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THE RELEVANCE OF SYNTHETIC AUXINS IN EXTENSIVE AGRICULTURE IN EUROPE

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RESUME

Les auxines synthétiques ont été les 1ers herbicides de synthèse sélectifs utilisés en agriculture grâce à des résultats d'essais officiels avec le 2,4-D dès 1945. Depuis, de nombreuses substances ont été découvertes dont 103 matières actives sont aujourd'hui homologuées en Europe (EU P. D., Feb 2019), 15 appartenant au Groupe HRAC O. Ce sont des herbicides dotés d'un excellent mode d'action (MoA) pour lutter entre autres contre les dicotylédones majeures tels que le gaillet, les coquelicots et les chardons. Ceci est particulièrement crucial aujourd'hui alors que le nombre de cas de résistance aux inhibiteurs de l'acétolactate synthéthase (ALS) ne cesse de croître (32% des cas). Le risque de résistance aux auxines synthétiques peut être considéré comme moyen (Moss S., 2018) ou faible (Hugh B., 2007). Ce qui est confirmé par le fait que seuls 7 des 345 cas publiés impliquent ce groupe d'herbicides. Cependant un programme spécifique de lutte intégrée contre les mauvaises herbes, basé sur la rotation des cultures, l'alternance des herbicides avec des modes d'action différents et l'utilisation de pratiques agronomiques non chimiques doit être mis en œuvre pour limiter le développement des populations résistantes dans l'avenir.

Mots clés : auxines synthétiques, herbicides, modes d'action, résistance, lutte intégrée.

ABSTRACT

Synthetic auxins were the first used selective herbicide in agriculture from public testing of 2,4-D in 1945. Several active substances have been discovered since then and there are currently 103 actives approved as herbicide in Europe (EU P. D., Feb 2019). 15 actives belong to the synthetic auxins HRAC O group. These are herbicides with an excellent mode of action (MoA) to control key broadleaf weeds like *Galium aparine, Papaver rhoeas, Cirsium arvense* among others. This is especially relevant now that the level of ALS resistance in becoming a tough issue (32% of cases). Herbicide resistance risk can be consider medium (Moss S., 2018) or low (Hugh B., 2007) in case of synthetic auxins. This is also demonstrated by the fact that only 7 of 345 published cases involved this herbicide group. However, a specific integrated weed management program based on rotation involving crops and herbicides with different MO as well as non-chemical control needs to be implemented to avoid significant issues in the future.

Key words: synthetic auxins, herbicides, modes of action, resistance, integrated weed management.

INTRODUCTION

Weeds started to be an issue from the very beginning of the agricultural era, almost 10.000 B.C. Man understood that yield was higher when he removed non-desired plants from the field. Additionally weeds can affect human activity and reduce his human efficiency like *Ambrosia* spp. causing allergy (Hay 1974).

Several practices were implemented by farmers since then from hand-weeding, tools to destroy or remove weeds and chemical control recently in history. Potential yield losses due to weeds are estimated in 37% and thanks to weed control practices are considered only 8.93% (Oerke, EC. 2006).

Chemical weed control started with the use of inorganic compounds such us sulfuric acid, salts of heavy metals or oil wastes to control all plants appearing in transportation networks (Green et al. 1987). But these solutions were not safe to the crop in most of the cases. Use of selective herbicides has been the primary way to control weeds in agriculture from the discovery and introduction of synthetic herbicides (2,4-D, 2,4,5-T and MCPA) during the 1940's by four groups of researches from two countries, U.S.A. and U. K. (Troyer, J.R.; 2001).

Several actives belonging to this chemical group have since been discovered and there are now 15 actives which belong to the group O herbicides (Herbicide Resistance Action Committee classification) currently in Europe (Table 1). Most of the actives belong to the phenoxy carboxylic acids family (2,4-D, 2,4-DB, dichlorprop-p, MCPA, MCPB and mecoprop-p) and the pyridine carboxylic acid family (aminopyralid, clopyralid, fluroxypyr, picloram and triclopyr).

