1. Introduction

Systemic insecticides were first developed in the 1950s, with the introduction of soluble organophosphorus (OP) compounds such as dimethoate, demeton-S-methyl, mevinphos and phorate. They were valuable in controlling sucking pests and burrowing larvae in many crops, their main advantage being their translocation to all tissues of the treated plant. Systemic carbamates followed in the 1960s with aldicarb and carbofuran. Since then, both insecticidal classes comprise a large number of broad-spectrum insecticides used in agriculture all over the world. Nowadays, OPs are the most common pesticides used in tropical, developing countries such as the Philippines and Vietnam, where 22 and 17% of the respective agrochemicals are ‘extremely hazardous’ [126], i.e. classified as WHO class I. Systemic insect growth regulators were developed during the 1980-90s, and comprise only a handful of compounds, which are more selective than their predecessors. Since 1990 onwards, cartap, fipronil and neonicotinoids are replacing the old hazardous chemicals in most developed and developing countries alike [137].

Through seed coatings and granular applications, systemic insecticides pose minimal risk of pesticide drift or worker exposure in agricultural, nurseries and urban settings. Neonicotinoids and fipronil are also preferred because they appear to be less toxic to fish and terrestrial vertebrates. Initially proposed as environmentally friendly agrochemicals [129], their use in Integrated Pest Management (IPM) programs has been questioned by recent research that shows their negative impact on predatory and parasitic agents [221, 258, 299]. New formulations have been developed to optimize the bioavailability of neonicotinoids, as well as combined formulations with pyrethroids and other insecticides with the aim of broadening the insecticidal spectrum and avoid resistance by pests [83]. Indeed, as with any other chem-
ical used in pest control, resistance to imidacloprid by whitefly (Bemisia tabaci), cotton aphids (Aphis gossypii) and other pests is rendering ineffective this and other neonicotinoids such as acetamiprid, thiacloprid and nitenpyram [247, 269].

This chapter examines the negative impacts that systemic insecticides have on organisms, populations and ecosystems. The efficacy of these products in controlling the target pests is assumed and not dealt with here – only the effects on non-target organisms and communities are considered.

2. Exposure to systemic insecticides

Unlike typical contact insecticides, that are usually taken up through the arthropod’s cuticle or skin of animals, systemic insecticides get into the organisms mainly through feeding on the treated plants or contaminated soil. Thus, monocrotophos and imidacloprid are more lethal to honey bees (Apis mellifera) through feeding than contact exposure [143]. Residual or contact exposure affects also some pests and non-target species alike.

Systemic insecticides are applied directly to the crop soil and seedlings in glasshouses using flowable solutions or granules, and often as seed-dressings, with foliar applications and drenching being less common. Being quite water soluble (Table 1), these insecticides are readily taken up by the plant roots or incorporated into the tissues of the growing plants as they develop, so the pests that come to eat them ingest a lethal dose and die. Sucking insects in particular are fatally exposed to systemic insecticides, as sap carries the most concentrated fraction of the poisonous chemical for a few weeks [124], whereas leaf-eating species such as citrus thrips and red mites may not be affected [30]. Systemic insecticides contaminate all plant tissues, from the roots to leaves and flowers, where active residues can be found up to 45-90 days [175, 187], lasting as long as in soil. Thus, pollen and nectar of the flowers get contaminated [33], and residues of imidacloprid and aldicarb have been found at levels above 1 mg/kg in the United States [200]. Guttation drops, in particular, can be contaminated with residues as high as 100-345 mg/L of neonicotinoids during 10-15 days following application [272]. Because these insecticides are incorporated in the flesh of fruits, the highly poisonous aldicarb is prohibited in edible crops such as watermelons, as it has caused human poisoning [106].

As with all poisonous chemicals spread in the environment, not only the target insect pests get affected: any other organism that feeds on the treated plants receives a dose as well, and may die or suffer sublethal effects. For example, uptake of aldicarb by plants and worms results in contamination of the vertebrate fauna up to 90 days after application [41], and honey bees may collect pollen contaminated with neonicotinoids to feed their larvae, which are thus poisoned and die [125]. Newly emerged worker bees are most susceptible to insecticides, followed by foraging workers, while nursery workers are the least susceptible within 72 h of treatment [80]. Insects and mites can negatively be affected by systemic insecticides whenever they feed on:
1. pollen, nectar, plant tissue, sap or guttation drops contaminated with the active ingredient (primary poisoning);

2. prey or hosts that have consumed leaves contaminated with the active ingredient (secondary poisoning).

Parasitoids may be indirectly affected because foliar, drench or granular applications may decrease host population to levels that are not enough to sustain them. Furthermore, host quality may be unacceptable for egg laying by parasitoid females [54]. Small insectivorous animals (e.g. amphibians, reptiles, birds, shrews and bats) can also suffer from primary poisoning if the residual insecticide or its metabolites in the prey are still active. It should be noticed that some metabolites of imidacloprid, thiamethoxam, fipronil and 50% of carbamates are as toxic as the parent compounds [29]. Thus, two species of predatory miridbugs were negatively affected by residues and metabolites of fipronil applied to rice crops [159]. However, since systemic insecticides do not bioaccumulate in organisms, there is little risk of secondary poisoning through the food chain.

Apart from feeding, direct contact exposure may also occur when the systemic insecticides are sprayed on foliage. In these cases, using a silicone adjuvant (Sylgard 309) reduces the contact exposure of honey bees to carbofuran, methomyl and imidacloprid, but increases it for fipronil [184]. In general the susceptibility of bees to a range of insecticides is: wild bees > honey bee > bumble bee [185]. In reality a combination of both contact and feeding exposure occurs, which is more deadly than either route of exposure alone [152, 218].

In soil, residues of acephate and methomyl account for most of the cholinesterase inhibition activity found in mixtures of insecticides [233]. Fortunately, repeated applications of these insecticides induces microbial adaptation, which degrade the active compounds faster over time [250]. Degradation of carbamates and OPs in tropical soils or vegetation is also faster than on temperate regions, due mainly to microbial activity [46]. Some neonicotinoids are degraded by soil microbes [172], and the yeast Rhodotorula mucilaginosa can degrade acetamiprid but none of the other neonicotinoids [63], which are quite persistent in this media (Table 2).

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Group</th>
<th>Vapour Pressure (mPa, 25°C)</th>
<th>Solubility in water (mg/L)</th>
<th>Log Kow#</th>
<th>GUS index*</th>
<th>Leaching potential</th>
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<td>2.52</td>
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</tr>
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<td>Group</td>
<td>Vapour Pressure (mPa, 25°C)</td>
<td>Solubility in water (mg/L)</td>
<td>Log Kow#</td>
<td>GUS index*</td>
<td>Leaching potential</td>
</tr>
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<td>----------------------------</td>
<td>---------------------------</td>
<td>----------</td>
<td>------------</td>
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<td>8180000</td>
<td>-0.22</td>
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<tr>
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<td>10000</td>
<td>-0.74</td>
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<td>1200000</td>
<td>-0.74</td>
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<tr>
<td>phorate</td>
<td>OP</td>
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<td>3.86</td>
<td>1.4</td>
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<td>moderate</td>
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<td>OP</td>
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<td>200</td>
<td>3.15</td>
<td>0.37</td>
<td>low</td>
</tr>
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</tr>
<tr>
<td>fipronil</td>
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<td>0.002</td>
<td>3.78</td>
<td>3.75</td>
<td>2.45</td>
<td>moderate</td>
</tr>
</tbody>
</table>

Table 1. Physicochemical properties of systemic insecticides. C = carbamates; D = dithiol; IGR = Insect growth regulator; N = neonicotinoid; OP = organophosphate; PP = phenylpyrazole

