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STRESS AND USE OF HERBICIDES IN FIELD CROPS

M. P. Radchenko, I. G. Ponomareva, I. S. Pozynych, Ye. Yu. Morderer

Institute of Plant Physiology and Genetics NAS of Ukraine,
31/17, Vasylkivska Str., Kyiv, Ukraine, 03022

*E-mail: mradchenko.phd@i.ua *, iraskazka2014@ukr.net, pozychka@gmail.com, morderer@ifrg.kiev.ua*

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When herbicides are combined under natural conditions or applied in stress conditions (drought, for instance), the efficiency of their action may decrease which results in considerable yield losses. The reason thereto is that another herbicide or stressor can trigger the adaptation mechanism in weed plants, and they survive, resulting in weed infestation. In particular, it applies to such herbicides as acetyl-CoA-carboxylase inhibitors or so-called graminicides, which are effective only for grass weeds control. The efficiency of this groups of herbicides is heavily dependent on the environment and often decreases when combined with herbicides, efficient against dicotyledon weeds. It turns out that this occurs due to the fact their final phytotoxicity is not determined at the level of the site of action (herbicide target) but depends on the stage of herbicide-induced pathogenesis – processes, occurring due to the interaction between the herbicide and its site of action. The stress response of the weeds may make its contribution into herbicide-induced pathogenesis. Plants are known to respond to the action of various abiotic stressors in the form of non-specific stress response and depending on the intensity and duration of the stressor's action, a plant either adapts or dies. At present there are sufficient data, demonstrating that programmed cell death (PCD) is involved in the herbicide-induced pathogenesis. Reactive oxygen species (ROS) induce PCD in specific classes of herbicides. The participation of ROS and PCD in herbicide-induced pathogenesis allows for targeted effects on the phytotoxic action of herbicides, for instance, via combined application of herbicides with possible PCD inducers and prooxidants. The confirmation of the role of non-specific response in the development of phytotoxic action of herbicides is found in the phenomena of cross-adaptation (activation of antioxidant defense) and cross-synergism (activation of oxidative stress) under the application of herbicides. Based on our own research and literature data, the importance of cross-adaptation and cross-synergism in applying herbicides in drought conditions and to determine the nature of the interaction in herbicide complexes is discussed. In particular, the review discusses the reduction of phytotoxicity of the ACCase herbicides due to the phenomenon of cross-adaptation in drought conditions and in combination with herbicides, which are acetolactate synthase inhibitors. The results of investigations were presented about the reduction of antagonism in the mixtures of herbicides, which are ACCase and ALS inhibitors, because of the use of substances with prooxidant properties, as well as the inhibitor of the antioxidant enzyme superoxide dismutase. On the other hand, we analyzed the possibility of increasing the phytotoxic effect of herbicides, ACCase inhibitors, in combination with herbicides with prooxidant properties – inhibitors of electron transport in Photosystem 2 (FS 2) chloroplasts and protoporphyrinogen oxidase (PROTOX) inhibitors. It became the foundation for the elaboration of efficient herbicide compositions for wheat and onion fields. While combining herbicides, the issue of synergism is becoming relevant due to the problem of the spread of target-site resistance, since, to prevent this type of resistance, it is necessary to combine herbicides with different mechanisms of phytotoxicity. The presented data demonstrate that the increased activity of antioxidant defense systems, which is the result of a long process of evolutionary adaptation of weeds to the action of abiotic stressors, is an element of non-target-site-based resistance to herbicides. Possible ways to prevent the negative impact of non-specific stress response on the efficiency of herbicides, as well as the prospects of the chemical method of weeds control are discussed.

Key words: herbicides, induced pathogenesis, programmed cell death, reactive oxygen species, stress, superoxide dismutase, cross-adaptation, cross-synergism, non-target-site-based resistance to herbicides.

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INTRODUCTION

Crop protection from weeds is an obligatory condition of implementing the productivity potential of agricultural crops, since the competition between cultivated plants and weeds is the most relevant biotic stressor (Radosevich SR et al, 2007). It is a common fact that throughout the entire history of weeds control it has been a chemical method, envisaging the application of herbicides that has turned out to be the most effective and cost-efficient way to protect crops (Kraehmer H et al, 2014a; Vencil WK et al, 2012).

Herbicides are physiologically active substances, the phytotoxicity of which is implemented via inhibiting some metabolic reactions and physiological processes, relevant for plants. It is obvious that since the effect of herbicides brings damage and even death to sensitive plant species, herbicides are abiotic stressors for plants. According to the mechanism of action or so-called sites of action, modern herbicides are divided into 27 classes (Mallory-Smith CA and Retzinger EJ, 2003). The selectivity of herbicides, i.e. the presence of a toxic effect on weeds and the absence of the same effect on cultivated plants, is caused in the prevailing majority of herbicide classes by higher rate of detoxification of the active substances of herbicides in cultivated plants as compared with weeds (Morderer YeYu and Merezhinsky YuG, 2009; Kraehmer H et al, 2014a), though for some classes, for instance, for herbicides, ACCase inhibitors, the selectivity is determined by the specificities of the site of action (Delye C, 2005).

It has long been believed that the phytotoxicity of herbicides was clearly determined by the concentration of the active substance in the site of action and the inhibiting activity of herbicide in this site (Fedtke K., 1985). However, there is convincing evidence which suggests that the interaction between the herbicide and the site of action is not a direct factor of plant death, as the final phytotoxic action is realized due to the impairment in the vital metabolic pathway or a physiological function, conditioned by the interaction between the herbicide and the site of its action. To describe these processes, which directly bring damage and death of weeds in favorable conditions, the term "herbicide-induced pathogenesis" was suggested (Morderer YeYu et al, 2013). In addition to specific impairments, caused by the interaction between the herbicide and the site of its action, the development of induced pathogenesis may involve non-specific responses of plants to the effect of herbicides (Fig. 1).

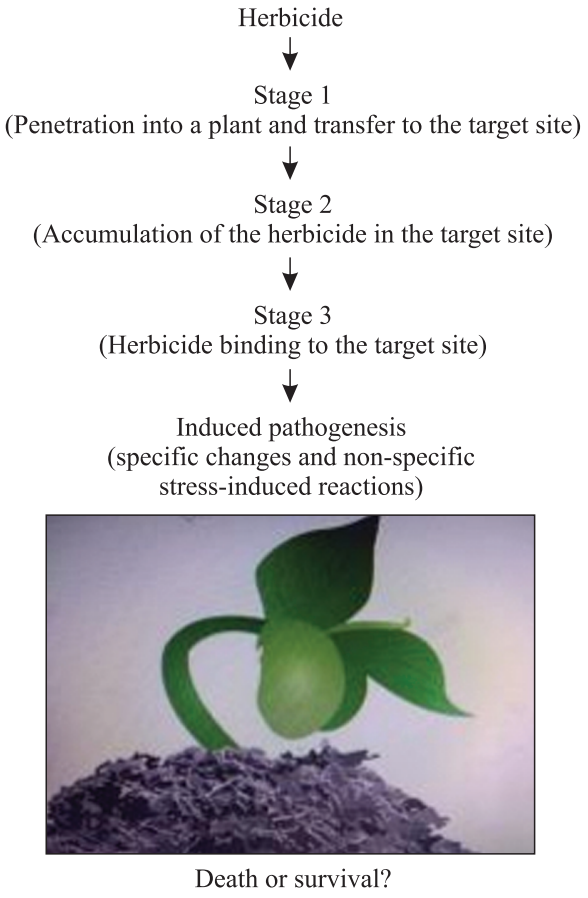

Fig. 1. The role of the herbicide-induced pathogenesis stage in the development of phytotoxic effect of herbicides

It is known that the response of plants to the effect of various stressors is related to the formation of ROS which, on the one hand, serve as a signal to switching on the systems of protection and non-specific increase in the resistance to the effect of the unfavorable factor (Gill, Tuteja, 2010; Kolupaev YuE and Karpets YuV, 2019), and on the other hand – may be a factor of damage and even death of plants (Gill S and Tuteja N, 2010; Sharma P, 2012; Caverzan A et al, 2019). A relevant component of the adaptive stress response is the increase in the activity of the antioxidant protection system of plants, which allows controlling the content of ROS. The consideration of the role of ROS and the activation of the antioxidant protection system is rather important for forecasting and modification of phytotoxicity and selectivity of herbicides under the effect of environmental factors and under combined application of herbicides.

