Sektion 6: Entwicklungen bei Herbiziden

Sektion 6: Developments in herbicides

Herbicide Safeners: an overview

Herbizid Safener: ein Überblick

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Abstract

A significant number of herbicides used in cereals, corn and rice owe their strong efficacy aligned with crop selectivity to safeners. The first commercial safener was 1,8-naphthalic anhydride used as a seed treatment in corn. Since then approximately 20 Safeners have been commercialized in monocot crops, although several were superseded. According to independent market research, in 2011 approximately 30% of herbicide use value from all companies in corn and cereals came from products containing safeners. In rice the percentage was 6%. Almost all safeners work by inducing the expression of genes which code for enzymes involved in herbicide detoxification. Thereby, herbicides are degraded rapidly enough to ensure a damaging concentration is not reached. This gene induction may occur in just one crop or several. For commercial success no significant induction of herbicide degradation should occur in the weeds. The actual molecular target(s) of safeners is/are not known and therefore the reasons for species specificity are unclear. Bayer CropScience has a strong track record of safener discovery and has developed product portfolios based on its safeners mefenpyr-diethyl, isoxadifen-ethyl and cyprosulfamide. Atlantis® WG and Laudis® OD are important Bayer CropScience-products in Germany. These contain mefenpyr-diethyl to safen wheat and isoxadifen-ethyl to safen corn, respectively. The safeners provide an enabling technology which together with strong herbicide molecules has helped farmers to optimize their crop productivity through improved weed management.

Keywords: Crop safety, herbicide detoxification, metabolism, phytotoxicity, safener, selectivity

Zusammenfassung

Eine bedeutende Anzahl von Herbiziden in Getreide-, Mais- und Reisanwendungen verdanken Safenern ihre Nutzpflanzenselektivität bei gleichzeitig starker Unkrautwirksamkeit. Der erste kommerziell angewandte Safener war 1,8-Naphthalinanhydrid, das als Samenbeizung in Mais Anwendung fand. Seitdem wurden annähernd 20 Safener in monokotyledonen Nutzpflanzen kommerzialisiert, obwohl mehrere inzwischen wieder vom Markt verdrängt wurden. Entsprechend unabhängiger Marktforschung wurden 2011 etwa 30 % des Herbizidnutzungswerts von allen Firmen in Mais und Getreide aus Safener-enthaltenden Produktmischungen generiert. In Reis betrug der prozentuale Anteil 6 %. Fast alle Safener wirken, indem sie die Expression von Genen induzieren, die für Enzyme kodieren, welche an der Herbiziddetoxifizierung beteiligt sind. Dadurch werden Herbizide schnell genug abgebaut, wodurch sichergestellt wird, dass keine schädigenden Konzentrationen erreicht werden. Eine derartige Geninduktion kann nur in einer oder auch in mehreren Nutzpflanzen erfolgen. Für den kommerziellen Erfolg sollte keine signifikante Induktion des Herbizidabbaus in Unkräutern oder Ungräsern erfolgen. Das aktuelle molekulare Target von Safenern ist nicht bekannt, wodurch der Grund für eine Nutzpflanzenspezifität noch unklar ist. Bayer CropScience kann auf eine starke Erfolgsgeschichte in der Safenerentdeckung zurückblicken und hat Produktportfolios entwickelt, die auf seine Safener Mefenpyr-diethyl, Isoxadifen-ethyl and Cyprosulfamid basieren. Atlantis® WG und Laudis® OD sind wichtige Bayer CropScience-Produkte in Deutschland. Diese enthalten zum einen Mefenpyr-diethyl um Weizen und zum anderen Isoxadifen-ethyl um Mais zu sichern. Die Safener liefern die technologische Voraussetzung, die es dem Landwirt erlaubt, mit starken Herbiziden seine Produktivität im Unkrautmanagement zu optimieren.

