets which ensures a wide aerial distribution of the substance [26].

> TP3: disinfectant for veterinary hygiene

This range of biocidal products is used to disinfect livestock premises and equipment, particularly when disinfecting installations during the crawl space between the reception of two batches of animals. Bactericides, virucides, or fungicides, they routinely prevent the appearance and spread of diseases, especially in intensive livestock farming. However, they are not supposed to be in contact with animal food and/or drink. They can also act as a barrier against external infectious agents, being applied in the form of foot baths for animals or vehicles decontamination units [25]. On the other hand, some TP3 products can be used directly on the animal as part of routine hygiene practices, particularly through foot and udder care (excluding preventive treatment of mastitis, which is a veterinary treatment). These disinfectants are most often made from formaldehyde, glutaraldehyde, quaternary ammonium, peracetic acid, hydrogen peroxide, chloromethylphenol, etc.

> Other types of biocidal products are likely to be used on livestock farms

Thus, TP19 (repellents or bait) can be used in veterinary hygiene, directly on the animal's body, or in their environment, to ensure protection against parasitic insects. However, they are not expected to have intrinsic toxic activity. TP4 (disinfectant for surfaces in contact with foodstuffs) is widely used in cattle husbandry to disinfect dairy equipment. More generally, they make it possible to ensure the hygiene of surfaces in contact with foodstuffs. The most common is bleach. Finally, TP14 (rodenticides), in the form of poisoned baits, are used to control rodents in and around the facilities.

We will, therefore, focus on TP18 biocides, specifically designed to kill insects. Its use in livestock farming is likely to expose non-target arthropod species.

B - TRANSITIONAL REGULATORY PERIOD

Regulation is in a transitional period, pending the examination and potential authorisation at European level of active biocidal substances. Hence, the objective of European Regulation N° 528/2012 is to make the marketing authorisation (MA) of biocidal products subject to an acceptable level of risk for humans and the environment, the absence of unacceptable effects (development of resistance, damage to non-target organisms, etc.) and sufficient efficacy [27][28].

The examination of the product is divided into two stages:

1) a Community evaluation of the active substance contained in the product which, if favourable, leads to its inclusion in the Community 'positive' list of authorised active substances

2) a national product evaluation with a view to issuing a marketing authorisation. This procedure distinguishes between pre-existing active substances, i. e. those present on the Community market on 14 May 2000, and new, i. e. subsequent active substances. The former, as well as products containing them, are authorised a priori on the market until the Community evaluation is completed and until the products are evaluated at a national level. On the other hand, active substances that were not already on the market in 2000 cannot be introduced before evaluation.

Thus, in practice, the placing on the market of a biocidal product does not require a national marketing authorisation during the examination of the active substance, but only a declaration and labelling. In France, an online platform, SIMMBAD, has been set up to enable distributors of these products to declare their placing on the market [29][30].

Special provisions may remain in force for certain types of products under specific regulations, in particular: biocidal products used against contagious livestock diseases, which are subject to mandatory declaration or to collective prophylaxis organised by the State. This is the case for products used during Bluetongue epizootics.

C- ACTIVE SUBSTANCES AND FORMULATIONS ON THE MARKET

As of 20/02/2018, there are 84 TP18 biocidal products with a French MA (according to the European Chemicals Agency [31]). They are formulated from 18 different insecticidal substances and have a wide variety of application methods: traps, gels, sprays, granules, fumigation, etc. The molecules that form the basis of most products are deltamethrin (21 products), imidacloprid (17 products), spinosad (a spinosyne, a recent family of macrocyclic lactones) (17 products) and fipronil (6 products). All four

active substances are highly toxic to bees (topical LD50s of 1.5 ng/bee [32]; 18 ng/bee [33]; 47 ng/bee[34] and 3.9 ng/bee [35] respectively). It should be noted that imidacloprid (a neonicotinoid), spinosad and fipronil are not authorised as veterinary medicinal products for livestock. As biocides, they are mainly used in the composition of traps and poisoned baits for ants, termites and cockroaches. Deltamethrin, on the other hand, is widely used in veterinary medicine for farm animals and has a greater diversity of biocidal uses. Thus, it is at the base of traps but also of less specific products, to be sprayed in solution.

However, since the transition period allows it, there are a large number of products on the French market that do not have marketing authorisations, listed on the SIMMBAD platform. Despite this tool, it is difficult to draw up an inventory, particularly because of their quantity. There are 133 deltamethrin products; 181 cypermethrin products; more than 500 permethrin products; 10 fipronil products; 44 imidacloprid products; 5 clothianidin products; 2 thiamethoxam products; 1 dinotefuran product [30]. Indeed, it is sufficient that the active substance is authorised at European level for the product to be placed on the French market. Therefore, it is interesting to consider the 41 TP18 insecticidal substances as authorised at European level. These include 4 neonicotinoids (clothianidin, dinotefuran, imidacloprid and thiamethoxam), 16 molecules for which acute toxicity to bees is documented, and 7 for which chronic toxicity to bees is documented.

The multiplicity of these insecticidal products, which do not have marketing authorisations and therefore for which the benefit/risk analysis has not been carried out, makes it difficult to assess the current situation regarding the use of TP18 biocidal products in livestock farming. This questions the potential risks that these products pose to farmers, their livestock and the environment.

Since the transition period allows it, there is a large number of products on the French market that do not have marketing authorisations.

B

DISTRIBUTION AND USES

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1 - QUANTIFICATION AND MARKET MONITORING

A - A NON-TRANSPARENT VETERINARY DRUG MARKET: IMPOSSIBLE QUANTIFICATION

With 38 companies accounting for 24% of the European market's €4.6 billion turnover, France is the leading research and manufacturing country for veterinary drugs in Europe [36]. As far as the consumption of pest control products is concerned, it was - since 2004 - second only to Germany, with 28.5 tonnes of active substances used in one year [37]. Nevertheless, this large market lacks clarity.

Information on the internal market for veterinary medicinal products and the quantities sold are held and protected by the Union of the Industry of Veterinary Medicines and Reactives (in French Syndicat de l'industrie du médicament vétérinaire et réactif, SIMV) and the Inter-professional Association for the Study of the Veterinary Medicines (in French Association interprofessionnelle pour l'étude du médicament vétérinaire, AIEMV) for reasons deemed to be commercial. Despite the very general figures provided annually by AIEMV, it is very difficult to establish a detailed follow-up [7][8][10].

However, it is known that in 2015, the French market for animal health products - whether or not subject to MA - was estimated by AIEMV at €1380 million [38]. Products for livestock accounted for 48.10% (pigs 8.44%; poultry 5.76%; ruminants 29.91%; horses 3.99%) of the total market and pets 51.80% (including pet food). In addition, all veterinary pesticides (internal pesticides 8.59%; insecticides & external pesticides 11.75%; and endectocides 6.96%) accounted for more than a quarter (27.30%) of the market share compared to 9.57% for anti-infectives (Figure 6). However, these figures cover the market as a whole, and not just the livestock sector. Finally, in 2015, 79.16% of the market shares were held by veterinarians themselves, compared to 6.78% by pharmacies, and 13.17% for groups and industries approved to supply veterinary drugs [38].

Despite the few very general figures provided by AIEMV, there is a glaring lack of public information on the market for veterinary pesticides. Hence, in 2016, the ANSES deplored that it did not have at its disposal the information regarding quantities of active substances sold [9]. This is an important distinction from veterinary antibiotics, which are subject to detailed monitoring - a consequence of greater awareness of their environmental impacts and the risks of developing resistant strains.

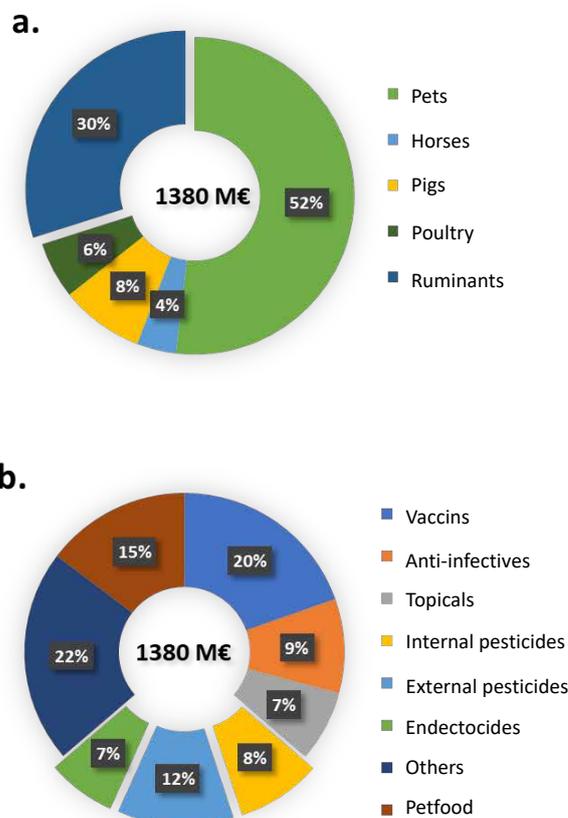


Figure 6. Market shares of animal health products in 2015, by species (a.) (ruminants - including cattle and sheep - increased), and by product type all sectors combined (b.) (increased pest control products). (AIEMV data[38])

B - COMPLEX AND POORLY MONITORED BIOCIDAL PRODUCTS MARKET IN TRANSITION

Similarly, there is no public quantitative monitoring of sales of biocidal products, and in particular insecticides, in France, despite an obligation for firms selling them to declare the quantities sold. This problem is reinforced by the amount of distributors and the free sale of these products, which is only subject to a declaration on the SIMMBAD platform. In 2010, the Ministry of the Environment also pointed out that «most biocidal products on the market today are not covered by a marketing authorisation scheme», as a consequence of the transitional mechanism set up by European regulations. To date, this situation remains unchanged, as confirmed by our interlocutors at the Ministry of the Environment. Therefore, «in the absence of a fully operational authorisation regime, many biocidal products are available over the counter without precise knowledge of the nature of

these products, their composition and uses» (MEEDDM, 2010 [9]). In 2010, the hearing by the French Agency on Sanitary Safety of Environment and Labour (in French Agence française de sécurité sanitaire de l'environnement et du travail) of the Union Chamber of Disinfection, Insect and Rodent Control (Chambre Syndicale de Désinfection, de Désinsectisation et de Dératisation, CS3D) even showed that these structures were unable to record this type of data [9].

Besides, certain products are supposed to benefit from additional supervision when their use is strictly professional, ensured by the obligation for the user to hold a «CertiBiocide» certification. However, this framework is not applied to the livestock sector. In fact, farmers are not required to be certified to use products for professional use on their own farms [39].

Despite the few very general figures provided by AIEMV, there is a glaring lack of public information on the market for veterinary pesticides.

2 - ACQUISITION OF PRODUCTS BY FARMERS

A - PRESCRIPTION AND DISTRIBUTION OF VETERINARY PRODUCTS, AND THEIR SUPERVISION

The prescription of veterinary treatments is carried out by a veterinary doctor in two ways[40]. The first is the prescription of drugs following an animal examination or a medical or surgical procedure. But the veterinarian may also prescribe treatments without prior clinical examination if she/he is responsible for the permanent health monitoring of the farm in question. This responsibility includes carrying out a health assessment of the farm, a care protocol, and follow-up through regular visits[41].

The delivery of these treatments is mainly carried out by the veterinarians themselves. However, they are not allowed to keep a pharmacy. As a result, they can only dispense drugs that they themselves have prescribed. However, they accounted for more than 80% of drug sales in 2015, aggregating livestock and companion animals [38]. This dual status of prescriber and distributor of drugs is regularly the subject of controversy. Indeed, it is sometimes suggested that this would encourage overuse of drugs. In second place are the groups of farmers approved to supply veterinary medicines (13%) [38]. Despite the fact that they are no longer authorised to deliver antibiotic treatments[41], they are able to dis-

tribute the other drugs included in their livestock health programs. These groups are of different nature: Health Defence Groups, agricultural cooperatives, breeders' associations[42], etc. Finally, the supply of veterinary products within pharmacies represents only a minority of the market share of these drugs (7%)[38].

The collective expert report «Occupational exposure to pesticides in agriculture» of the ANSES [9], underlines, in particular for the sheep sector, the difficulty of having a clear vision on the health practices of farmers - mainly because of the structural heterogeneity of the sector. In the regions studied, no organisation is responsible for the inventory and assessment of health interventions that do not fall within the scope of regulated diseases. As far as external antiparasitic treatments in sheep farming are concerned. Therefore, it seems impossible to draw a reliable picture of the situations in which people are exposed to toxic substances. Knowledge about the environmental impacts of these practices, which are even more difficult to assess, is therefore beyond the reach of institutions.

Moreover, even within sectors that are environmentally friendly, pest management health practices remain complex and not very restricted. Due to the inconvenience caused by parasitism, it would be difficult to

require abstinence from pest control products. Thus, since 2009, farms labelled as «Organic» have been authorised to apply antiparasitic treatments without a variety limit, provided that their use is justified and is applied in response to a proven infestation. Only the galenic form of bolus - with long-lasting action and re-release - is completely prohibited [4]. However, it should be noted that some endectocides such as moxidectin are allowed in organic dairy farming, even though the molecule is permanently released into cattle faeces [43]. Even if the use of phytotherapy and homoeopathy is preferred in «Organic» husbandry, the use of allopathic antiparasitic substances remains authorised with doubled waiting times [44].

B - BIOCIDAL TREATMENTS: FREE SALE AND SERVICE PROVIDERS

As previously observed, biocidal products are sold over the counter through mass distribution channels such as specialised networks, via the Internet and others. Farmers also have the possibility of using service providers, such as companies in the Farago network [45]. They are qualified to carry out biocidal disinfection and insect control treatments. However, farmers themselves are entitled, within their holdings, to apply products for use only by professionals [7].

The application of biocidal products for professional use typically requires the possession of a “Certibiocide”, but farmers are not subject to this regulation. It is considered that «The use of biocidal products during production or processing is not likely to expose uninformed populations to the possible risks that these products may present, and therefore does not make the possession of Certibiocide mandatory for its user». It means that the use of these products in agriculture and agri-food production does not require certification [39]. It is important to note that the “Certibiocide” training is distinct from the “Certiphyto” one required for the use of plant protection products applied to plants. Because of the risks associated with the toxicity of TP18 insecticide products to those who handle them and to the environment, the lack of specialised training for farmers is a concern.

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3 - WAYS OF APPLICATION

The details provided here mainly concern the cattle and sheep farming sectors. These sectors, which are large in scale (about 8 million dairy and suckler cows; 5 million dairy and lactating ewes in 2011 [46]), seem to be among the most likely to generate a risk of ecotoxicity for bees and other pollinators, particularly during grazing. However, it would be appropriate to extend the study to other sectors, because they are even more important and sometimes more industrial, such as the poultry and pig sectors.

A - PATHOLOGIES AND GALENIC FORMS OF ASSOCIATED TREATMENTS

The different types of treatments administered to livestock are clearly related to the supply chain and the different infestations of animals. Thus, the main pathologies that require the use of insecticide treatments are myases and scabies [9] [4].

In sheep, the fight against this external parasitism remains first and foremost assured thanks to treatments applied through bathing, spraying and extreme-pressure showers. These treatments are carried out using solutions of relatively old drugs: organophosphates (including dimpylate and phoxime), pyrethroids, amitraz [9]. They involve large-scale treatment sites (Figure 7), particularly during insecticide baths. For example, the RCP of the acaricide product DIMPYGAL® (Qalian) stipulates that the bathing application must involve all animals in the herd, which follow one another in a pool with the drug solution [13]. After being held there for between 30 seconds and one minute, with two immersions of the head, the sheep leave the fleece loaded with acaricide substance.

Finally, in the case of sheep, the injection or oral intake of macrocyclic lactone is more marginal, rather used as a last resort, in case of failure of external treatments [9]. In cattle, treatments can also be carried out by administering organophosphates and pyrethroids, by spraying and pour-on (application on the back line) [4]. Pyrethroids can also be administered as earplugs. Also, there is a vast abundance of veterinary drugs for cattle based on macrocyclic lactones: doramectin, ivermectin, moxidectin and éprinomectin (zero withdrawal time in milk), applied in pour-on or by subcutaneous injection [13].

On the other hand, the application of ivermectin by bolus - a large dose administered orally - is no longer permitted due to a significant and sustained release into the faeces. Indeed, this device is installed in the digestive system of animals in order to durably release its active



Figure 7 : External treatment sites for sheep scabies: (a.) permanent bathing treatment device; (b.) spray treatment device [47].

MAIN PATHOLOGIES CAUSED BY ARTHROPOD PARASITES

MITES

Scabies is a skin condition caused by mites of the genera *Sarcoptes*, *Psoroptes* or *Chorioptes*, parasites that colonise the skin of animals causing lesions and itching. Weight loss and yield losses manifest the nuisance to the animal. Although scabies - obligatory parasites - do not survive for long outside a host, the infestation is nevertheless highly contagious. Scabies, therefore, requires coordinated treatment of herds of cattle or sheep to avoid re-contagions [47][48].

