

# Unexpected Side Effects of Herbicides: Modulation of Plant-Pathogen Interactions

Andreas Kortekamp

*DLR Agricultural Research Station, Department of Phytomedicine*

*Neustadt/Weinstrasse*

*Germany*

## 1. Introduction

Herbicides are widely used as an important alternative to prevent excessive growth of weeds in agricultural crop land, particularly where conservation tillage is adopted. Weeds reduce crop yield and quality, interfere with cultivation and harvest operations and seem to be the most economically important of all pests with respect to sales of pesticides worldwide. As an interesting side effect, the biological activity of herbicides extends beyond their effect on target organisms and herbicides may influence plant-pathogen interactions through their effect on the pathogen, the plant, or on the surrounding soil organisms including symbiotic interactions. This phenomenon was first observed in the early 1940s by Smith et al. (1946) and described in more detail since 1960. Several studies examining the direct effects of various herbicides on plant pathogens and disease development have been published.

The objective of this chapter is to summarise publications in which herbicide applications have resulted in a direct effect on fungal plant pathogens *in vitro* or in the field or on disease development by influencing the metabolism of the plant. The question that arises is if the direct or indirect effect of herbicides on microorganisms is a general feature of these agrochemicals, also provoking some kind of stress that leads to a reprogramming of the plant's physiology, or if the observed effect relates to a distinct mode of action within a given plant-pathogen relationship. In some cases, herbicide-resistant plants were used to specify the effect on pathogens and plants when herbicides are applied at field rates. Even though the application of field doses may represent the true situation in the field where herbicide-resistant crops are planted, the effect of sublethal doses on non-transformed plants and pathogens remains more or less obscure. Thus, some hormetic effects, although defined as side effects of putatively toxic compounds but playing an important role regarding plant health, plant growth, or even harvest, can not be explained. Some, if not many herbicides seem to provoke hormetic effects (Duke et al., 2006). Hormesis refers to stimulatory effects caused by toxic compounds. Paracelsus, an ancient leader in toxicology, declared that all things are poison and are not poison. Only the dose matters and it is only the dose that makes a thing not to be a poison. He considered that substances, although toxic at higher concentrations or doses, can be stimulatory or even beneficial when used at low doses. Even though this phenomenon was recognised a long time ago, hormesis was mainly discussed in the biomedical literature, especially in toxicology and radiation biology. Sublethal doses of

toxic compounds or radiation, for instance, were found to provoke stimulatory responses instead of reducing the vitality of human cells (Calabrese & Baldwin, 2002). However, hormesis is not restricted to mammals and can be found within all groups of organisms, from higher plants and animals to bacteria and fungi (Calabrese, 2005). Interestingly, herbicides seem to induce hormesis in both, plants and pathogens (Duke et al., 2006). Stimulations have been shown for various physiological and biochemical parameters such as gene expression and enzyme activity (Ahn, 2008), growth, biomass, and protein content (reviewed in Duke et al., 2006), and chlorophyll content in plants (Kortekamp, 2010). Several highly informative reports considering side effects of herbicides have been published in recent years (e.g. Duke et al., 2007; Sanyal & Shrestha, 2008). However, a big part of the work was done with herbicide-resistant plants, not representing biochemical processes in non-transformed plants as mentioned above. Furthermore, mainly pathogens able to grow on artificial media were used. Even though the direct effect of the active compound, the additive(s) and/or the formulated product can be tested *in vitro* very easily in most cases, only a few details about the mechanisms that are involved when the pathogen enters its host are known. Moreover, especially the underlying mechanisms playing an important role in case for biotrophic pathogens (that can not be investigated without the respective host) are still far from being well known. Therefore, some examples, e.g. the grapevine-downy mildew interaction representing a biotrophic plant-pathogen relationship, are picked out to throw some light on these highly sophisticated plant-pathogen-herbicide interactions.

## 2. Herbicides with antifungal properties

### 2.1 Glyphosate

Glyphosate (N-[phosphonomethyl]glycine), mainly sold under the trade name Roundup, is a systemic broad-spectrum herbicide that inhibits 5-enolpyruvyl shikimate 3-phosphate synthase (EPSPS), a key enzyme in the biosynthesis of aromatic acids and secondary metabolites. Blockage of this pathway results in massive accumulation of shikimate in affected plant tissues leading to a deficiency of significant end-products such as lignins, alkaloids, and flavonoids and a decrease in CO<sub>2</sub> fixation and biomass production in a dose dependant manner (Olesen & Cedergreen, 2010). EPSPS is also present in fungi and bacteria, but not in animals, and organisms with glyphosate-sensitive EPSPS may be affected by glyphosate. In plants, glyphosate is readily translocated throughout the plant within a few days after treatment and thus affects roots or rhizomes even after foliar application. One reason for the popularity of glyphosate is that glyphosate-resistant plants had been developed. In such a case, glyphosate can be applied over the top to glyphosate-resistant plants as a postemergence herbicide to kill unwanted weeds without affecting the crop. In most cases, the use of glyphosate on resistant crops reduces the need for pre-emergence herbicides and other postemergence herbicides.