Stichwörter: Nutzpflanzensicherheit, Herbiziddetoxifizierung, Metabolismus, Pflanzentoxizität, Safener, Selektivität

Introduction

In herbicide research, new test compounds synthesized by chemists face many hurdles before they might reach the market place. First and foremost they must have herbicidal activity at rates that permit cost effective use. The weed spectrum has to fit the commercial targets for prospective use scenarios, and increasingly compounds must also control herbicide resistant weed biotypes. The compound must meet regulatory criteria (toxicology, ecotoxicology and environmental fate) so as to allow registration. All these hurdles together mean the chance of any specific new molecule reaching the market is extremely low. When a new area of chemistry with herbicidal potential is discovered, exploration and fine tuning will usually provide stronger and weaker compounds. To fulfill the weed control hurdles, only the stronger compounds are likely to be of interest. However, these more active and broader spectrum compounds are more likely to damage crops and therefore not be commercially viable. It is this fundamental problem of compromise between weed control and crop safety that has been the driving force behind the commercial success of safeners - chemicals which prevent crop injury without significantly reducing weed control (HATZIOS and HOAGLAND, 1989; DAVIES and CASELEY, 1999; ROSINGER *et al*., 2012). Using safener technology may therefore enable a range of the strongest compounds to be used without crop injury, and so significantly increase the chance that a particular area of chemical research can deliver a selective herbicide product to the farmer. The aim of this article is to provide an overview of safener technology, including a brief history, the mode of action and, using commercial examples from the herbicide market in Germany, their commercial utility.

Why Safeners?

There are many hurdles which new herbicide molecules must overcome between the research chemists bench and the farmers field. In aiming for strong weed control, it is likely that crop plants will also become injured. Alternatively compounds with good crop tolerance (even in only a single crop) will tend to have weaker overall activity and/or gaps in the spectrum of weeds needing to be controlled. An example of this can be seen from Bayer CropScience herbicide research into 4-Hydroxyphenylpyruvate Dioxygenase (HPPD) inhibitors (Fig. 1).

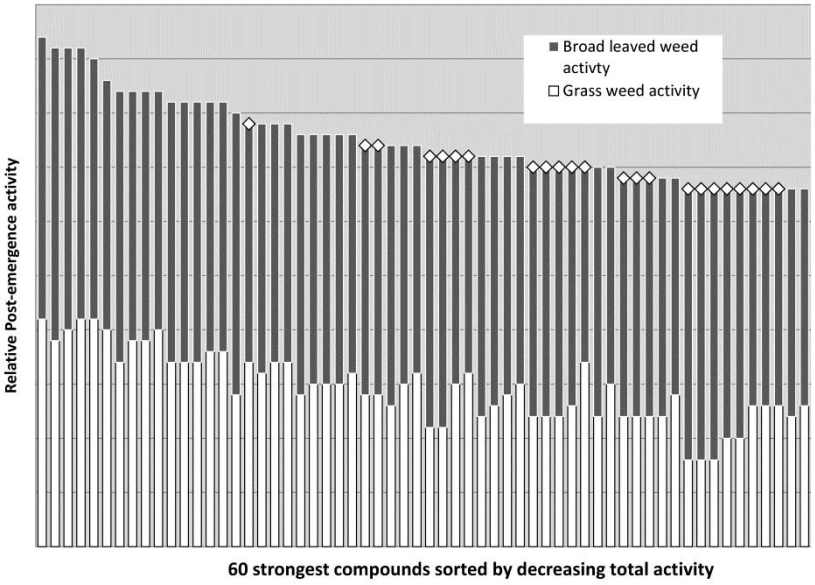

Fig. 1 Selectivity in wheat of 60 HPPD inhibitors sorted by total post-emergence activity.

Abb. 1 *Selektivität in Weizen von 60 HPPD Inhibitoren sortiert nach Gesamtwirkung im Nachauflauf.*

The herbicidal activity against a selection of target grass and broad-leaved weeds was assessed after post-emergence applications in the glasshouse. The 60 strongest compounds were ranked according to overall relative efficacy and then the post-emergence selectivity in wheat was overlaid onto the efficacy data. Selectivity was defined as injury (bleaching/necrosis) under 10% at the dose rate used for ranking weed control. Based on this definition only one compound from the 20 most active was selective in wheat. Out of the next 20 compounds 8 were selective, but from the remaining weaker compounds 14 were selective. During the investigation of herbicidal chemical classes usually many thousands of compounds will be prepared, but the tendency shown by this example remains true.

Even herbicides which do reach field testing for selective use in crops can have selectivity limitations. For example, crop damage may be increased under adverse weather conditions or on particular soils. Also, crop varieties can vary strongly in their tolerance towards a specific herbicide. This can be exemplified by tembotrione applied post-emergence at a dose of 300 g/ha (3x of maximum registered rates) to 71 corn varieties in field trials (Fig. 2). In the absence of safener most varieties (59) showed either no injury or less than 10% which was considered acceptable. Whilst, this clearly indicates a high level of crop tolerance for the compound, 12 varieties did show unacceptable damage greater than 10%, with some showing up to 50% injury. The addition of a safener (in this case 150 g of Isoxadifen-ethyl) reduced crop injury even in the most sensitive varieties to an acceptable level.

