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Pesticide Mode of Action Classification: Understanding Resistance Action Committees (RACs)[1]

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This publication defines the concept of a pesticide mode of action and provides several examples. It emphasizes the importance of identifying and differentiating modes of action for pesticide resistance management and defines the development and goals of the three resistance action committees for insecticides (IRAC), herbicides (HRAC), and fungicides (FRAC). It describes each group's pesticide mode of action classification scheme. Finally, it provides an example of a pesticide label and instructions for applicators on how to use mode of action classification schemes for pesticide rotation and resistance management.

Pesticides

According to the Environmental Protection Agency (EPA), "A pesticide is any substance or mixture of substances intended for preventing, destroying, repelling or mitigating any pest; Use as a plant regulator, defoliant, or desiccant; or use as a nitrogen stabilizer." Pesticides are composed of both active and inert ingredients. Active ingredients are the components of a pesticide that directly destroy, repel, or desiccate the pest. Active ingredients are described by the types of pests they target. For example, insecticides target insects, herbicides target plants, and fungicides target fungi. The inert ingredients do not have pesticidal activity but are important for things such as shelf life and usability. Before registration, each pesticide is assessed based on its identity, composition, potential adverse effects, and environmental fate. All ingredients (active and inert) and the pesticide's ultimate formulations are evaluated thoroughly by the EPA. Basic information about pesticides and their ingredients can be found in this EPA publication: https://www.epa.gov/ingredients-used-pesticide-products/basic-information-about-pesticide-ingredients.

What is a mode of action?

The "mode of action" (MoA) is how, on a molecular and physiological level, the active ingredient kills the pest. Therefore, the active ingredient and MoA are not the same thing. For example, permethrin is an active ingredient in some insecticides. This means that permethrin is the component of the pesticide formula that kills the target insect. Inside the insect, permethrin works by closing the insect's voltage-gated sodium channels. This is the MoA, or how it works. To remember this, think of the active ingredient as *what* kills the pest and the MoA as *how* the pest is killed. Another example is the active ingredient glyphosate which is widely used in herbicides. Glyphosate is what kills the plant. How glyphosate kills the plant is its MoA. It blocks amino acid synthesis in plants by binding to the plant enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSP). Without this enzyme, three of the plant's essential amino acids are blocked. Without these essential amino acids, the plant can no longer function properly and eventually dies.

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Pesticide Resistance

Resistance to pesticides was first noted in 1914 with insecticide resistance appearing in scale insects (Melander 1914). Pesticide resistance is not a new problem but continues to be a very serious one. According to the IRAC, pesticide resistance is a heritable change in the sensitivity of a pest population to a product used at the label-recommended rate for that species. This change is noted when the product doesn't achieve the anticipated level of control. Resistance to pesticides is most likely to develop when pest populations are exposed repeatedly to products with the same MoA. This is in part because nature is always producing variation, or mutations, in individuals.

Occasionally, a mutation that naturally occurs in an individual allows it to survive a pesticide application (Figure 1A). When this happens, that survivor may reproduce and pass on its mutation, adding more resistant individuals to the population (Figure 1B). If the same MoA is used repeatedly, the cycle will continue, and the population will eventually be composed of more resistant individuals than susceptible individuals (Figure 1C).

These mutations can allow a population to survive in a few ways. The weed goosegrass, *Eleusine indica*, for example, has a mutation in which the shape of the EPSP enzyme is changed in a way that greatly reduces the binding of glyphosate in the enzyme. The reduction of bound glyphosate allows the enzyme to bind to the normal substrates in the plant and function properly. Another plant, Palmer amaranth, *Amaranthus palmeri,* has a mutation that results in an overproduction of the EPSP enzyme. Palmer amaranth produces so much EPSP enzyme that even with glyphosate binding, enough unbound enzyme allows the plant to function properly.

The most obvious tool available to avoid pesticide resistance is to avoid using the same MoA repeatedly without some alternative control strategy. In the example below, if the surviving "resistant" individuals were controlled with some alternative strategy, that resistant trait would fail to thrive in the population. Using another pest control strategy, such as mechanical control, biological control, or any of the other strategies of a robust integrated pest management program will help to prevent populations from becoming resistant. Additionally, the use of a different MoA, one that targets a different life process, would also prevent the "resistant" trait from thriving. Being able to quickly identify alternate strategies and alternate MoAs is essential to resistance management.