The first issue, related to the effect of stressors on the activity of herbicides, lies in determining the involvement of non-specific stress responses of plants in the development of herbicide-induced pathogenesis in

plants, sensitive thereto. It should also be considered that the selectivity of herbicides is not absolute, so the effect of herbicides may induce a stress response in resistant cultivated plants as well. Therefore, the stress response of plants may affect both the development of the phytotoxic impact on weeds and the selectivity of herbicides regarding cultivated plants.

Practice demonstrates that the efficiency of the applying herbicides is considerably dependent on environmental conditions (Varanasi A et al, 2016.) In actual non-simulated conditions of cultivation, it is quite possible that both cultivated plants and weeds would be stressed at the moment of treating the field with herbicides. Therefore, it is possible that the effect of environmental factors on the phytotoxicity of herbicides is conditioned by the interaction between the stress response of plants to their effect and the herbicide-induced pathogenesis. Due to higher stress load of the effect of several stressors, the phytotoxic action may increase, but there may also be the opposite phenomenon of cross-adaptation or cross-tolerance, which, as per the definition of Hale (Hale HB, 1969), means the formation of organism resistance to one unfavorable factor due to the effect of the other.

The simultaneous action of two or even more stressors on plants also takes place under combined application of herbicides, used to enhance the efficiency of weeds control (Morderer YeYu and Merezhinsky YuG, 2009), and to prevent the occurrence of resistance to herbicides (Norsworthy JK et al, 2012; Vencil WK et al, 2012). When combined, the phytotoxicity of herbicides may change due to the interaction effects: the phytotoxic effect may increase due to the synergism, or, vice versa, decrease if the interaction is antagonistic (Morderer YeYu and Merezhinsky YuG, 2009). The antagonism phenomenon is twice more frequent than synergism (Zhang J, 1995). In some cases, the interaction effects may be explained by changes in the intake, translocation, and activity of herbicides in the sites of action, but a considerable part of interaction effects occurs under herbicide-induced pathogenesis (Morderer YeYu, 2005; Morderer YeYu and Merezhinsky YuG, 2009). It is obvious that the latter case may involve the phenomenon of cross-adaptation.

Recently the occurrence of herbicide resistance in weeds has been considered the main problem of the chemical weeds control method. The most dangerous and least studied type of resistance is non-target-site-based resistance (NTSR) of herbicides (Vencil WK et al, 2012). NTSR may be caused by mutations, increasing the rate of herbicide detoxification (Yu Q and Powles S, 2014), but there is also evidence of the involvement of antioxidant protection systems of plants in NTSR implementation (Shaaltiel YA et al, 1988; Hart J and Di Tomaso J, 1994; Preston C, 1997; Maroli AS et al, 2015; Keith BK et al, 2017; Piasecki C et al, 2019).

Therefore, the *aim* of this review is to analyze the data about the role of stress responses of plants, including the formation of ROS and adaptive increase in the activity of antioxidant protection systems, in the development of herbicide-induced pathogenesis, in the changes in the phytotoxicity of herbicides because of unfavorable environmental factors under the combined application of herbicides and in case of NTSR.

The nature of stress: the role of ROS and antioxidant protection in defining the response of plants to abiotic stressors

The term “stress” was first introduced by Walter Cannon, an American physiologist, in 1920s, but the concept of stress was formulated in more detail by Hans Selye, a Canadian scientist, a decade later (Selye HA, 1936). According to his observations, the organism responds to various stressors in the form of both specific and, first and foremost, non-specific response which together form the “general adaptation syndrome”. According to Selye, a stress is the combination of all non-specific changes, occurring in the organism under the impact of different factors, and the adaptation is the common trait of all the organisms (Selye HA, 1960). P.A. Henkel introduced the term “phytostress” – the response of a plant organism proper to unfavorable environmental factors. A phytostress starts with the response phase and if the stress intensity does not reach threshold values, the adaptation phase and then the restoration phase follow. If the stress intensifies to lethal values, there comes the phase of destruction and death (Henkel PA, 1978). However, it should be noted that the result of the stressor action depends not only on the stress degree, but also on the sensitivity of the organisms (sensitive, tolerant or resistant) (Lichtenthaler HK, 1996; Steinberg CEW, 2012). The formation of thermal hysteresis proteins under low temperatures or the synthesis of phytochelatins in response to the effect of heavy metals may be referred to specialized mechanisms of adaptation. But the functioning of general resistance mechanisms proper allows a plant to avoid immense energy losses due to the need to form specialized mechanisms of adaptation in response to any deviation of the conditions of organism existence from the normal ones (Kuznetsov VV, 2001). These include

the changes in protein-synthesizing system, phytohormonal balance, activity of enzymes, etc. (Kosakivska IV, 2003).

The effect of the stress is often mediated by oxidative damage, initiated by ROS, such as superoxide anion radicals (SAR), hydroxyl radicals (HR), hydrogen peroxide (HP) and single oxygen (SO) (Gill S and Tuteja N, 2010), formed due to the action of different abiotic stressors, including the effect of herbicides (Caverzan A et al, 2019). It is noteworthy that a certain basic level of ROS is necessary for a cell and may be involved in various important biological processes (Mittler R, 2017). However, ROS in high concentrations are highly reactive and may cause DNA mutations, protein denaturation, chlorophyll losses, and lipid peroxidation (LP) (Sharma P, 2012). LP is believed to be the most destructive process in living organisms, changing the permeability of membranes via the destruction of membrane proteins, inactivation of receptors and other enzymes and ion channels (Gill S and Tuteja N, 2010; Czarnocka W and Karpinski S, 2018). It is also known that ROS are universal inducers of PCD which is a factor of plant cell death due to both biotic and abiotic stressors (Gadjev I et al, 2008; De Pinto M et al, 2012).

A relevant component of general protection systems is antioxidant enzymes. The role of many antioxidant enzymes in stress situations lies in controlling ROS accumulation (ROS-transforming enzymes), thus limiting the damage of oxidative stress (Sharma P, 2012). These include superoxide dismutase (SOD, KF 1.15.1.1), catalase (CAT, KF 1.11.1.6), ascorbate peroxidase (APO, KF 1.11.1.11), glutathione peroxidase (GP, KF 1.11.1.9), peroxidase (PO, KF 1.11.1.7). In addition to antioxidant enzymes, a relevant role in protecting from oxidative damage is played by non-enzymatic antioxidants: glutathione, ascorbic acid, proline, flavonoids (Gill S and Tuteja N, 2010; Czarnocka W and Karpinski S, 2018). Under normal conditions, a multicomponent antioxidant system protects the photosynthetic apparatus of plants from free-radical oxidation: ascorbate and glutathione protect from single oxygen, SAR and HR; SOD catalyzes the transformation of SAR into HP, further breakage of which is done by peroxidases and catalase. The antioxidant enzymes also include glutathione-S-transferases (GST, 2.5.1.18) (Mittler R, 2002) which are isoenzymes, known to protect the cells from chemically induced toxicity (Kumar S and Trivedi P, 2018).

Therefore, if the stress intensity does not reach threshold values, the plant can activate a wide spectrum of antioxidant protection and the adaptation phase takes place. One of the examples of non-specific response of plants is enhanced resistance of plants, called cross-resistance or adaptation, when moderate preliminary treatment of plants by one type of stressors causes further increase in their resistance to many others (Sabehat A et al, 1998; Allan AC et al, 2006; Hossain MA et al, 2016; Kolupaev YuE et al, 2018, 2019). Noteworthy is the fact that the occurrence of cross-adaptation is also possible between biotic and abiotic stress (Foyer CH et al, 2016). In case of cross-adaptation, the antioxidant systems get activated and the content of oxidative stress indices decreases (ROS, TBA-reactive substances, etc.). However, the nature of stress is twofold and, in addition to cross-adaptation, there is another possible type of interaction between stresses – cross-synergism, when the result of combined effect of stressors may be not the occurrence of resistance, but on the contrary – the acceleration of plant death. On the contrary, the content of oxidative stress indices increases under cross-synergism, respectively. Depending on the stress intensity, the same stressors may lead either to cross-adaptation or to cross-synergism. The article of Obozniy OI et al. discusses the impact of indurating and damaging heat and osmotic stress and the contribution of ascorbate-dependent component of the antioxidant system into the formation of cross-resistance of wheat seedlings to hyperthermia and osmotic shock (Obozniy OI et al, 2012).