Some studies have shown that the application of glyphosate on glyphosate-resistant plants alters the susceptibility of such plants towards plant pathogens. Reports of both enhanced and reduced disease severity have been published and glyphosate seem to have preventative and curative properties. Furthermore, the formulation and adjuvants used to enhance the efficiency of the active compound can dramatically affect germination, growth, and propagation of fungal plant pathogens (Smith & Hallett, 2006; Weaver et al., 2006; Weaver, et al., 2009; Wyss et al., 2004). Interestingly, glyphosate has also been reported to

control mammalian pathogenic fungi (Nosanschuk et al., 2001) and was active against apicomplexan parasites that cause diseases such as malaria and toxoplasmosis (Roberts et al., 2002).

### 2.1.1 Soil pathogens

There are several reports indicating that glyphosate inhibits fungal species involved in soilborne diseases. *Sclerotium rolfii*, for instance, is a common soilborne plant pathogen known to persist on crop residues. Banana growers noted that rotting residues inadvertently sprayed with glyphosate had little mycelial growth and fewer sclerotia than those not sprayed with the herbicide. Growth of *Sclerotium rolfii* was retarded on culture plates amended with benomyl or glyphosate, each at the commercial rate of application. Both amended media reduced the radial growth of *S. rolfii* compared to the control; however, glyphosate-amended medium had the greater inhibitory effect (Westerhuis et al., 2007). Radial growth of other pathogens such as *Pythium ultimum* and *Fusarium solani* f.sp. *pisi* was also retarded with increasing concentrations of the herbicide (Kawate et al., 1992), which also referred to conidial germination and sporulation in *F. solani* f.sp. *glycines* (Sanogo et al., 2000). In contrast to the results described above, Harikrishnan and Yang (2001) found no negative effect of glyphosate on vegetative growth of several *Rhizoctonia solani* isolates and anastomosis groups. However, the herbicide influenced the production of fruiting bodies of this pathogen. The number of sclerotia produced was higher but these sclerotia remained smaller in the presence of the herbicide compared to the untreated control.

Even though inhibitory effects of glyphosate on several plant diseases have been reported, some pathogens were unaffected and/or glyphosate increased disease severity of host plants. In some cases, glyphosate affected growth and reproduction of a given pathogen *in vitro* but showed an adverse effect in the field. Glyphosate inhibited, for instance, the development of *Nectria galligena* mycelium *in vitro* but increased the number of lesions when apple shoots were inoculated with a mycelium derived from a medium containing glyphosate (Burgiel & Grabowski, 1996). Thus, even though glyphosate exhibit a negative effect towards distinct pathogens in some test systems, this herbicide may show other effects *in vivo*. In greenhouse studies using glyphosate-resistant sugar beet, increased disease severity was observed following glyphosate application and inoculation with *Rhizoctonia solani* and *Fusarium oxysporum* (Larson et al., 2006). This increase in disease was not fungal mediated, since there was no direct effect of glyphosate on both fungal species as tested in *in vitro* studies. Thus, the herbicide seems to reduce the plant's ability to protect itself against pathogens. Glyphosate was also shown to be phytotoxic to sugarcane and herbicide treatment resulted in increased disease severity caused by *Pythium arrenomanes* (Dissanayake et al. 1998). Furthermore, glyphosate application caused injury and death of *Lolium multiflorum* as a result of increased Pythium root rot (Kawate and Appleby, 1987). Even sublethal doses of glyphosate inhibited the expression of resistance in soybean to *Phytophthora megasperma* f.sp. *glycinea* (Keen et al., 1982), in bean to *Colletotrichum lindemuthianum* (Johal & Rahe, 1990), and in tomato to *Fusarium* spp. (Brammal & Higgins, 1988). Furthermore, glyphosate applied to the soil increases the disease symptoms caused by *Cylindrocarpon* sp. in grapevine (Whitelaw-Weckert, 2010).

Despite the fact that glyphosate may have a direct effect on a crop plant and the respective pathogens, repeated glyphosate use has also an impact on the microbial community composition. Repeated applications favour species belonging to the group of Proteobacteria in glyphosate-treated soils than occurring in untreated control soils (Lancaster et al., 2010);

glyphosate mineralisation was reduced when glyphosate was applied several times. Gimsing et al. (2004) found that glyphosate mineralisation rates are positively correlated with *Pseudomonas* spp. population size. However, results of Lancaster et al. (2010) indicate that a repeated application of glyphosate is associated with an increase of those soil microorganisms capable of metabolising the herbicide. Altered microbial community may repress *Pseudomonas* species such as the beneficial species *P. fluorescens* and may modulate plant-pathogen interactions as well.

### 2.1.2 Leaf pathogens

There are several cases of inhibitory effects of glyphosate on certain leaf diseases in various crops. Transgenically modified wheat with tolerance to glyphosate showed very low infection rates regarding leaf rust caused by *Puccinia triticina* and stem rust caused by *P. graminis* f.sp. *tritici* when treated with field doses one day prior to inoculation with the pathogen (Anderson & Kolmer, 2005). The leaf rust control by glyphosate decreased with reduced application rates and longer periods of time between herbicide application and rust inoculation indicating a direct toxic effect. However, control of leaf rust in wheat conditioned by glyphosate is effective for at least 21 days (Anderson & Kolmer, 2005), but how glyphosate inhibits rust infection was not investigated. The herbicide may act as a systemic fungitoxic compound itself or may induce a systemic resistance, since also non-treated leaves were protected after herbicide application. In wheat straw, Sharma et al. (1989) reported an inhibition of *Pyrenophora tritici-repentis* pseudothecia production by glyphosate. Glyphosate has been shown to reduce sporulation, growth, and disease development caused by other cereal fungal pathogen such as *Septoria nodorum* on wheat (Harris & Grossbard, 1979), Rhizoctonia root rot (Wong et al., 1993), and take-all of wheat caused by *Gaeumannomyces graminis*, as well as *Rhynchosporium secalis* and *Drechslera teres* on barley (Toubia-Rahme et al., 1995; Turkington et al., 2001).

