Milestones in the Development of Herbicide Safeners*

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The concept of using chemical safeners to improve herbicide selectivity became widely known in 1969 with the introduction of naphthalic anhydride (NA) to improve the tolerance of maize to thiocarbamate herbicides. Soon thereafter dichlormid was also developed as a safener for thiocarbamates in maize. At present there are at least eight different chemical safeners that have been developed commercially. Many of these safeners have been most effective for chloroacetamide or thiocarbamate herbicides in monocotyledonous crops such as maize or sorghum. Some are like dichlormid and have been developed as physiologically selective safeners that can be combined in the formulation with the herbicides. Others, like NA, are either less selective or less active in the soil and must be used as dressings on the crop seed. Most of the presently used safeners are for soil active herbicides. The challenge for the future will be to develop safeners that are effective for the newer postemergence herbicides in dicotyledonous as well as monocotyledonous crops.

Introduction

Chemical herbicides have had an immense impact on agricultural productivity and the key reason for their importance is selectivity. No other approach to weed control is as selective and efficient for the control of numerous species of weeds with such a low risk of crop injury. Even in crops that are inter-row cultivated, banded applications of selective herbicides can increase yields an additional 10% to 15%.

During the 1960's and early 1970's, many new herbicides were developed each year, and agriculturalists presumed it was only a matter of time before a highly selective herbicide was developed for every major crop. These expectations have gradually been realized and herbicide use has increased steadily as a result. In fact, during the 1990's, herbicide use for selective weed control may account for at least two thirds of all pesticide use in agriculture.

Although selectivity is the major reason for the importance of herbicides in general, there is not yet a single herbicide that is perfectly selective. Theoretically, it should be possible to exploit the unique physiology or biochemistry of a very major crop like maize (*Zea mays* L.) and to design a herbicide that no plant species except maize can tolerate. However, no presently available herbicides are the product of such an approach and perfect herbicide selectivity can't be expected. Repeated use of the same herbicide or even the same mixture of herbicides eventually allows population increases in weeds that are closely related or similar to the tolerant crop.

At present, chemical safeners or antidotes offer the greatest potential for achieving perfectly selective weed control with herbicides. In fact in some situations, the technology with safeners for herbicides already exists! As one example, application of chemical safeners (dichlormid, naphthalic anhydride) to a particular variety of maize seed can permit the use of various herbicides (EPTC, butylate, metazachlor) to selectively control volunteer seedlings of other maize varieties. Thus, if or when, the perfectly selective herbicide is developed for a crop, plant breeders may still choose to use seed applied safeners to selectively protect some breeding lines but not others.

During the 1970's and 1980's several herbicide safeners were developed as either formulation additives or as seed treatments and there is promise for an even greater application of the concept during the 1990's.

The use of safeners to improve the biochemical tolerance of crop plants to herbicides may seem like a new concept to many agriculturalists. However, the origin of the concept goes back to the

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1940's during the very beginning of the "herbicide era" in weed control. Hatzios and Hoagland [1] have edited a recent and very thorough review of the field. The following is a brief summary of the major developments or "milestones" that have helped put this marvellous concept into agricultural practice.