To determine the fact of cross-adaptation or synergism by the indices of oxidative stress, the cumulative effect is determined by the following formula – $(A + B)/B \times 100$, where $(A + B)$ – % to control under the combined effect of stressors, and B – the effect of the stressor, which caused more significant changes in the parameter under investigation. If the cumulative effect > 100, the interaction should be considered cross-synergism, and on the contrary, if it is < 100, it is cross-adaptation (Alexieva V et al, 2003). The experiments on cross-adaptation are the evidence of general resistance systems to two or several stressors. For instance, it was demonstrated that short-term thermal treatment of cotton plants was accompanied with their enhanced resistance to further salinization. On the other hand, the adaptation of plants to salinization led to their enhanced thermotolerance (Kuznetsov et al, 1993). Short-term hyperthermia increases the resistance to heavy metals and UV-light (Neumann et al, 1994), and moderate drought may lead to enhanced resistance to herbicides (Boydston RA, 1992).

It should be noted that the phenomenon of cross-adaptation allows using various growth regulators to enhance the resistance of plants to different unfavorable environmental factors. It may be applied to enhance the selectivity of herbicides. For instance, the treatment of peanut plants with salicylic acid enhanced the selectivity of herbicide bazagran due to the activation of the general antioxidant activity (GAC) (Radwan DEM, 2019).

The process of herbicide-induced pathogenesis and possible involvement of stress response of plants in its development

Numerous studies on the physiology of the effect of herbicides and the nature of mutations, determining the occurrence of resistance to herbicides found specific sites, the interaction with which defines the presence of herbicide activity in some chemical substances (Morderer YeYu and Merezhinsky YuG, 2009; Vencil WK et al, 2012; Kraehmer H et al, 2014ab). At the same time, it was found that the death of plants due to herbicides is not directly related to the interaction between the herbicide and the site of its action, rather it is conditioned by the processes, induced due to this interaction. The death of plants due to herbicides, having different interaction with the photosynthesis process, is conditioned by the increase in the rate of ROS formation, caused by photosynthesis disorganization by herbicides (Dan Hess F, 2000). At the effect of herbicides, acetolactate synthase (ALS) inhibitors, the death of plants is related to the deficit of aminoacids with the branched chain, not to inhibiting ALS activity (Zhou Q et al, 2007). The obtained data demonstrated that the changes in phytotoxic action of herbicides were not obligatorily conditioned by the changes in the inhibiting activity in the site of action (Bjelk L and Monaco T, 1992) but may occur due to the change in the processes, induced by the interaction between the herbicide and the site of its action. The very realization of this fact triggered the study on the nature of these processes, using the term, suggested to describe them, – "herbicide-induced pathogenesis" (Morderer YeYu et al, 2013; Sychuk AM et al, 2013 b).

There are six known classes, whose phytotoxic activity is related to light and photosynthesis process. It was found for all these herbicides that their phytotoxic activity was mediated by ROS formation (Dan Hess F, 2000; Caverzan A et al, 2019). ROS, whose content is controlled by the antioxidant protection systems, are always formed in a small amount during the photosynthesis process. Under the effect of herbicides, disorganizing the photosynthesis process, ROS formation gets accelerated and there are conditions, in which antioxidant systems cannot control the content of prooxidants. As a result, there is fast uncontrolled increase in the content of all ROS – the content of triplet chlorophyll, single oxygen, HR, SAR, HP which, in its turn, leads to accelerating LP reactions (Dan Hess F, 2000).

The involvement of ROS in induced pathogenesis was also determined for herbicides, whose action is not related to photosynthesis, including herbicides, ACCase inhibitors. It was shown that antioxidants decrease while prooxidants increase the phytotoxic action of herbicides, ACCase inhibitors (Morderer YeYu et al, 2008). It was found that under the effect of herbicides, ACCase inhibitors, there was an increase in ROS content in root meristems of sensitive plants which preceded the necrotization of these tissues. The treatment with the antioxidant ionol decreased and that with hydrogen peroxide increased the intensity of ROS formation under the effect of the herbicide (Palanitsya MP et al, 2009).

It is known that under the effect of physiological factors, including various biotic and abiotic stressors, the death of cells occurs due to the PCD activation (Yoshida Y, 1961; Lam E, 2008; Locato W and De Gara L, 2018). There are different mechanisms of PCD initiation, but ROS is a universal PCD inducer in different organisms (Gadjev I et al, 2008; De Pinto M et al, 2012). Thus, it was quite predictable that the first evidence of PCD involvement in induced pathogenesis was obtained for herbicides, whose phytotoxicity was related to the photosynthesis process and mediated by ROS formation (Chen S and Dickman M, 2004; de Freitas D et al, 2007; Chichkova NV et al, 2010). For instance, it was found that after the administration of animal antiapoptosis gene Bcl-2 into tobacco chloroplasts, there was an increase in their resistance to herbicides paraquat (electron interceptor from natural acceptor of FS I), acifluorfen, sulfentrazone (inhibitors of protoporphyrinogen oxidase, PROTOX). While the control tobacco plants died under the effect of these herbicides with apoptosis traits, the transgenic plants survived without the manifestation of any apoptosis traits (Chen S and Dickman M, 2004). When the bioballistics method was used to introduce the antiapoptosis gene *p53* of baculovirus into the genome of passion fruit plants, the resistance of plants to herbicide gluphosinate was enhanced (de Freitas D et al, 2007). A relevant apoptosis marker in animals is the activation of caspases. The

studies of Chichkova et al. first demonstrated the activation of phytaspase – a protease with caspase specificity under the effect of paraquat – in plants (Chichkova NV et al, 2010).

Recently the evidence has been obtained to demonstrate the involvement of PCD in the pathogenesis, induced by herbicides, ACCase and ALS inhibitors. It is known that internucleosomal DNA fragmentation is a feature of apoptosis-like PCD, and the non-systematic DNA degradation is remarkable for PCD, occurring by the necrosis mechanism (O'Brien et al, 1998). The electrophoresis was used to demonstrate that under the effect of herbicide, ACCase inhibitor haloxyfop-R-methyl in the sensitive root meristems of corn and ALS inhibitor tribenuron in pea leaves, there is both degradation and internucleosomal DNA fragmentation (Morderer YeYu et al, 2013; Sychuk AM et al, 2013 b). The hydrolysis of genomic double-stranded DNA is a terminal irreversible stage of PCD. During the PCD process in plants, DNA hydrolysis occurs due to the activation of two classes of endonucleases – Zn^{2+}-dependent ("acid") and Ca^{2+}, Mg^{2+}-dependent ("alkali") (Sugiyama M et al, 2000). During coleoptile aging, which is a typical example of apoptosis-like PCD in plants, DNA fragmentation mainly takes place due to the activation of acid nucleases (Aleksandrushkina NI et al, 2009). When TUNEL method was used under the effect of ACCase and ALS inhibitors on the background of increasing intensity of DNA fluorescence, which is an indicator of its fragmentation degree, it demonstrated the increase in the general activity of endonucleases (Radchenko et al, in print). Under the effect of ALS inhibitor, there was activation of Ca^{2+}, Mg^{2+}-dependent and Zn^{2+}-dependent nucleases, whereas under the effect of ACCase inhibitor – only of Zn^{2+}-dependent ones. These data clearly demonstrate the involvement of PCD in the pathogenesis, induced by herbicides, ACCase and ALS inhibitors. At the same time, it is obvious that the mechanisms of PCD, induced by ACCase and ALS inhibitors, have some differences. The involvement of PCD in induced pathogenesis was also determined under the effect of mixtures of herbicides, inhibiting the polymerization of microtubules of dinitroaniline derivatives with herbicides, ACCase inhibitors (Ozheredov SP et al, 2010).

Therefore, there are all reasons to assume that the PCD process is involved in herbicide-induced pathogenesis with different mechanisms of phytotoxicity. The involvement of PCD in herbicide-induced pathogenesis opens new possibilities for targeted effect on the phytotoxic action of herbicides, for instance, via combined application of herbicides with possible PCD inducers. The elicitor chitosan is known to induce Ca^{2+}-dependent PCD in plant cells (Zuppini A et al, 2004). It was found that chitosan enhances the phytotoxic effect of the mixture of the herbicide, ACCase inhibitor, fenoxaprop-p-ethyl, and the herbicide, electron transport chain (ETC) inhibitor, metribuzin (Trach VV et al, 2011). It is also known that low concentrations of nitrogen monoxide (NO) inhibit, whereas high concentrations induce PCD (Duboskaya LV et al, 2007). It was demonstrated that NO donor – nitroprusside – may enhance the phytotoxic effect of herbicides, ACCase and ALS inhibitors (Sychuk AM et al, 2013a).