# Partition coefficients between n-octanol and water (Kow) indicate bioaccumulation potential when Log Kow > 4.

*The Groundwater Ubiquity Score (GUS) is calculated using soil half-life (DT50) and organic-carbon sorption constant (Koc) as follows: GUS = log(DT50) x (4-log Koc). A compound is likely to leach if GUS > 2.8 and unlikely to leach when GUS < 1.8; other values in between indicate that leaching potential is marginal.
<table>
<thead>
<tr>
<th>Chemical</th>
<th>Group</th>
<th>Water Photolysis (pH 7)</th>
<th>Hydrolysis (pH 5-7)</th>
<th>Field Water-sediment</th>
<th>Soil (range)</th>
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<td>25</td>
<td>2</td>
<td>4 (3-20)</td>
</tr>
<tr>
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<td>C</td>
<td>Stable</td>
<td>stable</td>
<td>-</td>
<td>4 (1-8)</td>
</tr>
<tr>
<td>butoxycarboxim</td>
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<td>Stable</td>
<td>18 (510-16)</td>
<td>-</td>
<td>42</td>
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<td>9.7</td>
<td>14 (1-60)</td>
</tr>
<tr>
<td>ethiofencarb</td>
<td>C</td>
<td>-</td>
<td>16</td>
<td>52</td>
<td>37 (34-131)</td>
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<td>C</td>
<td>Stable</td>
<td>stable</td>
<td>4</td>
<td>7 (5-30)</td>
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<td>195</td>
<td>9 (5-13)</td>
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<td>&lt;1</td>
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<td>cartap</td>
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<td>-</td>
<td>-</td>
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<td>3</td>
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<td>-</td>
<td>-</td>
<td>28</td>
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<td>68 (156-4)</td>
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<tr>
<td>omethoate</td>
<td>OP</td>
<td>Stable</td>
<td>17</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>oxydemeton-methyl</td>
<td>OP</td>
<td>222</td>
<td>73 (96-41)</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>phorate</td>
<td>OP</td>
<td>1</td>
<td>3</td>
<td>-</td>
<td>63 (14-90)</td>
</tr>
</tbody>
</table>
Aquatic organisms take up easily whatever residues reach the waterbodies, through runoff from treated fields or contaminated groundwater. Some 20% systemic insecticides are prone to leaching, and 45% are mobile in wet soils (Table 1). For example, acephate leaches more easily than methamidophos [305], and so acephate should be restricted or avoided in tropical areas and rice crops [46]. Residues of aldicarb and methomyl in groundwater can have sublethal effects in mammals [215]. Even if residue levels of systemic insecticides in rivers and lakes are usually at ppb levels (μg/L), persistent compounds such as fipronil, neonicotinoids and growth regulators can have chronic effects due to their constant presence throughout several months in the agricultural season [123]. For example, about 1-2% of imidacloprid in treated soil moves into runoff after rainfall events, with the highest concentrations recorded at 0.49 mg/L [12]. Systemic carbamates and OPs do not last long in water because they breakdown through photolysis or hydrolysis in a few days, or are taken up and degraded by aquatic plants [100]. In any case, their presence and frequency of detection in water depends on local usage patterns [39, 171]. The acute toxicity of most systemic compounds is enhanced in aquatic insects and shrimp under saline stress [22, 253].

A characteristic feature of most systemic insecticides –except carbamates– is their increased toxicity with exposure time, which results from a constant or chronic uptake through either feeding or aquatic exposure (Figure 1). Effects are more pronounced some time after the initial application [16], and could last up to eight months [286]. Also, as a result of chronic intoxication, there may not be limiting toxic concentrations (e.g. NOEC or NOEL) in compounds that have irreversible mechanism of toxicity, since any concentration will produce an effect as long as there is sufficient exposure during the life of the organism [274]. This is precisely their main advantage for pest control: any concentration of imidacloprid in the range 0.2-1.6 ml/L can reduce the population of mango hoppers (Idioscopus spp.) to zero within three weeks [291]. However, it is also the greatest danger for all non-target species affected, e.g. predators, pollinators and parasitoids. By contrast, contact insecticides act usually in single exposures (e.g. spray droplets, pulse contamination after spraying, etc.) and have the highest effects immediately after application.

### Table 2. Degradation of systemic insecticides expressed as half-lives in days. Compounds with half-lives longer than 100 days are considered persistent (Sources: Footprint database & [284]. a for pH 9C = carbamates; D = dithiol; IGR = Insect growth regulator; N = neonicotinoid; OP = organophosphate; PP = phenylpyrazole)

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Group</th>
<th>Water</th>
<th>Field</th>
</tr>
</thead>
<tbody>
<tr>
<td>phosphamidon</td>
<td>OP</td>
<td>-</td>
<td>36 (60-12)</td>
</tr>
<tr>
<td>thiodetion</td>
<td>OP</td>
<td>-</td>
<td>22</td>
</tr>
<tr>
<td>vamidothion</td>
<td>OP</td>
<td>-</td>
<td>119</td>
</tr>
<tr>
<td>fipronil</td>
<td>PP</td>
<td>0.33</td>
<td>stable</td>
</tr>
</tbody>
</table>

* for pH 9C = carbamates; D = dithiol; IGR = Insect growth regulator; N = neonicotinoid; OP = organophosphate; PP = phenylpyrazole
3. Modes of action of systemic insecticides

Before describing their impacts on organisms and ecosystems, a description of the mechanisms of toxicity of systemic insecticides is briefly outlined.

3.1. Acetylcholinesterase inhibitors

Carbamates and organophosphorus compounds are inhibitors of the acetylcholinesterase enzyme (AChE), thus blocking the transmission of the nervous impulse through the neuronal synapses. The binding of carbamates to the enzyme is slowly reversible and temporary, i.e. < 24 h [197], whereas that of alkyl OPs is irreversible. The binding of methyl-OPs does not last as long as that of alkyl-OPs, and this feature is compound specific [182]. Given their mode of action, all these compounds are broad-spectrum insecticides, extremely toxic to most animal taxa, from worms to mammalian vertebrates. Avian species are often more susceptible to these compounds due to relatively low levels of detoxifying enzymes in birds [207, 297]. Thus, recovery of ducklings exposed to a range of carbamate and OP insecticides occurred within eight days after being depressed 25-58% following dosing [91].

3.2. Insecticides acting on nicotinic acetylcholine receptors (nAChR)

Neonicotinoids are derived from nicotine, which is found in the nightshade family of plants (Solanaceae), and particularly in tobacco (Nicotiana tabacum). They all are agonists of the nicotinic acetylcholinesterase receptor (nAChR), which mediate fast cholinergic synaptic transmission and play roles in many sensory and cognitive processes in invertebrates. Binding of neonicotinoids to these receptors is irreversible in arthropods [40, 307]. Given that nAChRs are embedded in the membrane at the neuronal synapses, their regeneration seems unlikely.
because neurons do not grow. The lower affinity of neonicotinoids for mammalian nAChRs has been attributed to the different ionic structure of the vertebrate subtypes [283]. The high toxicity of neonicotinoids to insects and worms is comparable to that of pyrethroids, but aquatic crustaceans, particularly waterfleas, are more tolerant [119, 136].

Cartap is a dithiol pro-insecticide that converts to nereistoxin, a natural toxin found in marine *Nereis* molluscs. Both cartap and nereistoxin are antagonists of the nAChR in insects and other arthropods [164], blocking irreversibly the neuronal functions of these receptors. Unlike neonicotinoids, cartap appears to be very toxic to fish and amphibians [235].

### 3.3. GABA-R antagonists (fipronil)

Fipronil is a phenylpyrazole antagonist of the γ-aminobutyric acid (GABA)-gated chloride channel, binding irreversibly to this receptor and impeding the nervous transmission [56]. Its mode of action, therefore, appears to be identical to that of cyclodiene organochlorins (e.g. endosulfan), but fipronil is mostly systemic whereas all cyclodienes are insecticides with contact activity. Interestingly, while aquatic organisms (e.g. cladocerans, fish) are quite tolerant of fipronil, vertebrates are more susceptible to this compound than to the old organochlorins [235].

### 3.4. Insect growth regulators (IGR)

Hexaflumuron, novaluron and teflubenzuron are the only systemic benzoylureas in the market. They are chitin inhibitors, blocking the biosynthesis of this essential component of the arthropod’s exoskeleton. As a consequence, insects and other arthropods cannot moult and die during their development. Since their mode of action is restricted to arthropods, benzoylureas are not very toxic to any other animal taxa, e.g. molluscs, vertebrates, etc. [235].

Halofenozide is the only systemic compound among the hydrazines, a group of chemicals that mimic the steroidal hormone ecdysone, which promotes moulting in arthropods [71]. The premature moulting in larvae of some insect taxa, particularly in Lepidoptera, prevents them from reaching the adult stage. Toxicity of halofenozide is selective to insects only.