Early Discoveries

A. *NA, the first herbicide safener to be used commercially*

In the minds of many weed scientists, the herbicide antidote or safener era began in 1969. It was the Weed Science Society of America meetings in February of that year, that Otto Hoffman [2] made big news with his paper on the use of NA (1,8-naphthalic anhydride) seed treatments to selectively protect maize seedlings from carbamothioate herbicides. NA as the product PROTECT (Table I) soon became the first commercially marketed herbicide safener. However, the year 1969 was far from the beginning of this new approach to achieving greater herbicide selectivity. The earliest published reports appeared in the early 1960's when Hoffman [3] und Matsunaka [4] published their initial studies on safeners for barban in wheat and amitrole in rice, respectively. According to Otto Hoffman [5], his interest in developing herbicide safeners originated as early as 1947. He recalls entering his greenhouse on a hot summer afternoon of that year and discovering that most of the tomatoes (*Lycopersicon esculentum* Mill.) in his experiments had accidentally been injured by vapours of 2,4-D. In fact, the only tomatoes not injured were those that had been treated with 2,4,6-T, an analogue of 2,4-D that was later shown to act as an anti-auxin. Hoffman's interest was further aroused with a later discovery that 2,4-D was very antagonistic to barban in wild oats (*Avena fatua* L.) [5]. However, the challenge was always to find antagonistic herbicide-safener mixtures that were selective (antagonistic on the crop but not on the weeds) or safeners that were effective and non-injurious as selective applications to crop seed. Numerous greenhouse tests over a span of ten or more years eventually led to the development of NA as the first safener for herbicides in maize. NA has moderate activity as a safener for a number of types of herbicides such as carbamates, chloroacetamides, carbamothioates, imidazolinones, and sulfonyl ureas in various monocotyledonous crops such as maize, sorghum (*Sorghum bicolor* L. Moensch), oats (*Avena sativa* L.), wheat (*Triticum aestivum* L.), barley (*Hordeum vulgare* L.) or rice (*Oryza sativa* L.) [6–8]. Although it never became widely important as a commercial product, its diversified activity has made it a very important research tool (Table I).

Table I. Herbicide safeners that have been developed commercially.

Manufacturer	Common name Trade name	Application[a] method	Herbicide(s) counteracted	Crop(s) protected	References
BASF	*LAB-145,138*	selective spray	metazachlor	maize	[13]
CIBA-GEIGY	*Cyometrinil* Concept I	seed treatment	metolachlor	sorghum	[11]
	Oxabetrinil Concept II	seed treatment	metolachlor	sorghum	
	CGA-133205 Concept III	seed treatment	metolachlor	sorghum	
	CGA-154281	selective spray pre.	metolachlor	maize	[15]
	Fenclorim	selective spray	pretilachlor	rice	[14]
Gulf Oil	*Naphthalic Anhydride* Protect	seed treatment	carbamothioates	maize	[2]
Hoechst	Fenchlorazoleethyl	selective spray post.	fenoxaprop-ethyl	wheat	[18]
Kumiai	Methoxyphenone	selective spray pre.	benthiocarb	rice	[16]
Monsanto	*Flurazole* Screen	seed treatment	alachlor	sorghum	[12]
Nitrokemia	MG-191	selective spray PPI	carbamothioates	maize	[17]
Stauffer	Dichlormid	selective spray PPI	carbamothioates	maize	[9]

[a] Pre., post., and PPI mean preemergence, postemergence, and pre-plant-soil incorporated, respectively.

B. *Dichlormid (R-25788), the first selective herbicide safener for maize*

A few years after the introduction of NA, Pallos *et al.* [9] patented dichlormid (known for many years by the code R-25788) and other chloroacetamides as safeners for carbamothioate herbicides in maize. Dichlormid was also effective as a seed applied safener but unlike NA, it was much more effective and selective when applied as a tank mixed spray and incorporated right along with the herbicides in the soil [10]. These properties permitted its development as SUTAN$^+$. Largely because of its selectivity for protecting maize but not weeds, dichlormid was a much greater commercial success than was NA. It permitted Stauffer Chemical Company to market two "new" herbicide products with "improved" selectivity in maize for the control of difficult weeds such as nutsedge (*Cyperus esculentus* L.), shatter cane (*Sorghum bicolor* L.) and various annual grasses. Dichlormid has activity as a safener for many of the same types of herbicides as does NA [8]. However in contrast to NA, it has only marginal safening activity for monocotyledonous crops other than maize [8] (Table I).

Other Herbicide Safeners that have been Developed Commercially

A. *Safeners for chloroacetamide herbicides*

The development of NA and dichlormid stimulated a major expansion of research in this field. Researchers within various companies began the search for chemical safeners to improve the selectivity of their herbicides in additional crops. These efforts have been more successful for the chloroacetamides than for any other group of herbicides. In the early 1980's Ellis *et al.* at CIBA-GEIGY [11] developed various oxime ether compounds as safeners for metolachlor and Sacher *et al.* at Monsanto [12] developed various thiazole carboxylates as safeners for alachlor. Both of these safeners are most effective as seed applications to protect sorghum from metolachlor or alachlor and the treated sorghum seed is the marketed product. Wurtzer *et al.* [13] at BASF have now developed BAS 145,138, a dichloroacetamide, as a safener for metazachlor in maize and Quadranti and Ebner [14] at CIBA-GEIGY have developed fenclorim as a safener for pretilachlor in rice. Peek *et al.* [15] at CIBA-GEIGY have also developed CGA-154281 to improve the selectivity of metolachlor in maize. These latter three safeners are all selective and are marketed as components in the formulations of the respective herbicides (Table I).