Since the invention and commercialization of herbicide tolerant (HT) crops (using genetic modification or natural mutant selection) the question arises whether safeners are still required. Because safeners had been used for over 20 years before HT was developed, companies with proprietary safeners tested them for safening effects on their newer herbicides. Where safening was adequate, the extensive R and D necessary to provide HT solutions could be avoided and a product portfolio could be developed based on individual safeners. Thus, despite the introduction of HT technology, safeners still capture significant market values in cereals, corn and to a lesser extent rice.

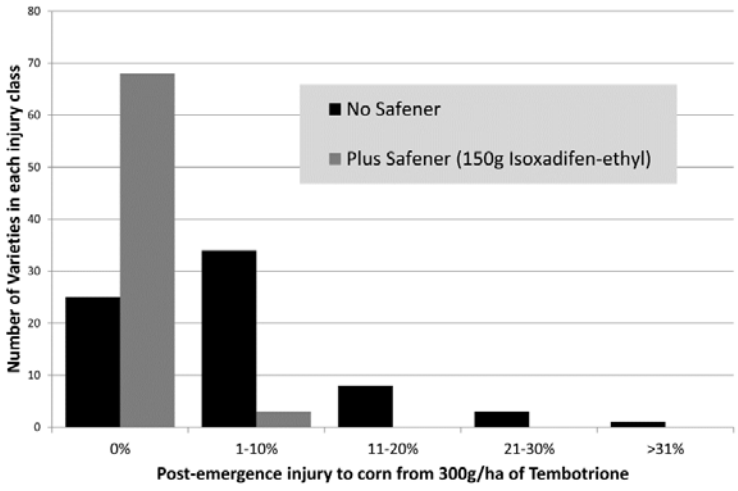

Fig. 2 Effect of safener on post-emergence field injury in 71 corn varieties from 300 g/ha tembotrione.

Abb. 2 *Schäden von 300 g/ha Tembotrione in 71 Mais-Sorten im Nachauflauf alleine und mit Safener.*

History of Safeners

The history of safeners, including structures and properties, has been the subject of several extensive reviews (HATZIOS and HOAGLAND, 1989; DAVIES and CASELEY, 1999; ROSINGER *et al.*, 2012; JABLONKAI, 2013). Therefore, this section gives just a brief summary of the commercial safeners. The first safener was 1,8-naphthalic anhydride (NA). It was launched in 1971 by Gulf Oil Company under the trade name Protect®, and it was used as a seed treatment in corn (HOFFMAN, 1969). Safening was provided against pre-emergence thiocarbamate herbicides such as EPTC, butylate and vernolate from Stauffer (now Syngenta). The 1970s and 80s saw the launch of five further commercial safeners that were used in seed treatment in corn and sorghum. The first was cyometrinil, an oxime ether launched as Concep I® in 1978 by Ciba-Geigy (now Syngenta). It was used to safen sorghum against the Ciba-Geigy chloroacetanilide pre-emergence herbicide metolachlor. Whilst safeners applied to the crop seeds have little or no potential for antagonism of weed control, they can have negative effects on crop germination and emergence. This was the case with cyometrinil and in 1982 Ciba-Geigy replaced it with a better tolerated analogue, oxabetrinil (Concep II®). This was then also replaced in 1986 by a third analogue, fluxofenim (Concep III®). In 1983 Monsanto launched the safener flurazole, also for sorghum seed treatment. Although it comes from a different chemical class to the oxime ethers, it also had a pre-emergence chloroacetanilide herbicide as the target for safening; namely the Monsanto compound alachlor. The oxime ethers and flurazole were produced by the same companies as the herbicides to be safened and therefore provided a sustainable value capture model that was not the case for NA from Gulf.