### 4. Effects on organisms and ecosystems

#### 4.1. Direct effects on organisms

Mortality of non-target organisms exposed to insecticides is mostly due to acute toxicity, particularly in the case of carbamates. However, with systemic compounds there are many observations of long-term suppression of populations that suggest a chronic lethal impact over time. The latter impacts are likely due to persistence of residual activity in the soil, foliage or water in the case of reversible toxicants (i.e. carbamates), or to irreversible and persistent binding in other cases. (note: all application rates and concentrations here refer to the active ingredient).
4.1.1. Acetylcholinesterase inhibitors

These compounds can have serious impacts on soil organisms of various taxa. Aldicarb and phorate applied to a cotton crop soil at 0.5 and 1 kg/ha, respectively, eliminated or reduced significantly non-target mesofauna, including mites and springtails. Populations of the latter taxa were reduced for more than 60 days (phorate) and 114 days (aldicarb) [17, 225], with the highest effects peaking after 18 days [16]. Granular applications of phorate (250 mg/kg dry soil) killed almost all earthworms, Collembola, Acarina, free-living saprophytic and parasitic nematodes and Protozoa, with populations of Collembola recovering only when residues went below 2 mg/kg [300]. After a single aldicarb application to soil at 2.5 g/m², Gamasina predatory mites went to extinction within a year [148]. Bendiocarb impacts on predaceous arthropods and oribatid mites were less severe and temporary compared to the impacts of non-systemic OPs, but increased trap catches of ants two weeks after application [55], possibly as a result of a longer-term effect. Many soil arthropods, in particular mites and springtails, were the most affected by dimethoate –and its metabolite omethoate– residues in soil after sprays of 1-2 ml/L in the farms of the Zendan valley, Yemen [4]. Similar observations were made when dimethoate was sprayed on vegetation of arable fields [85] or in soil microcosms [180]; the springtail populations recovered but attained lower densities a year later, while their dominance structure had changed. However, dimethoate or phosphamidon applied in mustard fields produced only a temporary decline, compared to the long-lasting effect of monocrotophos [141]. Collembola populations do not seem to be affected by pirimicarb applications on cereal crops [95].

Earthworm populations were affected initially after application of phorate and carbofuran to turfgrass, but not thiofanox, and their numbers recovered subsequently [53]. Reduction of earthworm populations by bendiocarb was the highest (99% in one week) among 17 insecticides applied at label rates on turfgrass, with significant effects lasting up to 20 weeks [216]. Juveniles and species living in the surface layers or coming to the soil surface to feed (e.g., Lumbricus terrestris) are most affected, since a high degree of exposure is usually found in the first 2.5 cm of soil [288]. However, systemic carbamates can be selective to plant-parasitic nematodes without affecting fungal or microbial communities [296]. Thus, cholinesterase inhibitors do not have significant impacts on bacteria, fungi and protozoa in soil [133], and consequently do not alter the soil biochemical processes [79]. Nevertheless, a combined dimethoate-carbofuran application reduced active hyphal lengths and the number of active bacteria in a treated forest soil [58].

Populations of beneficial predators can be decimated initially as much as the target pests, but they usually recover quickly. For example, thiodicarb or its degradation product, methomyl, applied at 0.5 kg/ha on soybean crops, significantly reduced populations of the predatory bugs Tropiconabis capsiformis and Nabis roseipennis within two days after treatment only [25]. Demeton-S-methyl reduced populations of predatory insects on strawberry patches, whereas pirimicarb and heptenophos had no significant effect on spiders, staphylinids and anthocorids, or on hymenopteran parasitoids [76]. While populations of web spiders and carabid beetles are severely reduced by dimethoate applied to cabbage fields and cereal crops [144], pirimicarb does not seem to have much impact on these taxa [97, 195], affecting
mainly aphids [131]. Pirimicarb on wheat crops does not impact on ladybirds, but larvae of *Episyrphus balteatus* are affected [135]. By contrast, longer impacts have been observed with acephate applied at 0.5 kg/ha on rice paddies, which reduced populations of predatory bugs (*Cyrtozophilus lividipennis* and *Paederus fuscipes*) for at least 10 days [155]. Similar rates of acephate on rice and soybean crops reduced spiders populations for three weeks, but they recovered afterwards [181]. In addition, acephate is deadly to three species of whitefly parasitoid species [267].

Direct mortality of bumble bees (*Bombus terrestris*) in short exposures to dimethoate is much higher than for heptenophos or ethiofencarb [132]. However, what matters most is the chronic toxicity to the entire bee colony not just the workers. For example, methamidophos contaminated syrup (2 mg/L) produced significant losses of eggs and larvae of honey bees without any appreciable loss of workers after one week of exposure; the colonies would recover completely within 13 weeks if the insecticide was applied only once [301], indicating a long-term impact on the colony. Similarly, the mortality of non-target adult chrysomelid beetles (*Gastrophysa polygoni*) after foliar treatment with dimethoate on the host plants was low (1.9-7.6%), but because this insecticide was most toxic to the egg stage, the overall beetle population decreased over time due to hatching failure [146].

Primary poisoning of birds and mammals by ingestion of OP and carbamate granules or coated seeds is still a problem despite the many attempts to reduce these impacts [189, 190]. For example, mortality of birds that ingested granules of carbofuran in a corn field was extensive, affecting waterfowl, small songbirds and mice within 24 hours. Residues up to 17 mg/kg body weight (b.w.) were found in the dead animals [19]. The granular formulation of this carbamate was banned in the mid-1990s by the US EPA after numerous cases of direct poisoning by animals; however, the liquid formulation applied to alfalfa and corn is just as deadly to bees, because this systemic insecticide is present in the pollen of those plants [208]. Phosphamidon sprayed at 1 kg/ha to larch forests in Switzerland caused many bird deaths [243]; large bird mortality was also observed in Canadian spruce forests sprayed with phosphamidon (0.55 kg/ha), particularly among insectivorous warblers. There was good evidence that birds picked up the insecticide from sprayed foliage within a few hours of application [94]. Carbofuran and phosphamidon were the most common pesticides implicated in deaths of wild birds in Korea between 1998-2002 [157], and ducklings died in large numbers when phorate was applied to South Dakota wetlands [73]. Usually birds die when their brain AChE depression is over 75% [92, 114]. Thus, 11 out of 15 blue jays (*Cyanocitta cristata*) which had depression levels ranging 32-72% after disulfoton was sprayed to pecan groves would die [302], but their carcasses would probably not be found. In orchards sprayed with methomyl, oxamyl or dimethoate, the daily survival rates for nests of Pennsylvania mourning dove (*Zenaida macroura*) and American robin (*Turdus migratorius*) were significantly lower than in non-treated orchards, and the species diversity was also lower. Repeated applications of these and other insecticides reduced the reproductive success of doves and robins and may have lowered avian species diversity [93].

Secondary poisoning with bendiocarb was attributed to 22 birds that had depressed AChE activity after eating contaminated mole crickets and other soil organisms on the applied
turfgrass [224]. Several species of raptors were killed or debilitated after consuming waterfowl contaminated with phorate – the fowl had ingested granules of the insecticide that were applied to potato fields a few months earlier [84]. Equally, ladybugs (Hippodamia undecimnotata) fed upon Aphis fabae, which were reared on bean plants treated with carbofuran, experienced a 67% population reduction due to secondary poisoning [206]. Pirimicarb caused 30-40% mortality of Tasmanian brown lacewing (Micromus tasmaniae) larvae when feeding on contaminated 1st instar lettuce aphid (Nasonovia ribisnigri) for three days [298].

Impacts on aquatic organisms usually do not last more than a month. For example, thiodicarb applied at 0.25-1.0 kg/ha had severe impacts on copepods, mayflies and chironomids in experimental ponds for three weeks, but not so much on aquatic beetle’s larvae; eventually there was recovery of all populations [7]. Pirimicarb can be lethal to common frog (Rana temporaria) tadpoles, but does not appear to have chronic effects [139]. However, vamidothion and acephate are most lethal to non-target organisms in rice crops, and are not recommended in IPM programs [153]. Carbofuran and phorate are very toxic to aquatic invertebrates [140], particularly amphipods and chironomids but not so much to snails, leeches or ostracods [72, 249]. Small negative effects in zooplankton communities (cladocerans copepods and rotifers) were observed in rice paddies treated with carbofuran at recommended application rates, but fish were not affected [107]. Carbofuran should not be used in rice paddies, whether in foliar or granular formulations: not only induces resurgence of the brown planthoppers (Nilaparvata lugens) [122], but it is also more toxic to the freshwater flagellate Euglena gracilis than the non-systemic malation [15]. It reduces populations of coccinellid beetles, carabid beetles, dragonfly and damselfly nymphs, but does not impact much on spiders [255]. However, it appears that carbofuran at 0.2% per ha can double the densities of Stenocypris major ostracods in rice paddies, whereas other insecticides had negative effects on this species [168]. Repeated applications of carbofuran can also have a significant stimulation of the rhizosphere associated nitrogenase activity, with populations of nitrogen-fixing Azospirillum sp., Azotobacter sp. and anaerobic nitrogen-fixing bacteria increasing progressively up to the third application of this insecticide [142].