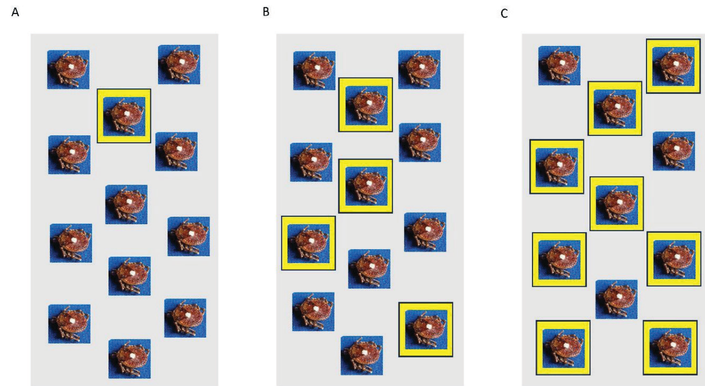

Figure 1. A) In this figure an individual has arisen with a natural mutation. It is represented by the image of the tick with the yellow frame and black border. Most of the population is made of susceptible individuals (ticks without frames and borders). B) The resistant and susceptible individuals reproduce, resulting in a mixed population. C) If the same MoA is used for management, the number of resistant individuals increases compared to the number of susceptible individuals, resulting in a population of mostly resistant individuals.
Credits: Tyler Jones and Emily Kraus, UF/IFAS

Resistance Action Committees

There are several organizations that have been formed to assist pesticide applicators to prevent the development of pesticide resistance, or resistance management. They are the Fungicide Resistance Action Committee (FRAC), the Herbicide Resistance Action Committee (HRAC), and the Insecticide Resistance Action Committee (IRAC). Each of these organizations is administered by CropLife International, an organization whose goal is to protect crop yields and quality by supporting pesticide resistance management offices around the world. CropLife International has developed an MoA classification scheme as a key part of their global resistance management strategy. The goal is to encourage pesticide applicators to use this classification scheme and rotate MoAs to prevent the development of resistance. In addition to educating users about the various MoAs, resistance action committees offer alternative control strategies to further reduce the selection pressure associated with repeated applications of the same pesticide.

MoA Group Classification

This classification scheme involves the designation of MoA groups, chemical classes, and active ingredients (Figure 2A, 2B, 2C, Table 1). As stated above, the MoA groups are based on how the active ingredient affects the target organism and the physiological or molecular site. The MoA is represented by a group number. For example, HRAC classifies the inhibition of cellulose synthesis as group 29 (Figure 2B, Table 1). This MoA group includes the chemical classes alkylazines and nitriles. The chemical class includes active ingredients with similar molecular structures. In this case, indaziflam and triaziflam have similar structures and are in the chemical class alkylazines (Figure 2B, Table 1). Each numbering system is unique to the resistance action committee. For example, a group 5 in HRAC has no relation at all to a group 5 in IRAC. There are some small differences between the MoA schemes of each of the RACs because the chemistries of insecticides, herbicides, and fungicides differ from one another. HRAC had been using letters but has recently moved to a system using numbers like IRAC and FRAC. HRAC has indicated that there are some active herbicide ingredients that are not currently assigned to a chemical class. These are indicated with a white background (Figure 2B). FRAC has some slight differences as well due to the unique physiology of fungi. Detailed information on fungicides and FRAC can be found in the publication "Fungicide Resistance Action Committee's Classification Scheme of Fungicides According to Mode of Action." FRAC has also indicated that there are some active ingredients in fungicides that are not currently assigned to a chemical class. Like HRAC, FRAC uses a white background for unassigned active ingredients (Figure 2B).

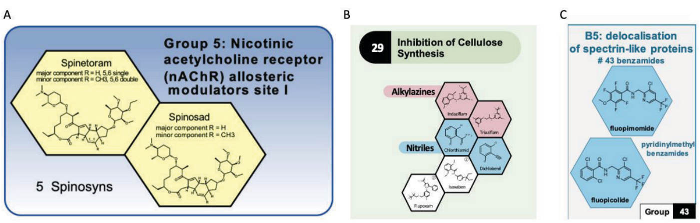

Figure 2. A) IRAC MoA group 5. B) HRAC MoA group 29. C) FRAC MoA group 43. The images that were used to create this figure came from the IRAC, HRAC, and FRAC brochures and posters (Linked in Additional Resources).

