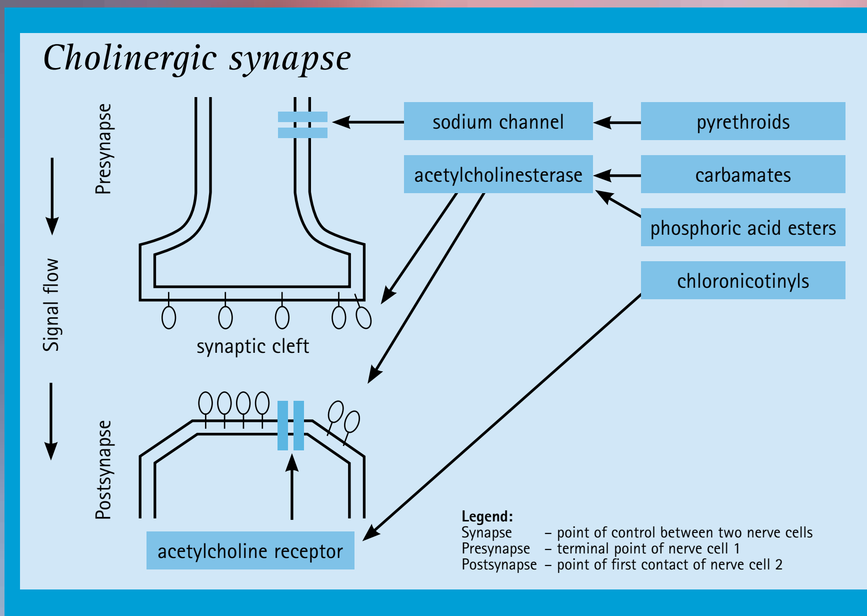
Synapses transmit electrical signals from one nerve cell to the next. When an electrical signal reaches a synapse, it triggers the release of chemicals called neurotransmitters (red) from vesicles in the terminal swelling of the presynaptic cell. The vesicles burst through the membrane, and the neurotransmitters cross a microscopic gap called the synaptic cleft, and bind to the receptor nerve cell. The neurotransmitter changes the permeability of the postsynaptic membrane, causing it to propagate an electrical impulse.



The differences of the modes of action

How **insecticides** work

Outbreaks of pest insects continue to affect agricultural crops such as oilseed rape, potato and cereals, often causing serious harvest losses. Achieving the optimal level of control through careful timing of applications is becoming more difficult, because the activity of some insecticides is being lost to resistance. But this problem can be countered if the entire product portfolio is brought into play.

Most insecticides interfere with the nervous systems of insects by inhibiting or blocking enzymes. They act against the adult insects, or against their various developmental stages (from egg to larva). The best-known active substances belong to the pyrethroid and nicotinoid group of substances.

Insecticides can enter the pest's body in a variety of ways: as an ingested, contact or inhaled poison. Some are actively taken up by the insect in food, entering its tissues via the gastrointestinal tract; others penetrate as a vapour, via the breathing holes (spiracles); contact insecticides are simply absorbed as soon as the insect touches treated surfaces with its antennae, cuticle, proboscis or legs). Systemic active substances are initially taken up by the plant: activity against insects then follows as the result of their sucking or feeding activities. Pests that live inside the plant are also killed off. Some insecticides are specifically active against the eggs and larvae of certain insects.

A simple classification of substances according to the mode of uptake into the insect – ingestion, inhalation or contact – is difficult, if not impossible, for modern insecticides. Rather, a distinction is made between the major chemical groups of substances:

- organophosphorus compounds (e.g. chlorpyrifos and parathion),
- natural and synthetic pyrethroids (deltamethrin, beta-cyfluthrin, lambda cyhalothrin, tau-fluvalinate),
- carbamates (methiocarb, pirimicarb),
- neonicotinoids (imidacloprid, thiacloprid)
- pymetrozines
- flonicamide
- oxadiazines

Insecticides with only local activity must arrive directly where the pest is located, or they must be distributed very evenly over the plant surfaces from which the pest is likely to take them up. Many insecticides have a good penetrative activity: they enter into leaf tissues, thus reaching even individuals hidden within the leaf tissues (e.g. the maggot of the beet fly) or those situated on the lower leaf surface. Examples of insecticides with predominantly local activity can be found among the phosphoric acid esters and the carbamates.