4.1.2. Insecticides acting on nAChR

Direct toxicity of cartap to fish species is not as high as that of other neurotoxic insecticides, with 3-h LC50s between 0.02 and 6.8 mg/L [161, 308]. However, cartap affects negatively several species of Hymenoptera and aphid parasitoids used to control a number of crop pests [14, 77, 147, 270]. This insecticide also inhibits hatching of eggs of the nematode Ag nemermis unka, a parasite of the rice pest Nilaparvata lugens [50], and reduces significantly the populations of ladybugs and other predatory insects in cotton crops when applied at the recommended rates, i.e. 20 g/ha [109, 169]. In rice paddies, cartap hydrochloride reduced populations of coccinellid beetles, carabid beetles, dragonflies and damselflies by 20-50% [255]. Pollinators such as honey bees and bumble bees can also be seriously reduced in numbers when feeding on crops treated with cartap hydrochloride, which is included among the most toxic insecticides to bees after neonicotinoids and pyrethroids [179, 278]. For all its negative impacts on parasitoids and predatory insects it is hard to understand why cartap was
the third most common insecticide (19% of all applications) used in IPM programs in Vietnam a decade ago [31], and is still among the most widely used in rice farms in China [308].

Cumulative toxicity of neonicotinoids over time of exposure results in long-term pest control compared to the impact of cholinesterase inhibitor insecticides. For example, soil treated with clothianidin at 0.05-0.15% caused increasing mortality in several species of wireworms (Coleoptera: Elateridae), reaching 30-65% after 70 days, whereas chlorpyrifos at 0.15% produced 35% mortality within 30 days but no more afterwards [292]. Soil application of imidacloprid did not eliminate rapidly Asian citrus psyllid (Diaphorina citri) and leafminer (Phyllocnistis citrella) populations, but resulted in chronic residues in leaf tissue and long-term suppression of both pests [245]. Also, soil applications of neonicotinoids are very effective in controlling soil grubs and berry moths (Paralobesia viteana) in vineyards provided there is no irrigation or rain that washes off the insecticide [289]. For the same reason, however, the impact of neonicotinoids on non-target organisms is long-lasting. For example, repeated corn-seed treatment with imidacloprid caused a significant reduction in species richness of rove beetles in three years, even though the abundance of the main species was not affected [88]. In addition to long-term toxicity, acute toxicity of acetamiprid, imidacloprid and thiamethoxam to planthopper and aphid species is similar to that of synthetic pyrethroids, and higher than that of endosulfan or acetylcholinesterase inhibitors [219, 246]. Thus, combinations of pyrethroid-neonicotinoid have been hailed as the panacea for most pest problems as it suppresses all insect resistance [70]. Mixtures of imidacloprid and thiacloprid had additive effects on the toxicity to the nematode Caenorhabditis elegans but not on the earthworm Eisenia fetida [108].

Acute toxicity of imidacloprid, thiamethoxam, clothianidin, dinofuran and nitenpyram to honey bees is higher than that of pyrethroids, while toxicity of acetamiprid and thiacloprid is increased by synergism with ergosterol-inhibiting fungicides [134, 242] and antibiotics [116]. Thus, neonicotinoids can pose a high risk to honey bees, bumble bees [176, 263] and wasps [90]. Bees can be killed immediately by direct contact with neonicotinoid droplets ejected from seed drilling machines. Thus, numerous worker bees were killed when seed was coated with clothianidin during drilling of corn in the Upper Rhine Valley (Germany) in spring 2008 [102]. The same problem happened in Italy with thiamethoxam, imidacloprid and clothianidin [105, 285], leading to the banning of this application method on sunflower, canola and corn during 2008-09 [20]. However, most of the time bee colonies are intoxicated by feeding on contaminated pollen and nectar [9, 228]. It has been observed that bee foraging was notably reduced when Indian mustard was treated with 178 mg/ha imidacloprid [10]. Imidacloprid residues in sunflowers are below the no-adverse-effect concentration to honey bees of 20 μg/kg at 48-h [241], with surveys in France showing residue levels in pollen from treated crops in the range 0.1-10 μg/kg and average in nectar of 1.9 μg/kg [33]. However, bees feeding on such contaminated pollen or nectar will reach first sublethal and later lethal levels, with 50% mortality occurring within 1-2 weeks [228, 266]. Such data was disputed [89, 240] as it was in conflict with some long-term field observations of honey bees feeding on sunflowers grown from imidacloprid-treated seeds at 0.24 mg/seed [256]. However, recent evidence suggest that chronic lethality by imidacloprid is implicated in the colo-
ny collapse disorder (CCD) that affects honey bees [174]. Based on the fast degradation of imidacloprid in bees (4-5 hours), it is assumed that honey bees which consume higher amounts of imidacloprid die already outside of the hive, before the colony’s demise and before samples are taken, though residues of imidacloprid in bees at 5-8 μg/kg have been found in some cases [111]. Clothianidin residues of 6 μg/kg in pollen from canola fields reduced the number of bumble bee (Bombus impatiens) workers slightly (~20%) [96], but exposure to clothianidin-treated canola for three weeks appeared not to have affected honey bee colonies in Canada [61]. Thiamethoxam applied to tomatoes (~150 g/ha) through irrigation water does not have impacts on bumble bees (Bombus terrestris) [244], whereas pollen contaminated with this insecticide causes high mortality and homing failure [125].

Negative impacts of neonicotinoids on non-target soil arthropods are well documented. A single imidacloprid application to soil reduced the abundance of soil mesofauna as well as predation on eggs of Japanese beetle (Popillia japonica) by 28-76%, with impacts lasting four weeks. The same level of impact was observed with single applications of clothianidin, dinotefuran and thiamethoxam, so the intended pest control at the time of beetle oviposition runs into conflict with unintended effects – disruption of egg predation by non-target predators [210]. Among several insecticides applied to home lawns, only imidacloprid suppressed the abundance of Collembola, Thysanoptera and Coleoptera adults, non-oriibatid mites, Hemiptera, Coleoptera larvae or Diptera taxonomic groups by 54-62% [209]. Imidacloprid applied to the root of eggplants (10 mg/plant) greatly reduced most arthropod communities and the species diversity during the first month. Small amounts of soil residues that moved into the surrounding pasture affected also some species; however, non-target ground arthropods both inside and outside the crop showed significant impacts only in the two weeks after planting [238], probably due to compensatory immigration from nearby grounds.

Foliar applications of thiamethoxam and imidacloprid on soybean crops are preferred to seed treatments, as neonicotinoids appear to have lesser impacts on non-target communities than pyrethroids [204]. However, a foliar application of thiacloprid (0.2 kg/ha) to apple trees reduced the population of earwigs (Forficula auricularia), an important predator of psyllids and woolly apple aphid, by 60% in two weeks, while remaining below 50% after six weeks [294]. Branchlets of hemlock (Tsuga canadensis) treated with systemic imidacloprid (1-100 mg/kg) reduced the populations of two non-target predators of the hemlock woolly adelgid (Adelges tsugae) and had both lethal and sublethal effects on them [78]. Clothianidin, thiamethoxam and acetamiprid were as damaging to cotton crop predators as other broad-spectrum insecticides and cartap [169]. All neonicotinoids are lethal to the predatory mirid Pilophorus typicus, a biological control agent against the whitefly Bemisia tabaci, since their residual activity can last for 35 days on the treated plants [201]. The ladybug Serangium japonicum, also a predator of the whitefly, is killed in large numbers when exposed to residues of imidacloprid on cotton leaves applied at the recommended rate (40 ppm) or lower; apparently, the predator was not affected when imidacloprid was applied as systemic insecticide [120]. Clothianidin is 35 times more toxic to the predatory green miridbug (Cytorhinus lividipennis 48-h LC50 = 6 μg/L) than to the main pest of rice (Nilaparvata lugens 48-h LC50 = 211 μg/L), thus questioning seriously its application in such crops [221]. Not surprisingly, popu-
lations of predatory miridbugs and spiders suffered an initial set back when rice paddies were treated with a mixture of ethiprole+imidacloprid (125 g/ha), and their recovery was slow and never attained the densities of the control plots [154]. Mixtures of ethiprole+imidacloprid and thiamethoxam+λ-cyhalothrin on rice paddies are also highly toxic to mirid and veliid natural enemies of rice pests, with 100% mortalities recorded in 24 h [159].

