VLCFA-inhibitors (HRAC Group 15)

Working Group Update - July 2025

Roland Beffa (Independent Scientist), **Laurent Cornette** (Gowan), **Gael Le Goupil** (Syngenta), **Mike Grenier** (Gowan), **Bianca Martins** (Bayer**), Ricardo Pavon** (UPL), and **Atul Puri** (FMC)

Group 15 results from the merger in 2020 of legacy groups N and K3. All Group 15 herbicides share the same MoA in the target plants: they inhibit the synthesis of the Very Long Chain Fatty Acids (VLCFAs) by interfering with the elongation process in the Endoplasmic Reticulum.

VLCFAs are fatty acids with an acyl chain of 18 carbons and longer. The chain length, degree of unsaturation, type of polar head and associated lipids provide the structural and functional diversity of fatty acids. In plants, VLCFAs are found in triacylglycerols as seed storage lipids, they are involved as membrane constituents and signalling molecules in sphingolipids and phospholipids and they are necessary for the production of cuticular waxes and suberin, two extracellular biopolymers preventing plants from desiccation or external aggressions (*Bach 2010*).

Their elongation uses palmitic acid (C16) and stearic acid (C18) as precursors after they migrate from the chloroplast to the endoplasmic reticulum (*Tanetani 2009*). VLCFAs are synthesized by the sequential addition of two carbons through four successive enzymatic reactions within a protein complex named the elongase. Several elongase systems must exist in a given plant. For example the *Arabidopsis* genome contains 21 genes coding for elongases (*Krähmer 2019*), sorghum has got 25, peanut 30 and cotton 58 (*Batsale 2023*). This provides a high diversity of binding sites for Group 15 herbicides.

Trenkamp 2004 reported that each of the 6 elongases she tested was inhibited by several herbicides, thereby revealing its individual pattern of active inhibitors. Conversely, some compounds inhibited a spectrum of several elongases. For example, flufenacet and cafenstrole inhibited all elongase activities tested but inhibition was observed only with former class K3 herbicides while none of the class N herbicides inhibited elongase activities.

Little is known on the exact site of action of Group 15 herbicides. Though they show similar physiological effect, they may inhibit different elongases and/or involve different binding sites in the elongase complex. These elongases being essential, it could explain why there has not been any report of target-site resistance (TSR) to group 15 herbicides, so far, despite some of them having been used for more than 50 year. Indeed, all cases of resistance reported to date involve either enhanced metabolism or reduced metabolism and are thus considered non-target site resistances (NTSR)*. See table below from weedscience.org.

Further investigations are going on under HRAC's Working Group 15's supervision in order to identify which of the VLCFA inhibitors act on elongases and which of them act elsewhere. This work could lead to a future split of the group between two different modes of action (MoAs).

In conclusion, Group 15 herbicides are suspected to target a multi-enzyme process and therefore are less prone to evolve TSR. Unlike other HRAC groups that are often defined by a very precise site of action (an enzyme or a specific site of an enzyme), the definition of the MoA of Group 15 herbicides is very broad. They basically show similar physiological effect but are thought to act on a diversity of sites of action which still need to be precisely identified.

For all the reasons mentioned above, VLCFA inhibitors represent a rather unique group and recommendations on how to use them in programs may differ from other groups. In fact, they can play a crucial role in herbicide programs by preventing the development of resistance to other mode of action herbicides.

HRAC acknowledges that VLCFA inhibitors are a very important tool in the management of herbicide resistance risk. Consequently, HRAC supports combinations or sequences of products containing active ingredients from the former HRAC Groups N and K3 (all belonging to new Group 15) as per the attached position paper published in 2021.

* NTSR is so far the main mechanism of resistance affecting VLCFA inhibitors. This is a non-specific mechanism of resistance that cannot be prevented through the usual HRAC recommendations of use but is less prone to evolve.

Bibliography

Bach L and Faure J-D. (2010). Role of VLCFAs in plant development, when chain length does matter. C.R. Biologies, 333. 361-370.

Batsale M at al. (2023). Tackling functional redundancy of Arabidopsis fatty acid elongase complexes. Frontiers in Plant Science, Jan 2023, pp 14.