2,4-D was one of the original actives of the group O herbicides approved in Europe (almost 72 years ago) and it is still fundamental to control key weeds in several crops (Peterson 2016) like cruciferae species and *Centaurea cyanus* in winter cereals, *Taraxacum officinale* in pastures or *Ambrosia artemisiifolia* in corn.

Table 1. Active ingredients belonging to the HRAC O group approved in Europe (up to June 2019). Matières actives appartenant au groupe HRAC O homologuées en Europe (jusqu'à juin 2019).

Active ingredient	HRAC chemical family	Crops
Halauxifen-methyl	arylpicolinate	Cereals, oil seed rape, sunflower (emergence use approval in 2019)
Florpyrauxifen-benzyl	arylpicolinate	Rice (emergence use approval in 2019)
Dicamba	Benzoic acid	Cereals, corn, pastures, minor uses
2,4-D	Phenoxy carboxylic acid	Cereals, corn, pastures
2,4-DB	Phenoxy carboxylic acid	Legume crops
Dichlorprop-P	Phenoxy carboxylic acid	Cereals, pastures
MCPA	Phenoxy carboxylic acid	Cereals, corn, pastures, perennials, rice, flax
MCPB	Phenoxy carboxylic acid	Pastures, cereals, legume crops
Mecoprop-P	Phenoxy carboxylic acid	Cereals, pastures
aminopyralid	Pyridine carboxylic acid	Cereals, corn, oil seed rape, pastures
clopyralid	Pyridine carboxylic acid	Cereals, sugar beet, corn, pastures, sorghum, flax, brassica crops
fluroxypyr	Pyridine carboxylic acid	Cereals, corn, pastures, perennials, poppies, onion, sorghum, sugar cane
picloram	Pyridine carboxylic acid	Brassica crops
triclopyr	Pyridine carboxylic acid	Pastures, rice
quinclorac	Quinoline carboxylic acid	Rice (last emergence use approvals in 2017)
quinmerac	Quinoline carboxylic acid	Brassica crops, sugar beet, sunflower

Note: non-agricultural uses have been excluded in this table summary.

Synthetic auxins mode of action

Herbicides can be classified depending on several factors. One of those is their mode of action. The mode of action of herbicides is a biochemical and physiological mechanism by which herbicides regulate plant growth at tissue and cellular level (Jablonki, I., 2011). There are several level of complexity also in terms of herbicide mode of action. It can be very simple by binding to and inactivating a key enzyme. Or as complex as having several sites of action but involving also absorption and translocation (Streibig, J.C., 2003).

Auxin is a plant hormone (growth regulator) participating in several processes of the plant. Synthetic auxins are growth regulator herbicides that substitute plant growth hormone (basically indole-3-acetic acid, IAA) affecting the entire growth process of the plant primarily acting like an over-dose of auxin (Streibig, J.C., 2003).

The phenotypic response of sensitive plants to auxin herbicides are mainly loss of apical dominance, effects on cell elongation, cell division and adventitious root formation (Davies P., 1995; Johri, M., 2016). This includes stem and petiole twisting (epinasty), leaf malformations, swelling and splitting of the stem, root growth inhibition and eventually plant death (Schmitzer, P., 2016).

Binding differences among synthetic auxins

Actives from the synthetic auxin group are binding different receptors. Three different types of auxin receptors have been described in recent studies: (a) auxin-binding protein 1 (ABP1) mainly localized at the ER (endoplasmic reticulum) and outer cell membrane interface; (b) auxin-signaling F-box (TIR1/AFB) receptor in the nucleus; (c) and S-phase kinase-associated protein 2 (SKP2) also in the nucleus (Peterson, M., 2016).