MoA Groups and Pesticide Labels

Using this information for resistance management is easy! Find the MoA group number on the pesticide label. An example of a label is below with the group number inside the yellow box (Figure 3). If an applicator was using this product for insect management, they would see the label showing MoA Group 6. For subsequent applications, the applicator should consider products that would be effective in this situation (to be able to control the target pest) with any other MoA group number besides 6 (ex: 3, 5, 9) or combinations of those numbers. Some products have multiple ingredients that fall into different MoA groups. If such a product was used and it included both groups 3 and 4, it would be ideally followed with products that do not have either MoA Groups 3 or 4. The numbering system for FRAC, HRAC, and IRAC make keeping track of what was used very easy.

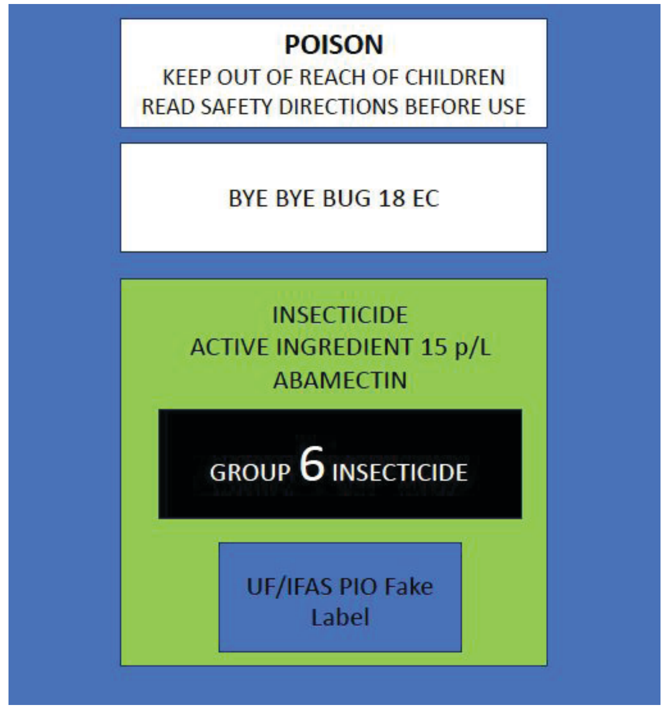

Figure 3. This is an imitation pesticide label with the IRAC MoA indicated on the black square. An applicator should note it is MoA Group 6. To practice good resistance management, future applications would use products with any group other than 6.

Conclusion

Pesticide resistance management is vital to the protection of chemistries used in pest control. There are currently resistant populations of pests in essentially every aspect of the pest control industry. It is imperative applicators are educated and assisted on product stewardship. This education begins with understanding pesticide resistance, modes of action, and the importance of rotation. A particular point of confusion has been differentiating between active ingredients and modes of action. Extension professionals and educators should place an additional effort into clarifying these points as we attempted to do in this publication here. IRAC, HRAC, and FRAC have a variety of resources including posters, brochures, and videos to assist with pesticide resistance management.

Additional Resources

HRAC Mode of Action Classification 2022 https://hrac-global.com/files/HRAC_MOA_Poster_January_6_2022.pdf

FRAC Classification of Fungicides

https://www.frac.info/

A World Without Pesticides

https://blogs.ifas.ufl.edu/pesticideinformation/2022/04/14/a-world-without-pesticides/

The EPA's pesticides page

https://www.epa.gov/pesticides

Reference

Melander, A. L. 1914. "Can insects become resistant to sprays?" *Journal of Economic Entomology* 7:167–173. https://doi.org/10.1093/jee/7.2.167

Table 1. The mode of action (MoA) scheme for the three pesticides portrayed in Figure 2 is repeated here in table form to further clarify the MoA, groups, chemical classes, and active ingredients.

Pesticide Type	Mode of Action	Group	Chemical Class(es)	Active Ingredients	Figure
Insecticide	Nicotinic acetylcholine receptor (nAChR) allosteric modulators –site 1	5	Spinosyns	Spinosad, Spinetoram	2A
Herbicide	Inhibition of Cellulose Synthesis	29	Alkylazines, Nitriles	Indazilflam, Triaziflam, Chlorthiamide, Dichlobenil, Isaxaben, Flupoxam	2B
Fungicide	Delocalisation of spectrin-like proteins	43	Pyridinylmethyl benzamides	Flupimomide, flupicolide	2C