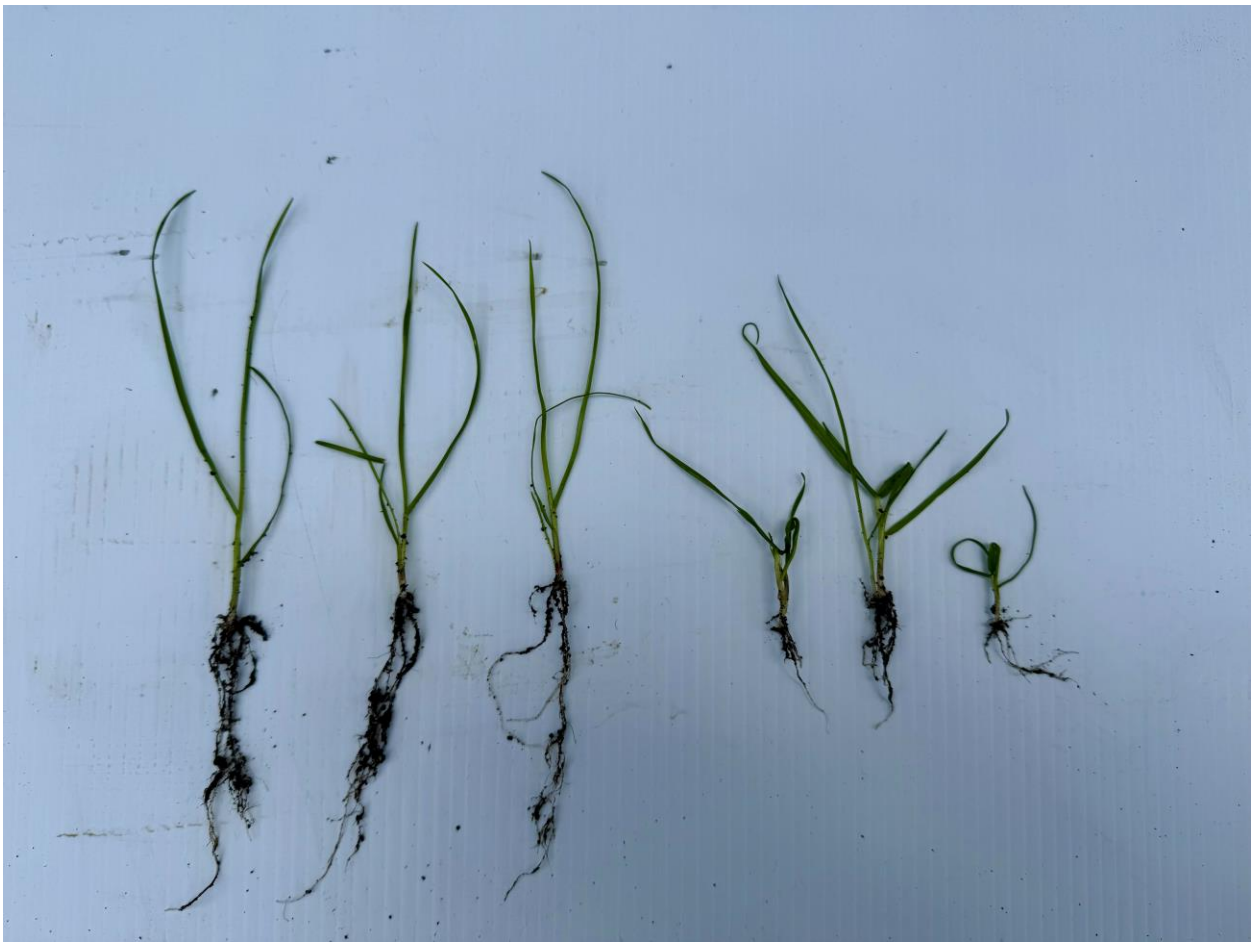
Krähmer at al. (2019). Inhibitors of the Synthesis of Very-Long-Chain Fatty Acids (VLCFAs). Modern Crop Protection Compounds, Third edition. 351-363.

Tanetani Y. at al. (2009). Action mechanism of a novel herbicide, pyroxasulfone. Pesticide Biochemistry and Physiology, 95. 47-55.

Trenkamp S., Martin W, and Tietjen K. (2004). Specific and differential inhibition of very long chain fatty acid elongases from Arabidopsis thaliana by different herbicides. Proceedings of the National Academy of Sciences, USA 101. 11903- 11908.