Feng et al. (2005) showed by using glyphosate-resistant wheat and soybeans that rust infections and symptoms caused by *Puccinia striiformis* f.sp. *tritici*, *Puccinia triticina*, and *Phakopsora pachyrhizi*, respectively, can be suppressed when plants had been sprayed with formulated glyphosate. The authors proposed that when rust spores became exposed to the herbicide, glyphosate was able to inhibit fungal EPSPS, thus, through the same mechanism described for its herbicidal activity. Their studies with glyphosate-resistant wheat revealed that rust control activity of glyphosate is not mediated through the induction of SAR (systemic acquired resistance) genes, but that glyphosate provided both preventative and curative activities in greenhouse experiments and in the field. However, rust control seemed to depend on the systemic glyphosate concentration in the host plant during germination of rust spores and the first infection events. Thus, rust spores just entering the plant in order to receive nutrients have to be exposed to a lethal concentration of glyphosate. Furthermore, field data obtained from glyphosate-resistant soybeans suggest that rust control by glyphosate is influenced by environmental conditions, and rust races may differ in glyphosate sensitivity (Feng et al., 2008). Also species-specific differences in glyphosate sensitivity seem to exist, so that rust control in soybean requires higher doses than rust control in wheat (Feng et al., 2008). There are also intra-specific variations in *R. solani* as shown by Verma and McKenzie (1985).

Since glyphosate is originally used as an herbicide to prevent growth of unwanted weeds, the use of fungi and bacteria as biological control agents was tested as an alternative to chemical herbicides or, much more interesting, in combination with herbicides. In many

cases, weed control and disease incidence were enhanced when the biocontrol agent was applied after glyphosate treatment (Boyette et al., 2006; Boyette et al., 2008a; Boyette et al. 2008b). The authors demonstrated that an application of glyphosate prior to *Myrothecium verrucaria* provided better weed control in kudzu (*Pueraria lobata*), redvine (*Brunnichia ovata*), and trumpetcreeper (*Campis radicans*). This was also the case for green foxtail, which was sufficiently controlled when treated with glyphosate prior to *Pyricularia setariae* inoculation (Peng & Byer, 2005). These results suggest that timing of glyphosate application in relation to combined treatment with a bioherbicide is important. Wyss et al. (2004) reported that certain pesticides and their adjuvants affected spore germination and growth of *Phomopsis amaranthicola*, an effective bioherbicides against *Amaranthus* species. Several herbicides such as glyphosate had also negative effects on spore germination of *P. setariae* (Peng & Byer, 2005). Thus, one strategy to overcome direct toxic effects of herbicides is a sequential rather than simultaneous application of the synthetic herbicide and the bioherbicides. Applying glyphosate prior to pathogen application would allow the absorption, translocation, and the full action of the herbicide (with minimised degradation) and reduces its possible toxicity to the biocontrol agent. Furthermore, glyphosate interactions with bioherbicides were found to be synergistic. Sharon et al. (1992) showed that glyphosate suppressed the plant's defence by lowering phytoalexin production and biosynthesis of other phenolics. Even a sublethal dose of glyphosate suppressed the shikimate pathway in sicklepod (*Cassia obtusifolia*) infected with *Alternaria cassiae*, thus reducing the resistance of this weed (Sharon et al., 1992). Numerous examples in the literature have correlated production or transformation of preformed phenolic compounds and plant defence. In most cases, an activation of the enzyme phenylalanine ammonia-lyase (PAL) plays a pivotal role, and compounds that inhibit PAL activity have caused increased susceptibility to disease (Hoagland, 2000). This seems also to refer to crop plants such as soybean. Glyphosate was able to block resistance to *Phytophthora megasperma*, even in an incompatible interaction by lowering the glyceollin production, an important phytoalexin and part of the resistance machinery in soybean (Keen et al., 1982).

## 2.2 Glufosinate ammonium

The non-selective herbicide glufosinate ammonium is an ammonium salt of phosphinothricin and used as a postemergence contact herbicide currently being marketed under the trade name Basta® or Liberty®. Glufosinate ammonium efficiently kills various kinds of plants, since it is a glutamic acid analog that inhibits glutamine synthetase by irreversible binding (Hoerlein, 1994). Glutamine synthetase is also a target to control bacteria pathogenic to humans such as *Mycobacterium tuberculosis* (Nilsson et al., 2009). The inhibition of glutamine synthetase in plants results in an accumulation of toxic ammonium that disturbs electron transport systems and induces production of free radicals (Krogmann et al., 1959). Free radicals in turn cause lipid peroxidation and cell death (Devine et al., 1993; Hess, 2000).