ABP1 influences some cellular response to auxins and seems to be essential for early embryonic development. But its molecular activity has remained elusive and proteins interacting with ABP1 have not yet been identified. Thus, it is difficult to classify ABP1 as receptor (Woodward, A., 2005). A receptor for auxin was identified as the F-box protein TIR1 (transport inhibitor response 1) is a component of cellular protein complex (SCF^{TIR1}) (Dharmasari, N., 2005; Tan et al., 2007). TIR1 was reported to recognize synthetic auxin analogues such as 2,4-D (Jablonki, I., 2011). In addition to that, five additional F box proteins (AFB1, AFB2 and AF3: Dharmasari, N., 2005 and AFB4 and AFB5, Prigge et al., 2016) regulates auxin response. Recently the S-phase kinase-associated protein 2 (SKP2) has been indentified as an auxin binding protein that connects auxin signaling with cell division in plants (Jurado et al.,2010). This reflect the complexity associated to the binding preferences associated to synthetic auxins.

However, the binding affinities of most of the synthetic auxins have been studied during the last years. It was identified that picloram is mainly acting on AFB5 but also on AFB4 receptors although the response is greater on AFB5 than on AFB4. The affinity on receptors TIR1 and AFB2 was low (Prigge et al., 2016). Only TIR1-1 and AFB5 were resistant to dicamba, and this resistance was additive in the double TIR1-1/AFB5 mutant. TIR1-1 but not AFB5 was resistant to 2,4-D (Gleason et all., 2011). Mutations in AFB5 confer selective resistance to picolinate auxins, especially picloram, while conferring very low or no cross-resistance to 2,4-D. The TIR1-1 mutant was slightly more resistant to picloram than halauxifen-methyl, but this resistance was considerably less than the strong resistance of AFB5 (Walsh et al., 2006). Fluroxypyr and triclopyr also supported stronger AFB5 co-receptor assembly compared with that of IAA (Lee S. et all, 2014). Different binding affinity can be observed on Table 2.

Table 2. Binding preference of most of the different O group actives (HRAC classification). Préférence de liaison de la plupart des matières actives du groupe O (classification HRAC).

Compound	TIR1 Binding Affinity	AFB5 Binding Affinity
halauxifen-methyl	low	high
florpyrauxifen-benzyl	low	high
dicamba	high	medium
2,4-D	high	low
dichlorprop-P	high	medium
MCPA	medium	low
mecoprop-P	high	medium
aminopyralid	low	medium
clopyralid	low	high
fluroxypyr	medium	high
picloram	medium	high
triclopyr	medium	high

Spectrum of control of synthetic auxins

Several weeds are predominantly controlled by synthetic auxins. This is clearly known from the common use of some of them in the European market. Fluroxypyr is an excellent active controlling *Galium aparine* at post emergence in cereals (Radivojevic L., 2006). Aminopyralid provides very good control on annual dicotyledonous weeds such as *Matricaria* spp., *Papaver rhoeas* and *Centaurea cyanus* (Zots A., 2016). Clopyralid had the maximum effect on *Solanum nigrum* and *Portulaca oleracea* (Chitband A.A. et al. 2014). Halauxifen-methyl and clopyralid provide superior control of a wide range of important annual broad-leaved weeds in winter oilseed rape, including *Centaurea cyanus*, *Galium aparine, Geranium* spp., *Matricaria* spp. and *Papaver rhoeas* (Zots A., 2018). The highly significant effects of clopyralid on *Cirsium arvense* density reduction are supported by several findings (Anzer et. al., 2018). Halauxifen-methyl should be an effective tool for management of glyphosate resistant *Erigeron canadensis* (McCauley C. et al., 2018). There are specific official recommendation from sugar beet institutes to use clopyralid in case of difficult weeds to control like *Cirsium* spp, *Xanthium* spp, *Matricaria* spp., volunteer sunflower or volunteer potatoes (AIMCRA, ITB, BBRO, SFZ CBS).