Working Group 15

Typical symptoms resulting from Group 15 herbicide treatments

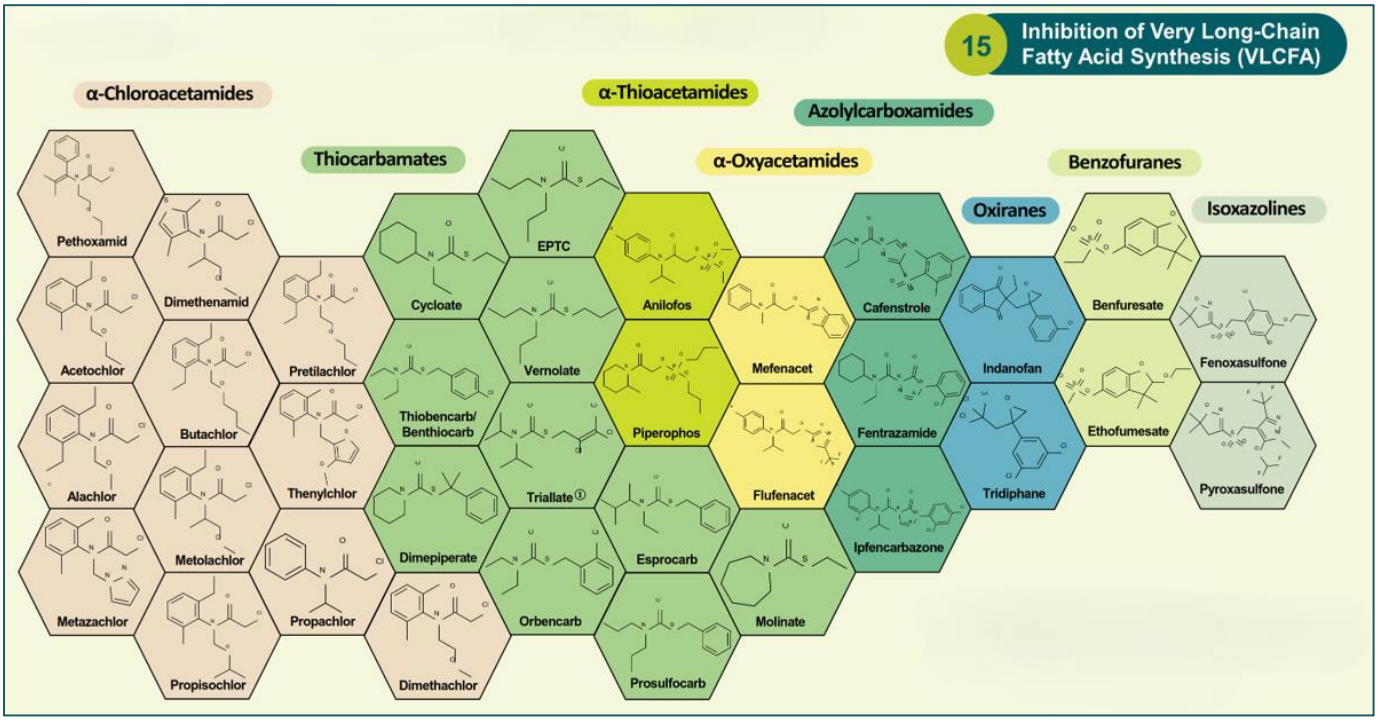


Tri-allate symptoms on *Lolium rigidum* (leaf twisting, thickening of base, enriched green colouration)
The 3 specimen on the left are untreated, the 3 specimen on the right are treated with tri-allate

33 cases of resistance to VLCFAs have been reported along the years, involving 10 weed species, 10 countries and 10 active ingredients. Most cases are unexplained or attributed to non-target site resistance (either enhanced or reduced metabolism) as per the below table from weedscience.org.

#	Species	Year	Country	Resistant to MoAs	Group 15 Actives	Type for MoA 15
1	Alopecurus myosuroides	2007	Germany	1, 2, 5, 15	Flufenacet	Enhanced metabolism
		2011	Sweden	1, 2, 15	Flufenacet, prosulfocarb	Enhanced metabolism
		2020	France	15	Flufenacet, prosulfocarb	Unknown
2	Amaranthus palmeri	2016	USA	2, 3, 9, 14, 15	S-metolachlor	Unknown
		2017	USA	15	S-metolachlor	
3	Amaranthus tuberculatus	2016	USA	15	Acetochlor, Dimethenamid, pyroxasulfone, S-metolachlor,	Enhanced metabolism
4	Avena fatua	1989	Canada	0, 15	Triallate	Elevated level of gibberellins or reduced metabolism or unknown
		1990	USA	0, 15	Triallate	
		1993	USA	0, 15	Triallate	
		1996	Canada	15	Triallate	
		1996	Canada	1, 2, 15	Triallate	
		1997	Canada	15	Triallate	
		1997	Canada	0, 1, 2, 15	Triallate	
		1998	Canada	1, 2, 15	Triallate	
		2015	Canada	1, 2, 14, 15	Pyroxasulfone, triallate	
5	Echinochloa crus-galli var. crus-galli	1993	China	15	Butachlor	Unknown
		1993	China	15	Thiobencarb	
		1998	Thailand	5,15	Butachlor	
		2000	USA	1,15	Molinate, thiobencarb	
		2005	Philippines	5,15	Butachlor	
6	Echinochloa oryzoides	2000	USA	15	Molinate, thiobencarb,	Unknown
7	Echinochloa phyllopogon (=E. oryzicola)	1998	USA	15	Thiobencarb	Unknown
		2000	USA	1,15	Molinate, thiobencarb	
8		2005	USA	1, 2, 15	Flufenacet	Unknown