Systemically-acting insecticides are taken up by plants relatively quickly via the roots or above-ground parts, and are then transported and re-distributed within the vascular system. They can also move between cells by diffusion. The subsequent duration of action and speed of breakdown of an active substance depends on environmental conditions. Insecticidal active substances applied as a layer in a seed coating acts as a depot, providing sustained protection for the seed.

Pyrethrum is obtained from the flowers of Chrysanthemum species. Chemically, it is a mixture of six different esters, the main component among which is pyrethrin I. Pyrethrum is a contact poison and entering the insect's body e.g. via the spiracles, after which a rapid enzymatic detoxification of this substance occurs.

Synthetic pyrethroids are among the most effective insecticides available. In order to obviate the disadvantages of natural pyrethrum (i.e. low light stability and high production costs), these substances were chemically synthesized and modified. Synthetic pyrethroids act as contact- and ingested toxins, but they are not inhaled toxins, because their vapour pressure is too low.

There are two types of pyrethroids that differ simply by a C-N bond. Type I lacks a C-N bond. In contrast, in Type II, this bond is built into the chemical backbone in order to strengthen the activity. There are also overlaps between the two types I and II.

Fiproles are insecticides that act on the chloride channels of nerve cells. Examples include the phenylpyrazoles (e.g. fipronil) and cyclodienes/polychlorocycloalkanes.

Organophosphates and carbamates are insecticides that affect the messenger molecules which travel between nerve

The majority of insecticides used around the world are active against various different targets in the insect nervous system. The most common target is the cholinergic synapse (see the much simplified representation).
In insects, acetylcholine is the most important among the neurotransmitters active in signal transmission.
Although chloronicotinyls are among the insecticides that target the insect nervous system, their molecular mode of action is more insect-specific than those of other substances, meaning that they are correspondingly less toxic to humans.

cells: they induce a constant stimulation of downstream cells.

Organophosphates are predominantly ingested and contact poisons. But their high vapour pressures mean that these substances can also be toxic by inhalation (e.g. dichlorvos). Most insecticides of the **carbamate** group are also contact and ingestion poisons, but in contrast to the organophosphates, they possess enzyme-inhibiting properties.

Neonicotinoids: examples of active substances belonging to this group include thiacloprid and imidacloprid. They act on the central nervous system of insects and block enzymes involved in the transmission of nerve signals. No cross-resistance to carbamates, organophosphates or synthetic pyrethroids is recorded.

Portfolio of active substances for agriculture

Various other modes of action exist beyond those listed above. For example energy blockers, which influence energy production in many types of cells, rather than affecting nerve cells specifically. Insect growth regulators (IGR) act against the larval stage by interfering with certain insect biochemical growth processes, such as larval and pupal ecdysis (molting) and the transition between different developmental stages. Chitin synthesis inhibitors disrupt the development of the outer cuticle by suppressing chitin production. In the course of their development, insects must exchange their chitin covering several times. After taking up the active substance, the insect larvae at first continue to behave normally. Only when the next molt takes place does the newly-developed cuticle burst, because no chitin has been deposited, and the cuticle's stability is thus lost. The first larval stage is particularly sensitive to this effect.

If you consider the number of insecticides that are currently registered, you will gain the impression of a broad palette of active substances, and you might assume that many different chemical groups with a range of modes of action are present on the market. If this were true, then there would be no difficulty in following flexible resistance management programmes. New insecticides with different target sites in the insect's body have indeed been developed and registered. But a more detailed analysis is necessary – you have to consider the individual indications and biological demands made of the products too.

In practice, only two groups of active substances provide the mainstay of agricultural needs: pyrethroids and neonicotinoids. Substances from these groups are generally broad-spectrum, so they can be widely used against a broad range of pests. Pyrethroids are present on the market almost exclusively in the form of sprayed products. In contrast, neonicotinoids have been used for many years in seed treatment products (e.g. imidacloprid). Nowadays, there are very few insecticidal seed treatment products that do not contain active substances from this chemical group; neonicotinoids are also receiving increasing numbers of registrations for spray applications.

As target beetle species develop stronger resistance to pyrethroids, more and more alternative neonicotinoid-based products tend to be brought in to control them. The selection pressure on this group of substances increases correspondingly. The product palette for controlling the Colorado beetle has recently been extended to include the non-neonicotinoid active substance metaflumizone, meaning that six different chemical modes of action are now available (along with the biological control products based on *Bacillus thuringiensis* and neem).

Besides broad-spectrum insecticides such as Biscaya®, selectively-acting products are available for controlling aphids and the Colorado beetle. These are based on active substances from other chemical groups that do not show any known cross-resistance to pyrethroids and neonicotinoids. These special products should be used in alternation with other groups of active substance.