In 1972 the first safener which could be used in mixture with the herbicide was launched by Stauffer. This was the dichloroacetamide compound dichlormid which safened corn against pre-emergence thiocarbamate herbicides. In addition to dichlormid several further dichloroacetamide safeners were commercialized in the 1980s and early 1990s for pre-emergence use in corn. The most important of these are benoxacor, furilazole and AD67, all of which safen corn against chloroacetanilide herbicides. MG191 is another pre-emergence corn safener still in use. It is from a slightly different chemical class, but is also a dichloro-substituted low molecular weight compound. It was commercialized by the state run institute in Hungary in the 1980s. The use of safeners in co-formulation products versus seed treatment was a significant step forward in simplifying safener technology from both the farmer and manufacturer perspective. The farmer could apply the product just as if the herbicide were *per se* selective without the added complication of a seed treatment. For the manufacturer it meant better control of the product performance containing its herbicides (e.g. optimum herbicide/safener ratios). On the other hand the safener had to fulfill criteria that the seed treatment safeners did not. In particular the physico-chemical properties must allow co-formulation compatibility with the herbicide and of course no negative effect on control of target weeds. In addition, the soil and plant uptake characteristics of pre-emergence and seed treatment safeners will need to be different. In 1983 the first safener which could be used in rice was launched by Ciba-Geigy. This was fenclorim, and it safened the crop against the pre-emergence herbicide pretilachlor. It is a phenyl-pyrimidine unrelated to the above mentioned pre-emergence corn safeners, and has no appreciable safening activity in that crop. Daimuron (Dymron), cumyluron and dimepiperate are actually registered as herbicides. However, all three have a safening effect in rice especially against sulfonylurea (SU) herbicides like bensulfuon and azimsulfuron. Certainly the safening activity was discovered serendipitously as herbicide mixture concepts were being developed for the SU herbicides.

Tab. 1 List of commercialized safeners.

Tab. 1 *Auflistung von kommerzialisierten Safenern.*

Safener	Crop	Main timing	Safener	Crop	Main timing
Naphthalic anhydride	Corn	Seed treatment	Daimuron (Dymron)	Rice	Water surface application
Cyometrinil	Sorghum	Seed treatment	Cumyluron	Rice	Water surface application
Oxabetrinil	Sorghum	Seed treatment	Dimepiperate	Rice	Water surface application
Fluxofenim	Sorghum	Seed treatment	Fenclorim	Rice	Pre-emergence
Flurazole	Sorghum	Seed treatment	Cloquintocet-mexyl	Cereals	Post-emergence
Dichlormid	Corn	Pre-emergence	Fenchlorazole-ethyl	Cereals	Post-emergence
Benoxacor	Corn	Pre-emergence	Mefenpyr-diethyl	Cereals	Post-emergence
Furilazole	Corn	Pre-emergence	Isoxadifen-ethyl	Corn/Rice	Post-emergence
AD67	Corn	Pre-emergence	Cyprosulfamide	Corn	Pre- and post-emergence
MG191	Corn	Pre-emergence	Dietholate	Rice/Cotton	Seed treatment

In the late 1980s the next big step in safener technology was made by Hoechst AG (now Bayer CropScience AG) and Ciba-Geigy. Both companies discovered and commercialized safeners that could be used for the first time post-emergence and in cereals. For Hoechst it was fenchlorazole and for Ciba Geigy, cloquintocet-mexyl. Although these are from different chemical classes, both were introduced to safen against ACCase inhibitors (fenchlorazole with fenoxaprop-ethyl and cloquintocet with clodinafop-propargyl). Hoechst AG subsequently replaced fenchlorazole with mefenpyr-diethyl which had significantly better safening ability in barley. In the years since mefenpyr-diethyl and cloquintocet-mexyl were launched which have been used to safen newer herbicides from various chemical classes. For mefenpyr-diethyl prime examples are mesosulfuron-methyl and pyrasulfatole, and for cloquintocet-mexyl, pinoxaden and pyroxsulam.

Isoxadifen-ethyl was commercialized in 2002 by AgrEvo (now Bayer CropScience AG) and is the first safener with strong multi-crop (corn and rice) and multi-herbicide (e.g. fenoxaprop-ethyl, foramsulfuron, tembotrione) activity. In all cases isoxadifen-ethyl is used in post-emergence products. The most recently commercialized safener is cyprosulfamide which was launched by Bayer CropScience AG in 2009. It is strongly active in corn and sorghum and is particularly interesting because it can safen both pre- and post-emergence herbicides. The final safener of note is dietholate from FMC. This is used in several crops, most especially rice and cotton, to safen against clomazone. As far as the author is aware this is the only commercial safener used in a dicot crop.

The value of safeners?