Glufosinate ammonium resistant plants have been produced successfully by introducing a *bar* gene from the soilborne microbe *Streptomyces hygrosopicus* or the *pat* gene from *S. viridochromogenes*. The genes encode the phosphinothricin acetyl transferase, which converts glufosinate ammonium to a nonphytotoxic acetylated metabolite (Murakami et al., 1986; Thomson et al., 1987). Glufosinate ammonium-resistant crops allow the control of weeds through an application of suitable amounts of the herbicide. As a beneficial side effect, glufosinate ammonium can also reduce fungal diseases in plants. Wang et al. (2003) had

shown that glufosinate significantly reduced disease development of *Rhizoctonia solani* and *Sclerotinia homoeocarpa* on transgenic bentgrasses expression the *bar* gene under controlled conditions. Glufosinate ammonium also reduced Pythium blight caused by *Pythium aphanidermatum* in transgenic bentgrasses expressing the *bar* gene, even though the herbicide did not alter mycelial growth *in vitro* (Liu et al., 1998).

In rice, two important diseases, blast and brown leaf spot, were also diminished in transgenic rice when treated with glufosinate ammonium (Ahn, 2008). The herbicide inhibited the formation of appressoria of the two pathogens *Magnaporthe grisea* and *Cochliobolus miyabeanus* in a dose-dependant manner; but the same treatment did not affect conidial germination of both pathogens. However, glufosinate ammonium almost completely inhibited mycelial growth of both fungi *in vitro* and triggered the transcription of pathogen related (PR) genes and hydrogen peroxide accumulation in rice and *Arabidopsis thaliana* (Ahn, 2008). Furthermore, a pretreatment with glufosinate ammonium 24 h prior to infection greatly increased blast protection. These results indicate that the herbicide is able to activate the resistance response of the plant, and that the induced mechanisms are more effective after a time lag between application and infection. Thus, both direct inhibition of pathogen infection and activation of the defence system by glufosinate ammonium seem to be responsible for disease protection in transgenic rice. Other reports also showed that treatments with glufosinate ammonium enhanced resistance against rice sheath blight caused by *R. solani* on *bar*-transgenic rice (Uchimiya et al., 1993). In that case, herbicide treatment led to a substantial suppression of blight symptoms, even when applied two days after inoculation, indicating a curative capacity of glufosinate ammonium.

Even though the direct effects of glufosinate ammonium on plant pathogens are not well understood in most cases, this herbicide may inhibit glutamine synthetase activity in fungi or fungal like organisms similar to inhibition of glutamine synthetase in plants. Consistent with amino acid biosynthesis being the primary target of glufosinate ammonium, inhibition of glutamine synthetase in the presence of the herbicide leads to a reduced nitrogen metabolism, a reduced hyphal protein content, and thus to a restricted growth and biomass yield of various *Trichoderma* species (Ahmad et al., 1995). Furthermore, especially the expression of those genes involved in protein biosynthesis and energy production seem to be important for oomycetous pathogens during germination and at the onset of a biotrophic or hemibiotrophic infection. Whereas the amino acid biosynthetic genes are expressed at basal levels during release of zoospores (that are produced in sporangiospores or sporocysts), they are upregulated in germinated cysts of *Phytophthora* species, indicating a requirement of elevated amino acid production and metabolism at the early infection events. Among those genes expressed at early infection stages, glutamine synthetase was also upregulated in germinated cysts of *P. nicotianae* (Shan et al., 2004). During the biotrophic phase of the *P. infestans*-potato interaction, the free amino acid pool within the plant leaf increases, that corresponds with the expression of host amino acid biosynthesis genes (Grenville-Briggs & Van West, 2005; Grenville-Briggs et al., 2005). As infection progresses, there is a decrease in the level of free amino acids within the infected plant tissue and a corresponding increase in the expression of both host and pathogen amino acid biosynthesis genes (Grenville-Briggs & Van West, 2005; Grenville-Briggs et al., 2005) which attests the need of high levels of amino acids for a sufficient growth of the pathogen. Interestingly, growth and propagation of oomycetous pathogens such as *P. infestans* and *Pythium ultimum* were also inhibited by glufosinate ammonium *in vitro*, especially when cultivated on media containing low amounts of nutrients (Kortekamp, 2008).

Direct inhibition of mycelial growth was also observed for several fungal species putatively pathogenic to grapevine. *Botrytis cinerea*, *Guignardia bidwellii*, *Penicillium expansum*, and

*Phomopsis viticola* were exposed to various concentrations of glufosinate ammonium in an *in vitro* assay (Albrecht & Kortekamp, 2009). The herbicidal compound caused reduction of mycelial growth in a dose-dependant manner as it was shown for other phytopathogenic fungi. However, *G. bidwellii* seem to be extremely sensitive, since mycelial growth was reduced about of 80%, even when the pathogen was exposed to a 500fold diluted solution of glufosinate ammonium normally applied to the field. Even though the pathogen *P. expansum* seemed to be less sensitive towards this herbicidal compound with regard to mycelial growth, spore production of this fungus was nearly completely inhibited when exposed to the same low concentration used to suppress growth of *G. bidwellii*, maybe allowing an effective control of this challenging pathogen late in the growing season. An application of glufosinate ammonium also caused severe effects on growth and development of the obligate biotrophic grapevine pathogen *Plasmopara viticola* in a dose-dependant manner (Kortekamp, 2008; Kortekamp, 2010). High doses were unacceptable phytotoxic, but low doses did not cause any visible negative effect on grapevine leaf samples. Moreover, low doses increased chlorophyll concentrations as a result of a hormetic-stimulatory response.