Resistance development

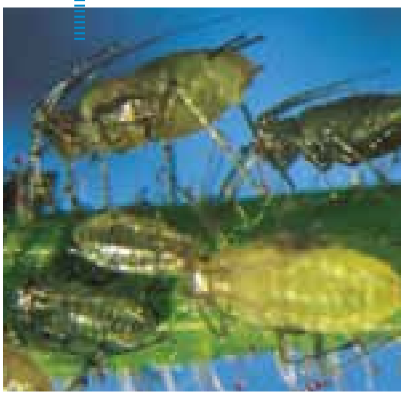
Every population of pest insects contains individuals that vary in their sensitivity to xenobiotics. Only when an insecticide is used repeatedly does the selection pressure rise - and the more rapid the reproduction rate of the insect, the quicker the population becomes adapted in response. The following factors play a role in the development and spread of resistance:

- the number of applications of insecticides sharing the same target site or mode of action;
- amount of active substance applied
- application conditions
- pest developmental stage
- environmental conditions, etc.

Repeated use of products based on the same mode of action is particularly favourable for resistance development. And this is exactly what has been happening in recent years because of the limited choice of substances available: situations of severe selection pressure have arisen over and over again. For example, in some mid-European regions where growers of oilseed rape only had products available that were based predominantly on the pyrethroid group and the number of applications within a season was also high (pollen beetles are usually present in the crop at all spring spray timings), the proportion of resistant individuals within the population

Pollen beetle (Meligethes aeneus)

Rose-grain aphid (Metopolophium dirhodum)



Testing the activity of insecticides in the glasshouse.

Target-site classification of insecticides used in agriculture

Carbamates	Organophosphates	Pyrethroids	Neonicotinoids	Pymetrozines Flonicamide	Oxadiazines Semicarbazone	
Pirimor	*Perfektion* *Pyrinex* *Reldan 22*	*Bulldock* *Decis flüssig* *Fastac* *Fury* *Karate Zeon Mavrik* *Sumicidin* *Talstar* *Trebon*	*Actara* *Biscaya* *Cruiser 350 FS* *Dantop* *Monceren* *Poncho*	*Plenum*	*Alverde* *Steward*	
1A*	**1B***	**3***	**4***	**BB, BC***	**22A, 22B***	**(*IRAC-groups)**
Inhibition of cholinesterase-activity	*Inhibition of acetylcholine-cholinesterase-activity*	*Blockage of sodium channels*	*Blockage of acetylcholine-receptors*	*Blockage of sucking ability*	*Blockage of sodium channels*	

increased markedly. Nearly all types of pest insects are capable of this type of loss of sensitivity if they are exposed to repeated insecticide treatments. Moreover, the mobility of insects means that resistance can spread rapidly over large areas.

Discussions of resistance development as the result of insecticide applications often fail to consider temporal and spatial aspects. The rotations used in various situations can mean that pests are indeed exposed successively to the same groups of active substances: for example, neonicotinoids are applied to control aphids both as a seed-treatment in sugar beet and as spray-applications or seed-treatments in potato crops. Oilseed rape, which is also seed-treated with the same active substances, might also be grown in the same region, exposing the insects further. This results in selection pressure towards neonicotinoid resistance, for example in the green peach aphid. In the meantime, the virus problem means that grain aphids are coming into contact more with these substances because of the higher proportion of seeds receiving treatment. Selection can also occur if aphids on volunteer cereals growing in oilseed rape are caught by insecticide sprays applied to the rape crop. A similar situation occurs when, for example, pollen beetles present in flowering potato crops come into contact with the insecticides applied to them. Thus in designing insecticide programmes, careful consideration should be made of which insecticidal active substances are due to be applied on the farm, and the circumstances of each application.

Managing resistance

In order to delay or at best to prevent the development of resistance, so-called resistance management strategies are needed that ensure that an alternation of insecticides takes place, bearing in mind the need to use active substances with different modes of action. As nearly all pyrethroids share the same mode-of-action, it doesn't make sense simply to alternate between different pyrethroid products within a spray programme. Successive sprays need to be made with the full use of available products with different modes of action. For example, pyrethroids, organophosphates and neonicotinoids all have different modes of action. These three chemical classes are all different, and even if resistance arises to one class, the other two should continue to be effective. In other words, insecticides belonging to these separate classes do not show cross-resistance with each other. ◀