Secondary poisoning with neonicotinoids reduces or eliminates eventually all predatory ladybirds in the treated areas, compromising biological control in IPM programs. Indeed, exposure of larval stages of Adalia bipunctata to imidacloprid, thiamethoxam, and acetamiprid, and adult stages to imidacloprid and thiamethoxam, significantly reduced all the demographic parameters in comparison with a control –except for the mean generation time–, thus resulting in a reduced coccinellid population; adult exposures produced a significant population delay [162]. Eighty percent of 3rd and 4th instar larvae of the ladybug Harmonia axyridis died after feeding for 6 hours on corn seedlings grown from seeds treated with clothianidin, compared to 53% mortality caused by a similar treatment with thiamethoxam; recovery occurred only in 7% of cases [196]. Survival of the ladybird Coleomegilla maculata among flower plants treated with imidacloprid at the label rate was reduced by 62% [251], and Hippodamia undecimnotata fed upon aphids reared on bean plants treated with imidacloprid, experienced a 52% population reduction [206]. Equally, 96% of Tasmanian brown lacewing (Micromus tasmaniae) larvae died after feeding on 1st instar lettuce aphid (Nasonovia ribisnigri) for three days. Low doses did not increase mortality but from days 3 to 8, lacewing larvae showed significant evidence of delayed developmental rate into pupae [298].

Recent evidence of the negative impacts of neonicotinoids on parasitoids reinforces that these insecticides are not suitable for IPM [271]. All neonicotinoids are deadly to three whitefly parasitoid species (Eretmocerus spp. and Encarsia formosa), with mortality of adults usually greater than the pupae [267]. Thiamethoxam appears to be less toxic to whitefly parasitoids compared to imidacloprid [202]. Imidacloprid, thiamethoxam and nitenpyram appeared to be the most toxic to the egg parasitoids Trichogramma spp. [231, 299]. For example, the acute toxicity of thiomethoxam and imidacloprid to Trichogramma chilonis, an egg parasitoid of leaf folders widely used in cotton IPM, is about 2000 times higher than that of other insecticides used in rice crops in India, such as acephate or endosulfan [220]. Acute toxicity of imidacloprid is more pronounced on Braconidae parasitoids than on T. chilonis, whereas thiacloprid only reduced the parasitization on Microplitis mediator [192]. Thiacloprid is as toxic to the cabbage aphid Brevicoryne brassicae as to its parasitoid (Diaeretiella rapae), whereas pirimicarb and cypermethrin are more toxic to the aphid and are, therefore, preferred in IPM [3].

Neonicotinoids pose also risks to aquatic taxa. The synergistic toxicity of imidacloprid+thiacloprid on Daphnia magna [173] implies the combined effect of neonicotinoids on aquatic arthropods would be higher than expected, even if Daphnia is very tolerant of neonicoti-
noids [119]. Other contaminants, such as the nonylphenol polyethoxylate (R-11) act also synergistically with imidacloprid [49]. Thiacloprid causes delayed lethal and sublethal effects in aquatic arthropods, which can be observed after 4 to 12 d following exposure to single 24-h pulses [28]. Thus, its 5% hazardous concentration (0.72 μg/L) is one order of magnitude lower than predicted environmental concentrations in water [35]. Also, thiacloprid LC50 for survival of midges (Chironomus riparius) is only 1.6 μg/L, and EC50 for emergence 0.54 μg/L [160], so both acute and chronic toxicity reduce the survival and growth of C. tentans and Hyalella azteca [265]. Acute toxicity of neonicotinoids to red swamp crayfish (Procambarus clarkii) is 2-3 orders of magnitude lower than that of pyrethroids [23]; comparative data such as this gives the neonicotinoids an apparent better environmental profile. However, experimental rice mesocosms treated with imidacloprid at label rates (15 kg/ha) eliminated all zooplankton communities for two months, and their recovery did not reach the control population levels four months later. Equally, mayflies, coleoptera larvae and dragonfly nymphs were significantly reduced while residues of imidacloprid in water were above 1 μg/L [117, 237]. Similarly, streams contaminated with a pulse of thiacloprid (0.1-100 μg/L) resulted in long-term (7 months) alteration of the overall invertebrate community structure [27]. However, while aquatic arthropods with low sensitivity to thiacloprid showed only transient effects at 100 μg/L, the most sensitive univoltine species were affected at 0.1 μg/L and did not recover during one year [167].

4.1.3. Fipronil

Fipronil is very efficient in controlling locust outbreaks, but causes more hazards than chlorpyrifos and deltamethrin to non-target insects in the sprayed areas, although it is more selective to specific taxa [214, 252]. Thus, abundance, diversity and activity of termites and ants were all reduced in northern Australia after spraying several areas with fipronil for locust control [262], and 45% of the termite colonies died within 10 months of a spraying operation with fipronil for controlling locusts in Madagascar [214]. Reducing the recommended application rates by seven times (0.6-2 g/ha) still achieves 91% elimination of locusts while having lesser impacts on non-target organisms, comparable to those inflicted by carbamate and OP insecticides [18].

Despite its selectivity, fipronil in maize crops reduced the abundance of arthropod populations of the soil mesofauna more significantly than other systemic insecticides, i.e. carbofuran [59], although springtails are little affected as they avoid feeding on litter contaminated with fipronil and are more tolerant of this insecticide [232]. When applied to citrus orchards, fipronil was among the most detrimental insecticides affecting two Euseius spp. of predatory mites [112]. In rice crops, the effectiveness of fipronil in controlling pests was overshadowed by its negative impact on the predatory miridbugs Cytorhinus lividipennis and Tytthus parviceps [159].

Of greater concern is the impact of this systemic chemical on honey bees and wild bee pollinators. With an acute contact LD50 of 3.5 ng/bee [166] and acute oral LD50 of 3.7-6.0 ng/bee [2], fipronil is among the most toxic insecticides to bees ever developed. Even more worrying is the finding that the adjuvant Sylgard, used to reduce the toxicity of most insecticidal
products on bees, increases the toxic effects of fipronil [184]. The systemic nature of this chemical implies that chronic feeding of the bees on nectar contaminated with fipronil caused 100% honey bee mortality after 7 days, even if the residue concentration was about 50 times lower than the acute lethal dose [8]. Residues of fipronil in pollen have been measured as 0.3-0.4 ng/g, which are 30-40 times higher than the concentration inducing significant mortality of bees by chronic intoxication [33]. Unlike neonicotinoids, no residues of fipronil have been found in guttation drops [272].

The acute toxicity of fipronil to cladocerans is similar to the toxicity to estuarine copepods, with 48-h LC50 in the range 3.5-15.6 μg/L [47, 259], but the chronic toxicity with time of exposure is what determines the fate of the populations exposed. For example, populations of Daphnia pulex went to extinction after exposure to 80 μg/L for 10 days, equivalent to LC75 [259], and 40% of a population of grass shrimps (Palaemonetes pugio) died in 28 days after being exposed to fipronil concentrations of 0.35 μg/L in marsh mesocosms, and none of the shrimps survived when exposed to 5 mg/L during the same period [303]. Such impacts on zooplankton are likely to occur in estuaries, where waters have been found to contain 0.2-16 μg/L of fipronil residues [45, 163], even if no apparent effect on amphipods, mussels nor fish has been observed [37, 303]. Fipronil sprays on water surfaces to control mosquito larvae have negative impacts not only on cladocerans but also on chironomid larvae exposed to chronic feeding on contaminated residues [183, 264]. Studies on rice mesocosms have shown that significant population reductions due to fipronil application at the recommended rates (50 g per seedling box) are not restricted to zooplankton and benthic species, but affect most species of aquatic insects. Moreover, fipronil impacts on aquatic arthropods were more pronounced after a second application in the following year [118], indicating persistence of this insecticide in rice paddies. Chronic toxicity over time explains the long-term toxicity of this systemic compound, so it is not surprising that concentrations of 1.3 μg/L in paddy water were sufficient to kill 100% of dragonfly (Sympetrum infuscatum) nymphs in nine days [138].

4.1.4. Insect growth regulators

There is little information about the effect of systemic chitin inhibitors on non-target organisms. Obviously these compounds are harmless to fish at levels above 1 mg/L for a week-long exposures [290], and to all vertebrates in general. IGRs affect mainly the larval stages of Lepidoptera, Coleoptera and Hymenoptera, and their activity last longer than that of other pest control products [178]. The effectiveness of these compounds in controlling target pests is demonstrated by comparing the dietary LC50 of hexaflumuron (0.31 mg/L) to the target cotton worm (Helicoverpa sp.), which is 35 times lower than that of the systemic carbamate thiodicarb and less damaging to non-target predators [64]. Aquatic communities of non-target arthropods in rice fields (e.g. Cladocera, Copepoda, Odonata, Notonectidae, Coleoptera and Chironomidae taxa) were not affected by teflubenzuron applied at rates to control mosquitoes (5.6 mg/ha), even though this IGR remained active for several weeks during autumn and winter periods [239].

