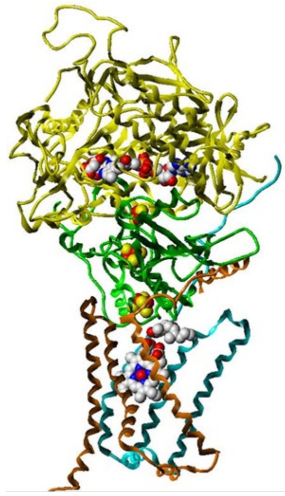
Mode of action explained

What does it mean when it comes to pesticides?



Definition: what do we mean by "mode of action"?

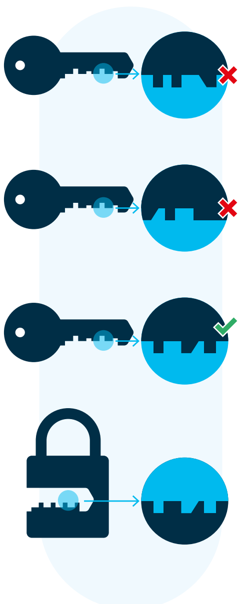
// In general, "mode of action" describes a series of key events that takes place at the **cellular or molecular level** after a living organism is exposed to a substance. These events can lead to **functional or anatomical change** in the cells.

// However, it takes a lot more than this change at the molecular or cellular level before an effect upon an organ, or indeed the entire organism, can occur.

Mode of action: what happens at the molecular level?

At the molecular level, there needs to be an interaction between a molecule of the substance (i.e. a molecule of the pesticide) and a specific molecular target in the organism. Broadly speaking, a molecular target can be a receptor or an enzyme that responds to the interaction with the substance.

How does this interaction happen? We can consider it as something like a key fitting into a lock. The molecular target has a binding site – this the "lock". Part of the pesticide molecule – the "key" – needs to fit into that site and successfully bind to it in order to trigger a response. When this binding happens, it is known as the "molecular initiating event".