Other mites, ticks, parasitise animals only temporarily during a blood meal. However, they also pose a threat and can lead to yield losses because of the diseases they can transmit.

INSECTS

Myases are parasitoses associated with infestation by larvae of several families of diptera (*Calliphoridae*, *Oestridae*, *Sarcophagidae*). Adult flies lay their eggs directly on the surface of the animals' skin, especially on wounds. Parasitic larvae hatch and feed on the flesh. The infestation can cause deep wounds that can be superinfected. Parasitised animals are weakened and lose weight. Be-

sides, in the event of a very pronounced infection, the lesions or septicaemia can cause the animal's death. These diseases affect both cattle and sheep [48][49][9].

Head lice infestations, though less severe, can also cause production declines due to the itching it causes. These parasitic insects proliferate mainly in winter in livestock farms during housing. A distinction is made between biting lice (cattle: *Hematopinus eurysternus*, *Linognathus vituli*, *Solenopotes capillatus*; sheep: *Linognathus pedalis ovillus*) which feeds on blood, and crushing lice (cattle: *Bovicola bovis*; sheep: *Damaliana ovis*) which feeds on skin debris. Therefore, they are not sensitive to systemic veterinary drugs.

Other serious parasitoses, causing significant yield losses, are associated with internal parasites such as nematodes (including strongles), cestodes (tapeworms), and trematodes (flukes). By infesting the respiratory or gastrointestinal tract, these helminths cause weight loss, diarrhoea and infections that can weaken the host and lead to its death. Their treatment uses internal antiparasitic agents by oral solution or cutaneous injection. The effectiveness of endectocides in controlling these internal parasites and skin parasitism, simultaneously, justifies the attraction of these substances, such as macrocyclic lactones [9][50].

principle into the body of the bovine treated continuously or sequentially. Nevertheless, formulations based on Moxidectin (CYDECTINE® - Zoetis France) with long release in the faeces are still available [51][10].

In practice, the most commonly used application methods today for cattle and sheep seem to be, respectively, the pour-on form and bathing [10]. This confirms that the substitution of external antiparasitic agents by endectocides is only partial. The choice of technique for treatment remains complex and requires weighing efficiency concerns such as the difficulty of administration, drug costs, waiting times and, for conscientious livestock farmers, ecotoxic risks [9].

Insecticide/acaricide baths in sheep appear to be a risky application method for the escape of ecotoxic substances into the environment. The quantities are large and the animals come out with fleeces loaded with product. Moreover, despite the obligation to collect and treat residues/effluents, they are not systematically well managed [9]. Indeed, these treatments target, among other things, myases, which are summer pathologies. They are therefore often conducted in summer pastures, on large herds of thousands of heads. Since the disposal of bath effluent is difficult, large quantities could be released directly to the site.

Spraying and pour-on also entail risks. Both involve significant quantities of products, applied in a relatively imprecise manner. Sometimes, the doses administered are voluntarily increased to compensate for flow losses [10]. Similarly, the effluents discharged during the operation are not always treated, and the animals come out loaded with products that may leak [10][9].

In addition, it is sometimes advisable, even in the RCPs of products (DIMPYGAL® - Qalian), to use the residual insecticide solutions to treat livestock premises and equipment, but also elements of the external environment likely to come into contact with animals (fences, scrapers, poles, trees, etc.) [13]. Such advice admittedly leads to direct contamination of the external environment.

In comparison, injectable, oral products, or earrings may appear to limit the substances to the animal's body. However, these molecules are then excreted in urine and faeces and released into the environment.

B - APPLICATION METHODS FOR BIOCIDES USED IN LIVESTOCK FARMING

TP18 biocides used in animal husbandry [25]

These biocidal products can take the form of toxic bait, mainly against crawling insects and ants. Trapped or

granulated, they often involve limited quantities of toxic substances.

Many insecticidal biocidal treatments are applied as liquids to be brushed, sprayed, or nebulised (cloud spraying of extremely fine droplets). The use of these biocidal products for the treatment of livestock buildings must be frequent, particularly in the context of the crawl space between the reception of two batches of animals. It should be considered that, given the cost of these products, the quantities applied are never unlimited. Therefore, their use may be restricted to a limited area of the farm (e. g. milking parlour). In theory, the application environment is therefore limited, and the effluents are controlled. The use of insecticide solutions for the treatment of vehicles is more punctual, according to testimonies, often reluctantly carried out under regulatory obligations [10][52]. In particular, it is implemented during vector control campaigns and may be accompanied by treatment of the farm's external surroundings. Insecticidal substances are then released directly into the environment.

TP18 insecticidal biocides are also used as larvicides in manure and slurry from livestock operations. These residual products are applied in the form of sprays or granules. They target in particular dipteran larvae, including «tailworms», larvae of pollinating hoverflies of the genus *Eristalis*. The fate of these manures and slurries then raises serious ecotoxicity issues.

TP3 Biocides for Veterinary Hygiene [25]

TP3 surface disinfectants, intended for veterinary hygiene, are essential for the systematic disinfection of premises, means of transport and livestock equipment. When applied during a crawl space or in the presence of animals, these bactericidal solutions must not come into direct contact with the food and drink of the animals. TP3 bactericides are also used in solution in foot baths to disinfect the feet of animals, or vehicle disinfection units, through which motorized equipment passes. Foot care can also be carried out more finely by the direct application of solution (e.g. iodine tincture) to the feet of the animals by the farmer.

Mandatory insect control for vector control and the use of larvicides in manure can be further explored. Indeed, they involve the non-targeted use of large quantities of insecticides, sometimes directly in the outdoor environment [52].

4 - EPIZOOTICS AND VECTOR CONTROL

A - EXAMPLE OF BLUETONGUE: VECTOR INVOLVEMENT AND VECTOR CONTROL

Bluetongue is a vector-borne disease caused by the «Bluetongue virus» (BTV). Transmitted to ruminants by the bite of a midge of the genus *Culicoides*, it has been the source of epizootic diseases affecting Western Europe since the early 2000s. Previously considered an exotic disease, it strikes France from 2007 to 2010, especially during warm periods of high vector activity. During these years, viral serotypes 1 and 8 of BTV cause significant margin losses for farmers, with a particularly marked pathogenicity in sheep [53]. The increase in outbreaks has led to sanitary measures restricting animal transport and insect control, as well as vaccination campaigns. These measures, combined with natural immunity, finally contained the outbreak. Since then, the disease has reappeared in 2013 in Corsica (serotype 1) [54], in 2015 in Allier (serotype 8) [55] and in 2017 in Haute-Savoie (serotype 4) [56].

In 2008-2009, in Ariège, mandatory vector control as part of the measures against the BT epizootic caused a strong objection from beekeepers [53]. Indeed, the latter have witnessed high mortality rates in their colonies, installed near treated herds [1] (Figure 8). The affected colonies were healthy and had good reserves. Faced with these losses, which could not be explained by other conditions, such as varroasis, insecticide poisoning was suspected. Thus, residues of permethrin and deltamethrin were detected in samples of dead bees and honey collected by beekeepers from affected hives, respectively.

Nevertheless, the additional analyses carried out three months after the deaths were too late to confirm intoxication, and were criticised by beekeepers[1]. Since this episode, beekeepers have regularly reported their concern for the health of their livestock in the face of the excessive use of insecticide substances in vector control. Finally, in addition to these vast, poorly targeted eradication campaigns, a multitude of pollinating arthropod species (bumbees, solitary bees, lepidopterans, etc.) and aquatic organisms could be mistakenly exposed to insecticides used on a large scale in the same geographical area [57].

Moreover, Bluetongue is not the only vector-borne disease that affects livestock animals. For example, the Schmallenberg virus, also transmitted to livestock by *Culicoides*, causes neonatal malformations. Following



Figure 8. Bee deaths observed in December 2008 by Ariège beekeepers @Nicole Russier

In 2008-2009, in Ariège, mandatory vector control as part of the measures against the BT epizootic caused a strong objection from beekeepers.

an outbreak in 2012, resistance gradually developed in part of the French livestock population [58]. However, the virus continues to spread to previously unaffected areas. Besnoitiosis, on the other hand, is a pathology caused by a coccidia (protist) transmitted to cattle by hematophagous gadflies and flies, causing fevers and oedema. It continues to expand geographically to the north, the control of which being difficult with ineffective vector control [59]. However, unlike

Bluetongue, these diseases are not among the regulated, reportable and vector-controlled diseases [60].

B - SYSTEMATIC VECTOR CONTROL IMPOSED, INADEQUATE AND INEFFECTIVE

In the event of a suspected outbreak of Bluetongue, insecticide treatment of the holding is required by Community legislation [27]. Indeed, a European directive prescribes, in this case, the treatment of animals, as well as livestock buildings and their surroundings (European Directive 2000/75/EC article 4 d) iii)[52]). Thus, the use of systematic antivectorial measures, through veterinary and biocidal means, is one of the foundations of the control of this regulated arbovirus. The policies to control this infectious agent are based on the eradication of the vector[53]. The products recommended

in this control are often insecticides of the pyrethroid family: deltamethrin, lambda-cyhalothrin, cyfluthrin, alpha cypermethrin, permethrin [61].

However, neither direct treatments of animals with insecticides nor treatments of livestock buildings and environments have been proven effective in the control of BT. This is the opinion of the Emergency Expert Group «Bluetongue», following a self-report by the AFSSA in 2009[62][53]. It establishes that the effectiveness of insecticide application in the treatment of livestock buildings, their surroundings and means of transport cannot be assessed. Direct applications to animals could only be effective if the treatments could be distributed in sufficient concentrations over the entire body surface. However, this is not conceivable in view of the constraints of use and the costs involved, making this measure ineffective against the transmission of BTV strains. The Expert Group concludes that such mandatory and systematic use of insecticide products is not relevant in a context where vaccination is proving effective.

Nevertheless, the re-emergence of bluetongue virus serotype 8 in Auvergne in September 2015 led once again to the implementation of vector control measures provided for in the regulations [63][64]. As part of these animal health measures, the application of insecticides to animals and their immediate environment (vehicles, livestock buildings, slaughterhouses) was, therefore, required again. This measure with unknown and potentially serious environmental consequences has therefore been applied despite suspicions of ineffectiveness. Indeed, no veterinary speciality has so far had marketing authorisations against the midge vector of the BT. The effectiveness of the treatment of livestock buildings and transport vehicles has never been demonstrated. Finally, the treatment applied to the animal protects it from the biting insect, but this is neither complete nor sustainable (Appendix 3 of the N.S. DGAI/SDSPA/2015-753 of 9 September 2015 [65]).

More recently, faced with the failure of the eradication strategy used against the BTV4 serotype in 2017, and the inevitable spread of the virus, the policy to control this very low pathogenic form of BT has been forced to adapt. Thus, the vaccination obligation and restrictions on the movement of animals within the national territory have been abandoned. Nevertheless, the regulation of the systematic application of insecticides has not been reviewed and is still based on Directive 2000/75/EC [66].

5 - LARVICIDAL TREATMENTS OF MANURE

Larvicidal treatments are applied, often in granular form, directly to the manure. The objective is to eliminate fly larvae (mainly *Musca domestica*) and tailworms (dipteran larvae of the genus *Eristalis* - whose adult stages are generalist pollinators)[67].

Their presence in manure and slurry applied to plant crops is taken into account when assessing the risks required for marketing authorisations for biocidal products (OECD Risk Assessment Guidelines[68]). These risks depend largely on the storage time of manure, and how it is applied in the field. However, the degradation phenomena of larvicides in manure are not well known, so little is known about their persistence. Thus, the evaluation guidelines emphasise that "direct application is not recommended because beneficial arthropods associated with manure can be killed. However, if manure cannot be kept dry or disposed of on a weekly basis, larvicides can be used."

These larvicidal products are traditionally formulated with growth-inhibiting insecticides, such as cyromazine and diflubenzuron. Cyromazine, as a biocidal substance, was approved at the European level in 2016. Slightly toxic to bees (LD50 > 25,000 ng/adult bee topically[32]), it is highly soluble (13,600 mg/L[69]) and mobile in soils (Koc=756 [69]), and degrades poorly (half-life 63 days in aerobic soil[69]). Therefore, cyromazine is likely to pollute surface waters. In contrast, diflubenzuron, while it may be more toxic to bees (LD50= 2420 ng/adult bee[70]), is less soluble (0.08 mg/L[69]) and mobile (Koc= 4620[69]), and degrades more rapidly (half-life 3 days in aerobic soil [69]).

The non-specific use of these insecticides in manure and slurry is significant. It is associated with risks of mortality of non-target arthropods during storage and application of these elements. It also raises the question of the risk of soil and water pollution.

C

EXPOSURE AND ECOTOXICITY

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1 - FATE OF INSECTICIDES USED IN LIVESTOCK FARMING

Excretion of active substances and release into the environment

Insecticidal substances administered to livestock can be metabolised in their bodies, even if they have been applied externally [71]. These molecules, therefore, undergo metabolism and transformation, which depend on the type of substance, the species of animal treated, but also on its physical condition. If the metabolism in the animal's body is incomplete, the insecticide substance can be excreted unchanged through urine and faeces, while retaining its full pesticidal potential [4]. Consequently, in general, the excreta of treated animals may contain a mixture of the parent compounds administered to them and the metabolites of these molecules [72]. This mixture has lethal or sublethal toxic effects on the entomofauna.

For the same active ingredient, the duration and intensity of faecal elimination depend on the pharmaceutical form used. Thus, the administration of a bolus of intra-ruminal ivermectin with continuous diffusion is followed by intense faecal elimination lasting more than 120 days, which entails a very high toxic risk for coprophagous beetles [73][74], hence its prohibition in France since 2003 [4]. Insecticidal substances administered by injectable solutions are also affected by this faecal elimination, which occurs for about ten days after injection.

Thus, during the treatment of sheep, cattle or pigs by intraruminal or subcutaneous injection of ivermectin, nearly half of the initial amount of the administered substance is unchanged in the faeces. In these faeces, up to 351 µg of ivermectin per kilogram of faeces can be detected one week after a subcutaneous injection [75]. Even external insecticide treatments carried out by pyrethroids can cause the excretion of substances still active in the urine and faeces of livestock. In dairy cows, cypermethrin levels in the faeces can reach 5 mg/kg in the days following treatment with pour-on. However, the substance can persist in the animal's body and be detectable in its faeces even 3 months after administration, up to 10 mg/kg [71][76].

External insecticide treatments, on the other hand, can lead to more direct environmental contamination. Applied during bathing, spraying and very high-pressure showering operations, they generate insecticide flows in solution. When they are not properly managed and treated, they lead to the contamination of soil and surface water. Also, in the case of sheep, the animals emerge from these processing operations with fleeces loaded with product. Simple runoff from treated body surfaces is fatally loaded with active substances, especially in the event of rain. Besides, these active substances may be persistent in animal fleeces. This is evidenced by the high concentrations detected on the hands of sheep farmers

who handled their cattle one month after spraying dicyclanil (growth inhibitor) or 15 days after showering with dimpylate [9]. This observation is also valid in the case of pour-on treatments [4].

When biocides are applied directly to the external environment of livestock farms, they are indeed likely to generate significant pollution for ecosystems and cause an ecotoxic risk for non-target species.

Dissemination in the environment

Once released into the environment, pest control substances and their degradation products are distributed in air, water, soil and sediment, based on a combination of factors such as the physicochemical properties of these substances and the characteristics of the environment [72]. Thus, among the intrinsic properties of the molecules that determine their mobility are water solubility, volatility, and the ability to be absorbed into the soil. The latter parameter is measured by the adsorption-desorption coefficient, K_d , which describes the intensity of leaching of the substance through the soil, also depending on the nature of the soil. A more standardised K_{oc} is also used, which indicates the retention potential of the active substance on soil organic matter.

In addition, substances leached through the soil are likely to migrate into surface waters and end up in puddles, rivers, streams, and other bodies of water. They cause pollution that is worrying for public health and the environment. Thus, in a study conducted in 2015 in partnership with ONEMA, sometimes significant concentrations of macrocyclic lactones were identified in rivers in two Breton catchment areas [43]. Although detected with low to moderate probabilities of occurrence, éprinomectin and ivermectin were detected in both areas at high concentrations. Also, during the flooding of the Kervidy-Naizin basin, 15% of the samples contained ivermectin, with an average concentration of 1010 ng/L; and 31% of the samples contained éprinomectin, with an average concentration of 415 ng/L.