After application of IGRs to a crop, affected insect pests are prey to many species of spiders, some of which are also susceptible to the toxicity of these products, in particular the ground
hunter spiders [211]. Larvae and eggs of pests contaminated with systemic IGR are consumed by a number of predators, including earwigs, which undergo secondary poisoning and stop growing beyond the nymph stage [226]. Chitin inhibitors only show effects on the larvae of predatory insects that had consumed treated-prey, not on the adult insects. As a consequence, predatory populations collapse, as it happened with the ladybeetle *Chilocorus nigritus* that fed on citrus red scales (*Aonidiella aurantii*) in African orchards that had been treated with teflubenzuron [177]. Teflubenzuron sprayed at 16.4 g/ha for locust control in Mali did not affect the non-target arthropods in the herb layer, whereas ground-living Colembola, Thysanura, Coleoptera and Lepidoptera larvae were reduced by about 50% [151]. Moreover, teflubenzuron has multigenerational impacts: experiments with springtails exposed to artificial soil contaminated with this IGR showed that the F2 generation suffered significantly from its effects even when only the F0 generation had been exposed for 10 days [42]. Secondary poisoning with chitin inhibitors can be detrimental also to parasitoids such as *Diadegma semiclausum*, which may fail to produce enough cocoons in the treated hosts, but do not seem to affect the parasitism of other Hymenoptera [98]. For instance, novaluron did not affect the parasitisation of *Trichogramma pretiosum* on mill moth’s caterpillars, a pest of tomato crops [44]. On the other hand, teflubenzuron appears to be harmless to predatory mites [32]. IPM programs must always consider the implications of using systemic chitin inhibitors to control specific pests without destroying their natural predators in the first place.

Halofenozide does not appear to cause any acute, adverse effects through topical, residual, or dietary exposure of the ground beetle *Harpalus pennsylvanicus*. In contrast to the negative effects of other systemic insecticides (i.e. imidacloprid), the viability of eggs laid by females fed halofenozide-treated food once, or continuously for 30 days, was not reduced [156].

### 4.2. Sublethal effects

Very often, sublethal effects of systemic insecticides are a first step towards mortality, as they are caused by the same neurotoxic mechanisms. Apart from these, there may be other effects on reproduction, growth, longevity, etc. when organisms are exposed to low, sublethal doses or concentrations. These effects are only observable in individuals that survive the initial exposure, or in species that are tolerant to insecticides. For a review see [69].

#### 4.2.1. Acetylcholinesterase inhibitors

Longevity of the parasitoid *Microplitis croceipes* that fed on nectar from cotton treated with aldicarb was affected for at least 10 days after application, and its foraging ability of the parasitoid’s host was severely impaired for 18 days [257]. Carbofuran caused a significant reduction of adult weight and longevity of the predator ladybug *Hippodamia undecimnotata*, as well as a 55% reduction in fecundity when fed on aphids contaminated with this insecticide [206]. Longevity and survival of *Aphidius ervi*, an important parasitoid of the pea aphid (*Acrystosiphon pisum*), were significantly reduced after treating with LC25 concentrations of dimethoate or pirimicarb [11]. A significant reduction in body size of females of the predator carabid *Pterostichus melas italicus* and altered sexual dimorphism were observed after long-term exposure in olives groves treated with dimethoate at a rate that caused 10% mortality.
after three days [104]. Unlike other insecticides, no behavioural effects of dimethoate or triazamate on honey bees were recorded [67].

Earthworms (*Lumbricus terrestris*) experienced significant reduction in growth rate and total protein content after soil applications of aldicarb at LC10 or LC25, but only small amounts of residues were detected in the worms [198]. Aldicarb and phorate can also increase infections by *Rhizoctonia* stem canker in potato fields [280].

A typical pattern of sublethal intoxication was revealed when red-winged blackbirds (*Agelaius phoeniceus*) were exposed to increasing doses of dimethoate: 2 mg/kg b.w. doses produced ataraxia, defecation and diarrhea; neuromuscular dysfunctions and breathing complications appeared at 3 mg/kg, and by 5 mg/kg muscle paralysis and death occurred. The estimated LC50 was 9.9 mg/kg, and all birds died at doses above 28 mg/kg [38]. Although sublethal AChE depression by acephate (25% brain) did not affect the attack behaviour in American kestrels (*Falco sparverius*) [229], nor did alter breeding behaviour in American robins (*Turdus migratorius*) [65], exposure to 256 mg/kg b.w. acephate impaired the migratory orientation of the white-throated sparrow (*Zonotrichia albicollis*) [295]. Similarly, low doses of demeton-S-methyl did not affect starlings (*Sturnus vulgaris*) behaviour [279], but doses of 2.5 mg/kg b.w. of dicrotophos administered to female starlings significantly reduced their parental care and feeding of nestlings [113]. Carbofuran orally administered to pigeons (*Columbia livia*) had profound effects on flight time, with pigeons falling off the pace of the flock when doses were between 0.5 and 1.0 mg/kg b.w. [36].

AChE activities in adductor muscle were depressed in freshwater mussels (*Elliptio complanata*) exposed for 96 h at concentrations as low as 0.1 mg/L and 1.3 mg/L of aldicarb and acephate respectively, while increasing the water temperature from 21 to 30 °C resulted in mortality [199]. High AChE inhibition (70%) by acephate was not associated with immobility of *Daphnia magna*, but increasing the concentration of acephate further had a strong detrimental effect on mobility, suggesting that binding sites other than AChE may be involved in acephate toxicity [222].

Exposure of bluegill fish (*Lepomis macrochirus*) to 30 μg/L carbofuran decreased significantly adenylate parameters in gill, liver, muscle and stomach tissues after 10 days, and then returned to normal [128]. Also, concentrations of carbofuran at half the LC50 dose for fathead minnow (*Pimephales promelas*) larvae caused reductions in swimming capacity, increased sensitivity to electric shocks, and a reduction in upper lethal temperature [121]. Enzymes of protein and carbohydrate metabolism were altered (some increased, others decreased) in liver and muscle tissues of the freshwater fish, *Clarias batrachus* when exposed to 7.7 mg/L of carbofuran for six days, recovering later to normal levels [26]. Exposure of guppies (*Brachydanio rerio*) to half the recommended dose for dimethoate (0.025 μl/L) caused morphological changes in hepatocytes within three days, as well as necrosis and other abnormalities [227]. When exposed to a range of monocrotophos concentrations (0.01-1.0 mg/L), male goldfish (*Carassius auratus*) showed higher levels of 17-β-estradiol and vitellogenin and lower levels of testosterone than normal, interfering with gonadotropin synthesis at the pituitary gland [281]. Eggs of the toad *Bufo melanostictus* exposed to acephate hatched normally, but the tadpoles exhibited deformities such as tail distortions and crooked trunk; decreased pigmenta-
tion, peeling of the skin, inactivity, delay in emergence of limbs and completion of metamorphosis were also apparent [103].

Insecticide mixtures can enhance not only the acute but also the sublethal effects. For example, disulfoton together with endosulfan caused cytological and biochemical changes in liver of rainbow trout (Oncorhynchus mykiss), independently of their respective modes of action [13]. Mixtures of aldicarb and other insecticides enhanced significantly the establishment of parasitic lungworm nematodes (Rhandias ranae) in leopard frogs (Rana pipiens) some 21 days after infection [101], as the frog’s immune response was suppressed or altered [51]. Similarly, laboratory rats exposed to sublethal mixtures of aldicarb, methomyl and a herbicide (metribuzin) showed learning impairment, immune response and endocrine changes [215].

4.2.2. Insecticides acting on nAChR

Laboratory experiments have shown a number of abnormalities such as less melanin pigmentation, wavy notochord, crooked trunk, fuzzy somites, neurogenesis defects and vascular defects in zebrafish (Danio rerio) embryos exposed to a range of cartap concentrations. The most sensitive organ was the notochord, which displayed defects at concentrations as low as 25 μg/L [308]. It is obvious that essential enzymatic processes are disturbed during embryo development, among which the inhibition of lysyl oxidase is responsible for the notochord undulations observed.