The mechanisms of herbicide-induced PCD in plants require further studies. In particular, noteworthy is the probable role of non-specific stress responses of plants in initiating PCD under the effect of herbicides. ROS formation is a known element of the plant response to the effect of stressors (Gill S and Tuteja N, 2010; Kolupaev YE, 2019). At the same time, ROS induces PCD which is involved in the development of herbicide-induced pathogenesis (Gadjev I et al, 2008; De Pinto M, 2012). On the other hand, the activity of antioxidant systems, controlling the ROS content in plants, affects the sensitivity of plants to the effect of stressors, including PCD induction inhibition. For instance, it was found that transgenic tobacco plants with overexpression of SOD gene survived under the effect of ozone (Van Camp V et al, 1994), whose toxic effect on plants was realized via PCD induction (Langebartels C et al, 2002). In addition, in the transgenic plants, differing in their level of catalase and ascorbate peroxidase activity, PCD induction under the effect of pathogens and ozone also had negative correlation with the activity of these antioxidant enzymes (Mittler R et al, 1999; O'rvar BL et al, 1997). It was determined that there was a connection between the activity of antioxidant protection and the systems, directly controlling PCD induction in plants. For instance, double mutants with inhibited activity of catalase and cytosolic ascorbate peroxidase (apx1/cat2) started having resistance to oxidative stress, DNA-damaging factors, including the effect of herbicide norflurazole (the inhibitor of the synthesis of carotenoids). It was found that the resistance of these mutant plants to the effect of the mentioned stressors was conditioned by the activation of antiapoptosis proteins of Bcl 2 family (Vanderauwera S, 2011).

A question arises – in what way will ROS, formed due to a stress response of plants to the effect of her-

bicides, impact the phytotoxic action of the latter, including the promotion of PCD induction? The study on the possible role of ROS in the development of the phytotoxic action of herbicides, ALS inhibitors, demonstrated that antioxidants decreased the phytotoxic effect of these herbicides. Here the sensitivity of ALS inhibitors to the effect of antioxidant was much lower than that for herbicides, ACCase inhibitors (Morderer YeYu et al, 2008). It was found that different sensitivity of ALS and ACCase inhibitors to exogenous antioxidants may be explained by different sources of ROS formation under the effect of these herbicides. The primary formation of ROS in plant cells under the effect of stressors is known to relate to the activation of NADPH-oxidase (Sagi M and Fluhr R, 2006). The study on the dynamics of ROS accumulation (Palanitsya MP et al, 2009) and the activity of NADPH-oxidase under the effect of herbicides, ACCase inhibitors, demonstrated that the activation of NADPH-oxidase may be responsible for the increase in the ROS content only at the initial stage of developing the phytotoxic effect (Radchenko MP et al, 2016). At the same time, it was found that the increase in the content of such ROS as SAR under the effect of ACCase inhibitor lasted during the whole period of pathogenesis development till the start of necrotization in meristem cells (Palanitsya MP et al, 2009). To determine the role of stress ROS in the development of pathogenesis, induced by herbicides, ACCase and ALS inhibitors, there was an investigation of the impact of the specific inhibitor of NADPH-oxidase, diphenyleneiodonium chloride (DPI), and the calcium-channel blocker, lanthanum chloride ($LaCl_3$) and calmodulin antagonist, chlorpromazine (CP) on the effect of these herbicides (Sychuk AM et al, 2017). Calcium antagonists were used along with DPI since NADPH-oxidase is a calcium-dependent enzyme (Sagi M and Fluhr R, 2006; Glyanko AK et al, 2009). It was found that under the effect of DPI, $LaCl_3$ and CP the phytotoxic effect of ALS inhibitor decreased considerably, while the decrease in the phytotoxic effect of ACCase inhibitor was not so significant (Sychuk AM and Morderer YeYu, 2017). The data obtained clearly demonstrated that the pathogenesis, induced by herbicides, ALS inhibitors, involved ROS, formed due to non-specific stress response of plants. The stress response may be merely an additional source of ROS formation for the phytotoxic action of herbicides, ACCase inhibitors. The main source of ROS formation under the effect of herbicides, ACCase inhibitors, is likely to be electron transport chains of plastids, whose functioning is impaired due to the inhibition of ACCase activity by these herbicides, and the corresponding blocking of the synthesis of fatty acids, required for maintaining the normal condition of plastid membranes.

Obviously, under the effect of herbicides, whose phytotoxicity is conditioned by the photosynthesis disorganization and thus mediated by ROS formation, it is rather hard to isolate the contribution of ROS, formed due to the stress response to the herbicidal effect. However, it is probable that these ROS may affect the functioning of the systems, impacting the sensitivity of plants to the herbicidal effect. For instance, one of the factors, limiting the efficiency of the action of herbicides, ETC inhibitors, in photosystem 2 (FS 2) of chloroplasts, is a high rate of the restoration of D1 protein, which is the site of action for these herbicides (Chen S et al, 2007). At the same time, it is known that ROS, formed due to abiotic stressors, inhibit the restoration of D1 protein in FS 2 of chloroplasts (Takahashi S, Murata N, 2008; Takahashi S, Badger M, 2011). Thus, it is quite probable that a fast stress response of plants to herbicides, ETC inhibitors, may lead to inhibiting the rate of D1 protein restoration and thus promote the development of the phytotoxic action of these herbicides.

The discovery of the nature of endogenous auxin receptors facilitated the determination of the mechanism of action for herbicides from the class of synthetic auxins (Kepinski S and Leyser O, 2005; Badescu GO and Napier RM, 2006; Guilfoyle T, 2007; Tan X et al, 2007; Chapman EJ and Estelle M, 2009; Mithila J et al, 2011; Sauer M et al, 2013) and the presence of a stress component in the changes of expression for auxin-dependent genes was clearly defined (Shi Q et al, 2020). Nevertheless, the issues of the role of ROS in the development of phytotoxic effect of auxin-like herbicides (ALH) (Pazmiño DM et al, 2012; McCarthy-Suárez I., 2017) and the herbicides from other classes, including glyphosate, the inhibitor of enolpyruvylshikimate phosphate synthase (EPSPS) (Cobb AH and Reade PHR, 2010), are yet to be investigated.

To date, there are enough data to demonstrate that similar to the effect of other stressors (Kültz D, 2005), the death of plants under the effect of herbicides from different classes, including photosynthesis inhibitors, ACCase and ALS inhibitors, occurs via apoptosis-like PCD. It allows increasing their phytotoxicity due to the substances of PCD inducers. The involvement of ROS in herbicide-induced pathogenesis gives the possibility to regulate the phytotoxic action of herbicides using the substances with antioxidant and prooxidant action.

The role of stress in determining the effect of environmental factors on the phytotoxic action of herbicides

Global climate changes and higher competitiveness of weeds under these conditions (Amare T, 2016) pose a threat due to better adaptation potential of weeds and require adjustments in agrotechnologies and methods of protecting fields from weeds (Varanasi A et al, 2016). In some cases, the impact of environmental factors on the phytotoxic action of herbicides may be explained by the impact on the processes, determining the herbicide concentration in the site of its action. For instance, corn-selective herbicides from the class of fatty acid synthesis inhibitors with a long chain, chloroacetanilide derivatives, may inhibit this crop considerably under low temperatures and high moisture content in soil. This effect may be explained by the fact that in case of a temperature decrease, there is a sharp drop in the rate of chloroacetanilide detoxification, which leads to corn inhibition by these herbicides (Rowe L et al, 1991; Viger P et al, 1991; Stefanovic L and Zaric L et al, 1991). However, there are also data about the dependence of the phytotoxic action of herbicides on environmental conditions, which is not related to changes in herbicide content in the sites of their action and changes in the impact of herbicides on these sites (Coupland D, 1989; Kells JJ et al, 1984; Kidder DW and Behrens R, 1988; Boydston RA, 1992).