On the other hand, on livestock farms, livestock manure is often collected in the form of manure or slurry. These large quantities of organic matter can be stored, in manure or tanks, for varying periods of time before being applied to plant crops. During this storage phase, the active substances and their metabolites may undergo further degradation. However, some insecticidal substances are very persistent in manure and slurry, such as ivermectin, which can persist for several months. This raises the risk of contamination of large areas of plant crops during land application if toxic substances are not completely degraded [72]. A study of the contamination of pollen and nectar in these plants would be necessary.

Degradation in the environment

Veterinary and biocidal insecticides can degrade biotically or abiotically in soils and surface waters. In general, degradation processes generate fewer toxic products than parent compounds. However, some degradation products exhibit similar or greater toxicity to the latter (e.g. fipronil sulfone, hydroxy-imidacloprid). It should also be noted that after degradation in organic matrices such as manure, some substances can perform the reverse reaction and thus reconstitute their parent compounds [72].

Degradation processes vary considerably from one molecule to another. Thus, while some insecticidal substances such as dimpylate degrade rapidly, others, such as ivermectin, persist in the soil. Besides, these processes are largely dependent on environmental conditions, such as temperature, soil type and acidity (pH). Thus, ivermectin degradation is slower in winter conditions than in summer conditions, and slower in marly soils than in sandy soils [72].

In a study conducted in 2015 in partnership with ONEMA, sometimes significant concentrations of macrocyclic lactones were identified in rivers in two Breton catchment areas.

Table 1 lists the intrinsic properties of the molecules that determine their fate in the environment for the main insecticidal substances used in livestock farming: how they are excreted; their solubility and mobility (expressed by the retention potential in organic matter in the soil, K_{oc}) that determines their leaching or persistence in the soil; and their degradation dynamics.

SUBSTANCE	METABOLISATION	SOLUBILITY	MOBILITY	DEGRADATION
Ivermectine	Most of the dose is excreted unchanged in the faeces [77]. Main metabolites: 24-OH-H2B1a, 24-OH-H2B1a-MS, 24-OH-H2B1b [78]	Not very soluble 4 mg/L [15]	Low mobility: Clay soil K_{oc} =12600 Silty soil K_{oc} =15700 [79]	Long to very long HL _{mix soil-feces summer} = 7-14 days HL _{mix soil-feces winter} = 9 1-217days [79] HL _{sandy soil} = 14-28 days HL _{sol argileux} =28-56 days [79]
Cypermethrin	Elimination is done by faecal means [71]. Main metabolites: cis and trans (DCVA), 3-phenoxybenzoic acid (3PBA) & 3-(4'-hydroxy-phenoxy) benzoic acid (4OH3PBA) [80]	Very little soluble 0.004 mg/L [80]	Very low mobility K_{oc} =20 800-503 000 [80]	Long to very long HL from 4 to 56 days in soils [80] HL _{hydrolyse} = 179 days [79]
Deltamethrin	4D-HO-deltamethrine & Decamethrinic acid [69]	Very little soluble 0,0002 mg/L [69]	Very low mobility K_{oc} =460 000 - 16 300 000 [79]	Long HL _{aerobie} =21-25 days HL _{anaerobie} =31-36 days [79]
Dimpylate	2-Isopropyl-4-methyl-6-hydroxypyrimidine & Diazoxon (still active cholinesterase inhibitor) [69]	Not very soluble 60 mg/L [69]	Average mobility K_{oc} =1580 [69]	Longue HL _{hydrolyse} =138 days - HL _{aerobie} =40 days, HL _{anaerobie} =16 days [69]
Phoxime		Not very soluble 1,5 mg/L [69]	High mobility K_{oc} =686 [69]	Moderate HL _{hydrolyse} =7,2 days HL _{aerobie} =6 days [69]
Amitraze	2,4-dimethylphenyl formamide (2,4-DMPF) & 2,4-dimethyl aniline (2,4 DMA) [69]	Très peu soluble 0,0094 mg/L [69]	High mobility K_{oc} =951 [69]	Long HL _{hydrolyse} =67days [69]

Table 1: Fate of insecticidal substances used in livestock production after metabolization and release into the environment (HL: Half-life)

2 - ROUTES OF EXPOSURE AND TOXICITY TO NON-TARGET INSECTS

A - A THREAT TO COPROPHAGOUS INSECTS

There are still no specific studies evaluating the exposure of bees and wild pollinators to insecticides used in animal husbandry. The risk of bees being poisoned by these substances is therefore unknown, hence the interest of the BAPESA study [3]. On the other hand, other insects with more obvious exposure pathways have been of more significant concern, leading to a better understanding of the ecotoxicity of insecticides used in livestock production: coprophagous insects.

The impact of veterinary antiparasitic drugs on non-target coprophagous fauna has been the subject of controversy since the 1970s, which has led to an awareness illustrated by the withdrawal of the ivermectin bolus from the French market in 2003[4]. Indeed, macrocyclic lactones induce significant lethal and sublethal effects on beetles and coprophagous diptera. Thus, dipteran larvae are found to be extremely sensitive to endectocidal residues, even in low concentrations, which can lead to mortality[81][82]. These lethal consequences caused at «normal» doses can endanger populations of coprophagous diptera[83]. Similarly, in beetles, larvae are significantly more sensitive than adults, showing very high mortality rates[81][83][84]. Despite greater resistance, adults can also be sublethally affected through reduced fertility[81][84].

According to Floate et al. (2002)[18], coprophagous insects have lethal effects in response to all macrocyclic lactones - moxidectin, éprinomectin, ivermectin and doramectin - here classified by increasing ecotoxicity. The most toxic, doramectin and ivermectin, also have similar ecotoxic effects on other groups of non-target invertebrates, such as collembola and nematodes[85]. In addition, external pesticides such as pyrethroids and growth regulators have also shown negative impacts on non-target coprophagous wildlife [86][81][87]. The impact of these pest control products on coprophagous wildlife may depend on the time of treatment. If it occurs during the period of maximum insect activity, the lethal and sublethal effects will be exacerbated. Thus, spring treatments are the most harmful for coprophagous beetles, which reproduce during this period [4].

The obvious consequence of eliminating non-target coprophagous fauna is to slow down the degradation processes of excreta [88][89][90]. For example, Floate (1998)[90] found that the degradation of a cow's dung enriched with a «normal» dose of ivermectin took more

than 340 days, compared to 80 days without treatment. The weakening of the decomposition service provided by coprophagous fauna then raises problems of hygiene and pasture management.

Finally, contamination of livestock excreta with insecticides can cascade down food chains and disrupt the ecosystem. Indeed, coprophagous fauna is a food resource for many predators. If toxic substances in dung deprive them of this resource or indirectly intoxicate them, populations of these animals may be affected [91][92]. Among these species are birds, such as the skylark and the red-backed shrike, and mammals, such as the European hedgehog and the great rhinolopher [93][94]. Some are emblematic, and already threatened by the degradation and fragmentation of their habitat[4][95].

Given this abundance of scientific literature on the damage caused by insecticides used in animal husbandry on coprophagous fauna, the bibliography on their ecotoxic consequences on bees appears very rare.

B - POTENTIAL EXPOSURE ROUTES FOR BEES: WATER RESOURCES AND FLOWER CONTAMINATION

The potential for exposure of bees to insecticides used in animal husbandry is unknown and has never been quantitatively monitored. Nevertheless, considering the use practices of these products and the behaviour of bees, it is possible to establish links and explain the occasional presence of certain pest control substances in hives. For example, during the winter of 2013-2014, toxicological studies detected several insecticidal substances in the matrices of beekeepers' hives in the Midi-Pyrénées and Languedoc-Roussillon [96]. Initiated following a mortality episode that affected 79% of the colonies of 58 beekeepers, these studies were designed to respond to the suspicion of poisoning by veterinary products, in a context far from any plant culture [97]. They revealed traces of neonicotinoids (imidacloprid, thiacloprid and acetamiprid) -used as plant protection and biocides-, but also pyrethroids (cypermethrin, permethrin and lambda-cyhalothrin) -used as plant protection, biocides and even veterinary use for cypermethrin-.

Bees require significant water resources (30-70L per year per colony), which they collect within a radius of 500 m to 1 km around the hive [1][98][99][100]. The water is extracted without the need for purity. On the contra-

According to a 1998 study, the degradation of a cow's dung enriched with a «normal» dose of ivermectin took more than 340 days, compared to 80 days without treatment.

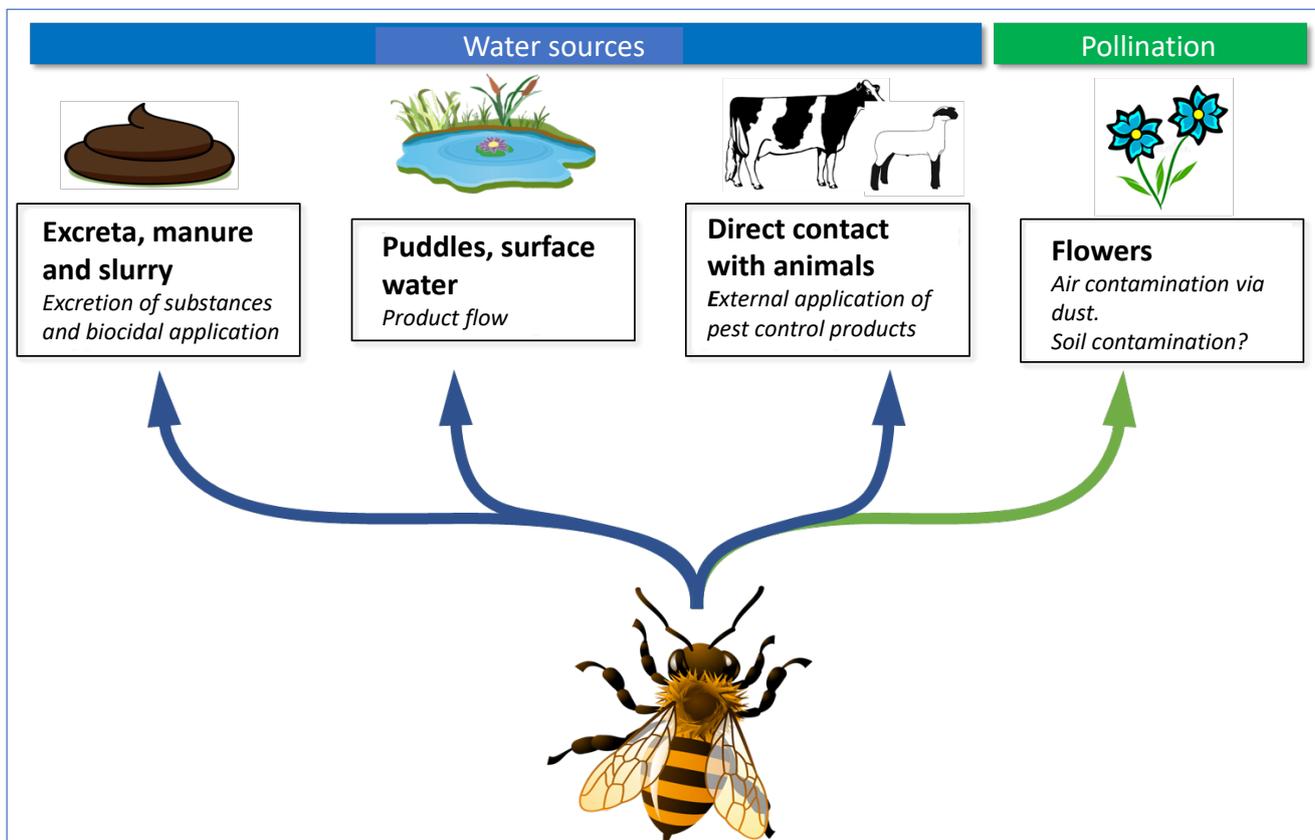


Figure 9. Potential routes of exposure of bees to insecticides used in animal husbandry

ry, Butler showed already in 1940 that bees showed a preference for water sources rich in sodium, ammonium, and magnesium, as is the case with puddles filled with decomposing organic matter, wastewater, and faeces [101][102].

Thus, the aqueous effluents from the insecticide treatment operations mentioned above can represent the water resources of choice for bees (Figure 9). Whether these flows are generated by sprays, showers, bath drains[103] or by biocidal sprays from buildings and vehicles, they spread solutions that can be attractive to bees foraging for water [99]. The same is true when residues of the insecticidal bathing solution are used to treat outdoor installations that may come into contact with animals - such as fences and «scrapers» [47]. It should also be noted that old outdoor bathing sites can generate lasting ecotoxicological risks if contaminated with very persistent products [104]. Also, bees can also drink directly from the wet fleeces of treated animals, or from the fluids that flow from them.

The preferences of water foragers also suggest water-collecting behaviour directly on the dung of livestock, or on manure and slurry stored and spread on outdoor plots. Under these conditions, workers are likely to bring back to the hive water that, even though has been contaminated by insecticidal substances from contaminated sources, is attractive to bees.

On the other hand, recent studies have raised the issue of the air transport of veterinary pharmaceutical substances through suspended particles. Thus, the dust generated by cattle farms on the American Great Plains seems to carry a great diversity of active substances [105][106]. The latter, by settling, can then contaminate large areas. This is evidenced by the detection of several active substances (including moxidectin), on wildflowers [107] and in wetlands[108] around large Texas livestock farms. This contamination by air is probably favoured by an arid climate conducive to the fragmentation of dried faeces.

2 - ROUTES OF EXPOSURE AND TOXICITY TO NON-TARGET INSECTS

C - ACUTE, CHRONIC, SUBLETHAL TOXICITIES FOR BEES AND WILD POLLINATORS

Although little data is available on the exposure of bees to insecticides used in livestock farms, the scientific literature on the toxicity of these molecules is very extensive. The results of numerous laboratory studies on the *Apis mellifera mellifera* bee are available. Most often, experiments focus on determining the acute toxicity of insecticidal substances to bees. Chronic exposure toxicity and sublethal effects are rarely identified in longer, more detailed and more costly studies.

Table 2 lists the acute and chronic toxicity values, as well as the sublethal effects in bees caused by the main insecticidal substances included in the present report. As stated above, these molecules, belonging to the families of macrocyclic lactones, pyrethroids, or organophosphates, are highly effective neurotoxic insecticides. Their deleterious effects on bees are notoriously substantial, as these data show.

ACTIVE INGREDIENT	ACUTE TOXICITY	CHRONIC TOXICITY	SUBLETHAL EFFECTS
Ivermectin	Very high CL50=570 ng/mL (oral, 24h) [109] DL50=0,002µg/bee (topical) [110] DL50=0,011 µg/bee (abamectine, oral) [111]		Reduced long-term olfactory memory [112]
Cyperméthrin	High DL50= 110-560 ng/bee (oral) [32] DL50=23-130 ng/bee (oral) [32]	Demonstrated [113]	
Deltamethrin	Very high DL50=1,5 ng/bee (topical) [22] [32] DL50=50,65 ng/bee (topical) [114] DL50=850 ng/bee (oral 24h) [111] DL50=620 ng/bee (oral 48h) [115] Suspected synergy with organophosphates [116]	Demonstrated [117]	Disorientation [118] Reducing fertility and slowing development [119] Disruption of learning abilities [120]
Dimpylate	High DL50=200 ng/bee (oral) [32] DL50=52-233 ng/bee (topical) [121] [122]		
Phoxime	Mentioned but not quantified [13]		
Amitraze	Moderate DL50=14830 ng/bee (oral) [123] DL50=3660 ng/bee (topical) [124]		Damages heart function and resistance to viral infections [125]

Table 2 : Toxicity to bees of the main insecticidal substances used in animal husbandry (LC50: concentration sufficient to kill 50% of individuals; LD50: dose sufficient to kill 50% of individuals).

3 - RISK ASSESSMENT AND REGULATION

A - PROCEDURES FOR ECOTOXIC RISK ASSESSMENT OF VETERINARY MEDICINAL PRODUCTS

In order to obtain a marketing authorisation (MA), a veterinary medicinal product must be subject to a benefit/risk analysis in accordance with European Directive 2001/82/EC [126], as amended by Directive 2004/28/EC, and subsequently Directive 2009/9/9/EC [127][128]. Thus, any firm applying for MA must study the risks to the environment of its medicinal product “in order to assess the possible harmful effects that the use of the veterinary medicinal product could have on the environment and to identify the risks related to these effects”. “The assessment must also seek all precautions for use that may reduce these risks”. (Directive 2001/82/EC Annex I, Part 3, Article 6.1 [126]). To this end, the section of the MA dossier dedicated to environmental risk assessment is based on two guidelines published by the Veterinary International Conference on Harmonisation (VICH), an international body. The first guideline, VICH GL6, is for the assessment of environmental and non-target species exposure to the veterinary product in question [129]. The second, VICH GL38, deals with the assessment of the effects resulting from this exposure [130]. These guidelines provide a common basis that benefits administrations and industrialists in the different countries involved, to guide the assessment of the ecotoxic risk of veterinary medicinal products.