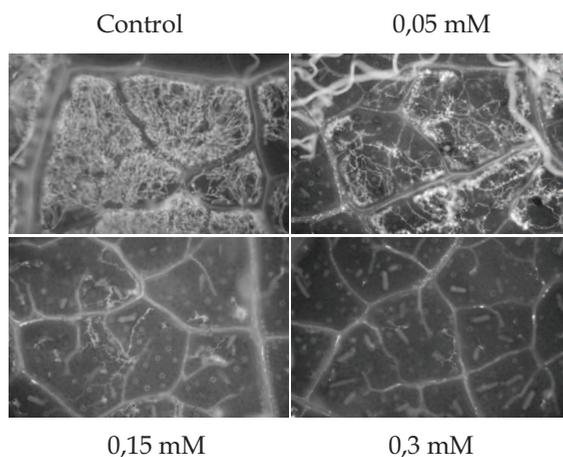


Fig. 1. Mycelial growth of *P. viticola* 7 day post inoculation. Incubation of leaf discs on glufosinate ammonium led to a retarded hyphal growth in a dose-dependant manner.

Even though germination of sporangiospores and zoospore release of the pathogen was not effected when exposed to low concentrations, spreading of the intercellular mycelium was reduced also leading to a dramatically reduced sporulation (Kortekamp, 2010). However, higher doses up to the rate normally applied to the field completely inhibited each developmental step of the disease cycle. Interestingly, glufosinate ammonium exhibited preventative and curative features. Pre- and postinfectious treatments resulted in significant reduced sporulation rates. The inhibitory effect of glufosinate ammonium on spore production decreased with increasing time intervals between inoculation and treatment, since the pathogen was able to establish a dense network of hyphae within the infected tissue and started to sporulate after few days. However, if the herbicide was applied prior to inoculation, the preventative effect increased with increasing time intervals between treatment and inoculation. This suggests an activation of defence mechanisms in

the plant. Alternatively or in addition, an application of the herbicide might cause an uncomfortable and improper environment due to a reduced level of amino acids, reduced nitrogen availability in general, an altered pH and/or an accumulation of ammonium. Especially changes in the pH, nitrogen availability, and ammonium concentrations have been suggested as a regulatory factor for colonisation of pathogenic fungi.

Ammonification (the active secretion of ammonium) of the host tissue leading to an alkalisation of the host environment has been suggested to be a key factor in the enhancement of pathogenicity of several fungi such as *Alternaria* and *Colletotrichum* (Duan et al., 2010; Eshel et al., 2002; Prusky et al., 2001). Both fungi are necrotrophic pathogens that are able to degrade cells or cell components to receive small fragments suitable for their own nutrition. This degradation of host cells seem to depend on suitable pH values, since most lytic enzymes are pH-sensitive regarding their maximum activity. Furthermore, changes in host pH are signals activating the production of pathogenicity factors via the regulation of gene expression (Kramer-Haimovich et al., 2006). It was recently shown that ammonium secretion and accumulation plays a key role as a pathogenicity factor during infection of tomato by *Colletotrichum* species and induces the transformation of the biotrophic to a necrotrophic infection (Alkan et al., 2008). Furthermore, addition of ammonium to a plant-pathogen system induces appressorium formation in *Alternaria alternata* and enables the pathogen to overcome defence mechanisms even in a resistant tobacco cultivar (Duan et al., 2010). Ammonium accumulation in plants is also associated with senescence promotion due to a decrease of glutamine synthetase activity (Chen and Kao, 1996; Chen et al., 1997). Plant tissues undergoing senescence are suitable resources for necrotrophic pathogens and saprophytes but do not represent adequate environments for biotrophic pathogens which rely on living host cells. Thus, high ammonia levels seem to favour necrotrophic fungi but maybe suppress the growth of biotrophic pathogens such as *P. viticola* on grapevine.

### 2.3 Triazine herbicides

The principle mode of action of triazine herbicides is the inhibition of photosynthesis. The triazines were shown to inhibit PSII but have no effect on PSI (Trebst, 2008). Several effects of triazines on soil organisms, especially on fungi causing soilborne diseases, were reported in the 1960s and 1970s. Especially atrazine had high inhibitory effects on *Fusarium moniliforme*, *F. oxysporum*, and *Aspergillus* species (Curl et al., 1968; Bozarth and Tweedy; 1971; Kabana and Curl, 1970; Rattanakreetakul et al., 1990). Several *Aspergillus* species were also repressed in soil by cyanazine, an herbicide that inhibits the growth of at least six other important soil fungi at field doses (Abdel-Fattah et al, 1983). Interestingly, this effect was not observed in artificial media. However, atrazine and other triazine herbicides seem to have an impact on growth and the production or viability of spores and fruiting bodies in soil cultures and on artificial media. Beam et al. (1977) demonstrated that enzyme activities and mycelial growth of *Rhizoctonia solani* were significantly reduced by prometryn and sclerotium production of *Sclerotium rolfsii* was reduced or even repressed by atrazine. This was also the case for *S. sclerotiorum* when triazine herbicides were applied to soil or media. Atrazine, simazine, and metribuzin inhibited mycelial growth or the development of normal apothecia and sclerotia at low concentrations (Casale and Hart, 1986). In another study, sclerotia germination was stimulated by triazine herbicides (Radke and Grau, 1986). Simazine and atrazine enhanced stipe formation but stipes and apothecia were malformed, whereas metribuzin enhanced stipe and mycelial growth without malformations. These

