

Herbicide and Pharmaceutical Relationships

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For many years, virtually all pharmaceutical companies had an agrochemical division. This was partly to maximize the benefits of expensive chemical synthesis efforts by searching for many types of useful biological activities. Leads for pharmaceuticals and pesticides often overlap, in some cases leading to similar compounds used for human health and weed management purposes. This review will focus on herbicides and herbicide classes that have potential pharmaceutical properties, both as therapeutic agents that act through human molecular target sites and those that act on infectious agents. An example of the first case is compounds that target plant acetyl coenzyme A carboxylases, inhibiting fatty acid synthesis, and similar compounds used in humans as anti-inflammatory agents. Another such example is the triketone class of compounds that can act both as herbicides and as treatments for the genetic disease tyrosinemia, targeting the same enzyme in both cases. Examples of the second case are the relatively large number of herbicides that have activity against the malaria protozoan (*Plasmodium* spp.). It turns out that *Plasmodium* spp. and related disease organisms have an organelle that is apparently analogous to the plant plastid, the apicoplast. Herbicides such as dinitroanilines are active against several protozoan parasites by the same mechanism by which they kill plants, interaction with tubulin to halt cell division and other tubulin-dependent processes. These and other multiple activities of various herbicides and herbicide classes provide perspective on the broad biological activity of herbicides and related compounds.

Key words: Disease, drug, herbicide, pharmaceutical.

Both pharmaceuticals and pesticides are designed to target particular biological functions, and in some cases these functions overlap in their molecular target sites, or they target similar processes or molecules. Shaner (2004) reviews molecular target sites for herbicides that are also found in mammals. Partly for this reason, most pharmaceutical companies until recently had pesticide divisions, sometimes with a different name (e.g., Eli Lilly and Elanco). All compounds generated by either division of the company were evaluated for both pesticide and pharmaceutical uses. Sometimes lead pesticides became pharmaceuticals and vice versa. However, little of this type of information was published and must usually be surmised from patent literature. One of the exceptions is fluconazole, a fungicide product discovered by the pharmaceutical sector that is now used as a pharmaceutical and patented as a crop production chemical (Delaney et al. 2006).

The physicochemical parameters used by industry as a first estimate of the probability of a molecule being a good pharmaceutical or pesticide are very similar (Lipinski et al. 1997; Tice 2001). In fact, the 20 most common chemical side chains of pharmaceutical molecules are the same as those for pesticides and are found in about the same relative frequency (Delaney et al. 2006). The molecular weight range of pesticides and pharmaceuticals is also very similar. This overlap made the synergy between the two discovery areas even greater. Perhaps the primary difference between pesticides and pharmaceuticals involves economics. Molecules that are costly to synthesize (e.g., more than one chiral center) are generally precluded from the pesticide market, whereas the pharmaceutical market can bear more expensive molecules.

Occasionally, certain analogs of a particular chemical class have been found to be good pharmaceuticals, whereas others are used as pesticides. In some cases, the molecular target sites are the same and in others they are different. For example, a triketone pharmaceutical, [2-nitro-4-(trifluoromethyl)benzoyl]-1,3-cyclohexanedione (NTBC), is structurally very

similar to the triketone herbicide mesotrione (Figure 1). Both compounds target the enzyme *p*-hydroxyphenylpyruvate dioxygenase (HPPD), although the enzyme has very different functions in plants and humans. Another example is the herbicide asulam and the sulfa drug sulfanilamide, which both target 7,8-dihydropteroate synthase (Figure 1). In this case, the enzyme is involved in folate synthesis in both plants and microbes. In other cases, such as the sulfonyleureas, the pharmaceutical and pesticide molecular targets are quite different.

This review will focus on the parallels between herbicides and pharmaceuticals, although similar parallels exist between other classes of pesticides and pharmaceuticals. This review does not recommend the use of any herbicide for any therapeutic use.

Pharmaceuticals for Infectious Diseases

One could consider pharmaceuticals used to kill disease organisms to be pesticides, in that they are used to kill unwanted organisms. In this case, the pest lives within us or on us. Examples of this category of pharmaceuticals include antimalarials, antivirals, antibiotics, and medicinal fungicides. Table 1 provides examples of herbicides that are active against various transmittable diseases.