Thus, the first step in the environmental risk assessment of a veterinary drug is dedicated to studying the exposure of ecosystems to the product under evaluation (phase I). According to the VICH GL6 guideline, the question then is whether this exposure is sufficient to generate a risk. In this case, the ecotoxicity studies recommended by the VICH GL38 guideline are required. Typically, the profile of the veterinary drug likely to cause high environmental exposure corresponds to the antiparasitic agents already described in this report: mass treatments done on livestock, poorly metabolised and marketable on a large scale. In detail, the VICH GL6 guideline introduces a quantitative indicator of exposure: the «Predicted Environmental Concentration» (PEC), which corresponds to the estimated concentration of the parent compound and its metabolites in each of the environmental compartments (water, soil and sediments), following normal use of the veterinary drug [127][129]. The value of PEC is derived from modelling using the farming method, treatment methods, substance characteristics, etc. This calculation is often controversial. For example, it has been found to be very underestimated in the case of neonicotinoids in crop treatment. In most cases, ecotoxicity studies (Phase II) are only necessary if the PEC is estimated to be greater than 100 µg/kg in soil or greater than 1 µg/L in the aquatic environment. Nevertheless, there is an exception for pest control treatments for livestock, which are of interest here. Indeed, whatever the PEC values associated with them, their evaluation requires

phase II studies to estimate their ecotoxicity according to the VICH GL38 guidelines. This exceptional regime, for once more restrictive, demonstrates a recognition of the environmental risks that result from the use of such pest control treatments. It also demonstrates the weakness of the PEC calculation, which often remains in use even though the measures are possible and give much more credible results.

Following the estimation of the exposure of the different environmental compartments and the calculations of the different PECs, the environmental risk assessment enters phase II-A aiming to study how the non-target species present in these environments are affected by substances derived from the veterinary medicinal product [127][130]. For convenience, this assessment, which follows the VICH GL38 guidelines, is only conducted on a few specific species selected as indicators or models. The latter are intended to be representative of taxa essential to the ecosystems in question, or particularly sensitive to ecotoxic risks. For each of them, the aim is to determine the «Predicted No Effect Concentration» (PNEC), which represents the concentration below which the active substance from the evaluated veterinary drug has no observable effect on the non-target species chosen as an indicator/model.

This assumes that the toxicity indicators have been well chosen and do not rule out some important sublethal effects (behaviour, reproduction, immunity, etc.). In any case, the PNEC value, identified experimentally in the laboratory, is then divided by a safety factor (usually 10), in order to prevent an underestimation of toxicity related to the uncertainty of the method, or the species tested. This provides a small precautionary margin since often the test species are not the most sensitive (e.g. imidacloprid and daphnia).

It is then possible to compare the PECs of each environmental compartment with the PNECs of the non-target species remaining there, by calculating the PEC/PNEC ratio, called the «Risk Quotient» (Figure 10). If the latter is less than 1 for a species, then it is considered that the concentrations of active substances released into its habitat are not sufficient to affect it. Otherwise, the veterinary drug presents a risk to this species. It is then necessary to carry out more complex and costly studies to refine the assessment of the impact of these substances, thus reducing the safety factor. This is phase II-B. Thus, while Phase II-A requires mainly acute and subacute toxicity studies, Phase II-B requires longer studies of chronic exposure, which include more species, in order to be more representative of real conditions [127].

Classically, the species selected as indicators/models in Phase II are algae and plants, whose growth inhibition by active substances is studied, and fish, crustaceans, daph-

3 - RISK ASSESSMENT AND REGULATION

nia and earthworms, for which acute or subacute toxicity is assessed [130]. The effect of the veterinary product on soil microorganisms is also studied. However, in the case of pest control treatments used on grazing livestock, ecotoxicity studies on beetle and dipteran coprophagous larvae are also recommended. Although the guidelines for these studies are less developed - no instructions are planned for Phase II-B - this indicates an awareness of the negative impact of parasite treatments on coprophagous fauna. However, no assessment is planned for pollinating fauna.

If the environmental assessment provides for a moderate ecotoxic risk, not considered "unacceptable", the MA may be issued with risk mitigation measures: administrative or issuing restrictions, monitoring conditions, warnings in the RCP [13][127]. The latter, a summary of the product characteristics, compiles scientific information from the marketing authorisation dossier and analysed by the competent authorities. It may contain warnings against direct illegal releases of the medicinal product into the environment, or indirect releases generated by its legal use. In the first case, the indications are intended to raise awareness of the harmful consequences of non-

compliance: e.g. "Extremely dangerous to fish and other aquatic organisms. Do not contaminate surface water or ditches with the product or used packaging" (mentioned in most RCPs for drugs containing macrocyclic lactones [13]). Under normal use, RCP warnings can act as a safety precaution to limit the ecotoxic risk of indirect releases: e.g. "The drug has harmful effects on coprophilic flies. Sheep should be kept away from watercourses for at least one hour after treatment. If this recommendation is not followed, there is a serious risk to the aquatic environment." (RCP of CLIK®- Elanco Europe, based on Dicyclanil[13]). Precautions for use may not directly concern the management of animals but their effluents: e.g. "manure from treated pigs must be kept for 3 months before spreading and incorporating it into the fields" (NUFLOR® RCP - Intervet, based on florfenicol[13]). Finally, the RCP warnings may sometimes compensate for the absence of a complete risk assessment, particularly when the active ingredient has demonstrated toxic effects in other formulations. For this reason, many livestock pest control products have been reported to be toxic to bees in RCPs, even though no bee risk assessment has been conducted to obtain the MA (e.g. BUTOX 7.5 POUR ON® RCP - Intervet, a deltamethrin-based drug for cattle and sheep).

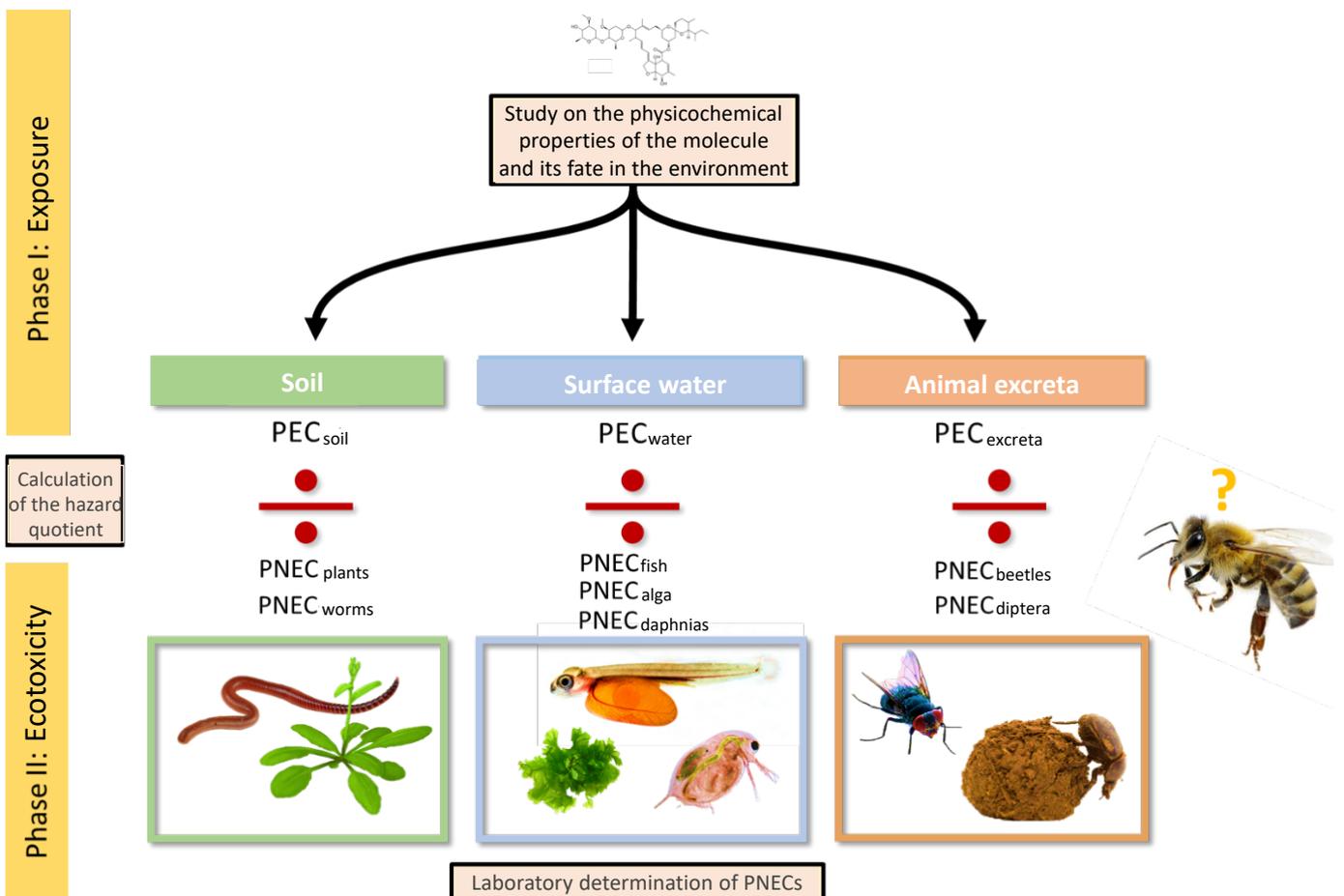


Figure 10. Outline of the environmental risk assessment process for veterinary drugs administered to grazing animals, phases I and II-A: calculation of the PEC/PNEC risk quotient for each non-target species considered [129][130].

B - PROCEDURES FOR ECOTOXIC RISK ASSESSMENT OF BIOCIDAL PRODUCTS

Like the environmental risk assessment of veterinary drugs, the environmental assessment of biocidal products is divided into two successive steps: exposure assessment to estimate PECs; and ecotoxicity assessment to determine PNECs. As before, the calculation of the PEC/PNEC risk quotient, for each non-target species considered, is decisive for judging the acceptability of the environmental risk associated with the use of the product. However, it remains based on two predictions. In the case of biocidal products, the evaluation procedure follows the guidelines provided by ECHA [131].

However, as with the environmental risk assessment of veterinary drugs, there are no guidelines for assessing the effects of biocidal products on bees and pollinators: "Non-target arthropods, bees and other non-target organisms are currently not covered in this guidance. The development of assessment methods for these species groups is currently under discussion" [131]. Thus, because of the lack of a method for assessing the risk posed by biocidal products to bees and other non-target arthropods, ECHA's guidelines suggest the possibility of implementing qualitative studies, based on the guidelines for the evaluation of plant protection products. This highlights the inadequacy of the current regulations for the risk assessment of biocidal products on non-target species. It also shows that biocides are assessed less rigorously than plant protection products, even though the evaluation of the latter is marred by major methodological shortcomings in the case of bees (EFSA Panel PPR; Scientific Opinion on the science behind the development of a risk assessment of Plant Protection Products on bees. EFSA Journal 2012).

C - INTEGRATE WILD BEES AND POLLINATORS INTO ASSESSMENTS

In the absence of quantification of the exposure of honeybees and wild pollinators to insecticides used in animal husbandry, it is not possible to conduct a true risk assessment for this non-target fauna, despite the abundance of experimental toxicity data. However, in the case of bees and other pollinating insects, it is difficult to quantify exposure to insecticidal substances spread by breeding activities [131]. Indeed, this exposure does not occur in an environment that can be considered continuous, such as soil, aquatic environments, sediments, and even animal excrement. Bees cannot, therefore, be attached to a single compartment of the environment (Figure 10). On the contrary, they actively visit water spots, plants, excreta, etc. In doing so, they are exposed to contamination of the soil, faeces, water, and air. It is therefore not relevant to reduce this exposure to PEC from a single compartment and compare it to the PNEC of bees.

It would be essential to adapt environmental risk assessment procedures to include ecotoxic risk issues for bees and other pollinating insects, starting with chronic exposure measurements over a beekeeping season.

The evaluation procedure described above cannot then be used to assess the risks associated with the use of veterinary medicinal products and biocidal products on non-target pollinating fauna. Under these conditions, how can the marketing authorisation of these products be made subject to "an acceptable level of risk for man and the environment" ? Hence, it would be essential to adapt environmental risk assessment procedures to include ecotoxic risk issues for bees and other pollinating insects, starting with chronic exposure measurements over a beekeeping season.

However, it is already possible to directly compare the levels of insecticides detected in livestock farms with the toxicity values of these molecules for honeybees. This exercise is simplistic because it assumes that bees consume all the substance released into the environment. Nevertheless, by transcribing a maximum risk, it raises questions about the potential harmfulness of insecticides released by livestock activities [132].

For example, Virilouvet et al. (2006) [71], quantified faecal excretion of cypermethrin in cattle following external treatment by pour-on. The peak excretion is obtained on the 5th day after treatment, with dung loaded with cypermethrin levels close to 1890 µg/kg dry matter. During the 8 days of maximum excretion, cows emit faeces loaded with an average of 1100 µg/kg of cypermethrin dry matter. At a rate of 12 dung per day, and 4 kg of dry matter per dung, a treated cow releases nearly 35200 µg of cypermethrin during the maximum excretion phase. Thus, considering an oral toxicity value (acute LD50) of 35 ng/bee [79], this contamination is equivalent to nearly one million times this LD50 [132].

Similarly, the dose of ivermectin excreted by a cow treated by subcutaneous injection can be estimated from the results of Tremblay & Wratten (2002) [75]. During peak excretion, fresh dung contains ivermectin levels up to 351 µg/kg, or around 5776 µg/kg of dry matter. With the same reasoning as above, such an excretion of ivermectin for 8 days, for such an animal, would lead to the release of nearly 184800 µg of ivermectin into the environment. By reproducing the above calculation for this molecule extremely toxic to bees, with an oral toxicity value (acute LD50) of 0.002 µg/bee [110], this contamination is equivalent to 92 million times this LD50 [132].

While it is difficult to imagine that bee colonies would be exposed to all of these quantities of insecticides released into the environment, these calculations nevertheless illustrate the extent of potential contamination over a short period of time for a single treated animal.

4 - PRACTICAL ALTERNATIVES?

After progress on the issue of antibiotics, the issue of the ecotoxicity of antiparasitic drugs used in livestock farming is beginning to be considered. Thus, various projects, bringing together the various stakeholders in livestock health, are being developed with the objective of managing pest infestations using of a more proportionate, responsible and sustainable control.

Solutions are being explored through projects such as the LIFE programme «Prairies bocagères» in Wallonia [93], or LIFE + «Chiro Med» in Camargue [95], in order to reduce the use of pesticides on livestock farms. This is based on rejecting the systematic use of pesticides by promoting the establishment of a host-parasite balance, which ensures that farm animal immunity is maintained while preserving their health. In addition, systemic pest control generates, through selection effect, the emergence of resistant parasites. More measured treatments thus make it possible to preserve the effectiveness of antiparasitic substances in the long term.

To allow the development of these alternative methods, care must be taken in the management of grasslands, whose parasitic load must be taken into account. This management may involve grazing rotations, sometimes involving several species of livestock, susceptible to different pests, and at reasonable densities [91]. This is accompanied by careful monitoring of the infestation status of the animals. If treatment is necessary, the focus should be on the molecules that are least harmful to non-target wildlife. For this reason, it is preferable to avoid treatments with broad-spectrum molecules by preferring specific treatments. In addition, it is essential

to know the life cycle of parasites in order to treat them at the optimal time, while avoiding periods when non-target wildlife is most sensitive.

These measures are similar to the good practices recommended by the Société Nationale des Groupements Techniques Vétérinaires (SNGTV), for the rational use of insecticides in vector control [57]. This use prohibits, in particular, direct applications of insecticides in the environment, manure treatments and uncontrolled drainage of contaminated water. On the contrary, it encourages the use of insecticides adapted to each situation, by controlling the dispersion of molecules and being aware of the possible environmental effects. As far as possible, SNGTV also advises favouring alternative methods to the use of insecticide treatments, through the use of insect repellents, brushing, maintaining the natural immunity of livestock, etc.

The adoption of such alternative practices is based on cooperation between breeders and veterinarians, as illustrated by the EleVE project "Controlling parasitism in herds while respecting the environment" [94]. This project, led by livestock farmers, veterinarians and environmental initiatives (Natura 2000 but also associations including the LPO, and ADA - in French Associations for the Development of Beekeeping), aims to reason the use of anti-parasite treatments in wetlands in Auvergne. Pest management is thus rethought through a case-by-case approach and reasoned and proportionate treatments. This results in a more economical approach for farmers, which also does not encourage the emergence of resistance in the long term.

CONCLUSION

Insecticides used in pest management on farms are highly toxic to bees. Their neurotoxic modes of action are not specific to parasitic insects and harm an entire non-target arthropod fauna. However, the conditions of use of these products are highly likely to cause exposure of this fauna to these molecules. Indeed, through indirect discharges into livestock excreta, or direct discharges from poorly managed effluents or large-scale applications, they are released into the external environment of farms.