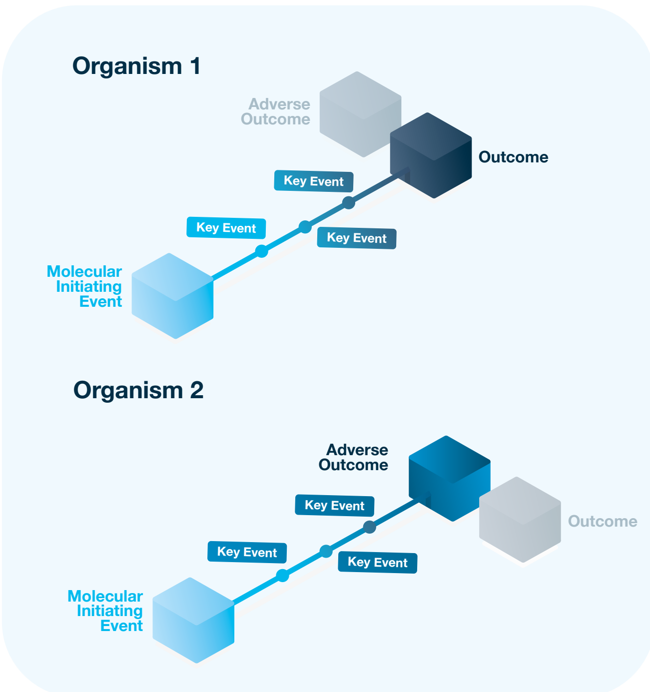


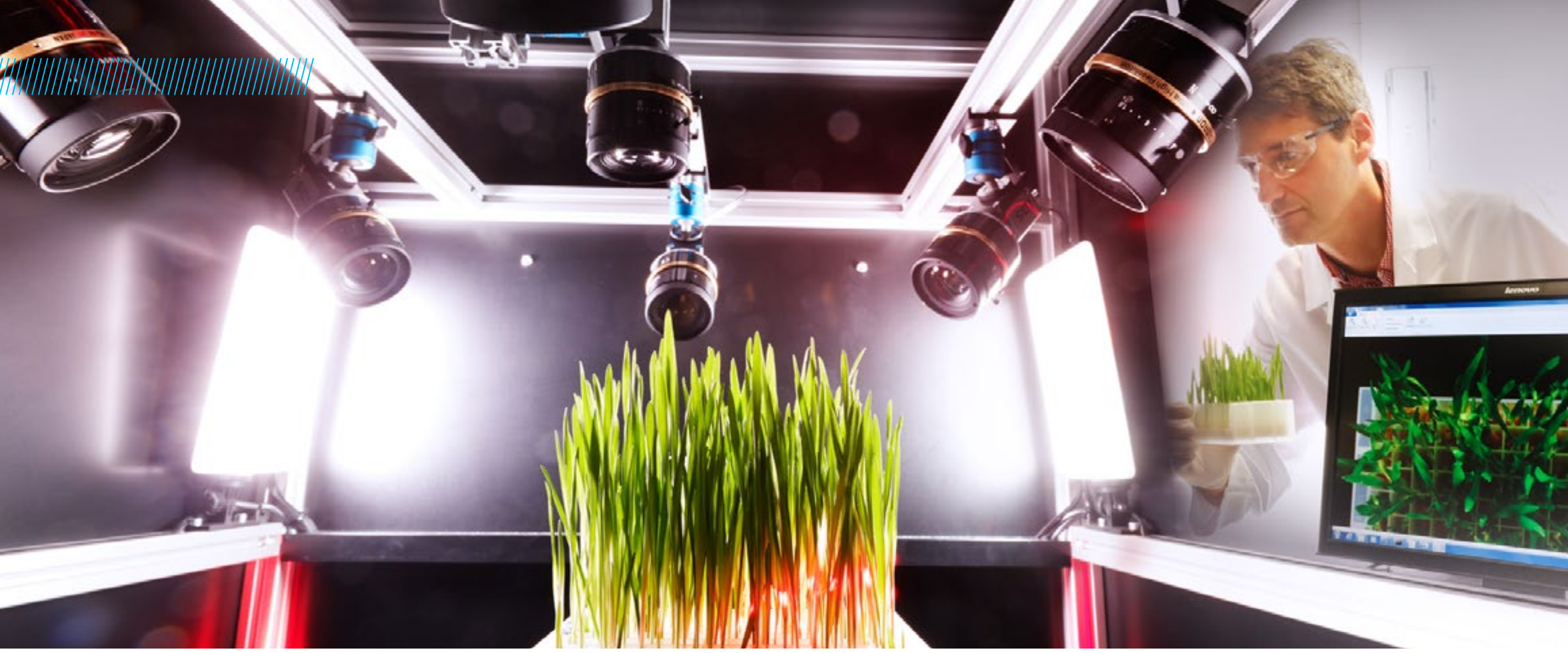
Only once the molecular initiating event has taken place (i.e. if the "key" fits into the "lock") can a response be initiated. However, this response and resulting effect or outcome will not be the same for every organism – even if the mode of action is similar or the same.

Why does the same mode of action not lead to the same outcome for every organism?

Not every substance will bind to the molecular target and when there is interaction, this does not happen the same way for every organism: just as a hotel will have a master key which opens the door to every guest room, while other keys will only open one specific door. Of course, if a substance does not bind at all, we cannot talk about mode of action. For example, if you stay in the car park in front of the hotel you will never unlock the door to your room.

When a substance successfully binds to a molecular target and initiates a response, this can potentially set off a chain of other events which can lead to many different outcomes, depending on many other factors along the way. Some of these outcomes can be adverse – and that is why it is essential that we understand the pathway that leads from the molecular initiating event to the possible adverse outcome(s).





Harnessing adverse outcomes to inform pesticide development

Scientists develop pesticides – also called plant protection products – to help farmers defend their crops against harmful pests, diseases or weeds. These harmful pests, diseases and weeds are known as "target species".

During research and development of plant protection products, a particular mode of action may be investigated because we know that it has the potential to trigger a chain of events that leads to adverse consequences in specific groups of organisms. Scientists explore these adverse consequences to identify how they can be harnessed and used against the target species.

Long, extensive research programs are carried out to discover a particular substance that, when used in a particular way, at a particular dose, will cause these adverse consequences only in the target species – and not in non-target organisms, such as humans or bees. In this way, scientists strive to develop substances which are specific and "selective" – meaning that they have special characteristics ensuring their activity is carefully targeted.