To control weeds in conventional (non-HT) crops, farmers have a range of selective herbicide products available. For the farmer it is not important that the selectivity comes innately from the herbicide or that a safener is included. From this viewpoint the safener has no value – the farmer

primarily pays for weed control! So what is the value of the safener? Various market research sources annually gather sales data on agrochemicals. Using this data it is possible to define the sales of products which contain safeners and those that do not. This can be broken down further per crop. Figure 3 shows the percentage values of safened products for 2011, where the total value of safened products was approximately 1,7bio €. This is probably a slight underestimate because it is not always clear whether a product contains a safener or not.

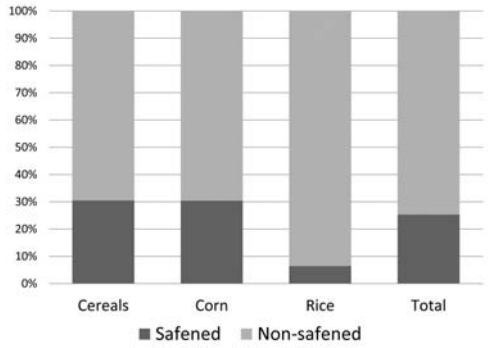

Fig. 3 Value of safened herbicide products in 2011 as a percentage of total herbicide sales.

Abb. 3 *Wert der auf Safenertechnologie-basierenden Herbizidprodukte im Jahr 2011 als prozentualer Anteil vom Gesamtherbizidumsatz.*

Safener mode of action

The way safeners reduce crop injury has been investigated for many decades and is the subject of several review articles (DAVIES and CASELEY, 1999). The idea that safeners might reduce herbicide uptake or translocation was tested extensively and in some cases effects were seen. However, as more data was gathered it became increasingly clear that almost all safeners primarily work by enhancing the degradation of the herbicides to inactive metabolites in the crop (RIECHERS *et al.*, 2010; ROSINGER *et al.*, 2012).

Several herbicides (e.g. isoxaflutole and many esters) are themselves not active at the target site. These can be termed prodrugs (or proherbicides) and they must first be transformed to the active principle in the plant or sometimes also in the soil. Once in the active form these herbicides, as well as those which are directly active, then undergo further metabolism to inactive compounds and conjugates. The speed of these transformations is the main reason for crop selectivity and weed control (DROBNY *et al.*, 2012). If the rate of metabolism to inactive forms in the crop is too slow then herbicidal damage will occur. On the other hand if detoxification is too fast in the weeds, then control is reduced or lost (e.g. metabolic resistance). Figure 4 shows theoretical curves for the concentration of active herbicide in the plant over time after a post-emergence application with and without an effective safener. With the safener added, the herbicide is more quickly metabolized and as a result the threshold which would cause visible crop damage is not reached.

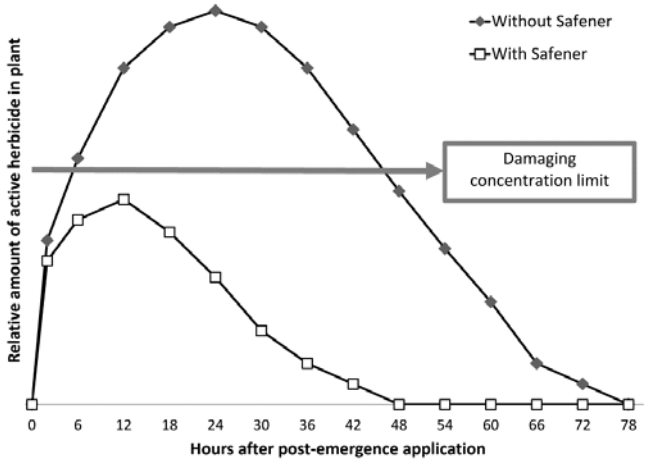

Fig. 4 Theoretical kinetics of herbicide concentration in crop plant.