Due to the difficulty of estimating the exposure of bees to these products and the lack of exposure data measured in various compartments, environmental risk assessments prior to the authorisation of these products are insufficient. Thus, they do not take into account the risks generated for pollinating insects. In comparison, the risks posed by veterinary drugs to insect coprophages in pastures are increasingly known and assessed. Considering these shortcomings in the risk assessment process, few precautions are taken to prevent bee poisoning. It is therefore imperative to carry out quantified monitoring of the use of these pesticides at a national level - or at least made it possible. This is not the case today, and it is very difficult to know the nature and quantity of these neurotoxic insecticides administered on livestock farms. The compartmentalisation between veterinary and biocidal uses further reduces this readability.

The present study focuses on the sheep and cattle grazing sectors. Other, sometimes more industrial sectors, such as the pig sector, could be studied, with particular attention to the management of potentially contaminated livestock manure. In addition, the focus was on neurotoxic insecticidal pest control products, designed for highly effective insect control. Other classes of pest control products with more unknown effects on insects, such as anthelmintics, may receive more attention in the future.

In the past, a "normal" use of these pesticides in livestock farming has probably already caused bee colony poisoning accidents and raised new fears among beekeepers. The latter, already suffering from many other problems - diseases, plant protection products and natural enemies - are thus facing an additional threat. As for wild pollinators, which do not benefit from the same monitoring, they can be the subject of substantial poisonings without anyone being aware of it. If insecticides used in livestock farming have already been implicated in the deterioration of the recycling function of grazing animal excreta, another major ecosystem function could be affected here: pollination. Essential for the reproduction of most wild and cultivated plants, it could suffer from the damage caused to insect communities by neurotoxic pesticides used in livestock farming.

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APPENDIX

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APPENDIX 1 - INVENTORY OF AUTHORISED VETERINARY ANTI-PARASITIC MEDICINAL PRODUCTS FOR LIVESTOCK [13]

Nom	Laboratoire	Numéro AMM	Date AMM	Procédure AMM	Mode d'application	Substances Actives	Espèces cibles	Type
CONCENTRAT V064 ALBENDAZOLE 30 BOVINS-OVINS	CEVA SANTE ANIMALE	FRV/4837 120 1/2002	05/02/2002	Nationale	Prémélange médicamenteux	Albendazole	Bovins, Ovins	ANTHELMINTHIQUE
DISTHELM 2,5 %	QALIAN	FRV/0195 210 8/1986	31/10/1986	Nationale	Suspension buvable	Albendazole	Caprins, Ovins	ANTHELMINTHIQUE
VALBAZEN BOVINS 5 %	ZOETIS FRANCE	FRV/9879 575 2/1980	18/02/1980	Nationale	Suspension buvable	Albendazole	Bovins	ANTHELMINTHIQUE
VALBAZEN DIX	ZOETIS FRANCE	FRV/5832 835 0/1983	02/11/1983	Nationale	Suspension buvable	Albendazole	Bovins	ANTHELMINTHIQUE
VALBAZEN MOUTONS ET CHEVRES 1,9 %	ZOETIS FRANCE	FRV/6310 474 5/1980	18/02/1980	Nationale	Suspension buvable	Albendazole	Caprins, Ovins	ANTHELMINTHIQUE
TAKTIC	INTERVET	FRV/9724 437 6/1982	09/02/1982	Nationale	Solution à diluer pour émulsion pour pulvérisation cutanée	Amitraz	Bovins, Caprins, Ovins, Porcins	INSECTICIDE
AMPROLINE 400 MG/ML SOLUTION POUR ADMINISTRATION DANS L'EAU DE BOISSON POUR POULETS ET DINDES	QALIAN	FRV/0796 434 5/2016	03/03/2016	DCP, FR=EMR	Solution pour administration dans l'eau de boisson	Amprolium	Dinde, Poule pondeuse, Poule reproductrice, Poules, Poulet de chair	COCCIDIOCIIDE
COCCIBAL 200 MG/ML SOLUTION POUR ADMINISTRATION DANS L'EAU DE BOISSON POUR POULETS ET DINDES	SP VETERINARIA	FRV/1142 130 6/2012	22/03/2012	RM, FR=EMR	Solution pour administration dans l'eau de boisson	Amprolium	Dinde, Poules	COCCIDIOCIIDE
COXAPROL	QALIAN	FRV/6959 048 5/2015	27/05/2015	Nationale	Solution à diluer pour solution buvable	Amprolium	Volailles	COCCIDIOCIIDE
EIMERYL 200 MG/ML SOLUTION POUR UTILISATION DANS L'EAU DE BOISSON POUR POULETS ET DINDES	GLOBAL VET HEALTH	FRV/5247 247 3/2012	23/03/2012	DCP, FR=EMR	Solution buvable	Amprolium	Dinde, Poules	COCCIDIOCIIDE
NEMAPROL	MERIAL	FRV/5336 886 7/1992	17/02/1992	Nationale	Solution buvable	Amprolium	Volailles	COCCIDIOCIIDE
ANIMEC D 10/100 MG/ML SOLUTION INJECTABLE POUR BOVINS	CHANELLE PHARMACEUTICALS MANUFACTURING	FRV/2963 916 8/2011	06/07/2011	RM, FR=EMC	Solution injectable	Closulone, Ivermectine	Bovins	ENDECTOCIDE
BIMECTIN D 10/100 MG/ML SOLUTION INJECTABLE POUR BOVINS	CROSS VETPHARM GROUP	FRV/8519 975 4/2016	01/06/2016	Nationale	Solution injectable	Closulone, Ivermectine	Bovins	ENDECTOCIDE
CEVAMEC D	CROSS VETPHARM GROUP	FRV/9864 064 7/2010	13/01/2011	RM, FR=EMC	Solution injectable	Closulone, Ivermectine	Bovins	ENDECTOCIDE
CHANECTIN D SOLUTION INJECTABLE	CHANELLE PHARMACEUTICALS MANUFACTURING	FRV/1563 730 3/2011	16/09/2011	RM, FR=EMC	Solution injectable	Closulone, Ivermectine	Bovins	ENDECTOCIDE
IVOMEC D	MERIAL	FRV/2584 338 3/1988	06/05/1988	Nationale	Solution injectable	Closulone, Ivermectine	Bovins	ENDECTOCIDE
VIRBAMEC D SOLUTION INJECTABLE	VIRBAC	FRV/2442 738 2/2005	30/05/2005	RM, FR=EMC	Solution injectable	Closulone, Ivermectine	Bovins	ENDECTOCIDE
FLUKIVER	LILLY FRANCE	FRV/8501 884 8/1981	12/08/1981	Nationale	Solution injectable	Closantel	Bovins, Ovins	ANTHELMINTHIQUE
SEPONVER	LILLY FRANCE	FRV/5195 635 8/1989	27/09/1989	Nationale	Suspension buvable	Closantel	Bovins, Ovins	ANTHELMINTHIQUE
SOLANTEL 50 MG/ML SUSPENSION BUVALE POUR OVINS	NORBROOK LABORATORIES	FRV/1545 591 2/2016	11/08/2016	DCP, FR=EMC	Suspension buvable	Closantel	Ovins	ANTHELMINTHIQUE
CLOSAMECTINE 5 MG/ML/125 MG/ML SOLUTION INJECTABLE POUR BOVINS ET OVINS	NORBROOK LABORATORIES	FRV/5138 990 9/2008	28/02/2008	RM, FR=EMC	Solution injectable	Closantel, Ivermectine	Bovins, Ovins	ENDECTOCIDE
VERMAX D	NORBROOK LABORATORIES	FRV/9829 328 1/2010	26/03/2010	Nationale	Solution injectable	Closantel, Ivermectine	Bovins, Ovins	ENDECTOCIDE
SUPAVERM	LILLY FRANCE	FRV/5114 443 0/1993	08/01/1993	Nationale	Suspension buvable	Closantel, Mébendazole	Ovins	ANTHELMINTHIQUE
DUOTECH	NORBROOK LABORATORIES	FRV/8345 859 2/2004	23/02/2004	RM, FR=EMC	Suspension buvable	Closantel, Oxfendazole	Ovins	ANTHELMINTHIQUE
ECTOFLY 12,5 MG/ML SOLUTION POUR-ON POUR OVINS	CROSS VETPHARM GROUP	FRV/4170 433 0/2012	02/04/2012	RM, FR=EMC	Solution pour pour-on	Cyperméthrine	Ovins	INSECTICIDE
ELECTRON A LA CYPERMETHRINE	VETOQUINOL	FRV/4983 555 7/1983	06/01/1983	Nationale	Plaquette auriculaire	Cyperméthrine	Bovins	INSECTICIDE
DECCOX DECOQUINATE 6 VEAU-AGNEAU SEVRES	ZOETIS FRANCE	FRV/3593 648 8/1992	07/08/1992	Nationale	Prémélange médicamenteux	Décoquinat	Agneau, Veau	COCCIDIOCIIDE
PM 14 DECOQUINATE 6 VEAU-AGNEAU SEVRES	DELTA VIT	FRV/1296 762 9/2001	03/09/2001	Nationale	Prémélange médicamenteux	Décoquinat	Agneau, Veau	COCCIDIOCIIDE
RUMICOX DECOQUINATE 6 VEAUX ET AGNEAUX SEVRES PREMELANGE MEDICAMENTEUX	CEVA SANTE ANIMALE	FRV/4810 334 5/2000	10/10/2000	Nationale	Prémélange médicamenteux	Décoquinat	Agneau, Veau	COCCIDIOCIIDE
UCAMIX V DECOQUINATE 6 VEAUX ET AGNEAUX SEVRES	QALIAN	FRV/4688 045 9/2001	03/01/2001	Nationale	Prémélange médicamenteux	Décoquinat	Agneau, Veau	COCCIDIOCIIDE
BUTOX 50	INTERVET	FRV/1423 534 8/1989	10/01/1989	Nationale	Solution à diluer pour application cutanée	Deltaméthrine	Bovins, Ovins	INSECTICIDE
BUTOX 50 POUR MILLE	INTERVET	FRV/6944 916 3/1986	10/10/1986	Nationale	Solution à diluer pour application cutanée	Deltaméthrine	Bovins, Ovins	INSECTICIDE
BUTOX 7,5 POUR ON	INTERVET	FRV/5414 469 9/1987	22/04/1987	Nationale	Solution pour pour-on	Deltaméthrine	Bovins, Ovins	INSECTICIDE
DECTOSPOT 10 MG/ML SOLUTION POUR-ON POUR BOVINS ET OVINS	CROSS VETPHARM GROUP	FRV/6739 546 0/2016	04/02/2016	DCP, FR=EMR	Solution pour pour-on	Deltaméthrine	Bovins, Ovins	INSECTICIDE
DELTANIL 10 MG/ML SOLUTION POUR POUR-ON POUR BOVINS ET OVINS	VIRBAC	FRV/7338 262 5/2013	19/04/2013	DCP, FR=EMC	Solution pour pour-on	Deltaméthrine	Bovins, Ovins	INSECTICIDE
DELTANIL 100 MG SOLUTION POUR SPOT-ON POUR BOVINS	VIRBAC	FRV/5858 053 4/2013	19/04/2013	DCP, FR=EMC	Solution pour spot-on	Deltaméthrine	Bovins	INSECTICIDE

INSECINOR 10 MG/ML SOLUTION POUR SPOT-ON POUR BOVINS ET OVINS	NORBROOK LABORATORIES	FRV/0013 122 1/2014	22/08/2014	DCP, FR=EMC	Solution pour spot-on	Deltaméthrine	Bovins, Ovins	INSECTICIDE
SPOTINOR 10 MG/ML SOLUTION POUR SPOT-ON POUR BOVINS ET OVINS	NORBROOK LABORATORIES	FRV/4515 307 5/2014	22/08/2014	DCP, FR=EMC	Solution pour spot-on	Deltaméthrine	Bovins, Ovins	INSECTICIDE
VERSATRINE	ZOETIS FRANCE	FRV/2996 804 2/1986	13/06/1986	Nationale	Solution pour pour-on	Deltaméthrine	Bovins, Ovins	INSECTICIDE
VECOXAN SUSPENSION ORALE 2,5 MG/ML	LILLY FRANCE	FRV/5395 150 6/1998	20/07/1998	RM, FR=EMR	Suspension buvable	Diclazuril	Agneau, Veau	COCCIDIOECIDE
CLIK	ELANCO EUROPE	FRV/5251 046 3/2002	25/03/2002	RM, FR=EMC	Suspension pour pour-on	Dicyclanil	Ovins	INSECTICIDE
CLIKZIN 1,25% SUSPENSION POUR POUR-ON POUR OVINS	ELANCO EUROPE	FRV/3885 778 4/2010	12/07/2010	DCP, FR=EMC	Suspension pour pour-on	Dicyclanil	Ovins	INSECTICIDE
DIMPYGAL	QALIAN	FRV/7212 234 5/1992	12/02/1992	Nationale	Solution pour application cutanée	Dimpylate	Bovins, Caprins, Chien, Ovins, Porcins	INSECTICIDE
DECTOMAX 10 MG/ML SOLUTION INJECTABLE POUR BOVINS OVINS ET PORCINS	ZOETIS FRANCE	FRV/4335 418 4/2012	09/07/2012	DCP, FR=EMC	Solution injectable	Doramectine	Bovins, Ovins, Porcins	EENDECTOCIDE
DECTOMAX 5 MG/ML SOLUTION POUR POUR-ON POUR BOVINS	ZOETIS FRANCE	FRV/9595 460 0/2012	09/07/2012	DCP, FR=EMC	Solution pour pour-on	Doramectine	Bovins	EENDECTOCIDE
DORANOR 5 MG/ML SOLUTION POUR-ON POUR BOVINS	NORBROOK LABORATORIES	FRV/4025 027 6/2013	12/11/2013	DCP, FR=EMC	Solution pour pour-on	Doramectine	Bovins	EENDECTOCIDE
NORADOR 5 MG/ML SOLUTION POUR-ON POUR BOVINS	NORBROOK LABORATORIES	FRV/9990 743 3/2013	12/11/2013	DCP, FR=EMC	Solution pour pour-on	Doramectine	Bovins	EENDECTOCIDE
TAURADOR 5 MG/ML SOLUTION POUR-ON POUR BOVINS	NORBROOK LABORATORIES	FRV/6420 513 9/2013	12/11/2013	DCP, FR=EMC	Solution pour pour-on	Doramectine	Bovins	EENDECTOCIDE
ZEARL	LILLY FRANCE	FRV/2691 324 5/1995	04/01/1995	Nationale	Solution injectable	Doramectine	Bovins, Ovins	EENDECTOCIDE
ZEARL POUR-ON	LILLY FRANCE	FRV/1225 541 8/1998	16/01/1998	RM, FR=EMC	Solution pour pour-on	Doramectine	Bovins	EENDECTOCIDE
EPRECIS 20 MG/ML SOLUTION INJECTABLE POUR BOVINS	CEVA SANTE ANIMALE	FRV/2517 136 5/2015	13/05/2015	DCP, FR=EMC	Solution injectable	Eprinomectine	Bovins	EENDECTOCIDE
EPRECIS 5 MG/ML SOLUTION POUR POUR-ON POUR BOVINS	CEVA SANTE ANIMALE	FRV/1482 427 6/2015	13/05/2015	DCP, FR=EMC	Solution pour pour-on	Eprinomectine	Bovins	EENDECTOCIDE
EPRINEX MULTI 5 MG/ML POUR-ON POUR BOVINS OVINS ET CAPRINS	MERIAL	FRV/7747 510 9/2016	27/07/2016	DCP, FR=EMC	Solution pour pour-on	Eprinomectine	Bovins, Caprins, Ovins	EENDECTOCIDE
EPRINEX POUR-ON POUR BOVINS	MERIAL	FRV/1998 779 2/1997	04/08/1997	Nationale	Solution pour pour-on	Eprinomectine	Bovins	EENDECTOCIDE
EPRIVALAN 5 MG/ML POUR-ON POUR BOVINS	MERIAL	FRV/5011 083 4/2013	18/09/2013	Nationale	Solution pour pour-on	Eprinomectine	Bovins	EENDECTOCIDE
EPRIZERO 5 MG/ML SOLUTION POUR-ON POUR BOVINS ET VACHES LAITIÈRES	NORBROOK LABORATORIES	FRV/3525 887 6/2013	19/02/2013	DCP, FR=EMC	Solution pour pour-on	Eprinomectine	Bovins, Vache	EENDECTOCIDE
EPROMECS 5 MG/ML SOLUTION POUR-ON POUR BOVINS	CHANELLE PHARMACEUTICALS MANUFACTURING	FRV/8709 207 5/2015	20/01/2016	RM, FR=EMC	Solution pour pour-on	Eprinomectine	Bovins	EENDECTOCIDE
NEOPRINIL POUR-ON 5 MG/ML SOLUTION POUR-ON POUR BOVINS	VIRBAC	FRV/4669 176 7/2014	28/02/2014	DCP, FR=EMR	Solution pour pour-on	Eprinomectine	Bovins	EENDECTOCIDE
ROBONEX 5 MG/ML SOLUTION POUR-ON POUR BOVINS ET VACHES LAITIÈRES	NORBROOK LABORATORIES	FRV/5681 414 5/2013	19/02/2013	DCP, FR=EMC	Solution pour pour-on	Eprinomectine	Bovins, Vache	EENDECTOCIDE
ZEPPRIPOUR 5 MG/ML SOLUTION POUR-ON POUR BOVINS	CHANELLE PHARMACEUTICALS MANUFACTURING	FRV/9131 744 9/2015	20/01/2016	RM, FR=EMC	Solution pour pour-on	Eprinomectine	Bovins	EENDECTOCIDE
RINTAL SUSPENSION 10 %	BAYER HEALTHCARE	FRV/2512 503 8/1982	17/05/1982	Nationale	Suspension buvable	Fébanfel	Bovins, Caprins, Ovins	ANTHELMINTHIQUE
CUROFEN 50 MG/G POWDRE ORALE POUR PORCS	UNIVET	FRV/9519 726 9/2015	15/10/2015	DCP, FR=EMC	Poudre orale	Fenbendazole	Porcins	ANTHELMINTHIQUE
GALLIFEN 40 MG/G PREMELANGE MEDICAMENTEUX POUR POULETS	HUVEPHARMA	FRV/0164 348 6/2016	08/12/2016	DCP, FR=EMC	Prémélange médicamenteux	Fenbendazole	Poules, Poulet de chair	ANTHELMINTHIQUE
PANACUR 10 %	INTERVET	FRV/4901 731 9/1985	08/01/1985	Nationale	Suspension buvable	Fenbendazole	Bovins, Equins	ANTHELMINTHIQUE
PANACUR 2,5 %	INTERVET	FRV/6213 550 8/1985	08/01/1985	Nationale	Suspension buvable	Fenbendazole	Bovins, Caprins, Ovins	ANTHELMINTHIQUE
PANACUR 250 OVINS-CAPRINS	INTERVET	FRV/0470 542 2/1995	17/11/1995	Nationale	Comprimé	Fenbendazole	Caprins, Ovins	ANTHELMINTHIQUE
PANACUR 4 %	INTERVET	FRV/4941 982 7/1985	08/01/1985	Nationale	Poudre orale	Fenbendazole	Bovins, Caprins, Ovins, Porcins	ANTHELMINTHIQUE
PANACUR AQUASOL 200 MG/ML SUSPENSION BUVABLE POUR UTILISATION DANS L'EAU DE BOISSON POUR PORCS ET POULETS	INTERVET INTERNATIONAL	EU/2/11/13 5	09/12/2011	Centralisée	Suspension buvable	Fenbendazole	Porcins, Poules	ANTHELMINTHIQUE
PANACUR EQUINE GUARD	INTERVET	FRV/8395 371 4/2000	01/09/2000	Nationale	Suspension buvable	Fenbendazole	Cheval	ANTHELMINTHIQUE
PANACUR PATE	INTERVET	FRV/9693 415 3/1985	12/11/1985	Nationale	Pâte orale	Fenbendazole	Cheval	ANTHELMINTHIQUE
PIGFEN 40 MG/G PREMELANGE MEDICAMENTEUX POUR PORCS	HUVEPHARMA	FRV/2572 559 1/2016	11/10/2016	DCP, FR=EMC	Prémélange médicamenteux	Fenbendazole	Porcins	ANTHELMINTHIQUE
ACADREX 60	ELANCO EUROPE	FRV/7554 327 5/1980	04/01/1980	Nationale	Solution à diluer pour application cutanée	Fenvalérate	Bovins	INSECTICIDE
CONCENTRAT V080 FLUBENDAZOLE 3 PORC-VOLAILE	CEVA SANTE ANIMALE	FRV/3617 757 8/1983	21/03/1983	Nationale	Prémélange médicamenteux	Flubendazole	Porcins, Volailles	ANTHELMINTHIQUE
CONCENTRAT V081 FLUBENDAZOLE 6 VOLAILE	CEVA SANTE ANIMALE	FRV/5701 173 6/1991	23/04/1991	Nationale	Prémélange médicamenteux	Flubendazole	Volailles	ANTHELMINTHIQUE
FLIMABEND 100 MG/G SUSPENSION BUVABLE POUR PORCINS ET POULETS	KRKA	FRV/4910 013 2/2013	14/01/2013	DCP, FR=EMR	Suspension buvable	Flubendazole	Porcins, Poules, Poulet de chair	ANTHELMINTHIQUE
FLIMABO 100 MG/G SUSPENSION BUVABLE POUR PORCINS ET POULETS	KRKA	FRV/9457 833 3/2013	14/01/2013	DCP, FR=EMR	Suspension buvable	Flubendazole	Porcins, Poulet de chair	ANTHELMINTHIQUE
FLUBENDAZOLE 3 PORC-VOLAILE FRANVET	QALIAN	FRV/2578 133 9/2005	02/06/2005	Nationale	Prémélange médicamenteux	Flubendazole	Dinde, Faisan, Porcins, Poules, Poulet de chair	ANTHELMINTHIQUE