Imidacloprid does not cause high mortality among eggs or adults of the parasitoid nematode Agamermis unka, but impairs the ability of the nematode to infect nymphs of the host brown planthopper (Nilaparvata lugens) [50]. Contrary to this, a synergistic effect of imidacloprid on reproduction of entomopathogenic nematodes against scarab grubs may increase the likelihood of infection by subsequent generations of nematodes, thereby improving their field persistence and biological potential to control grubs. Acetamiprid and thiamethoxam, however, do not show synergist interactions with nematodes [149]. Imidacloprid at 0.1-0.5 mg/kg dry soil disturbs the burrowing ability of Allolobophora spp. earthworms [43], and the highest concentration can also induce sperm deformities in the earthworm Eisenia fetida [306]. Reduction in body mass (7-39%) and cast production (42-97%) in Allolobophora spp. and Lumbricus terrestris have also been observed after 7 days exposure to relevant environmental concentrations of imidacloprid [74]. Residues of imidacloprid in maple leaves from treated forests (3–11 mg/kg) did not affect survival of aquatic leaf-shredding insects or litter-dwelling earthworms. However, feeding rates by aquatic insects and earthworms were reduced, leaf decomposition (mass loss) was decreased, measurable weight losses occurred among earthworms, and aquatic and terrestrial microbial decomposition activity was significantly inhibited, thus reducing the natural decomposition processes in aquatic and terrestrial environments [150].

The dispersal ability of the seven-spotted ladybirds (Coccinella septempunctata) sprayed with imidacloprid was compromised, and this may have critical consequences for biological control in IPM schemes [21]. A significant reduction of adult weight and longevity of the ladybug Hippodamia undecimnotata, as well as 33% reduction in fecundity were observed when this predatory bug fed on aphids contaminated with imidacloprid [206]. Imidacloprid and
fipronil had adverse effects on the immune response of the wolf-spider *Pardosa pseudoannulata*, reducing significantly its phenoloxidase activity, the total number of hemocytes and encapsulation rate [282]; the implications of such effects on this natural enemy of rice pests are unknown. When applied in the egg-larval or pupal stages, acetamiprid or imidacloprid reduced the parasitisation capacity of F1 and F2 generation females of *Trichogramma pretiosum* on mill moth’s caterpillars (*Anagasta kuehniella*), a pest of tomato crops [44]. Longevity of females of the parasitoid *Microplitis croceipes* that fed on nectar from imidacloprid-treated cotton was affected for at least 10 days after application, while the parasitoid’s host foraging ability was severely affected from day 2 onwards [257]. Exposure of western subtropical termites (*Reticulitermes hesperus*) to acetamiprid (1 mg/kg sand) or imidacloprid also impaired locomotion of termites within 1 hour [230].

Bumble bees (*Bombus terrestris*) interrupt their activity for several hours when exposed to imidacloprid sprayed on plants [132], and soil treatment at the highest recommended doses extended the handling times of *B. impatiens* on the complex flowers [194]. Such an impairment affects the bees foraging behaviour and can result in a decreased pollination, lower reproduction and finally in colony mortality due to a lack of food [193]. Although Franklin et al. [96] found that clothianidin residues of 6 μg/kg in canola pollen reduced the production of queens and increased the number of males in *B. impatiens*, their study did not find significant differences with controls due to a high variability in the results. Larval development in wild bees (*Osmia lignaria* and *Megachile rotundata*) was delayed significantly when fed pollen contaminated with either imidacloprid or clothianidin at 30 or 300 μg/kg [1]. Honey bees are more sensitive to neonicotinoids than bumble bees: at 6 μg/kg, imidacloprid clearly induced a decrease in the proportion of active bees [57], and 50-500 μg/L affect significantly their activity, with bees spending more time near the food source [273]. Other authors found that lower activity of honey bees during the hours following oral exposure to 100-500 μg/L imidacloprid in syrup is transitory [186]. In any case, that may explain the delayed homing behaviour of honey bees exposed to 100 μg/L imidacloprid in syrup and their disappearance at higher doses [34, 304]. Honey bees fed on syrup contaminated with acetamiprid increased their sensitivity to antennal stimulation by sucrose solutions at doses of 1 μg/bee and had impaired long-term retention of olfactory learning at 0.1 μg/bee. Contact exposure at 0.1 and 0.5 μg/bee increased locomotor activity and water-induced proboscis extension reflex but had no effect on behaviour [82]. Similar response was obtained with honey bees exposed to thiamethoxam by contact, having impaired long-term retention of olfactory learning at 1 ng/bee [8]. Winter bees surviving chronic treatment with imidacloprid and its metabolite (5-OH-imidacloprid) had reduced learning performances than in summer: the lowest-effect concentration of imidacloprid was lower in summer bees (12 μg/kg) than in winter bees (48 μg/kg), indicating a greater sensitivity of honey bees behaviour in summer bees compared to winter bees [68].

Honey bees infected with the microsporidian *Nosema ceranae* experienced 7 or 5 times higher mortality than normal when fed syrup contaminated with sublethal doses of thiacloprid (5 mg/L) or fipronil (1 μg/L), respectively [293]. *N. ceranae* is a key factor in the CCD in honey bees [127], and the synergistic effect of these systemic insecticides on *Nosema* is probably its
underlying cause [213]. Suppression of the immune system is not restricted to bees, as a massive infection of medaka fish by a protozoan ectoparasite (Trichodina spp.) when exposed to imidacloprid in rice mesocosms has been documented [236].

Imidacloprid residues in water as low as 0.1 μg/L are sufficient to reduce head and torax length in mayfly nymphs of Baetis and Epeorus, whether applied as pulses or in continuous exposures for 20 days [6]. At 1 μg/L the insecticides caused feeding inhibition. However, 12-h pulses induced emergence because of stress, whereas constant exposure reduced survivorship progressively. Also, the aquatic worm Lumbriculus variegatus experienced immobility during 4 days when exposed to 0.1-10 μg/L imidacloprid [5].

4.2.3. Fipronil

Apart from the extreme acute toxicity of this insecticide to bees, honey bees fed on sucrose syrup contaminated with fipronil (2 μg/kg) reduced significantly their attendance to the feeder [57]. It has also been demonstrated that sublethal concentrations of this insecticide as low as 0.5 ng/bee, whether orally or topically applied, reduce the learning performance of honey bees and impair their olfactory memory but not their locomotor activity [67, 82]. Furthermore, chronic feeding exposure at 1 μg/kg or 0.01 ng/bee reduced learning and orientation, whilst oral treatment of 0.3 ng/bee reduced the number of foraging trips among the exposed workers [66]. In addition to their activity, honey bees fed with sucrose syrup containing 1 μg/L fipronil increased significantly the mortality of bees infected with the endoparasite Nosema ceranae, suggesting a synergistic effect between the insecticide and the pathogen [293]. All these sublethal effects reduce the performance of the hive and help explain the decline in honey bee and wild bee pollinators in many countries [205], although fipronil is not alone in causing this demise – neonicotinoids are equally implicated.

Female zebra finches (Taeniopygia guttata) fed with single sublethal doses of fipronil (1, 5, and 10 mg/kg b.w.) failed to hatch 6 out of 7 eggs laid. The only chick born was underdeveloped and had fiprole residues in the brain, liver and adipose tissues. By contrast, 12-day-old chicken eggs injected with fipronil (5.5 to 37.5 mg/kg egg weight) hatched normally although the chicks from the highest dose group showed behavioural and developmental abnormalities [145].

Low residues of fipronil in estuary waters (0.63 μg/L) inhibited reproduction of the copepod Amphiascus tenuiremis by 73-89%, and this effect seems to be more prevalent on males than on females [45]. Even lower residue levels (0.22 μg/L) halted egg extrusion by 71%, whereas exposure to 0.42 μg/L nearly eliminated reproduction (94% failure) on this species. Based on these results from chronic and sublethal toxicity, a three-generation Leslie matrix model predicted a 62% decline in population size of A. tenuiremis at only 0.16 μg/L [47]. Unlike other insecticides, the stress on Ceriodaphnia dubia caused by predatory cues of bluegill fish (Lepomis macrochirus) was significantly exacerbated when the cladocerans were exposed to 80-160 μg/L of fipronil [223]; however, these concentrations are much higher than the residue levels usually found in waters [99, 163].
While fipronil applied at the recommended rates in rice fields induces biochemical alterations in carp (*Cyprinus carpio*), such metabolic disturbances do not appear to have any effect on growth nor mortality of this fish after 90 days exposure at <0.65 μg/L [52]. However, similar residue levels (<1 μg/L) reduced significantly the growth of adult medaka fish (*Oryzias latipes*) after two weeks of exposure, as well as growth of their offspring in the first 35 days, even if residues of fipronil by that time were below the analytical detection limit (0.01 μg/L) [117].

### 4.2.4. Insect growth regulators

Longevity of predatory bug *Podisus maculiventris* was reduced after preying on Colorado potato beetles that fed on foliage treated with novaluron at 85 g/ha. Females produced fewer eggs and their hatching was significantly suppressed, while 5th instars that also preyed on the beetles failed to moult into adults [62]. Novaluron and hexaflumuron significantly decrease (<30%) the total protists population in the guts of termites (*Reticulitermes flavipes*), thus upsetting their digestive homeostasis [165].