herbicides also induced the germination of *Cochliobolus sativus* spores which resulted in a loss of viability (Isakeit and Lockwood, 1989). *C. sativus* (*Bipolaris sorokiniana*) is the causal agent of a wide variety of cereal diseases. This pathogen can infect roots, leaves, stems, flowers, and head tissues just like other *Cochliobolus* species. Even though *C. sativus* was greatly affected by triazine herbicides, these herbicides had no influence on germination and viability of conidia of other *Cochliobolus* species such as *C. heterostrophus*, *C. carbonum*, and *C. victoriae* (Isakeit and Lockwood, 1989). There may be species differences among the genus *Cochliobolus*. Russin et al. (1995) reported that atrazine did also not reduce the production and germination of microsclerotia of *Macrophomina phaseolina* in sorghum but reduced fungal growth. Despite the fact that atrazine and other triazines could have a direct effect on fungal pathogens, they are able to modulate plant-pathogen interactions due to changes in the physiology of the plant. Atrazine applications to sugarcane plants growing in soils infested with *Pythium arrenomanes* resulted in increased root and shoot growth, even though root colonization by *P. arrenomanes* was unaffected by the herbicide. Furthermore, root rot symptom severity was not reduced. However, atrazine inhibited mycelial growth of *P. arrenomanes* *in vitro* when applied at the label rate (Dissanayake et al., 1998). The mechanism of root and shoot growth stimulation of triazine herbicides was shown to be an increase in the activity of nitrite reductase and transaminase (Ries et al., 1967) and seem also to refer to pea and sweet corn (Wu et al., 1972). Even though triazine and maybe other triazine herbicides are able to inhibit *P. arrenomanes* *in vitro*, such an effect was not observed in the field. If both, the herbicide and the pathogen are present, growth stimulation by atrazine seems to be greater than growth reduction induced by *P. arrenomanes*. Other data recently published indicate that herbicide treatments, especially when applied at field rates, may lower the effect of the fungicide. Heydari et al. (2007) conducted two field experiments to investigate the impact of three preemergence herbicides on the efficacy of commonly fungicides against *Rhizoctonia solani*. In one trial, the effectiveness of fungicides on fungal pathogenicity was reduced in the presence of prometryn and two dinitroaniline herbicides. The authors suggested that the herbicide-mediated suppression of fungicidal activity occurred perhaps because herbicides concentrations in the soil were high shortly after application but diminished gradually due to inactivation (Heydari et al., 2007). However, the fact that herbicides interfere with fungicidal activity of other pesticides may also be due to the presence of variable soil factors including texture, pH, temperature, moisture, and organic matter, which all might have an influence on microbial activity in soil.

Hill and Stratton (1991) tested the antifungal capacity of metribuzin towards *Alternaria solani*. Metribuzin was used for both preemergence and postemergence control of weeds in potatoes that can be affected by *A. solani*. The results presented for metribuzin indicated that this herbicide is relatively nontoxic towards *A. solani* *in vitro*. Interestingly, the herbicide interacted in an additive manner when applied at low doses together with a fungicide but antagonistically at higher doses. Thus, the type of interaction between triazine herbicides and fungicides seems to depend on the concentration of the components in mixtures. Reasons for this are still far from being well understood.

## 2.4 Dinitroaniline herbicides

Dinitroaniline herbicides are selective, wide-spectrum herbicides, which are used extensively in vegetable and field crops. The herbicidal effect results from an uptake by roots and the negative effect on root development. Dinitroaniline herbicides disrupt mitosis by binding to plant tubulin to form a complex, thus, inhibiting the formation of microtubules (Strachan & Hess, 1983).

Dinitroanilines have been reported to reduce disease incidence by different pathogens in various crops such as cherry, which can be affected by several *Phytophthora* species leading to a crown rot (Wilcox, 1996). Dissanayake et al. (1998) and Canady et al. (1986) reported that pendimethalin and trifluralin inhibited mycelial growth of *Pythium arrhenomones* and root colonization of *Macrophomia phaseolina*, respectively. However, both herbicides seem to be able to increase disease incidence of seedling damping-off caused by *Rhizoctonia solani* in cotton (Neubauer & Avizohar-Hershenson, 1973) and germination of sclerotia produced by *Sclerotinia sclerotiorum* (Radke & Grau, 1986). Trifluralin is also able to increase the severity of Fusarium root rot, since it induces hypocotyl swelling in soybean, which allows a more successful penetration of the pathogen *Fusarium oxysporum* (Carson et al., 1991). Even though trifluralin showed no effect on damping-off of cotton seedlings, pendimethalin lowered the effectiveness of fungicides applied in combination with the herbicide (Heydari et al., 2007).

In contrast to the results mentioned above, dinitroaniline herbicides may provoke a remarkable increase in resistance of pretreated plants to soil-borne pathogens, such as *Fusarium* species, even if applied at very low concentrations (Grinstein et al., 1976). Thus, this effect can not surely be attributed to a direct fungitoxic mode of action. However, the increase in resistance correlates with the amount of herbicide applied and correlates negatively with the production of ethylene. Ethylene seems to play an important role in inducing certain disease symptoms of wilt diseases (Cronshaw & Pegg, 1979; Cohen et al., 1986) by predisposing plant tissues to the damage of lytic enzymes or other fungal-derived pathogenicity factors. Even though a dose-dependent suppression of ethylene production and an induction of resistance in *Fusarium*-infected plants may be a result of different mechanisms, dinitroanilines are capable to induce the production of antifungal compounds leading to an occlusion of the pathogen (Grinstein et al., 1984).