	Lolium perenne ssp. multiflorum	2018	France	15	Flufenacet	Enhanced metabolism
		2018	UK	15	Flufenacet	Enhanced metabolism
		2018	USA	15	Flufenacet	Enhanced metabolism
		2018	USA	15	Flufenacet	Enhanced metabolism
9	Lolium rigidum	1982	Australia	1, 2, 3, 13, 15, 23	Metolachlor, triallate	Enhanced metabolism
		1984	Australia	15	Metolachlor	Unknown
		2015	Australia	15	Triallate	Unknown
		2015	Australia	15	Triallate	Unknown
10	Poa annua	1994	USA	15	Ethofumesate	Unknown



Global HRAC supports combination or sequence of active ingredients belonging to former Groups N and K3 (new Group 15)

R. Beffa (Bayer Crop Science), **L. Cornette** (Gowan Crop Protection), **G. Le Goupil** (Syngenta), **C.V.S. Rossi** (Corteva Agriscience) and **B. Sievernich** (BASF).

*Written in cooperation with Europe HRAC.

Weed control is an important method of safeguarding the yield and quality of crops. Herbicides provide farmers with an effective and economic weed control tool, which can be integrated with different cultural techniques in a flexible and sustainable way to ensure crop production is optimized. Maintaining the effectiveness of herbicides and reducing the risk of selecting for herbicide resistance requires the implementation of certain strategic elements. One of the most important of these is the careful rotation of herbicides with different modes of action (MoA) against the targeted weeds.

To enable farmers to identify a herbicide's mode of action easily and quickly, HRAC developed a letter-based classification system back in the 1980s. Since then, many new active ingredients, some with new modes of action, have entered the market. Additionally, new research methods have helped to further clarify the precise modes of action of herbicides already on the market. In order to capture all these new developments, in January 2020, following consideration of the latest scientific findings, HRAC updated the mode of action classification scheme, adding new mode of action classes and reviewing the correct positioning of each active ingredient.

Moreover, a transition from the former letter-based system to a new numeric based system was implemented to bypass the limitation in the number of classes set by the letter-based system and to foster use in geographical areas in which the Latin alphabet is not commonly used.

For HRAC group N – "Inhibition of lipid synthesis (not ACCase)" - it turned out that most of its active ingredients needed to be moved into HRAC group 15 (K3; Inhibition of Very Long-Chain Fatty Acid synthesis - VLCFAs) – and class N was deleted. However, in contrast to many other HRAC groups (e.g., 1 (A) – ACCase, 2 (B) – ALS, 6 (G) – EPSP, 27 (F2) – HPPD, etc.), the inhibition of VLCFAs takes place in a multi-enzyme system, which shows a complex pattern of substrate specificity to individual active ingredients. Specific target sites have not yet been identified (4). Indeed, it is believed that **herbicides in HRAC group 15 (K3) might exhibit a multi-site or at least a multi-enzyme mode of action, with several elongases being involved**, and that **there could be significant differences between the herbicides**. Further investigations are required to identify the specific target sites of the different members of group 15 (K3) in more detail. So far, weed resistance to inhibitors of VLCFAs has only rarely been observed and, in most cases, no cross-resistance was reported.

Combinations or sequences of products containing active ingredients from different HRAC groups are part of resistance management recommendations. In line with this advice, it is common practice for European farmers to tank-mix or sequence products of the former HRAC groups N and K3 to control grasses like *Alopecurus spp* or *Lolium spp*. A similar approach to broadleaves weeds (e.g. *Amaranthus* spp) applies to other regions of the World. Such an approach has been in use for years with only few cases of resistance evolving against group 15 inhibitors active on grasses (1, 2 & 3).

Based on this experience and the fact that HRAC group 15 (K3) covers a multi-enzyme mode of action with a complex pattern of substrate specificity, **combinations or sequences of products containing active ingredients from the former HRAC Groups N and K3 (new Group 15) are still supported by HRAC.**

Based on further investigation and their findings a review of HRAC group 15 (K3) might be required.

Bibliography

(1) Dücker R., Parcharidou E., and Beffa R. (2020). Flufenacet activity is affected by GST inhibitors in blackgrass (Alopecurus myosuroides) populations with reduced flufenacet sensitivity and higher expression levels of GSTS. Weed Science, 68 (5). 451-459.
(2) Dücker R. at al. (2019). Enhanced metabolism causes reduced Flufenacet sensitivity in black-grass (Alopecurus myosuroides Huds) field populations. Pest Manag Sci, 75. 2996-3004.
(3) Dücker R. at al. (2019). Glutathione transferase plays a major role in flufenacet resistance of ryegrass (Lolium spp.) field populations. Pest Manag Sci, 75. 3084-3092.
(4) Trentkamp S., Martin W, and Tietjen K. (2004). Specific and differential inhibition of very long chain fatty acid elongases from Arabidopsis thaliana by different herbicides. Proceedings of the National Academy of Sciences, USA 101. 11903- 11908.