Abb. 4 *Theoretische Kinetiken von Herbizidkonzentrationen in Kulturpflanzen.*

Herbicide detoxification often involves a three or four step enzymatic process (HATZIOS, 1991; VAN EERD and HOAGLAND, 2003) and it is known that safeners can increase the speed of at least the first three stages (ZHANG *et al*., 2007). Firstly, Cytochrome P450 catalyzed reactions can oxidize, reduce or hydrolyze the herbicide to introduce or expose a functional group. For many herbicides, just this first step produces inactive metabolites. However, for some pro-herbicides, as mentioned above, this step may be responsible for activation (e.g. hydrolysis of inactive fenoxaprop-P-ethyl to the active acid fenoxaprop-P). The next step involves conjugation reactions in which the herbicide or herbicide metabolite links with endogenous molecules such as glutathione (GSH), glucose (Glc) or amino acids. The enzymes which catalyze these reactions are primarily glutathione S-transferases (GSTs) and UDP-dependent glycosyltransferases (UGTs). GSTs are multi-functional enzymes in the cytosol and their main role in herbicide detoxification is that the resulting conjugates are primed for transport into the vacuole. Glucose conjugation can lead to O-, S-, and N-glucosides, glucose ester and malonyl-glucose-conjugates. Glucose conjugates can be subjected to secondary conjugation to form glucosyl-glucosides or, by malonyl-transferases, to 6-O-malonyl-glucosides. The third stage of herbicide detoxification is the transport of conjugates to the vacuole where further catabolic reactions can occur. This transport into vacuoles is frequently catalyzed by various ATP-binding cassette (ABC) transporters in the tonoplast or plasma lemma (TOMMASINI et al., 1997). Degradation of GSH conjugates in the vacuole, catalyzed by peptidases which remove the amino acid glycine and then glutamate are sometimes referred to as the fourth step in herbicide detoxification. Because safeners seem to only influence the speed of herbicide metabolism it is unsurprising that they do not alter the metabolic pathways. In other words, no new metabolites are found in safener treated plants.

The speed at which the herbicide detoxification occurs depend on the levels of the various enzymes mentioned above and these in turn are dependent upon the expression levels of the genes which code for them. There is now strong evidence that hundreds of genes encoding proteins involved in herbicide detoxification are induced within a few hours of safener application (KREUZ and TOMMASINI, 1996; THEODOULOU *et al.*, 2003; ZHANG *et al.*, 2007). This induction suggests that safeners work at the transcriptional level and surprisingly such gene activation is also seen in non safener target dicot species suggesting a common molecular safener mode of action for all plants (DERIDDER *et al*., 2002). Gene expression profiling experiments especially in Arabidopsis indicate parallels between the oxidative stress related oxylipin pathway and safener signaling (RIECHERS *et al*., 2010). In response to oxidative stress plants accumulate oxidized lipids (oxylipins,

cyclopentenones, phytoprostanes) derived from alpha-linolenic acid. These compounds were shown to induce the expression of genes involved in defense and detoxification reactions. It is suggested, that safeners could interfere with this signaling pathway and thus induce the expression of genes involved in detoxification of xenobiotics. There also seems to be a degree of overlap between safener induced gene expressions and the plant stress defense signaling pathway involving salicylic acid (SA). Indeed it could be shown that many safener-regulated genes are induced by salicylic acid (BEHRINGER *et al*., 2011). Therefore if appears that several signaling pathways may contribute to the full safener response in plants. However the primary target of safener signaling is still unknown. Future studies may provide a clearer understanding of these signaling cascades and also help to explain why safeners work well in specific crops, and not in weeds.

The mode of action of dietholate is rather unique. Before being introduced as a safener, it was used as an "extender" for thiocarbamate herbicides, working by inhibiting the cytochrome P450 activity of soil microbes which were responsible for rapid degradation of these soil applied herbicides. Commercially dietholate it is only used to safen clomazone which itself is not herbicidal. Research indicates that clomazone must be metabolized by cytochrome P450 to the herbicidally active 5-keto clomazone and that dietholate inhibits the cytochrome P450 in plants (FERHATOGLU *et al*., 2005; FERHATOGLU and BARRETT, 2006). Therefore, this safening mechanism relies on an opposite effect to other safeners (i.e. reduced rather than enhanced metabolism).