One of more significant consequences of global warming, affecting the performance of agricultural crops and efficiency of the measures in protecting the fields from weeds, is the increase in the frequency and duration of droughts during the vegetation period (Roeckner E, 1992). It is well known that the phytotoxic action of many classes of herbicides, including ACCase inhibitors, decreases under drought (West LD et al, 1980; Dickson RL et al, 1990; Kells JJ et al, 1984; Boydston RA, 1991, 1992; Rossi F et al, 1993; Collings LV et al, 2003; Shekoofa A et al, 2020; Alizade S et al, 2020). No significant differences were found in accumulation, absorption, translocation, and metabolism of ACCase inhibitors in plants under drought and without the latter (Coupland D, 1989; Kells JJ et al, 1984; Kidder DW and Behrens R, 1988; Boydston RA, 1992). Thus, Dastgheib et al. suggested that ACCase may become less sensitive to being inhibited by herbicides under drought (Dastgheib F, 1990). However, under other conditions, when the decrease in the phytotoxicity of graminicides was observed during their application with herbicides of other classes, it was determined that this response of plants was not related to the degree of ACCase activity inhibition (Bjelk L and Monaco T, 1992). It is obvious that the decrease in the phytotoxicity of ACCase inhibitors under drought may be conditioned by changes in the induced pathogenesis (Morderer YeYu, 2005). It should be noted that the intensity and duration of the stressor effect are relevant as the efficiency of controlling foxtail using fluazifop on Days 2, 4 after the administration of the herbicide under drought decreased by 40 and 50 %, respectively, while if drought lasted less than one day, the efficiency of controlling this weed using fluazifop did not decrease (Boydston RA, 1992).

Considering the role of ROS in the pathogenesis, induced by ACCase inhibitors (Palanitsya MP et al, 2009) and the data on increasing the activity of the antioxidant plant protection system under drought (Fu J and Huang B, 2001), it is possible to assume that the decrease in the phytotoxicity of herbicides, ACCase inhibitors, under drought may be conditioned by the increase in the activity of the antioxidant protection system. For instance, a significant increase in the activity of the antioxidant enzyme SOD and the tendency to the increase in the catalase activity under the effect of herbicide, ACCase inhibitor, fenoxaprop-p-ethyl under drought was determined. There was a strong negative correlation between the content of hydrogen peroxide and catalase activity which is known to decrease its content: the correlation coefficient between these indices on Day 10 after the beginning of drought was $r = -0.8$ (Radchenko MP et al, 2014).

Therefore, the results of the studies demonstrated that the decrease in the phytotoxic effect of herbicides, ACCase inhibitors, under drought was conditioned by the stress response of plants – the phenomenon of cross-adaptation. This cross-adaptation was caused by the increase in the activity of antioxidant enzymes SOD and catalase under drought, which are involved in eliminating reactive oxygen species – SAR and HP. It was determined that under combined effect of the herbicide and drought on Day 10 the cumulative effect for HP was 66 %, for SAR – 56 % which is under 100 % and is considered to be the cross-adaptation to the effect of these stressors (Alexieva V et al, 2003).

The involvement of stress responses of plants in the interaction effects under combined application of herbicides

Since some preparations cannot control the whole spectrum of weed species in the fields of cultivated

crops, it conditions the need for combined application of herbicides, whose spectra of action supplement each other (Morderer YeYu and Merezhinsky YuG, 2009). The combined application of herbicides with different mechanisms of phytotoxicity is considered to be the way to prevent herbicide-resistant weed biotypes (Norsworthy JK et al, 2012; Vencil WK et al, 2012). However, due to high ecotoxicological requirements, less than 1/3 of currently known classes of herbicides (Mallory-Smith CA and Retzinger EJ, 2003) are allowed for application in Ukraine, which limits the possibility of combining and requires new ways of searching for efficient and safe herbicides.

It is known that the phytotoxic effect of herbicides may vary in the combinations due to interaction effects (Zhang J, 1995; Morderer YeYu, 2000). Some interaction effects may be explained by changes in the intake, translocation, or metabolic detoxification of some components of herbicide complexes (Morderer YeYu and Merezhinsky YuG, 2009). However, there is evidence suggesting that the changes in the phytotoxic activity may also take place due to changes in the induced pathogenesis (Bjelk L, Monaco T, 1992).

The fields of many crops are protected with tank mixtures of herbicides, chloroacetanilide and dinitroaniline derivatives, efficient against cereal weeds, with the herbicides, s-triazine derivatives, efficient mainly against dicotyledon weeds (Morderer YeYu and Merezhinsky YuG, 2009; Morderer YeYu et al, 2014). The specificity of these mixtures lies in the fact that the phytotoxic effect of their components occurs at different phases of plant development which facilitates the determination of interaction effects considerably. Chloroacetanilide and dinitroaniline derivatives act at early phases of plant development, so, for our purpose, they can be named germination inhibitors (GI), and s-triazine derivatives are ETC inhibitors in FS 2 of chloroplasts, so their effect starts after the formation of the photosynthetic apparatus of plants. It is obvious that when these mixtures are applied, only GI-resistant plants are exposed to the effect of ETC herbicides. It was found that when used in the mixtures with GI, the phytotoxic effect of ETC herbicides on plant species, sensitive to them, does not change, and as for moderately resistant plant species – it decreases antagonistically. As the cultivated plants are resistant to both components of the mixture, this antagonism is useful since the probability of damaging cultivated plants with ETC herbicides decreases due to it. A series of studies on the mechanism of antagonistic decrease in the phytotoxic effect of ETC under combined application with GI did not find the effect of GI on the intake of ETC into plants (Morderer YeYu and Merezhinsky YuG, 2009). The assumption was made that enhanced plant resistance to the effect of ETC was conditioned by their stress response to GI. This assumption was based on the fact that antagonism manifestations were observed under some inhibiting effect of GI on the growth of plants, accompanied with the acceleration of LP reactions, which was expected to result in the enhanced antioxidant activity (AOA) of lipids. However, this assumption was not confirmed (Morderer YeYu and Merezhinsky YuG, 2009). The activity of antioxidant enzymes under GI was not determined, and the hypothesis on the role of the stress response of plants in the antagonistic decrease in the effect of ETC herbicides under combined application with GI herbicides was neither refuted nor confirmed.

Clear evidence, suggesting the role of adaptive increase in the activity of antioxidant protection systems in the interaction effects was obtained during the study on the mechanism of antagonistic decrease in the phytotoxic effect of herbicides, ACCase inhibitors, on cereal weeds, when these herbicides were applied in the mixtures with herbicides, ALS inhibitors, efficient against dicotyledon weeds (Radchenko MP et al, 2013ab; Morderer YeYu et al, 2014).

The specificity of herbicides, ACCase inhibitors, lies in the fact that their selectivity is determined by the specificities of the site of action. Only plastids of grass family (Poaceae) plants contain a sensitive eukaryotic form of ACCase, while the plastids of all other plant species have a resistant prokaryotic form of ACCase. Thus, the herbicides, ACCase inhibitors, affect only the plants of Poaceae family, so they are separated into a group of so called graminicides. The limitation of the action spectrum of ACCase inhibitors determines the need to combine them with herbicides, efficient against dicotyledon weeds. However, a significant hindrance in applying these mixtures is the antagonistic decrease in the effect of graminicides on cereals under combined application with synthetic auxins, herbicides, ALS, ETC inhibitors in FS 2 of chloroplasts (Dechamps JA et al, 1990; Baerg RJ et al, 1996; Zhang J et al, 1995; Morderer YeYu et al, 2009). To prevent failures in efficiency of controlling cereal weeds, graminicides and herbicides, efficient in fighting dicotyledon weeds, are often used consecutively, instead of mixtures (Morderer YeYu et al, 2014). The study of the physiological nature of antagonism demonstrated that it may be unrelated to changes in the intake, translocation, and de-

toxification of graminicides and to the decrease in the degree of inhibiting ACCase activity (Bjelk L and Monaco T, 1992). Thus, the antagonistic decrease in the phytotoxicity of graminicides may be caused by changes in the induced pathogenesis. As stated above, the development of the phytotoxic effect of graminicides under optimal conditions is related to the formation of ROS, including long-term increase in SAR content (Palanitsya MP et al, 2009). Therefore, an assumption was made, suggesting that the antagonistic decrease in their phytotoxicity in tank mixtures was caused by the increase in the activity of antioxidant systems, including SOD activity, and it was the result of a stress response of plants to the herbicide, efficient against dicotyledon weeds. It was found that the blocking of the activity of antioxidant enzyme SOD by the specific activity inhibitor resulted in changing the character of the interaction from antagonistic to additive in the mixture of graminicide fenoxaprop-p-ethyl with the ALS inhibitor, amidosulfurone, applied to protect wheat and barley fields, which can induce only moderate stress in cereals (Radchenko MP et al, 2013a). These results demonstrate that the antagonistic decrease in the phytotoxicity of graminicide fenoxaprop-p-ethyl in the mixtures is related to the stress response of plants to the effect of herbicides, ALS inhibitors. The antagonistic decrease in the phytotoxic effect of herbicide, ACCase inhibitor, in the mixture with herbicide, ALS inhibitor, is the manifestation of cross-adaptation similar to the decrease in the effect of this herbicide under drought (Radchenko MP et al, 2014). The evidence thereto is the cumulative effect of the combined action of herbicides, determined by the indices of oxidative stress markers – the content of TBA-active substances. The content of TBA-active substances in the antagonistic mixture of graminicide fenoxaprop-p-ethyl and ALS inhibitor, amidosulfurone, on Day 5 after treatment was considerably lower as compared with the application of graminicide only. SOD activation resulted in the decrease in SAR content and a relevant decrease in the oxidative stress level. As a result, the cumulative effect value was 53 % which confirmed the phenomenon of cross-adaptation (Radchenko MP et al, 2017).