Beside the effects of dinitroanilines on soil-borne pathogens, these herbicides seem also to interfere with the phyllosphere microflora. Population and species composition of microbial communities on leaf surfaces are mainly influenced by physico-chemical characteristics of the leaves. However, specific environmental conditions and agrochemicals can modify the leaf surface and, thus, its microflora. Shukla et al. (1988) showed that potato leaves treated with herbicides harbored lower population compared to the untreated control. Especially *Penicillium brevicompactum*, *Fusarium oxysporum*, *Mucor racemosus*, and *Rhizopus species* were repressed after fluchloralin (Basaline®) application, whereas other species such as *Oidiodendron echinulatum* were isolated only from herbicide treated plants. This indicates that some fungal species were directly affected by selected herbicides, but others are favored and find a more convenient habitat when the population of (most) other fungi diminished due to the effect of the herbicide. Interestingly, also bacterial populations seem to be affected by herbicides. In case of untreated potatoes, the population increased with time whereas the population decreased initially after an application of fluchloralin and other herbicides but recovered from herbicide treatment rapidly (Shukla et al., 1988).

## 2.5 Quaternary ammonium herbicides

The site of action for quaternary ammonium herbicides such as paraquat and diquat is in the chloroplast. Paraquat is known to act on the PS I within the photosynthetic membrane. The free electrons from the PS I react with the paraquat ion to give a free radical form that

interferes with oxygen leading to superoxides. The production of reactive oxygen species (ROS) in turn results in lipid peroxidation and photobleaching (Duke, 1990). Thus, paraquat acts in the presence of light and the herbicidal activity increases with increased light intensity. Inhibitory effects of paraquat on mycelial growth of pathogens were reported in *Rhizoctonia solani* (Black et al., 1996), *Rhizopus stolonifer* (Wilkinson and Lukas, 1969), *Sclerotium rolfsii* (Kabana et al., 1966), *Septoria nodorum* and *S. tritici* (Harris & Grossbard, 1979; Jones & Williams, 1971), and to a lesser extent in *Fusarium moniliforme* (Rattanakreetakul et al., 1990). Paraquat seems to enhance the toxicity of fungicides as reported by Awadalla & El-Refaie (1994). In pot tests, damping-off caused by *R. solani* was better controlled by fungicides when the soil was treated with paraquat or simazine. Both herbicides increased the toxicity of fungicides against mycelial growth of the pathogen maybe due to an increased concentration of ROS in the plant.

## 2.6 Protoporphyrinogen oxidase (PPO) inhibitors

This herbicide group consists of a large number of compounds that cause an uncontrolled autooxidation of protoporphyrinogen and a rapid lipid peroxidation (Sandmann & Böger, 1982; Duke, 1990). Therefore, these compounds were termed as peroxidising herbicides. They have a contact action and cause leaf burn, desiccation, cell death, and therefore also growth inhibition (Matringe et al., 1992). Several studies have reported that PPO inhibitors enhance the defence mechanisms in plants leading to a decrease in disease severity. Some of these results have been recently reviewed by Sanyal and Shrestha (2008). Nelson et al. (2002) conducted some experiments to determine the response in soybean after an inoculation with *Sclerotinia sclerotiorum* and an application with several PPO inhibitor herbicides. Lesions caused by *S. sclerotiorum* exhibited smaller sizes when treated with PPO inhibitors. Furthermore, some of these herbicides induced an increase in phytoalexin production, but only in leaves and not in stems (Nelson et al., 2002). Furthermore, even though these experiments include glyphosate resistant plants that should not differ in their response regarding a PPO inhibitor application, these plants produced more phytoalexins than near-isogenic glyphosate susceptible cultivars. Lesion size was not only reduced by all PPO inhibitors on the treated leaf but also on non-treated leaves of the same plant. The authors suggest that the herbicides induced a systemic resistance response and that these herbicides mimic a hypersensitive response due to an increased production of reactive oxygen species (ROS). The generation of ROS in turn can result in lipid peroxidation and cell wall lignification leading to a reinforcement of cell walls.

## 2.7 Other herbicides

Antifungal effects or effects on disease development have been reported for several other classes of herbicides including amide herbicides such as propyzamide (Burgiel & Grabowski, 1996), carbanilate herbicides such as desmedipham (Pakdaman et al., 2002), chloroacetanilide herbicides such as acetochlor, alachlor, and metolachlor (Cohen et al., 1996; Russin et al., 1995), diphenyl ether herbicides such as lactofen (Dann et al., 1999), and phenoxy herbicides such as clodinafop and 2,4-D (Pakdaman et al., 2002). Most of them showed broad antifungal effects and were able to inhibit the growth of fungal pathogens belonging to different taxonomical groups. Thus, their activity against phytopathogens or symbiotic organisms does not depend on their specific mode of action, even though the toxicity towards fungi may differ with regard to a given pathogen or distinct plant-pathogen interactions.