B. *Safeners for other herbicides*

In a unique approach to herbicide safening, Wakabayashi and Matsunaka [16] have developed methoxyphenone as a safener for the herbicide benthiocarb in rice. Rice can be injured when benthiocarb breaks down to a toxic dechlorinated metabolite in soil. Methoxyphenone is also an effective herbicide in rice but when it is used in combination with benthiocarb, it inhibits the microbial production of the toxic benthiocarb metabolite and injury to rice is prevented.

Studies of structure activity relationships among chloroacetamide safeners for herbicides in maize, led Dutka and Komives [17] to conclude that either the $Cl_2CH-CO-N=$ or the Cl_2CH-CO group was essential for safener effectiveness. They speculated that these groups could act *via* transacylation reactions. This hypothesis led to the synthesis and commercial development of MG-191 as an additional selective safener for carbamothioate herbicides in maize.

Most of the herbicide safeners that have been developed commercially act as either seed or soil treatments to prevent crop injury from soil active preemergence herbicides. Major exceptions to this are the new safener-herbicide combinations recently developed by Hoechst [18] and CIBA-GEIGY [19]. In the Hoechst system, fenchlorazole-ethyl is a selective safener for fenoxaprop-ethyl in wheat and barley and both safener and herbicide can be formulated as the new, more selective, postemergence herbicide, PUMA (Table I). Furthermore, while this combination is safened on wheat and barley, there is significant evidence that fenchlorazole-ethyl synergizes the activity of fenoxaprop-ethyl on some weed species [20, 21]. The CIBA-GEIGY herbicide, CGA-184, 927, is also an aryloxy phenoxy propanoate like fenoxaprop-ethyl that is particularly effective for control of grassy weeds but is not fully selective for use in cereals [19]. In combination with the safener, CGA 184, 927, this herbicide also has a wide margin of safety for use in wheat [19].

Future Challenges

A. *Herbicide safeners for dicotyledonous crops*

Hall and Soni [22] have recently been able to increase rapeseed (*Brassica napus* L. *cv*. Altex) tolerance to picloram by pretreating the plants with clopyralid, a closely related pyridine herbicide. In earlier research, Stephenson and Ezra [23] used subtoxic pretreatments with the herbicides, pyrazon and metribuzin, to increase the tolerance of beets (*Beta vulgaris* L.) and tomatoes, respectively, to later normally toxic rates of these same herbicides as postemergence treatments. Phatak and Vavrina [24] have increased the tolerance of soybeans and potatoes (*Solanum tuberosum* L.) to postemergence applications of metribuzin by preemergence treatment of these crops with the growth retardants, daminozide, triapenthenol and BAS 140,810.

Although, the studies mentioned above indicate some promise, there is not yet a herbicide safener that is very close to commercial use on dicotyledonous crops. Despite extensive research on the mode of action of safeners, few investigators have even offered hypothetical explanations for why it seems so easy to protect monocots as compared to dicots from various herbicides.

B. *Safeners for postemergence herbicides*

In the early research with barban, Hoffman [3] and later Chang *et al.* [26] employed seed applied safeners to increase the tolerance of wheat and oats to this postemergence herbicide for wild oats. However, with this approach, the efficacy of the seed applied safener was reduced in heavier, more adsorptive soils. Thus protection of the crop against a postemergence herbicide varied with the soil type [25]. The safeners being developed by CIBA-GEIGY [19] and Hoechst [18] (mentioned above) are the first safeners that are sufficiently effective and selective to be formulated along with postemergence herbicides.

With the expected trend toward greater use of postemergence herbicides, increased efforts to develop postemergence safeners would certainly seem warranted, particularly for dicotyledonous crops.

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