After this, scientists must then perform another vast array of tests to demonstrate to the authorities that products containing this substance are safe for humans and the environment when used correctly. In addition, a set of label instructions are written, and these must be followed so that the product can be used safely and effectively.

Only when the authorities are completely satisfied can the product be sold on the market to help farmers protect their crops from damaging pests, diseases and weeds.

In summary

// Many factors influence the effect that an active substance could have on an organism; mode of action is **only one piece of the puzzle.**

// Even if two separate substances have the same mode of action, the outcome or effect is not necessarily the same in different organisms or in different life-stages of the same organism. This is because a very **specific chain of sensitive events** needs to be triggered before a certain outcome will occur. A substance must be potent enough and present in sufficient quantity (dose) to exert its effect.

// Scientists conduct in-depth research on adverse outcome pathways to develop plant protection products which are selective. This means that a product's activity is carefully targeted to ensure that when used correctly, it only **works against the target species,** and not against any other organism.

Analogy: mode of action as a journey with differing outcomes

We can compare mode of action – and how it does not lead to the same outcome in every organism – with taking a car journey. We can consider that cars share a common mode of action as they are all designed to travel. Yet, how far or fast you will manage to travel depends on a series of other factors, regardless of this common mode of action.

In this analogy, we can consider that the intended outcome of your journey is to arrive on time for a job interview. To achieve this outcome, a specific chain of events needs to happen so that your drive goes smoothly and that you reach your intended destination as planned. Similarly, a series of conditions need to be met in order for a substance to have a specific final effect on an organism. Let's take a look at the factors that can impact the outcomes in each scenario.

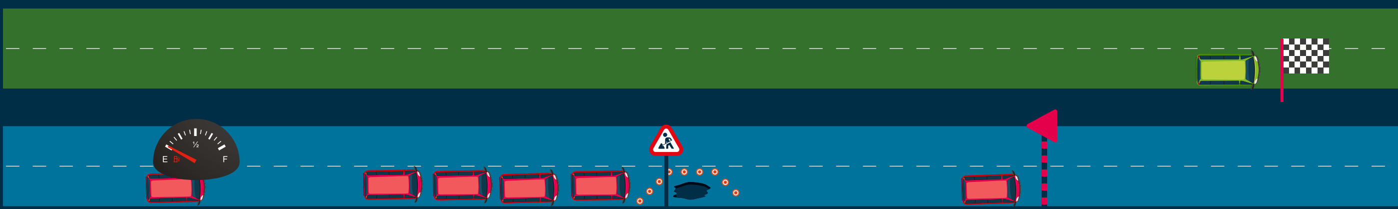
// If you do not have the correct car key, it will not fit in the ignition and you will not be able to start the engine. Your journey does not begin. → We can compare this to when the pesticide molecule does not "fit" and cannot bind to the target site in the organism. In this case there is no molecular initiating event, meaning that no response can be triggered, so the pesticide does not have an effect on the organism.

// If you have the correct car key and you turn it in the ignition, you can successfully start the car's engine. Your journey can begin. → We can compare this to the molecular initiating event, when the pesticide molecule "fits" and binds to the target site, allowing a response to be triggered.

However, simply starting the car is just one part of the journey: it still does not guarantee that you will end up at your intended destination on time. The drive itself and the destination can be influenced by many other events – just as many events beyond the molecular initiating event can influence the effect of a pesticide on an organism. During the journey you may need to refuel, take a break, pull over to check directions – we can consider these as key events along the way. For example:

// You do not have enough of the right fuel in sufficient quantities for the distance to travel, so your journey ends before you reach your a petrol station and therefore you do not reach your intended destination. → We can consider this as the organism being exposed to a dose of the substance which is too low to have any effect on its cells.

// You find roadworks on your route, so you get stuck and are forced to slow down, meaning you cannot reach your destination in time. → We can consider this as similar to the organism's metabolism kicking in to break down the substance very quickly. This causes a "diversion" from the next key event, so the intended outcome is not achieved.



In short, many factors can influence a car's journey and affect its destination, regardless of the fact that all cars are designed to travel. In a similar way, substances with a similar or common mode of action will not always lead to the same outcome in every organism or every circumstance. That is why scientists carry out in-depth research into the adverse outcome pathways, ensuring that they develop specific, selective plant protection products which are safe for non-target organisms when used correctly.