Synthetic auxin resistant weeds in Europe

Resistance issues associated to the use of herbicides are very well known in Europe. Several grasses and dicotyledonous species already are resistant to herbicides from the first case of *Chenopodium album* resistant to atrazine in Switzerland and *Senecio vulgaris* to simazine and metribuzin in United Kingdom in 1977 Heap I., 2019). There are today 347 documented cases of resistance weeds (Heap I., July 2019). 79.25% of those are involving group A, B and C1 mode of action groups. And only 2% (7 cases) are affecting group O mode of action herbicides. The seven O group resistant populations are listed in Table 3.

Table 3. Resistance cases involving O group herbicides in Europe (Heap I., July 2019).
Cas de résistance impliquant les herbicides du groupe HRAC O en Europe (Heap i., juillet 2019).

Weed	Year	Country	Crop	Active involved	Type of resistance
Cirsium arvense	1979	Sweden	cropland	MCPA	unknown
	1985	Hungary	pastures	2,4-D and MCPA	Unknown
Papaver rhoeas	1993	Spain	cereals	tribenuron-methyl and 2,4-D	Unknown
	1998	Italy	wheat	2,4-D, iodosulfuron methyl sodium and tribenuron-methyl	Not defined
	1998	Italy	wheat	2,4-D	Not defined
	2016	France	cereals	2,4-D, iodosulfuron-methyl-sodium, MCPA, mesosulfuron-methyl, and metsulfuron-methyl	Unknown and an altered target site
Centaurea cyanus	2012	Poland	wheat	Dicamba	Unknown

Broadleaved weeds resistance issues in Europe are led by *Papaver rhoeas.* This weed is probably the most important species and is resistant to herbicides with an ALS mode of action herbicides. ALS resistant populations of *Papaver rhoeas* are found in Belgium, Denmark, France, Germany, Greece, Italy, Poland, Spain, Sweden and United Kingdom (Heap I., 2019). Additionally, there are cases of *P rhoeas* resistant to the synthetic auxins in Southern European countries (Italy, France and Spain). Poppies are today a big issue in Spain where populations demonstrating resistant to both ALS and 2,4-D modes of action have been found in several areas (Torra J., 2010). Similar type of populations have been reported in small areas of Italy and recently in France (Délye C., 2016).

There are also cases of *Cirsium arvense* populations resistant to MCPA and 2,4-D published several years ago in Sweden and Hungary. Most recently a population of *Centaurea cyanus* resistant to dicamba has been published.

It is quite significant the low number of cases of resistance to synthetic auxins herbicides documented, considering they were the first class of herbicides used in agriculture (Vats B., 2016). Actives belonging to the O group are still one of the most used in the market together with G and B group mode of action (Busi et al., 2017) actives. Herbicide resistance risk can be consider medium taking in account the number of species involved (Moss S., 2018); or low when taking into account the numbers of cases (Hugh J. B., 2007) in case of synthetic auxins. This could also by attributed to multiple site of action of these actives, initial low frequencies of resistant alleles, low level of resistant conferred by resistance mechanism(s) or no reduction in plant fitness (Torra et al., 2017).

All cases related to synthetic auxins resistance in Europe affect 3 actives: MCPA, 2,4-D and dicamba. It means that only benzoic and phenoxy carboxylic acids families are involved in resistance in Europe. Aminopyralid, from the pyridine carboxylic acid family demonstrated excellent control on 2,4-D and ALS resistant populations of *Papaver rhoeas* (Corteva Agriscience proprietary sources, 2004-2011). It is unlikely that other actives from O group herbicides will be affected by cross-resistance because most are binding to different receptors (Lee et all, 2014) or maybe affected by an alternative resistance mechanism. The risk of additional herbicide-resistant biotypes developing with altered target sites (binding proteins, TIR1/AFB1‑5) remains relatively low (Busi et al., 2017). However, cross-resistance was already confirmed in the case of *Papaver rhoeas* in Spain (Rey-Caballero et al., 2016).