The determination of the mechanism of antagonistic decrease in the phytotoxic effect of graminicides demonstrated that to prevent the cross-adaptation and the failures of their efficiency, it is important for combinations to select herbicides, whose phytotoxic action on cereal weeds will be sufficient. For instance, the mixture of graminicide fenoxaprop-p-ethyl and ETC in FS 2, metribuzin, affecting both dicotyledons and cereal weeds, demonstrated the increase in the phytotoxic effect on cereals. The indices of the content of TBA-active substances showed the cross-synergism in the mixture of fenoxaprop-p-ethyl and ETC in FS 2, metribuzin, as under the combined action of two herbicides the cumulative effect was 141 %. Due to the introduction of metribuzin to the antagonistic mixture of fenoxaprop-p-ethyl with herbicides, ALS inhibitors, the antagonism was successfully overcome, which became the basis for the elaboration of technologies of combined application of herbicides in wheat fields (Radchenko MP et al, 2013b).

Cross-synergism may also be observed when the residues of herbicides with high prooxidant activity, like atrazine, remain in the fields. Atrazine belongs to herbicides, ETC inhibitors in FS 2 of chloroplasts, and its phytotoxic effect is directly related to ROS formation (Dan Hess F, 2000). It was shown that very low concentrations of atrazine, usually remaining in the field after the treatment with herbicide, increase the sensitivity of Arabidopsis plants to further treatment with doses, recommended for plant treatment in the field (Ivanov SV et al, 2005).

The protection from oxidative damages as a component of non-target-site-based resistance to herbicides

The occurrence of resistance to herbicides is the result of evolutionary adaptation of weeds populations to intense pressure, exerted by herbicides (Neve P et al, 2009; Dyer WE, 2018; Baucom RS, 2019). According to the data of Heap (Heap I, 2020), to date, there have been 515 unique cases of resistance to herbicides (up to 23 out of 26 known mechanisms of action) for 263 species of weeds (152 dicotyledon and 111 monocotyledon weeds). There is target-site-based resistance (TSR), leading to weeds acquiring resistance to herbicides with a certain mechanism of phytotoxicity, and non-target-site-based resistance (NTSR), which results in so called cross-resistance, i.e. the resistance of weeds to different herbicides (Vencil WK et al, 2012; Delye C et al, 2013a; Delye C, 2013b). While TSR may occur due to a mutation or overexpression of target enzyme gene, NTSR has polygenic character (Delye C et al, 2013a). Under the application of efficient doses of herbicides, ensuring a high level of controlling weeds, the occurrence of TSR is more probable, and under the introduction of low doses of herbicides or the effect of other factors (untimely introduction of herbicides, unfavorable weather conditions, etc.) the occurrence of

NTSR is more probable, when plants survive mainly due to their enhanced ability of metabolic detoxification of herbicides (Guralchuk ZhZ, and Morderer YeYu, 2015). NTSR develops gradually under strong selection, induced by herbicides, is controlled by multiple alleles and ensured by one or several constitutive and/or induced physiological mechanisms (Delye C, 2013b). Therefore, NTSR may be constitutive, which ensures the secondary metabolism of herbicides, and stress-induced or may be ensured by both ways (Cummins I et al, 2009).

The protection from oxidative damage, including the activation of antioxidant enzymes, may play a relevant role in NTSR (Delye C, 2013b). For instance, in the resistant biotype of foxtail (*Alopecurus myosuroides)* the content of hydrogen peroxide decreased at the effect of the herbicide, ACCase inhibitor, fenoxaprop-p-ethyl, and electron interceptor in FS 1, paraquat, while the content of hydrogen peroxide in the wild type of plants increased at the effect of these both herbicides (Cummins I et al, 1999). It was determined that the activity of glutathione peroxidase is a resistance factor for foxtail biotype to herbicide-mediated oxidative stress (Cummins I et al, 1999, 2009, 2013). It was shown that in several species of weeds the resistance to paraquat was conditioned by the activity of antioxidant enzymes (Shaaltiel YA et al, 1988; Hart J and Di Tomaso J, 1994; Preston C, 1997).

The increase in the activity of antioxidant enzymes was found in glyphosate-resistant biotypes of *Amarantus palmeri* and *Conyza bonariensis* (Maroli AS et al, 2015; Piasecki C et al, 2019). It should be noted that our previous studies demonstrated that cross-adaptation of oats plants to ACCase inhibitor, fenoxaprop-p-ethyl, was conditioned by the activation of SOD (Radchenko et al, 2013a, 2014, 2017), but Keith et al. found that one of the reasons for NTSR in oats plants to herbicides from 5 different classes was a much higher level of SOD gene expression as compared with sensitive weeds (Keith BK et al, 2017) (Fig. 2).

These data confirm the relevant role of the very gene, encoding SOD, in the evolution of resistance to herbicides and other stressors. Generally, the existence of universal strategies of responding to abiotic stress is remarkable for eukaryotes (Kültz D, 2005; Sulmon C et al, 2015). The universality of these strategies is conditioned by the fact that the increased activity of ROS-transforming enzymes is a factor of resistance of oats plants both to drought (Wendelboe-Nelson C and Morris PC, 2012), and to the effect of herbicides (Keith BK et al, 2017). As a consequence, in our studies the decrease in the phytotoxic activity of graminicide, fenoxaprop-p-ethyl, in the mixture with herbicide amidosulfuron, and the decrease in the phytotoxic effect of graminicide under drought was related to SOD activation (Radchenko et al, 2017).

To date, there are not much data about the genetic foundations of NTSR and some "omics" (genomics, transcriptomics, proteomics or metabolomics) are required to clarify them. Nevertheless, the application of inhibitors of enzymes, decreasing the rate of the oxidative stress, induced by herbicides, for instance, SOD inhibitors, is considered as a possible strategy of fighting NTSR **(**Rogachev I et al, 1998; Warshawsky A et al, 2001).

Possible ways of ensuring the efficiency of applying herbicides under the decrease in their phytotoxicity due to stress response of plants

Since during the last three decades no herbicides with new target sites of action have been found, combining herbicides may be the only method of preserving efficient control of weeds (Morderer YeYu et al, 2014) and preventing the occurrence of resistant biotypes of weeds (Norsworthy JK et al, 2012; Vencil WK et al, 2012). It should be noted that the need for combined application of herbicides had been studied in Ukraine long before the world acknowledged the necessity of combining herbicides due to resistance (Morderer YeYu and Merezhinsky YuG, 2009). However, while combining herbicides, the efficiency of controlling weeds using herbicides may decrease due to both global climatic changes (Amare T, 2016; Varanasi A et al, 2016) and the stress response of plants (Radchenko MP et al, 2013a, 2014). The decrease in the phytotoxicity of herbicides under drought requires adjusting agrotechnologies and technologies of protecting fields from weeds (Varanasi A et al, 2016), for instance, using irrigation or changes in the periods of herbicidal treatment (Alizade S et al, 2020).