APPENDIX 1 - INVENTORY OF AUTHORISED VETERINARY ANTI-PARASITIC MEDICINAL PRODUCTS FOR LIVESTOCK [13]

FLUBENDAZOLE 6 PORC-VOLAILE FRANVET	QALIAN	FRV/6096 514 5/2005	02/06/2005	Nationale	Prémélange médicamenteux	Flubendazole	Dinde, Faisan, Porcins, Poules, Poulet de chair	ANTHELMINTHIQUE
FLUBENOL 50 MG/G POUDRE ORALE POUR PORCINS	LILLY FRANCE	FRV/9438 166 7/2013	21/01/2013	DCP, FR=EMC	Poudre orale	Flubendazole	Porcins	ANTHELMINTHIQUE
PM 64 FLUBENDAZOLE 3 PORC-VOLAILE DELTAVIT	DELTAVIT	FRV/6286 135 7/1985	10/12/1985	Nationale	Prémélange médicamenteux	Flubendazole	Porcins, Volailles	ANTHELMINTHIQUE
BAYTICOL 1 % POUR-ON	BAYER HEALTHCARE	FRV/9135 260 0/1991	31/12/1991	Nationale	Solution pour pour-on	Fluméthrine	Bovins	INSECTICIDE
ALVERIN 18,7 MG/G PATE ORALE POUR CHEVAUX	ZOETIS FRANCE	FRV/4540 454 4/2014	23/07/2014	DCP, FR=EMC	Pâte orale	Ivermectine	Cheval	ENDECTOCIDE
BIMECTIN 10 MG/ML SOLUTION INJECTABLE POUR BOVINS OVINS ET PORCINS	CROSS VETPHARM GROUP	FRV/6922 284 9/2017	28/06/2017	Nationale	Solution injectable	Ivermectine	Bovins, Ovins, Porcins	ENDECTOCIDE
BIMECTINE PATE	CROSS VETPHARM GROUP	FRV/3138 155 6/2005	13/05/2005	RM, FR=EMC	Pâte orale	Ivermectine	Cheval	ENDECTOCIDE
CEVAMEC BOVINS OVINS SOLUTION INJECTABLE	CROSS VETPHARM GROUP	FRV/8943 423 9/2005	30/06/2005	RM, FR=EMC	Solution injectable	Ivermectine	Bovins, Ovins	ENDECTOCIDE
CEVAMEC PORCINS SOLUTION INJECTABLE	CROSS VETPHARM GROUP	FRV/4073 993 1/2005	30/06/2005	RM, FR=EMC	Solution injectable	Ivermectine	Porcins	ENDECTOCIDE
DIVAMECTIN 10 MG/ML SOLUTION INJECTABLE	ECO ANIMAL HEALTH	FRV/5808 111 2/2008	01/04/2008	RM, FR=EMC	Solution injectable	Ivermectine	Bovins, Ovins, Porcins	ENDECTOCIDE
DIVAMECTIN 18,7 MG/G PATE ORALE POUR CHEVAUX	ECO ANIMAL HEALTH	FRV/3520 608 6/2008	20/05/2008	RM, FR=EMC	Pâte orale	Ivermectine	Cheval	ENDECTOCIDE
DIVAMECTIN POUR-ON	ECO ANIMAL HEALTH	FRV/5294 397 1/2006	09/03/2006	RM, FR=EMC	Solution pour pour-on	Ivermectine	Bovins	ENDECTOCIDE
ECOMECTIN 6 MG/G PREMELANGE MEDICAMENTEUX POUR PORCS	ECO ANIMAL HEALTH	FRV/0026 980 7/2013	04/11/2013	RM, FR=EMC	Prémélange médicamenteux	Ivermectine	Porcins	ENDECTOCIDE
ECOMECTIN IVERMECTINE 18,7 MG/G PATE ORALE POUR CHEVAUX	ECO ANIMAL HEALTH	FRV/8211 881 9/2008	24/09/2008	RM, FR=EMC	Pâte orale	Ivermectine	Cheval	ENDECTOCIDE
ENDECTINE POUR-ON	ECO ANIMAL HEALTH	FRV/2611 768 3/2013	13/05/2013	RM, FR=EMC	Solution pour pour-on	Ivermectine	Bovins	ENDECTOCIDE
EQVALAN PATE	MERIAL	FRV/6151 318 9/1983	20/12/1983	Nationale	Pâte orale	Ivermectine	Equins	ENDECTOCIDE
EQVALAN PATE EQUIPACK	MERIAL	FRV/1741 204 5/2011	27/02/2012	Nationale	Pâte orale	Ivermectine	Equins	ENDECTOCIDE
ERAQUELL 18,7 MG/G PATE ORALE	VIRBAC	FRV/7101 113 0/2004	09/09/2004	RM, FR=EMC	Pâte orale	Ivermectine	Cheval	ENDECTOCIDE
ERAQUELL TABS 20 MG COMPRIMES A CROQUER POUR CHEVAUX	VIRBAC	FRV/4968 327 3/2009	23/06/2009	DCP, FR=EMC	Comprimé à croquer	Ivermectine	Cheval	ENDECTOCIDE
FUREXEL	MERIAL	FRV/3117 529 2/1996	19/07/1996	Nationale	Pâte orale	Ivermectine	Equins	ENDECTOCIDE
HIPPOECTIN 12 MG/G GEL ORAL POUR CHEVAUX	LE VET	FRV/2010 798 5/2008	02/12/2008	RM, FR=EMC	Gel oral	Ivermectine	Cheval	ENDECTOCIDE
IVERTIN BOVIN ET PORCIN	LABORATORIOS CALIER	FRV/3943 503 9/2005	29/09/2005	RM, FR=EMC	Solution injectable	Ivermectine	Bovins, Porcins	ENDECTOCIDE
IVOMECC	MERIAL	FRV/4157 043 2/1981	03/08/1981	Nationale	Solution injectable	Ivermectine	Bovins	ENDECTOCIDE
IVOMECC OVIN INJECTABLE	MERIAL	FRV/9721 844 1/1985	09/07/1985	Nationale	Solution injectable	Ivermectine	Ovins	ENDECTOCIDE
IVOMECC PORCIN	MERIAL	FRV/4576 133 3/1984	25/04/1984	Nationale	Solution injectable	Ivermectine	Porcins	ENDECTOCIDE
IVOMECC POUR-ON BOVIN	MERIAL	FRV/0337 844 3/1989	19/04/1989	Nationale	Solution pour pour-on	Ivermectine	Bovins	ENDECTOCIDE
IVOMECC PREMIX PORCIN 0,04 %	MERIAL	FRV/1143 590 1/1998	23/12/1998	Nationale	Prémélange médicamenteux	Ivermectine	Porcins	ENDECTOCIDE
MAGAMECTINE INJECTABLE	CHANELLE PHARMACEUTICALS MANUFACTURING	FRV/0616 621 0/2005	27/09/2005	RM, FR=EMC	Solution injectable	Ivermectine	Bovins, Porcins	ENDECTOCIDE
MECTAJECT PATE CHEVAUX	CROSS VETPHARM GROUP	FRV/8376 126 7/2016	19/10/2016	Nationale	Pâte orale	Ivermectine	Cheval	ENDECTOCIDE
NOROMECTIN 0,5 % POUR-ON	NORBROOK LABORATORIES	FRV/0681 919 0/2006	11/05/2006	RM, FR=EMC	Solution pour pour-on	Ivermectine	Bovins	ENDECTOCIDE
NOROMECTIN 1 % SOLUTION INJECTABLE BOVINS PORCINS	NORBROOK LABORATORIES	FRV/5933 884 0/2006	09/02/2006	RM, FR=EMC	Solution injectable	Ivermectine	Bovins, Porcins	ENDECTOCIDE
NOROMECTIN 1 % SOLUTION INJECTABLE OVINS	NORBROOK LABORATORIES	FRV/1722 865 9/2005	06/10/2005	RM, FR=EMC	Solution injectable	Ivermectine	Ovins	ENDECTOCIDE
NOROMECTIN 1,87 % PATE ORALE POUR CHEVAUX	NORBROOK LABORATORIES	FRV/6357 754 3/2005	09/12/2005	RM, FR=EMC	Pâte orale	Ivermectine	Cheval	ENDECTOCIDE
NOROMECTIN BUVALE OVINS	NORBROOK LABORATORIES	FRV/4505 414 5/2006	16/02/2006	RM, FR=EMC	Solution buvable	Ivermectine	Ovins	ENDECTOCIDE
ORAMECC OVIN SOLUTION ORALE	MERIAL	FRV/6902 498 2/1983	28/04/1983	Nationale	Solution buvable	Ivermectine	Ovins	ENDECTOCIDE
PARAMECTIN 10 MG/ML SOLUTION INJECTABLE BOVINS PORCINS	NORBROOK LABORATORIES	FRV/3989 921 9/2008	16/01/2008	RM, FR=EMC	Solution injectable	Ivermectine	Bovins, Porcins	ENDECTOCIDE
POUOMECC POUR ON	CHANELLE PHARMACEUTICALS MANUFACTURING	FRV/5818 367 8/2005	19/10/2005	RM, FR=EMC	Solution pour pour-on	Ivermectine	Bovins	ENDECTOCIDE
QUALIMECC 10 MG/ML SOLUTION INJECTABLE	ECO ANIMAL HEALTH	FRV/2968 829 8/2004	05/02/2004	RM, FR=EMC	Solution injectable	Ivermectine	Bovins, Ovins, Porcins	ENDECTOCIDE
QUALIMECC POUR-ON	ECO ANIMAL HEALTH	FRV/7879 631 9/2006	10/02/2006	RM, FR=EMC	Solution pour pour-on	Ivermectine	Bovins	ENDECTOCIDE
VETOMECC 10 MG/ML SOLUTION INJECTABLE	ECO ANIMAL HEALTH	FRV/4934 184 5/2004	05/02/2004	RM, FR=EMC	Solution injectable	Ivermectine	Bovins, Ovins, Porcins	ENDECTOCIDE
VIRBAMECC POUR ON	VIRBAC	FRV/4944 897 1/2004	03/05/2004	RM, FR=EMC	Solution pour pour-on	Ivermectine	Bovins	ENDECTOCIDE
VIRBAMECC SOLUTION INJECTABLE POUR BOVINS	VIRBAC	FRV/2516 622 0/2003	31/07/2003	RM, FR=EMC	Solution injectable	Ivermectine	Bovins	ENDECTOCIDE
VIRBAMECC SOLUTION INJECTABLE POUR PORCINS	VIRBAC	FRV/2639 786 3/2003	31/07/2003	RM, FR=EMC	Solution injectable	Ivermectine	Porcins	ENDECTOCIDE
EQUIMAX GEL ORAL POUR CHEVAUX	VIRBAC	FRV/4778 743 2/2004	15/04/2004	RM, FR=EMC	Gel oral	Ivermectine, Praziquantel	Cheval	ENDECTOCIDE