Resistance mechanisms to synthetic auxins in weeds and their molecular basis remain largely unknown for most species (Torra et al., 2017). And this could be due to the complexity and the difficulties to understand how synthetic auxins works, how many proteins are involved, what kind of resistant mechanism is involved or what are the binding preferences of the different actives.

How to manage the current situation in Europe?

Synthetic auxins herbicides are used approximately in 366 million ha ever year in the world (Corteva Agriscience proprietary sources, 2014) especially since the introduction of 2,4-D and dicamba tolerant crops in 2012 in Canada. Herbicides from this mode of action have been helping farmers to control weeds from the introduction of selective herbicides in 1940's. The level of efficacy achieved by these synthetic auxin molecules herbicides? is still excellent particularly on tough Key European weeds like *Galium aparine*, *Papaver rhoeas*, *Centaurea cyanus*, *Cirsium arvense* amongst others. Compared with ALS inhibitor, PSII inhibitor and ACCase inhibitor resistant weeds, resistance to the synthetic auxins has very little economic impact and they remain one of the least prone herbicide groups for the selection of resistance (Heap I., 2013).

However, the evolution of resistance especially to ALS inhibitors is increasing the use of herbicides with different modes of action in some areas and crops. Additionally, weeds are developing more resistance mechanisms and exhibiting multiple resistance to several actives (Powles et al., 2010). Precaution and specific actions need to be taken to extend the utility of these active ingredients.

The single most important factor leading to the evolution of herbicide resistance is overreliance on a single herbicide (or group of herbicides with the same MoA) s (Norsworthy J.K., 2012) and lack of diversity in the crop production systems. Therefore it is key that, robust weed management program and rotations are implemented not only when resistance occurs but prior to resistance developing.

Several cultural methods of control like crop rotation (winter crop follow by spring crop), sowing date, competitive varieties, plant density, row spacing, cover crops, fertilizer placement, sanitize farm equipment before moving to the next field or false sowing had been described as efficacious to suppress weed population (Taberner et al., 2008; WSSA 2011; Torra J., 2011; HRAC 2016; Reddy K.N., 2016). The scientific community have generated more information on the control of grasses with cultural methods due to these are causing major issues on crops and are more important for farmers. A deep ploughing is usually effective to reduce *Bromus* spp. population. But it is not so effective on *Avena* spp. due to the dormancy and ability to growth of each one of them. Additionally this labor is also very effective on broadleaved weeds like *Conyza* spp. This weed is very small and only able to emerge when seed are located in the first 2 cm of soil surface. One harrow operation reduced emergence compared to zero till by approximately 90% (Walker et al. 2012).

Chemical control is a fundamental part of the weed management and should be optimized at farm level. Most of the useful practices could include active substance rotation, combination of different application timing with different mode of action herbicides, adapt rate to the crop phenology by following label recommendations or build chemical strategy across seasons (WSSA 2011; Busi et al., 2017).

There are an increasing number of physical control methods that could be integrated into a weed management program. One of the most efficacious is the harvest weed seed control (HWSC) put in practice in Australia some years ago with populations densities reduced 60% on *Lolium rigidum* (Walsh M.J., 2017). Ploughing is very effective controlling *Conyza Canadensis* (Brown S.M., 1988). But this is not so effective on other species like *Papaver rhoeas* (Délye C., 2016). Hand weeding is very common in Africa, Asia and in some European rice areas it can be very effective in removing survivors of herbicide treatments/programs Mechanical weeding is very common and efficient in maize (Molher C.L., 1997; Rueda-Ayala et al. 2010).

Diversity in crop production systems and weed control is the key word used by most of the relevant researches in resistant management worldwide (WSSA 2011; Shaner D., 2013; Heap I., 2014; Reddy K.N., 2016; Délye C., 2016; Busi R., 2017). A combination of cultural, physical and chemical methods of control should be implemented. We maybe need to learn from the systems used by our grand-grandparents and implement relevant practices into 21st century agricultural to prolong the life of our crop protect products and maximize yields.

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