The contribution of the stress component into the herbicide-induced pathogenesis opens new ways to regulate selective phytotoxicity of herbicides. For instance, the application of antioxidant and prooxidant substances, controlling ROS content in plants, may regulate the phytotoxicity of herbicides, whose mechanism of action is mediated by ROS formation. The issue of combined application of herbicides is especially urgent for herbicides, ACCase inhibitors, since they affect only cereal weeds. However, the antagonism in the mixtures with most preparations, efficient against

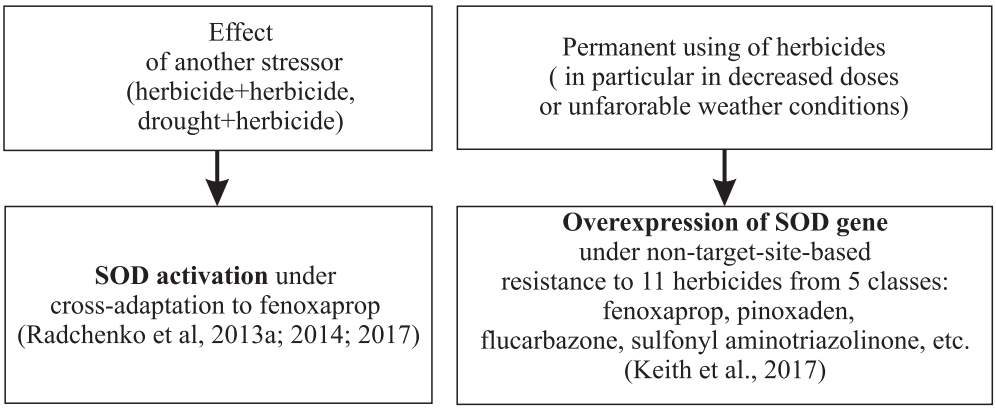

Fig. 2. The protection from oxidative damages (SOD activation) under cross-adaptation of oats plants to herbicide, ACCase inhibitor, and under NTSR of oats plants to the effect of herbicides from different classes

dicotyledons, is a considerable drawback for the application of these herbicides in the combinations. It is noteworthy that the issue of the contribution of a stress component into the decrease in the phytotoxicity of herbicides was raised long time ago. For instance, the fields of many crops are protected with tank mixtures of other herbicides, chloroacetanilide and dinitroaniline derivatives (GI), efficient against cereal weeds, with the herbicides, s-triazine derivatives (ETC), efficient mainly against dicotyledon weeds (Morderer YeYu and Merezhinsky YuG, 2009; Morderer YeYu et al, 2014). However, a frequent phenomenon in the mixtures of these herbicides is their antagonistic nature. The antagonism in the mixtures, for instance, s-triazine prometrin and dinitroaniline trifluralin was first determined by L.V. Khodeeva (Khodeeva LV et al, 1992). Although the antagonism in the mixtures resulted in the decrease in the effect on weeds, it was beneficial for the crop, as it decreased the negative impact of ETC which are generally characterized by low selectivity regarding cereal crops. The nature of this antagonism was not determined at the time, but the assumption was made that enhanced plant resistance to the effect of ETC was conditioned by their stress response to GI. We found the explanation of this fact later when we studied the reasons of a decrease in the phytotoxic effect of herbicides, efficient only against cereal weeds – graminicides with ALS inhibitors – under vegetative conditions. During a vegetative experiment we demonstrated a principal possibility of enhancing selective phytotoxicity of a graminicide fenoxaprop-p-ethyl while applying in the mixture with a synergist metribuzin and antagonists – herbicides inhibitors of ALS (Radchenko MP et al, 2013b). It was determined that under some ratio of concentrations of the active substances of mixture components the phytotoxic effect of fenoxaprop-p-ethyl on sensitive plants of oats, which served as a model of annual cereal weeds, increased synergetically, and the effect on resistant plants of winter wheat decreased antagonistically. The decrease in the negative effect of metribuzin on resistant plants of winter wheat was related to the activation of antioxidant protection of the cultivated crops. The activation of antioxidant protection must have been the reason for the decrease in the negative effect on the crop during the application of GI and ETC mixtures as well (Khodeeva LV et al, 1992). Judging from our studies, the simultaneous application of ACCase inhibitors and herbicides from other classes may lead to the synergic interaction in case, if the herbicide of another class is characterized with high prooxidant activity (Morderer et al. 2014). This fact became the basis for the development of technologies of new complex application of herbicides in wheat fields, since the addition of metribuzin to the antagonistic mixture of graminicide fenoxaprop-p-ethyl and ALS inhibitors was successful in overcoming the antagonism and enhancing the selective phytotoxicity of the mixture (Patent UA, 43543; Radchenko MP et al, 2013b; Morderer YeYu et al, 2013). For instance, in our field experiment, high efficiency of controlling a cereal weed, common windgrass (*Apera spica-venti*) and dicotyledon weeds, cleavers (*Galium aparine* L.) and flixweed (*Descurainia sophia* L.) in winter wheat fields was obtained by us in the variants with the mixture of graminicide fenoxaprop-p-ethyl with two anti-dicotyledon herbicides – metribuzin and inhibitors of ALS in the highest norms of introduction. It resulted in increasing the yield of winter wheat in these variants per 10 centners/ha as compared to the application of one graminicide (Morderer YeYu et al, 2013). No negative effect on wheat plants was determined in any

variant of the experiment, the value of the obtained yield of grain correlated with the efficiency of controlling weeds.

Therefore, the effect of interaction (whether the mixture will be antagonistic, synergic or additive) in combining graminicides and thus the efficiency of their application along with herbicides from other classes depends not only on herbicides, but also on the norms of their introduction. This is related to stress – since different norms of introducing herbicides may cause different stress responses in both weeds and crop plants. The effect of interaction between herbicides in the mixture may enhance both the efficiency of controlling weeds and the selectivity of herbicides regarding the crop which would collectively promote higher yields.

The herbicides, inhibiting PROTOX enzyme, are also characterized by high prooxidant activity (Dan Hess, 2000). The synergic interaction between herbicides was confirmed while using a graminicide haloxyfop and an inhibiting PROTOX herbicide oxyfluorfen in the mixture in onion field. Our field studies in the onion fields demonstrated that split fertilizing with herbicide oxyfluorfen was an efficient way to fight dicotyledon weeds, and the application of the mixtures of oxyfluorfen and graminicides ensures efficient destruction of annual and perennial cereal weeds. Our studies were used to elaborate the technology of combined application of a graminicide haloxyfop in the mixtures with a herbicide oxyfluorfen in onion fields (Morderer YeYu et al, 2014). Therefore, our previous studies promoted the elaboration of the strategies of protecting winter wheat and onions using synergic herbicide mixtures.

Combined application of herbicides and substances, capable of initiating PCD, is also a promising way of enhancing the phytotoxic effect of herbicides. For instance, it was found that the elicitor chitosan induces Ca^{2+} (calcium-dependent) PCD in plant cells (Zuppini et al, 2004). In our studies, the application of elicitor chitosan led to enhancing the phytotoxic effect of the mixture of herbicides, fenoxaprop-p-ethyl and metribuzin. , due to the stimulation of oxidative processes (Patent UA, 54664; Trach VV et al, 2011). It is also known that chitosan is a good complex former with adjuvant properties which may also promote the enhanced effect of herbicides on sensitive species of weeds. In addition, it was demonstrated that due to chitosan-induced oxidative stress there was an increase in the resistance of plants to phytopathogens (Xing et al, 2015) which is another valuable additional argument in favor of applying chitosan in the mixtures with herbicides on the fields of cereal crops.

As stated above, higher doses of administering herbicides may inhibit a crop due to the oxidative stress (Gar'kova AN et al, 2011; Langaro AC et al, 2017). It was demonstrated that the oxidative stress is a factor of decreased selectivity of herbicides, ALS inhibitors, for soya plants. For instance, due to the oxidative stress under the effect of herbicides, ALS inhibitors, the formation of the symbiotic nitrogen-fixation apparatus was inhibited, and its activity was decreased (Morderer YeYu et al, 2011). In this situation, antioxidant substances may be used to protect agricultural crops, thus decreasing the level of herbicide-induced oxidative stress in plant cells (Langaro et al, 2017; Radwan D, 2019). For instance, the antioxidant effect of NO and salicylic acid protects fields from the negative impact of different herbicides (Beligni and Lammatina 1999; Wang J et al, 2016).

As a stress contributes to NTSR as well, to prevent induced NTSR it is recommended to avoid the protection from oxidative damage, for instance, to use substances-inhibitors of SOD, considering its decisive role (Rogachev I et al, 1998; Warshawsky A et al, 2001). The efficiency of applying SOD inhibitor was confirmed in case of antagonism, related to a stress response of plants (Radchenko MP et al, 2013a). To avoid constitutive NTSR, it is recommended to search for substances, which are enzyme inhibitors (synergists), cleaving the herbicide molecules – cytochrome P450 (Preston C et al, 1998), glutathione transferase (Ezra G et al, 1985), hydrolase (Hoagland RE et al, 2004). The possibility of applying herbicides is based on the process of selective phytotoxicity, so these substances should correspond both to the toxicity and selectivity norms, besides, there is always an issue of economic feasibility.