### 3. Herbicide-bacteria interactions

Once herbicides are released into the environment, mainly to affect weeds as their primary targets, they have to be degraded and eliminated during time to avoid long-lasting negative effects regarding soil microbiology or groundwater safety. Since a large number of herbicides have been introduced during the past four decades, the fate of these compounds is becoming increasingly important. Thus, several results describing the metabolism of herbicides by microorganisms in soil and water have been published. Especially *Bacillus* and *Pseudomonas* species showed high capacities to degrade various herbicides (Wang et al., 2008; Moneke et al., 2010). However, herbicides are known to change the microbial community in soils (Sapundjieva et al., 2003), including those species relevant for symbiotic interactions with plants (Khan et al., 2004), and will surely affect phytopathogenic bacteria. This topic was excluded from this review and has to be considered in more detail elsewhere.

### 4. Conclusion

The mechanisms of herbicide-pathogen interactions are not well understood in most cases. Some herbicides seem to have fungitoxic or at least fungistatic properties and affect mycelial growth, production of spores or fruiting bodies, or spore germination, whereas others provoke indirect effects on soil and leaf organisms that are antagonistic to pathogens. In some cases, herbicides showed no effect *in vitro* but lowered disease incidence on the respective host plant. Thus, herbicides may also stimulate the physiology of the plant, e.g. by altering phytoalexin production, mineral and nutrient composition, or source-sink relationships. These alterations may lead to a reduced susceptibility due to physiological changes not favourable for a given pathogen or an induction of resistance and, thus, may affect the incidence of disease. On the other side, herbicides may cause an increase in diseases due to direct stimulatory effects on growth and reproduction of the pathogen, effects on the virulence of the pathogen (Ware, 1980) or by inactivating parts of the defence battery of the host plant.

Effects of herbicides described in this review are not restricted to distinct fungal pathogens, since effects have been observed in necrotrophic, hemibiotrophic, and biotrophic species, and many fungal pathogens are affected by various herbicides applied to different crops. Furthermore, antifungal capacities of the active compound and/or the adjuvants or the modulation of the physiology of the plant leading to increased or decreased disease severity do not depend on the plant tissue affected. Both effects, lowered or enhanced disease incidence, can be observed in case for phytopathogens infecting leaves, stems or roots. However, in some cases, results obtained from *in vitro* experiments differ from those generated in the field or on the host plant. Thus, future research may also include high throughput methods, such as chip based technologies, to illuminate all mechanisms involved in plant-pathogen interactions that are modulated by herbicides. This trilateral communication has to be considered as a molecular and biochemical crosstalk between the plant and the pathogen, the plant and the herbicide, and the pathogen and the herbicide. New information about mechanisms can be obtained by the generation of gene expression profiles, the observation of physiological and morphological changes at tissue level or even in single cells, and an analysis of all relevant compounds such as phenolics, phytoalexins, and proteins (metabolomic approach). In some cases the plant itself and its herbicide-modulated physiology play the predominant role within a given plant-pathogen interaction.

However, depending on the compound used the pathogen may represent the main target that will be arrested or even killed by the herbicide.

There are only few reports about additive or even synergistic effects of combined applications of herbicides together with fungicides (Hill & Stratton, 1991; Schuster & Schroder, 1990), even though these effects can be expected. With regard to the data presented by Hill and Stratton (1991) and Heydari et al. (2007), the simultaneous use of an herbicide and a fungicide to control diseases and weeds could lead to antagonistic interactions between these two kinds of pesticides. This could cause a reduction in the efficacy of both the fungicide and the herbicide. It would be useful to determine the potential herbicide-fungicide interactions in distinct plant-pathogen combinations and to use herbicides that interact synergistically with fungicides, thus they can be used to lower the amount of the fungicides necessary to prevent diseases. Unfortunately, only few data on the ecotoxic effects of pesticide combinations exist, even though considerable data have been published on the effects of individual agrochemicals towards non-target organisms and ecological processes. Thus, the investigation of herbicide-induced effects on plant-pathogen interactions, regardless if applied alone or in combination with other pesticides, requires a multidisciplinary approach combining plant physiology, plant pathology, biochemistry, microbiology, and weeds science and represents a highly interesting field in plant science.

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## **Herbicides and Environment**

Edited by Dr Andreas Kortekamp

ISBN 978-953-307-476-4

Hard cover, 746 pages

**Publisher** InTech

**Published online** 08, January, 2011

**Published in print edition** January, 2011

Herbicides are much more than just weed killers. They may exhibit beneficial or adverse effects on other organisms. Given their toxicological, environmental but also agricultural relevance, herbicides are an interesting field of activity not only for scientists working in the field of agriculture. It seems that the investigation of herbicide-induced effects on weeds, crop plants, ecosystems, microorganisms, and higher organism requires a multidisciplinary approach. Some important aspects regarding the multisided impacts of herbicides on the living world are highlighted in this book. I am sure that the readers will find a lot of helpful information, even if they are only slightly interested in the topic.

### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Andreas Kortekamp (2011). Unexpected Side Effects of Herbicides: Modulation of Plant-Pathogen Interactions, *Herbicides and Environment*, Dr Andreas Kortekamp (Ed.), ISBN: 978-953-307-476-4, InTech, Available from: <http://www.intechopen.com/books/herbicides-and-environment/unexpected-side-effects-of-herbicides-modulation-of-plant-pathogen-interactions>

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Slavka Krautzeka 83/A  
51000 Rijeka, Croatia  
Phone: +385 (51) 770 447  
Fax: +385 (51) 686 166  
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### **InTech China**

Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821

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