EQUIMAX TABS 150 MG/ 20 MG COMPRIMES A CROQUER POUR CHEVAUX	VIRBAC	FRV/6648 918 8/2008	25/06/2008	DCP, FR=EMC	Comprimé à croquer	Ivermectine, Praziquantel	Cheval	ENDECTOCIDE
EQVALAN DUO	MERIAL	FRV/1889 939 3/2004	20/10/2004	RM, FR=EMC	Pâte orale	Ivermectine, Praziquantel	Cheval	ENDECTOCIDE
EQVALAN DUO EQUIPACK	MERIAL	FRV/0334 369 6/2012	09/07/2012	RM, FR=EMC	Pâte orale	Ivermectine, Praziquantel	Cheval	ENDECTOCIDE
FUREXEL COMBI PATE ORALE	MERIAL	FRV/6524 375 6/2006	03/01/2006	RM, FR=EMC	Pâte orale	Ivermectine, Praziquantel	Cheval	ENDECTOCIDE
IVERPRAZ 18,7 MG/G + 140,3 MG/G PATE ORALE POUR CHEVAUX	NORBROOK LABORATORIES	FRV/1582 742 9/2013	02/09/2013	DCP, FR=EMC	Pâte orale	Ivermectine, Praziquantel	Cheval	ENDECTOCIDE
NOROMECTIN PRAZIQUANTEL DUO 18,7 MG/G + 140,3 MG/G PATE ORALE POUR CHEVAUX	NORBROOK LABORATORIES	FRV/4016 521 5/2013	02/09/2013	DCP, FR=EMC	Pâte orale	Ivermectine, Praziquantel	Cheval	ENDECTOCIDE
LEVISOLE TRANSCUTANE	QALIAN	FRV/1870 548 3/1986	07/07/1986	Nationale	Solution pour pour-on	Lévamisole	Bovins	ANTHELMINTHIQUE
NEMISOL TRANSCUTANE	MERIAL	FRV/2011 709 6/1989	19/04/1989	Nationale	Solution pour pour-on	Lévamisole	Bovins	ANTHELMINTHIQUE
NIRATIL POUR ON	VIRBAC	FRV/1966 699 6/2000	22/03/2000	Nationale	Solution pour pour-on	Lévamisole	Bovins	ANTHELMINTHIQUE
ANTHELMINTICIDE 15 %	LABORATOIRES BIOVE	FRV/5623 753 1/1986	17/03/1986	Nationale	Solution injectable et buvable	Lévamisole	Bovins, Ovins, Porcins, Volailles	ANTHELMINTHIQUE
BIAMINTHIC 5 %	LABORATOIRES BIOVE	FRV/4861 885 6/1986	14/02/1986	Nationale	Solution buvable	Lévamisole	Bovins, Ovins, Porcins, Volailles	ANTHELMINTHIQUE
CAPIZOL	VIRBAC	FRV/6693 705 6/1992	07/07/1992	Nationale	Solution buvable	Lévamisole	Bovins, Ovins, Porcins, Volailles	ANTHELMINTHIQUE
CHRONOMINTIC	VIRBAC	FRV/2414 462 9/1987	09/02/1987	Nationale	Dispositif intraruminal à libération continue	Lévamisole	Bovins	ANTHELMINTHIQUE
IVECIDE BUVABLE	MERIAL	FRV/6624 642 2/1990	01/10/1990	Nationale	Solution buvable	Lévamisole	Bovins, Ovins, Porcins, Volailles	ANTHELMINTHIQUE
LEVAMISOLE 3,75 % BUVABLE	QALIAN	FRV/8126 093 9/1984	13/12/1984	Nationale	Solution buvable	Lévamisole	Bovins, Ovins, Porcins, Volailles	ANTHELMINTHIQUE
LEVAMISOLE 5 % VIRBAC	VIRBAC	FRV/3386 507 0/1992	07/07/1992	Nationale	Solution buvable	Lévamisole	Bovins, Ovins, Porcins, Volailles	ANTHELMINTHIQUE
LEVASOLE 20	QALIAN	FRV/8948 018 6/2005	21/03/2005	Nationale	Poudre pour solution buvable	Lévamisole	Bovins, Ovins, Porcins, Volailles	ANTHELMINTHIQUE
LEVISOLE INJECTABLE	QALIAN	FRV/8591 736 3/1986	07/07/1986	Nationale	Solution injectable	Lévamisole	Bovins, Ovins	ANTHELMINTHIQUE
NEMISOL INJECTABLE	MERIAL	FRV/5424 399 0/1983	20/12/1983	Nationale	Solution injectable	Lévamisole	Bovins, Ovins, Porcins	ANTHELMINTHIQUE
NIRATIL INJECTABLE	VIRBAC	FRV/3682 856 6/1982	09/02/1982	Nationale	Solution injectable	Lévamisole	Bovins, Ovins, Porcins	ANTHELMINTHIQUE
POLYSTRONGLE POUVRE ORALE	MERIAL	FRV/5282 327 9/1989	27/09/1989	Nationale	Poudre pour solution buvable	Lévamisole	Bovins, Ovins, Porcins, Volailles	ANTHELMINTHIQUE
POLYVERMYL	LABORATOIRES BIOVE	FRV/6181 831 2/1984	21/05/1984	Nationale	Comprimé	Lévamisole	Volailles	ANTHELMINTHIQUE
THELMIZOLE 20 %	VIRBAC	FRV/7298 922 7/1984	11/07/1984	Nationale	Poudre pour solution buvable	Lévamisole	Porcins, Volailles	ANTHELMINTHIQUE
VERMIZOL L	MERIAL	FRV/1319 337 3/1991	14/05/1991	Nationale	Solution injectable et buvable	Lévamisole	Bovins, Ovins, Porcins, Volailles	ANTHELMINTHIQUE
IMENA L	INTERVET	FRV/8501 985 6/1986	26/12/1986	Nationale	Suspension buvable	Lévamisole, Oxytocanide	Bovins, Ovins	ANTHELMINTHIQUE
PARSIFAL BOVINS	ELANCO EUROPE	FRV/0376 114 8/1991	01/08/1991	Nationale	Suspension buvable	Lévamisole, Triclabendazole	Bovins	ANTHELMINTHIQUE
CYDECTINE 0,1 % SOLUTION ORALE POUR OVINS	ZOETIS FRANCE	FRV/5897 883 6/1995	13/10/1995	RM, FR=EMR	Solution buvable	Moxidectine	Ovins	ENDECTOCIDE
CYDECTINE 0,5 % SOLUTION POUR-ON POUR BOVINS	ZOETIS FRANCE	FRV/9745 491 9/1996	09/08/1996	RM, FR=EMR	Solution pour pour-on	Moxidectine	Bovins	ENDECTOCIDE
CYDECTINE 1 % SOLUTION INJECTABLE POUR BOVINS	ZOETIS FRANCE	FRV/6245 161 9/1994	30/12/1994	RM, FR=EMR	Solution injectable	Moxidectine	Bovins	ENDECTOCIDE
CYDECTINE 1 % SOLUTION INJECTABLE POUR OVINS	ZOETIS FRANCE	FRV/2011 560 1/1997	04/08/1997	RM, FR=EMR	Solution injectable	Moxidectine	Ovins	ENDECTOCIDE
CYDECTINE 10 % LA POUR BOVINS	ZOETIS FRANCE	FRV/5341 056 8/2005	17/01/2005	RM, FR=EMR	Solution injectable	Moxidectine	Bovins	ENDECTOCIDE
CYDECTINE LA 20 MG/ML SOLUTION INJECTABLE POUR OVINS	ZOETIS FRANCE	FRV/7672 854 5/2008	08/12/2008	DCP, FR=EMR	Solution injectable	Moxidectine	Ovins	ENDECTOCIDE
EQUEST GEL ORAL	ZOETIS FRANCE	FRV/0805 751 8/1997	04/08/1997	RM, FR=EMR	Gel oral	Moxidectine	Equins	ENDECTOCIDE
EQUEST PRAMOX	ZOETIS FRANCE	FRV/3281 212 3/2005	27/05/2005	RM, FR=EMR	Gel oral	Moxidectine, Praziquantel	Cheval	ENDECTOCIDE
CYDECTINE TRICLAMOXY 1 MG/ML + 50 MG/ML SOLUTION BUVABLE POUR OVINS	ZOETIS FRANCE	FRV/0822 223 7/2009	13/10/2009	DCP, FR=EMR	Solution buvable	Moxidectine, Triclabendazole	Ovins	ENDECTOCIDE
CYDECTINE TRICLAMOXY 5 MG/ML + 200 MG/ML SOLUTION POUR POUR-ON POUR BOVINS	ZOETIS FRANCE	FRV/0015 587 8/2011	20/12/2011	DCP, FR=EMR	Solution pour pour-on	Moxidectine, Triclabendazole	Bovins	ENDECTOCIDE
HAPADEX SUSPENSION ORALE 100 MG/ML	INTERVET	FRV/9201 288 8/1986	03/12/1986	Nationale	Suspension buvable	Nétobimine	Bovins, Ovins	ANTHELMINTHIQUE
HAPADEX SUSPENSION ORALE 150 MG/ML	INTERVET	FRV/1578 164 0/1986	03/12/1986	Nationale	Suspension buvable	Nétobimine	Bovins, Ovins	ANTHELMINTHIQUE
HAPADEX SUSPENSION ORALE 50 MG/ML	INTERVET	FRV/4434 884 3/1986	03/12/1986	Nationale	Suspension buvable	Nétobimine	Bovins, Ovins	ANTHELMINTHIQUE
DOVENIX	MERIAL	FRV/3894 021 5/1982	07/08/1982	Nationale	Solution injectable	Nitroxinil	Bovins, Ovins	ANTHELMINTHIQUE
OXFENIL 2,265 %	VIRBAC	FRV/3743 249 0/1996	24/09/1996	Nationale	Suspension buvable	Oxfendazole	Bovins, Caprins, Ovins	ANTHELMINTHIQUE

APPENDIX 1 - INVENTORY OF AUTHORISED VETERINARY ANTI-PARASITIC MEDICINAL PRODUCTS FOR LIVESTOCK [13]

OXFENIL 9.06 %	VIRBAC	FR/V/7749 035 7/1997	12/12/1997	Nationale	Suspension buvable	Oxfendazole	Bovins	ANTHELMINTHIQUE
REPIDOSE FARMINTIC 5-1250	INTERVET	FR/V/4174 466 6/1993	23/08/1993	Nationale	Dispositif intraruminal à libération séquentielle	Oxfendazole	Bovins	ANTHELMINTHIQUE
REPIDOSE FARMINTIC 5-750	INTERVET	FR/V/9648 488 9/1993	23/08/1993	Nationale	Dispositif intraruminal à libération séquentielle	Oxfendazole	Bovins	ANTHELMINTHIQUE
REPIDOSE FARMINTIC 6-1250	INTERVET	FR/V/8934 515 7/1995	26/06/1995	Nationale	Dispositif intraruminal à libération séquentielle	Oxfendazole	Bovins	ANTHELMINTHIQUE
SYNANTHIC	MERIAL	FR/V/2165 850 1/1979	05/12/1979	Nationale	Suspension buvable	Oxfendazole	Bovins, Caprins, Ovins	ANTHELMINTHIQUE
SYNANTHIC 9.06 IST	MERIAL	FR/V/5451 106 8/1982	08/03/1982	Nationale	Suspension buvable	Oxfendazole	Bovins	ANTHELMINTHIQUE
DACLO POWDRE	QALIAN	FR/V/9753 761 0/1985	09/07/1985	Nationale	Poudre pour solution buvable	Oxibendazole	Porcins	ANTHELMINTHIQUE
PIG HELM	QALIAN	FR/V/0863 047 2/1990	10/07/1990	Nationale	Poudre pour suspension buvable	Oxibendazole	Porcins	ANTHELMINTHIQUE
PREMELANGE MEDICAMENTEUX Z 56	QALIAN	FR/V/5384 847 9/1992	15/06/1992	Nationale	Prémélange médicamenteux	Oxibendazole	Porcins	ANTHELMINTHIQUE
DISTOCUR 34 MG/ML SUSPENSION BUVABLE POUR BOVINS	MERIAL	FR/V/6031 466 0/2015	13/05/2015	RM, FR=EMR	Suspension buvable	Oxyclozanide	Bovins	ANTHELMINTHIQUE
DOUVISTOME	CEVA SANTE ANIMALE	FR/V/0415 544 1/2002	02/10/2002	Nationale	Suspension buvable	Oxyclozanide	Bovins, Ovins	ANTHELMINTHIQUE
RUMENIL 34 MG/ML SUSPENSION BUVABLE POUR BOVINS	CHANELLE PHARMACEUTICALS MANUFACTURING	FR/V/5710 088 9/2017	15/12/2017	RM, FR=EMC	Suspension buvable	Oxyclozanide	Bovins	ANTHELMINTHIQUE
ZANIL SUSPENSION	INTERVET	FR/V/9273 440 3/1979	22/06/1979	Nationale	Suspension buvable	Oxyclozanide	Bovins, Ovins	ANTHELMINTHIQUE
BYEMITE	BAYER HEALTHCARE	FR/V/2385 846 0/2009	24/04/2009	DCP, FR=EMR	Solution à diluer pour pulvérisation d'une émulsion	Phoxime	Poule pondeuse	INSECTICIDE
SEBACIL 50 % SOLUTION	BAYER HEALTHCARE	FR/V/5882 196 3/1985	09/07/1985	Nationale	Solution pour application cutanée	Phoxime	Bovins, Caprins, Equins, Ovins, Porcins	INSECTICIDE
SEBACIL 7,5 % POUR ON	BAYER HEALTHCARE	FR/V/8458 556 5/2004	07/06/2004	RM, FR=EMC	Solution pour pour-on	Phoxime	Porcins	INSECTICIDE
PIPERAZINE 35 COOPHAVET	MERIAL	FR/V/8053 730 2/1992	21/07/1992	Nationale	Solution buvable	Pipérazine	Porcins, Volailles	ANTHELMINTHIQUE
CITRATE DE PIPERAZINE COOPHAVET	MERIAL	FR/V/0841 306 0/1992	06/08/1992	Nationale	Poudre pour solution buvable	Pipérazine	Chat, Chien, Porcins, Volailles	ANTHELMINTHIQUE
CESTOCUR SUSPENSION 2,5 %	BAYER HEALTHCARE	FR/V/7653 064 9/1999	19/03/1999	Nationale	Suspension buvable	Praziquantel	Ovins	ANTHELMINTHIQUE
DRONCIT 9 % GEL ORAL CHEVAL	BAYER HEALTHCARE	FR/V/8052 367 3/2001	01/02/2001	RM, FR=EMR	Gel oral	Praziquantel	Cheval	ANTHELMINTHIQUE
STRONGID CHEVAUX PATE ORALE	ZOETIS FRANCE	FR/V/1671 265 6/1984	07/06/1984	Nationale	Pâte orale	Pyrantel	Cheval	ANTHELMINTHIQUE
ACTI-METHOXINE	LABORATOIRES BIOVE	FR/V/2205 447 4/1992	21/07/1992	Nationale	Solution injectable	Sulfadiméthoxine	Bovins, Caprins, Ovins	COCCIDIOICIDE
AMIDURENE	LABORATOIRES BIOVE	FR/V/5834 046 8/1992	30/06/1992	Nationale	Solution buvable	Sulfadiméthoxine	Lapins, Volailles	COCCIDIOICIDE
EMERICID SULFADIMETHOXINE	VIRBAC	FR/V/9136 177 8/1987	17/06/1987	Nationale	Solution buvable	Sulfadiméthoxine	Agneau, Chevreau, Lapins, Veau, Volailles	COCCIDIOICIDE
METOXYL	VIRBAC	FR/V/1722 378 8/1992	24/07/1992	Nationale	Solution buvable	Sulfadiméthoxine	Agneau, Chevreau, Lapins, Veau, Volailles	COCCIDIOICIDE
SULFADIMETHOXINE 100-CR LAPIN-VOLAILLE-PORC ET AGNEAU-CHEVREAU SEVRES FRANVET	QALIAN	FR/V/8086 880 4/1991	14/05/1991	Nationale	Prémélange médicamenteux	Sulfadiméthoxine	Agneau, Chevreau, Lapins, Porcins, Volailles	COCCIDIOICIDE
SULFALON	VIRBAC	FR/V/9778 988 8/1984	11/07/1984	Nationale	Solution injectable	Sulfadiméthoxine	Bovins, Chat, Chien, Equins, Porcins, Volailles	COCCIDIOICIDE
SUNIX LIQUIDE	MERIAL	FR/V/5579 870 7/1982	01/12/1982	Nationale	Solution buvable	Sulfadiméthoxine	Lapins, Volailles	COCCIDIOICIDE
SUNIX AC POWDRE	MERIAL	FR/V/2352 345 8/1991	14/05/1991	Nationale	Poudre pour solution buvable	Sulfadiméthoxine	Agneau, Chevreau, Lapins, Porcins, Veau, Volailles	COCCIDIOICIDE
BIAPRIM BUVABLE	LABORATOIRE BIARD	FR/V/7596 936 7/1992	06/08/1992	Nationale	Solution buvable	Sulfadiméthoxine, Triméthoprime	Volailles	COCCIDIOICIDE
COMPOMIX V SulfAPRIM	QALIAN	FR/V/3847 983 2/1992	30/06/1992	Nationale	Poudre pour solution buvable	Sulfadiméthoxine, Triméthoprime	Agneau, Lapins, Porcins, Veau, Volailles	COCCIDIOICIDE
TRIMEDOXYNE ORALE	MERIAL	FR/V/4258 746 6/1992	18/06/1992	Nationale	Poudre pour solution buvable	Sulfadiméthoxine, Triméthoprime	Agneau, Chevreau, Lapins, Porcins, Veau, Volailles	COCCIDIOICIDE
TRIMETHOSULFA V	MERIAL	FR/V/8194 590 6/1992	24/07/1992	Nationale	Prémélange médicamenteux	Sulfadiméthoxine (sous forme de sel de sodium), Triméthoprime	Agneau, Chevreau, Lapins, Porcins, Veau, Volailles	COCCIDIOICIDE
TRIMETHOX	CEVA SANTE ANIMALE	FR/V/3166 166 5/1992	01/04/1992	Nationale	Solution buvable	Sulfadiméthoxine, Triméthoprime	Lapins, Volailles	COCCIDIOICIDE