While considering the need for combined application of herbicides, it is noteworthy that the latter is limited with the number of approved classes of herbicides due to high ecotoxicological requirements. It challenges conventional ways of searching for herbicides. The problem is – first of all, resistance occurs due to the fact that the conventional way of searching for herbicides has practically become obsolete which requires new approaches to the search for future herbicides. While in two decades, 1970–1990, during the period of maximal intensity in the development of the chemical method of weed management, more than 200 active substances of herbicides were invented and commercialized, in recent 30 years no new herbicide with the mechanism of

action, different from current ones, has been invented. One of modern strategies of creating new herbicides is the study of and cloning of genes, whose mutations are lethal or semi-lethal for plants (Duke SO, 2019). Another promising direction is the biological method of weed management, involving the application of allelochemicals of plants, phytopathogens or toxins, produced by them, to control weeds (Soltys D, 2013). However, the efficiency of applying these substances cannot be compared to the efficiency and economic feasibility of modern herbicides yet. For instance, a few grams of some herbicides of ALS inhibitors class may be sufficient for efficient weed management on the area of 1 ha. On the other hand, the study of allelopathy and the mechanisms of phytotoxic activity of toxins of rhizobial bacteria and fungi may be the source for creation of new herbicides.

The application of substances with prooxidant properties, including herbicides, to enhance the efficiency of herbicides in the mixtures or antioxidants to protect crops from the oxidative stress, is a possible way of managing a stress response and thus antagonism in the mixtures of herbicides or enhancing the selectivity. The application of substances, capable of inhibiting the process of protection from the oxidative damage or substances-synergists under NTSR, is a possible way of preventing NTSR problem (Delye C, 2013b). Nevertheless, the future of the chemical method of weed management lies in new ways of searching for herbicides, since global solutions to these problems require new sites of action, different from current ones.

CONCLUSIONS

Although herbicides mainly inhibit specific enzymes/proteins on the molecular level in plants, in many cases their final phytotoxicity will depend on passing the pathogenesis, induced by them. First and foremost, this is related to the presence of general mechanisms of resistance, by which plants respond to the effect of various abiotic stressors, including the effect of herbicides.

The relevance of studying the cross-adaptation and synergism under the application of herbicides is conditioned by the fact that under natural conditions plant organisms usually are exposed to the effect of not one but several stressors (for instance, herbicide+drought, herbicide+herbicide). Drawing conclusions on the problem of the interaction between stresses, one may state that short-term and soft treatment by one stress factor may eliminate the harmful impact of the subsequent stressors – probably since the former induces some protection mechanisms which result in enhanced resistance to further unfavorable factors (cross-adaptation). On the other hand, the treatment with a stronger stressor may also lead to enhancing the sensitivity of a plant organism to one or several stress factors, resulting in irreversible damage (cross-synergism). If a short-term and weak effect of stressors may lead to a short-term cross-adaptation to the herbicidal effect, then permanent application of herbicides in decreased doses or under unfavorable environmental conditions is the main reason for non-target-site-based cross-resistance to herbicides.

Therefore, the decrease in the efficiency of herbicides, including ACCase inhibitors under drought and under combining with herbicides from other classes as well as the protection against oxidative damage under NTSR are of general biological value, i.e. it is a part of the adaptation of plants to the effect of abiotic stressors. However, the nature of a stress is two-folded, which makes it possible to apply substances, capable of activating the oxidative reactions to enhance the phytotoxic effect of herbicides on weeds.

The article presents the analysis of the literature data and the results of our own studies according to the project “The study of molecular mechanisms of initiation, development and termination of the process of programmed cell death under herbicide-induced pathogenesis in plants” within the framework of the program of scientific studies of the NAS of Ukraine “Molecular and cellular biotechnologies for the needs of medicine, industry, and agriculture” for 2015–2019 (approved by the resolution of the Presidium of the NAS of Ukraine No. 22 dated February 11, 2015).

Стрес і застосування гербіцидів в посівах сільськогогосподарських культур

М. П. Радченко, І.Г. Пономарьова,
І.С. Позинич, Є.Ю. Мордерер

Інститут фізіології рослин і генетики
Національної академії наук України,
Вул. Васильківська, 31/17б Київ, Україна, 03022

e-mail: mradchenko.phd@i.ua*, iraskazka2014@ukr.net, pozychka@gmail.com, morderer@ifrg.kiev.ua

В природних умовах при комплексуванні гербіцидів чи при застосуванні гербіцидів в стресових умовах (наприклад, умовах посухи) ефективність дії гербіцидів може зменшуватися, що призводить до значних втрат врожаїв. Це пов’язано з тим, що інший гербіцид чи стресор, можуть запускати у рослин-бур’янів механізм адаптації і вони виживають, що в результаті призводить до забур’янення культур. Це, зокрема стосується гербіцидів інгібіторів ацетил-КоА-карбоксилази або так

званих граміцидів, які ефективні виключно проти злакових видів бур'янів. Ефективність цієї групи гербіцидів сильно залежить від умов навколишнього середовища і часто зменшується при комплексуванні з гербіцидами, ефективними проти дводольних видів бур'янів. Як виявляється, це пов'язано з тим, що остаточна фітотоксичність гербіцидів не визначається на рівні сайту дії (мішені гербіциду), а залежить від проходження етапу індукованого гербіцидами патогенезу – процесів, які відбуваються внаслідок взаємодії гербіциду з його сайтом дії. Свій вклад у індукований гербіцидами патогенез може вносити стресова реакція рослин-бур'янів. Загальновідомо, що рослини реагують на дію різноманітних абіотичних стресорів у формі неспецифічної стресової відповіді і в залежності від інтенсивності та тривалості дії стресора, рослина або адаптується або гине. На сьогодні достатньо даних, які свідчать, що в індукованому гербіцидами патогенезі задіяна програмована загибель клітин. Для певних класів гербіцидів індукторами програмованої загибелі клітин є активні форми кисню**.** Участь активних форм кисню та програмованої загибелі клітин у індукованому гербіцидами патогенезі дає можливість спрямованого впливу на фітотоксичну дію гербіцидів, зокрема за рахунок спільного застосування гербіцидів із сполуками, здатними бути індукторами програмованої загибелі клітин та речовин-прооксидантів. Підтвердженням ролі неспецифічної стресової реакції у розвитку фітотоксичної дії гербіцидів є випадки явища перехресної адаптації (активація антиоксидантного захисту) і перехресного синергізму (активація окиснювальних процесів) при застосуванні гербіцидів. На основі власних досліджень і літературних даних обговорюється значення перехресної адаптації та перехресного синергізму при застосуванні гербіцидів в умовах посухи та для визначення характеру взаємодії у гербіцидних комплексах. Зокрема, в статті обговорюється питання зменшення фітотоксичності гербіцидів інгібіторів ацетил-КоА-карбоксилази внаслідок явища крос-адаптації в умовах посухи та при комплексному застосуванні з гербіцидами інгібіторами ацетолактатсинтази. Наведені результати досліджень щодо зменшення антагонізму у сумішах гербіцидів інгібіторів ацетил-КоА-карбоксилази та ацетолактатсинтази в результаті використання речовин з прооксидантними властивостями, а також інгібітору антиоксидантного ферменту супероксиддисмутази. З іншого боку, проаналізовано можливість підвищення фітотоксичної дії гербіцидів інгібіторів ацетил-КоА-карбоксилази при їх комплексному застосуванні з гербіцидами з прооксидантними властивостями – інгібіторами транспорту електронів в фотосистемі 2 хлоропластів та інгібіторами протопорфіриноген оксидази. Це стало основою для розробки ефективних гербіцидних композицій у посівах пшениці і цибулі. Питання синергізму при комплексуванні гербіцидів набуває актуальності ще у зв'язку з проблемою поширення пов'язаної з сайтом дії резистентності**,** оскільки для подальшого запобігання цього типу резистентності необхідним є комплексування гербіцидів з різними механізмами фітотоксичності. Наведено дані, які свідчать, що підвищення активності систем антиоксидантного захисту, яке є результатом тривалого процесу еволюційної адаптації рослин бур'янів до дії абіотичних стресорів, є елементом непов'язаної з сайтом дії резистентності до гербіцидів. Обговорюються можливі шляхи запобігання негативного впливу стресової реакції на ефективність гербіцидів, а також перспективи хімічного методу контролювання гербіцидів.

Ключові слова: гербіциди, індукований патогенез, програмована загибель клітин, активні форми кисню, стрес, супероксиддисмутаза, перехресна адаптація, перехресний синергізм, непов'язана з сайтом дії резистентність до гербіцидів.

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