Two examples of safener based products from Germany

A manufacturer with access to one or more safeners and a strong herbicide research pipeline may be able to develop a significant range of safener-containing weed control products. For example, Bayer CropScience AG (BCS) has developed a wide range of products in cereals, corn and rice based on its three safeners, mefenpyr-diethyl, isoxadifen-ethyl and cyprosulfamide. In Germany safened products are sold in cereals (especially wheat) and corn. For BCS two important products can be used as examples; namely Atlantis® WG in cereals and Laudis® OD in corn. Atlantis® WG contains 30 g/kg mesosulfuron-methyl, 6 g/kg iodosulfuron-methyl sodium and 90 g/kg of the safener mefenpyr-diethyl. It is used for post-emergence grass and broad-leaved weed control in winter wheat, rye, triticale and spelt. Applications may be made in autumn or spring and dose rates range from 150 g/ha to a maximum of 500 g/ha. This maximum rate contains 15 g of mesosulfuron-methyl, 3 g of iodosulfuron-methyl and 45 g of safener. The safening power of mefenpyr-diethyl can be seen under glasshouse conditions in Figure 5. The experiment used 60 g/ha of mesosulfuron (4x max. field rate) applied post-emergence to wheat and barley with low rates of safener. The trial clearly shows why mesosulfuron plus mefenpyr-diethyl can be used in wheat (maximum injury reduced from 40-65% to 0% by the safener) but not in barley where safening was insufficient. The same experiment contained a lower rate of mesosulfuron combined with higher rate of mefenpyr-diethyl to check for antagonism in grass weed control. The efficacy level against *Avena fatua* (AVEFA), *Alopecurus myosuroides* (ALOMY) and *Lolium multiflorum* (LOLMU) was not changed significantly.

Laudis OD® (an oil dispersion formulation) contains 44 g/L tembotrione and 22 g/L isoxadifen-ethyl and is used post-emergence in corn to control grass and broad-leaved weeds. The application rate can range from 1.7 to 2.25 L/ha meaning a maximum dose of tembotrione of approximately 100 g/ha and 50 g/ha of safener. As shown in Figure 2, even at 3 times this maximum rate, tembotrione is extremely well tolerated by most corn varieties. However, a number of varieties show higher sensitivity, and in field trials the variety Lorenzo was identified as especially sensitive (50% injury at 300 g tembotrione). Figure 6 shows glasshouse results at various post-emergence rates of tembotrione and isoxadifen-ethyl on this sensitive variety and green foxtail (*Setaria viridis*) as an indicator of weed control levels. The 2:1 ratio of herbicide to safener, that was used in the final product, had no significant effect on weed control, whilst completely safening this highly sensitive corn variety.

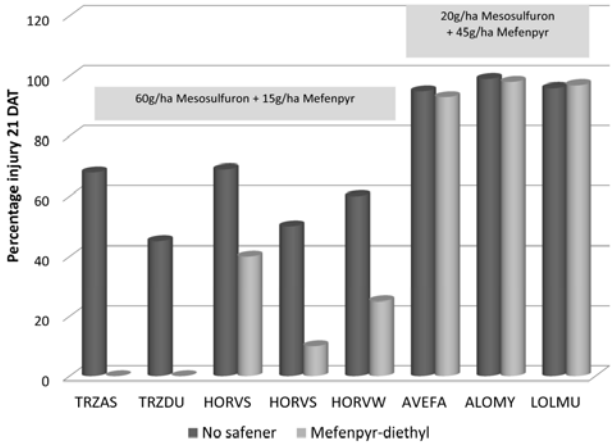

Fig. 5 Effect of mefenpyr-diethyl on crop injury and weed control of post-emergence mesosulfuron-methyl.

Abb. 5 *Einfluss von Mefenpyr-diethyl auf Kulturschäden und Unkrautbekämpfung von im Nachauflauf angewandtem Mesosulfuron-methyl.*

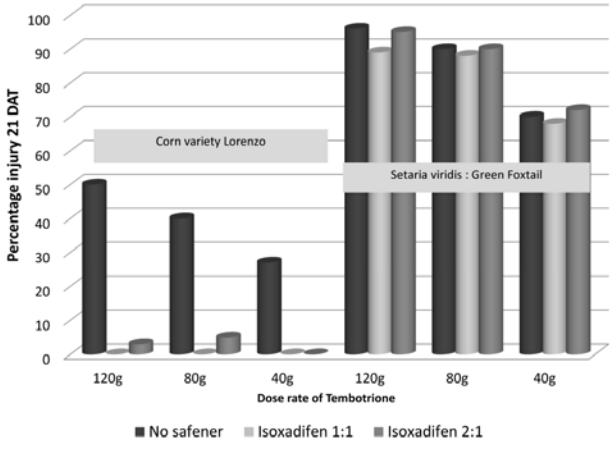

Fig. 6 Effect of Isoxadifen-ethyl on crop injury and weed control of post-emergence tembotrione.

Abb. 6 *Einfluss von Isoxadifen-ethyl auf Kulturschäden und Unkrautbekämfung von im Nachauflauf angewandtem Tembotrione.*

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