### 4.3. Indirect effects on populations and communities

Indirect effects result from the dynamics of ecosystems. Thus, applications of granular phosphate to soil eliminate most soil invertebrates (see 4.1) except for Enchytraeidae worms, which increase in large numbers and take over the leaf-litter decomposition function carried out by the eliminated springtails [300].

Resurgence or induction of pests by altering the prey-predator relationships in favour of the herbivore species is most common. When carbofuran was applied to corn plantations in Nicaragua, the population levels of the noctuid pest *Spodoptera frugiperda* increased because of lesser foraging activity by predatory ants [212]. Methomyl eliminated the phytoseid predatory mite *Metaseiulus occidentalis* for 10 days, thus causing an increase in Pacific spider mites (*Tetranychus pacificus*) and leafhopper (*Eotetranychus willamettei*) populations in the treated vineyards [130]. Unexpected outbreaks of a formerly innocuous herbivore mite (*Tetranychus schoenei*) were observed after imidacloprid applications to elms in Central Park, New York. A three-year investigation on the outbreaks showed that elimination of its predators and the enhanced fecundity of *T. schoenei* by this insecticide were responsible for that outcome [268].

The widespread use of insecticides usually tips the ecological balance in favour of herbivore species. For example, dimethoate sprayed on clover fields indirectly reduced the populations of house mice (*Mus musculus*) in the treated areas as the insect food source was depleted. However, herbivore species such as prairie voles (*Microtus ochrogaster*) and prairie deer mouse (*Peromyscus maniculatus*) increased in density levels [24], since they had more clover available due to either higher clover yields or through less competition with the house mice or both.

A reduction in arthropod populations often implies starvation of insectivorous animals. For example, densities of two species of lizards and hedgehogs in Madagascar were reduced 45-53% after spraying with fipronil to control a locust outbreak, because their favourite ter-
mite prey was almost eliminated (80-91%) by this chemical [214]. However, this type of indirect impact is difficult to observe and measure in birds, since they can move to other areas or change their resource diet. For example, hemlock forests treated with imidacloprid to control hemlock woolly adelgid (Adelges tsugae) reduced significantly Hemiptera and larval Lepidoptera, but not other insect taxa. Although larval Lepidoptera are the primary prey for insectivorous foliage-gleaning birds, many birds were able to find other food resources in the mixed hemlock-deciduous stands that were not treated [87]. Similarly, post-treatment with fipronil for grasshopper control in Wyoming did not affect bird densities, perhaps due to the large initial insect populations; fipronil plots generally had higher avian population densities (nongregarious, insectivores and total birds) than other areas treated with carbaryl [203]. Although some early studies found that fipronil did not have much impact on aquatic communities of Sahelian ponds [158], nor in predatory invertebrates in the Camargue marshes, herons in the latter region avoid rice fields treated with fipronil because of the scarcity of invertebrate food in there [188].

Food aversion to pesticide-treated seeds or plants is a mechanism that may indirectly ameliorate the toxic effects of systemic insecticides such as carbofuran in mice and other small rodents [170]. Some Collembola species (i.e. Folsomia fimetaria) avoid dimethoate sprayed areas [86], and female parasitoids (Cotesia vestalis) are discouraged from getting to their host—the diamond-back moth (Plutella xylostella) – in turnip plants treated with methomyl, whereas clothianidin does not produce aversion [248]. Equally, dimethoate and oxydemeton-methyl sprayed on peach trees discourage honey bees from visiting in the first two days after application, while treatments with imidacloprid, acetamiprid and thiamethoxam allow honey bees visits [246]. This helps explain the high long-term impact of neonicotinoids on bees compared to the effect of OP insecticides, even if imidacloprid at high experimental concentrations in syrup (>0.5 mg/L) may also have repellent effect on honey bees [34].

5. Risk assessment of systemic insecticides

All systemic compounds have effects with time of exposure. However, only the persistent chemicals (fipronil, neonicotinoids, cartap and some OPs) have cumulative effects over time, since the non-persistent compounds are quickly degraded in soil and water.

For risk assessment of these compounds it is important to understand their chronic impacts. Unlike traditional protocols based on acute toxicity, the persistent activity of the parent and toxic metabolites requires that exposure time must be taken into consideration [115]. Concerns about the impacts of dietary feeding on honey bees and other non-target organisms are thus justified [9, 60, 228], because the accumulation of small residue levels ingested repeatedly over time will eventually produce a delayed toxic effect [276]. For example, bees that feed on contaminated nectar and pollen from the treated crops are exposed to residues of imidacloprid and fipronil in the range 0.7-10 μg/kg and 0.3-0.4 μg/kg respectively [33], which appear in 11% and 48% of the pollen surveyed in France [48]. Based on those findings an estimate of the predicted environmental concentrations that bees are ingesting in that
country can be made for each insecticide. Since there is a log-to-log linear relationship between concentration and time of exposure [234], the critical levels of residue and time of exposure can be determined.

The declining populations of predatory and parasitic arthropods after exposure to recommended applications of most systemic insecticides are worrying. In view of the above, it not so much the small concentrations they are exposed to but the time of exposure that makes the population decline progressively over weeks, months and even years of treatment, as described in this chapter. Lethal and sublethal effects on reproduction are equally implicated. This is the reason why systemic insecticides should be evaluated very carefully before using them in IPM schemes. Obviously, recovery rates are essential for the populations affected to come back, and this usually occurs by recolonisation and immigration of individuals from non-affected areas. For example, modelling based on recovery data after dimethoate application to wheat fields [277] demonstrates that a non-target organism that is reduced by only 20% but is unable to recover is likely to be far more at risk from exposure to a pesticide than an organism that is reduced 99% for a short period but has a higher recovery potential.

The above is also relevant to the impact of small residues of those systemic insecticides that have cumulative effects (e.g. neonicotinoids, fipronil and cartap) on aquatic ecosystems. Because of the short life-cycle of many zooplankton species, the negative population parameters that result from sublethal and chronic effects on such organisms can lead their local populations to extinction [260]. Immediate reductions in populations and species may not always be apparent due to the small residue concentrations and the delayed effects they cause. For example, in recent surveys of pesticide residues in freshwaters of six metropolitan areas of USA, fipronil appears regularly in certain states [254]. Fipronil and its desulfinyl, sulfide, and sulfone degradates were detected at low levels (≤ 0.18–16 μg/L) in estuary waters of Southern California [163], and make some 35% of the residues found in urban waters, with a median level of 0.2-0.44 μg/L, most frequently during the spring-summer season [99]. Imidacloprid was detected in 89% of water samples in agricultural areas of California, with 19% exceeding the US Environmental Protection Agency’s chronic invertebrate Aquatic Life Benchmark of 1.05 μg/L [261]. In the Netherlands, imidacloprid appeared in measurable quantities in 30% of the 4,852 water samples collected between 1998 and 2007 [287]. These figures indicate there is already a widespread contamination of waterways and estuaries with persistent systemic insecticides.

The first consequence of such contamination is the progressive reduction, and possible elimination, of entire populations of aquatic arthropods from the affected areas. As time is a critical variable in this type of assessment, it is envisaged that should this contamination continue at the current pace over the years to come the biodiversity and functionality of many aquatic ecosystems will be seriously compromised [191]. Secondly, as these organisms are a primary food source of a large number of vertebrates (e.g. fish, frogs and birds), the depletion of their main food resource will inevitably have indirect impacts on the animal populations that depend on them for their own survival. The case of the partridge in England is an example of how a combination of herbicides and insecticides can bring the demise
of a non-target species by indirectly suppressing its food requirements [217]. Therefore, warnings about the possible role of environmental contamination with neonicotinoids in steeply declining populations of birds, frogs, hedgehogs, bats and other insectivorous animals are not far fetched and should be taken seriously [275].

6. Conclusions

This review has brought some light on the direct, sublethal and indirect effects that systemic insecticides have on species populations and ecosystems. Some long-term impacts have been known for some time (e.g. carbofuran, phorate), but it is the rapid increase in the usage of neonicotinoids and other systemic products that poses a new challenge to the ecological risk assessment of agrochemicals. Indeed, current risk protocols, based on acute, short-term toxic effects are inadequate to cope with the chronic exposure and cumulative, delayed impacts of the new compounds. Awareness of the increasing contamination of the environment with active residues of these chemicals should help regulators and managers to implement new approaches for risk assessment of these substances.

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