TRISULMIX INJECTABLE	MERIAL	FR/V/9930 567 1/1992	07/07/1992	Nationale	Solution injectable	Sulfadiméthoxine, Triméthoprime	Bovins, Caprins, Ovins, Porcins	COCCIDIOCIDÉ
TRISULMIX LIQUIDE	MERIAL	FR/V/9018 281 9/1984	11/07/1984	Nationale	Solution buvable	Sulfadiméthoxine, Triméthoprime	Lapins, Volailles	COCCIDIOCIDÉ
TRISULMIX POUFRE	MERIAL	FR/V/0086 132 2/1992	18/06/1992	Nationale	Poudre pour solution buvable	Sulfadiméthoxine, Triméthoprime	Agneau, Chevreau, Lapins, Porcins, Veau, Volailles	COCCIDIOCIDÉ
SULFACYCLINE	LABORATOIRES BIOVE	FR/V/4618 122 4/1990	01/10/1990	Nationale	Solution injectable	Sulfadiméthoxine, Triméthoprime	Bovins, Caprins, Equins, Ovins, Porcins	COCCIDIOCIDÉ
SULFADIMETHOXINE- TRIMETHOPRIME 62,5-12,5 PORC ET VEAU-AGNEAU-CHEVREAU SEVRES SANTAMIX	QALIAN	FR/V/9576 303 5/1995	15/09/1995	Nationale	Prémélange médicamenteux	Sulfadiméthoxine, Triméthoprime	Agneau, Chevreau, Porcins, Veau	COCCIDIOCIDÉ
BAYCOX 2,5 %	BAYER HEALTHCARE	FR/V/4499 801 9/1989	27/09/1989	Nationale	Solution pour administration dans l'eau de boisson	Toltrazuril	Poules	COCCIDIOCIDÉ
BAYCOX 25 MG/ML SOLUTION POUR ADMINISTRATION DANS L'EAU DE BOISSON DES POULES ET DES DINDES	BAYER HEALTHCARE	FR/V/6131 279 3/2014	10/07/2014	DCP, FR=EMC	Solution pour administration dans l'eau de boisson	Toltrazuril	Dinde, Poules	COCCIDIOCIDÉ
BAYCOX 5 %	BAYER HEALTHCARE	FR/V/6682 470 7/2002	08/11/2002	RM, FR=EMC	Suspension buvable	Toltrazuril	Porcelet	COCCIDIOCIDÉ
BAYCOX BOVIS	BAYER HEALTHCARE	FR/V/8896 149 9/2007	07/02/2007	RM, FR=EMC	Suspension buvable	Toltrazuril	Veau	COCCIDIOCIDÉ
BAYCOX MULTI 50 MG/ML SUSPENSION BUVABLE POUR BOVINS OVINS ET PORCINS	BAYER HEALTHCARE	FR/V/0260 177 9/2016	19/10/2016	DCP, FR=EMC	Suspension buvable	Toltrazuril	Bovins, Ovins, Porcins	COCCIDIOCIDÉ
BAYCOX OVIS	BAYER HEALTHCARE	FR/V/6247 175 6/2008	22/10/2008	RM, FR=EMC	Suspension buvable	Toltrazuril	Agneau	COCCIDIOCIDÉ
BUSERIL 50 MG/ML SUSPENSION BUVABLE POUR PORCINS	VETPHARMA ANIMAL HEALTH	FR/V/8606 942 3/2013	21/10/2013	DCP, FR=EMC	Poudre pour administration dans l'eau de boisson	Toltrazuril	Porcins	COCCIDIOCIDÉ
CEVAZURIL 25 MG/ML SOLUTION BUVABLE POUR POULETS DE CHAIR, POULETTES ET REPRODUCTEURS	CEVA SANTE ANIMALE	FR/V/7570 250 4/2005	14/10/2005	Nationale	Solution buvable	Toltrazuril	Poules, Poulet de chair	COCCIDIOCIDÉ
CEVAZURIL 50 MG/ML SUSPENSION BUVABLE POUR PORCELETS ET VEAUX	CEVA SANTE ANIMALE	FR/V/8864 511 1/2009	15/06/2009	DCP, FR=EMR	Suspension buvable	Toltrazuril	Porcelet, Veau	COCCIDIOCIDÉ
DOZURIL 50 MG/ML SUSPENSION BUVABLE POUR PORCS	DOPHARMA RESEARCH	FR/V/1289 413 8/2013	25/10/2013	DCP, FR=EMR	Suspension buvable	Toltrazuril	Porcins	COCCIDIOCIDÉ
ESPACOX 50 MG/ML SUSPENSION ORALE POUR PORCINS	INDUSTRIAL VETERINARIA	FR/V/2455 090 9/2014	21/05/2014	DCP, FR=EMC	Suspension buvable	Toltrazuril	Porcins	COCCIDIOCIDÉ
TOLRACOL 50 MG/ML SUSPENSION BUVABLE POUR PORCINS, BOVINS ET OVINS	KRKA	FR/V/4543 072 5/2014	29/08/2014	DCP, FR=EMC	Suspension buvable	Toltrazuril	Bovins, Ovins, Porcins	COCCIDIOCIDÉ
TOLTRACOX 2,5 %	VIRBAC	FR/V/5989 973 0/2011	08/11/2011	Nationale	Solution buvable	Toltrazuril	Poule reproductrice, Poulet de chair	COCCIDIOCIDÉ
TOLTRAMAX 50 MG/ML SUSPENSION ORALE POUR PORCS	LAVET PHARMACEUTICALS	FR/V/6510 112 2/2012	19/03/2012	RM, FR=EMC	Suspension buvable	Toltrazuril	Porcins	COCCIDIOCIDÉ
TOLTRANIL 50 MG/ML SUSPENSION BUVABLE POUR PORCINS, BOVINS ET OVINS	KRKA	FR/V/8891 923 8/2010	28/06/2010	DCP, FR=EMC	Suspension buvable	Toltrazuril	Bovins, Ovins, Porcins	COCCIDIOCIDÉ
TRATOL 50 MG/ML SUSPENSION BUVABLE POUR PORCINS, BOVINS ET OVINS	KRKA	FR/V/4064 102 5/2011	14/02/2011	DCP, FR=EMC	Suspension buvable	Toltrazuril	Bovins, Ovins, Porcins	COCCIDIOCIDÉ
ZORABEL 25 MG/ML SOLUTION POUR ADMINISTRATION DANS L'EAU DE BOISSON POUR POULETS ET DINDES	VETPHARMA ANIMAL HEALTH	FR/V/4557 026 3/2013	21/10/2013	DCP, FR=EMC	Solution pour administration dans l'eau de boisson	Toltrazuril	Dinde, Poulet de chair	COCCIDIOCIDÉ
ZURITOL 25 MG/ML SOLUTION BUVABLE POUR POULETS	LABORATORIOS CALIER	FR/V/5272 018 5/2012	12/07/2012	RM, FR=EMR	Solution buvable	Toltrazuril	Poules	COCCIDIOCIDÉ
ZURITOL 50 MG/ML SUSPENSION BUVABLE POUR PORCINS	LABORATORIOS CALIER	FR/V/1749 643 6/2013	10/10/2013	RM, FR=EMR	Suspension buvable	Toltrazuril	Porcelet	COCCIDIOCIDÉ
FASCICUR 10 %	CHANELLE PHARMACEUTICALS MANUFACTURING	FR/V/9815 611 1/2003	23/07/2003	RM, FR=EMC	Suspension buvable	Triclabendazole	Bovins	ANTHELMINTHIQUE
FASCICUR 5 %	CHANELLE PHARMACEUTICALS MANUFACTURING	FR/V/1665 618 3/2003	23/07/2003	RM, FR=EMC	Suspension buvable	Triclabendazole	Ovins	ANTHELMINTHIQUE
FASCINEX 240	ELANCO EUROPE	FR/V/2861 908 8/2009	04/05/2009	Nationale	Suspension buvable	Triclabendazole	Bovins	ANTHELMINTHIQUE

Les abeilles des Pyrénées décimées par les pesticides

Le rôle des phytosanitaires a été mis en évidence grâce à des analyses financées par les apiculteurs

Mais où les abeilles vont-elles bien pouvoir se réfugier ? Même la nature sauvage des montagnes leur est devenue fatale. Cette mauvaise nouvelle arrive des Pyrénées-Orientales par le biais d'une enquête dont les résultats viennent d'être transmis aux apiculteurs. Leurs taux de perte atteignent des records, jusqu'à 100% de mortalité, en particulier chez ceux qui pratiquent la transhumance avec leurs ruches vers les hauts pâturages.

Près de 48 millions d'abeilles ramassées mortes, 1300 ruches touchées, soit une sur dix : c'est une hécatombe dans le département, et la situation est tout aussi alarmante en Ariège (5 000 colonies concernées), dans l'Hérault, l'Ardèche... « Nous avons constaté que les colonies ne souffraient ni de fortes attaques de parasites ni de maladie manifeste après la saison estivale, rapporte Marc-Edouard Colin, vétérinaire expert en pathologie de l'abeille. Elles présentaient en revanche des symptômes caractéristiques d'intoxication : troubles nerveux, faible reproduction... »

Les apiculteurs, réunis en collectif, ont alors décidé de financer des analyses pour en avoir le cœur net. Fin 2013-début 2014, 26 échantillons d'abeilles mortes, de pollen et de miel recueillis au sein de leurs colonies aux trois quarts moribondes ont été expédiés dans un laboratoire du CNRS à Solaize (Rhône). Ces analyses physiques et chimiques ont mis au jour des traces de pesticides dans 81% des cas, en cocktail ou non.

La plupart des douze molécules détectées sont des insecticides. Trois appartiennent à la famille des néonicotinoïdes. Mais plus inquiétant, quatre autres sont prosrites en France notamment le triphényl phosphate et le coumaphos que l'on trouve dans des préparations antiparasitaires, des produits importés illégalement d'Espagne.

Ces résultats peuvent surprendre : on associe davantage les pesticides aux grandes plaines vouées aux monocultures céréalières plu-

tôt qu'aux pâturages de montagne. En fait, qu'il s'agisse de lutter contre les acariens, les pucerons et autres larves d'insectes, les phytosanitaires ont tous recours aux mêmes familles de molécules chimiques. Dans les Pyrénées-Orientales, ce sont surtout les éleveurs qui y ont recours pour débarrasser leurs vaches laitières et leurs brebis de leurs parasites.

Cohabitation ancestrale

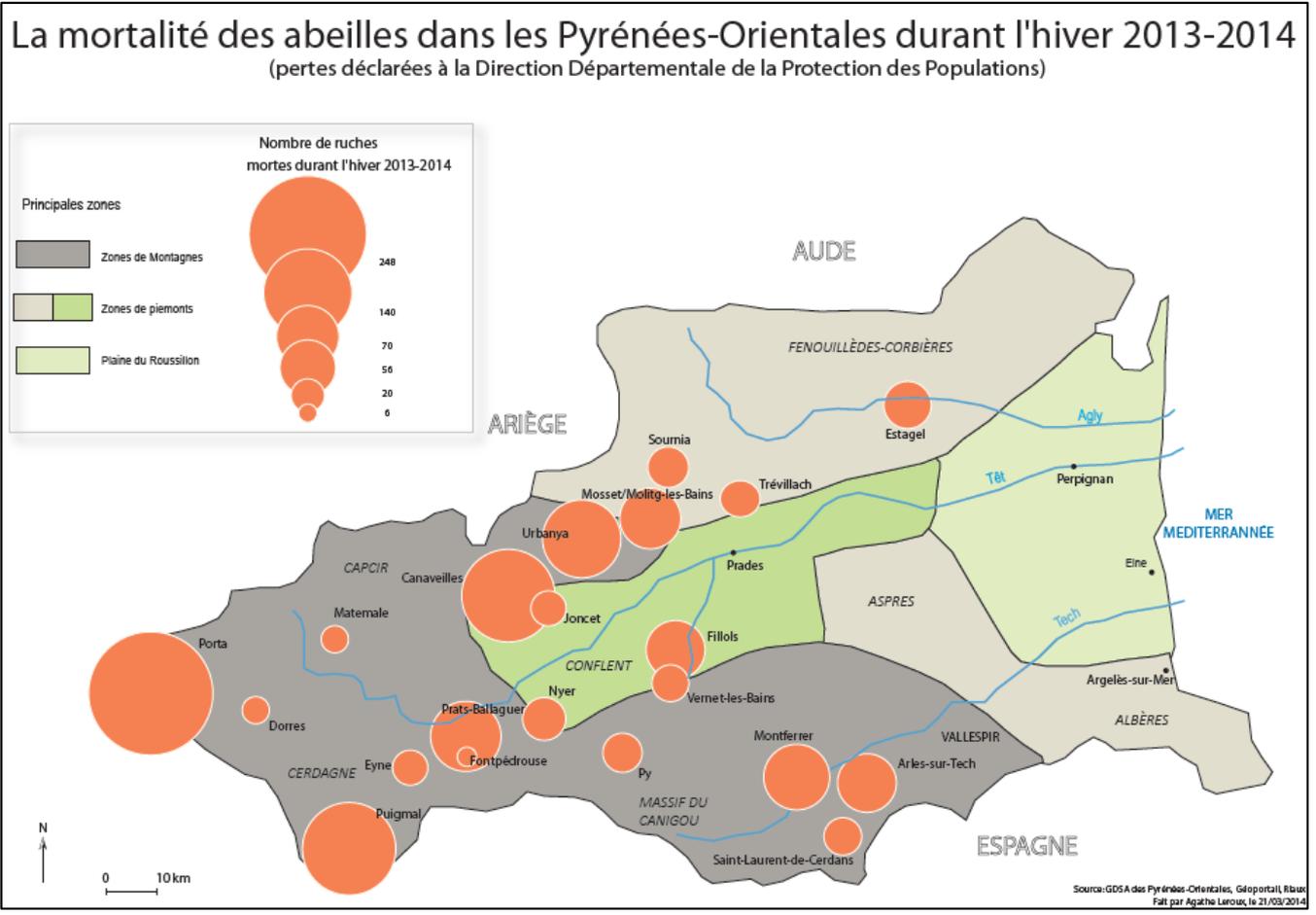
« Nous avons dû cesser de fréquenter les zones arboricoles et les vignes avec nos ruches, témoigne Jean Adestro, président du Groupement de défense sanitaire apicole du département. Puis en 2009, après une épizootie de fièvre catarrhale ovine, les bergeries ont été traitées à fortes doses. On a eu des mortalités anormales, nos abeilles, désorientées, essayaient d'entrer dans la ruche par l'arrière ! Cette fois-ci, on s'est dit qu'on ne tournerait pas le dos à nos cheptels morts et on a sorti 10 000 euros de nos poches pour les analyses. »

Les éleveurs du Roussillon se plaignent d'être publiquement montrés du doigt. La chambre d'agriculture des Pyrénées-Orientales a cependant diffusé, en juillet, un bulletin d'information rappelant à ses adhérents qu'il existe des alternatives aux traitements chimiques et incitant les apiculteurs à se concerter avec les éleveurs avant de se rendre en montagne. Retrouver les règles d'une cohabitation ancestrale ne semble pas totalement insurmontable.

« Le problème n'est ni les agriculteurs ni les éleveurs qui cherchent à protéger leurs animaux, mais les produits mis sur le marché : ils sont incompatibles avec les abeilles et la nature ! » dénonce Jean Adestro. C'est comme la course contre le dopage : chaque fois qu'un pesticide est retiré du marché, il est vite remplacé par deux autres. Nous sommes inquiets non plus seulement comme gardiens des abeilles, mais en tant que citoyens : il y a un problème de santé publique. » ■

MARTINE VALO

LE MONDE 15 Aout 2014





Bee Life

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HOW PESTICIDES USED IN LIVESTOCK FARMING THREATEN BEES

VETERINARY TREATMENTS, BIOCIDAL PRODUCTS & POLLINATING INSECTS

A UNAF REPORT
WITH THE COOPERATION OF BEE LIFE EUROPEAN
BEEKEEPING COORDINATION, CNTESA AND THE FRENCH
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