One of the first antibiotic classes was the sulfa drugs, including sulfanilamide. Sulfanilamide and the structurally related herbicide asulam (Figure 1) both target 7,8-dihydropteroate synthase, resulting in insufficient folic acid to sustain the target organism (Figure 2) (Brown 1962; Veerasekaran et al. 1981).

More recently, herbicides were found to have significant activity against apicomplexan parasites such as those associated with malaria, toxoplasma, and leishmania. This class of protozoan human disease organisms contains an organelle, the apicoplast, that is considered to have originated from an ancestor with an endosymbiotic photosynthetic blue-green alga (Fast et al. 2001). Plant plastids are thought to have originated and evolved in higher plants in a similar manner. The apicoplast genome of most apicomplexans encodes only

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Table 1. Examples of herbicides that have been reported to have activity against disease organisms.

Herbicide	Disease organism	Reference
Amiprofos-methyl	<i>Plasmodium falciparum</i>	Fennell et al. 2006
Clomazone	A long list of protozoans and bacterial pathogens	Singh et al. 2007
Endothall	<i>Plasmodium</i> spp. (malaria)	Bajsa et al. 2007
Glyphosate	<i>Plasmodium</i> spp. (malaria) <i>Toxoplasma gondii</i>	Roberts et al. 1998
Haloxypop	<i>T. gondii</i>	Zuther et al. 1999
Trifluralin	<i>Plasmodium</i> spp. <i>Cryptosporidium parvum</i> <i>Leishmania</i> spp. <i>Trypanosoma</i> spp. <i>Toxoplasma gondii</i>	Fennell et al. 2006 Benbow et al. 1998 Chen et al. 1993 Traub-Cseko et al. 2001 Stokkermans et al. 1996

about 60 proteins (Wilson et al. 2003), with most of the algal genes now being incorporated into the nuclear genome, with the gene products targeted to move into the plastid. This situation parallels that of plants and chloroplasts. Many of the nonphotosynthetic processes (e.g., amino acid synthesis) are common to both plant plastids and apicoplasts. Since most herbicides target plastid processes, herbicides have been evaluated as pharmaceuticals for apicomplexan diseases (e.g., Bajsa et al. 2007). Herbicides are also of particular interest for such pharmaceutical leads, because of the assumption that the molecular target site may not be found or, if present, be affected in humans.

In our survey of herbicide effects on the malaria organism *Plasmodium falciparum*, we found the most effective herbicide to be endothall (Bajsa et al. 2007). Endothall is a highly active protein phosphatase inhibitor in both plants and animals (Ayaydin et al. 2000; Li and Casida 1992), and protein phosphatases have been identified as promising targets for antimalarial drugs (Bajsa et al. 2008). Such a mode of action would indicate that it is generally cytotoxic. We find that the natural product cantharidin is more phytotoxic than its structural analogue endothall in the laboratory (J. Bajsa and S. O. Duke, unpublished data). From our survey of the anti-*Plasmodium* activity of a broad array of herbicides, we concluded that plastid site-based herbicides were not necessarily superior leads for antimalarial drugs.

Others have found that glyphosate is active against *P. falciparum* at about 1 mM (Roberts et al. 1998), a concentration above that of its effective herbicidal activity. The inhibition could be reversed by folate and *p*-aminobenzoate, indicating that the shikimic pathway is necessary for folate synthesis in this organism. We found essentially no activity of asulam, a specific inhibitor of folate synthesis, on

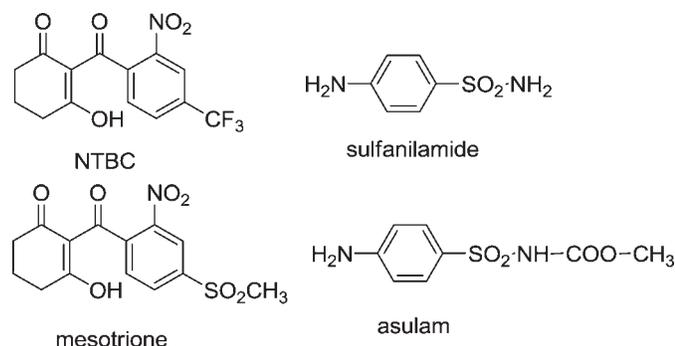


Figure 1. Structures of pharmaceuticals and structurally related herbicides.

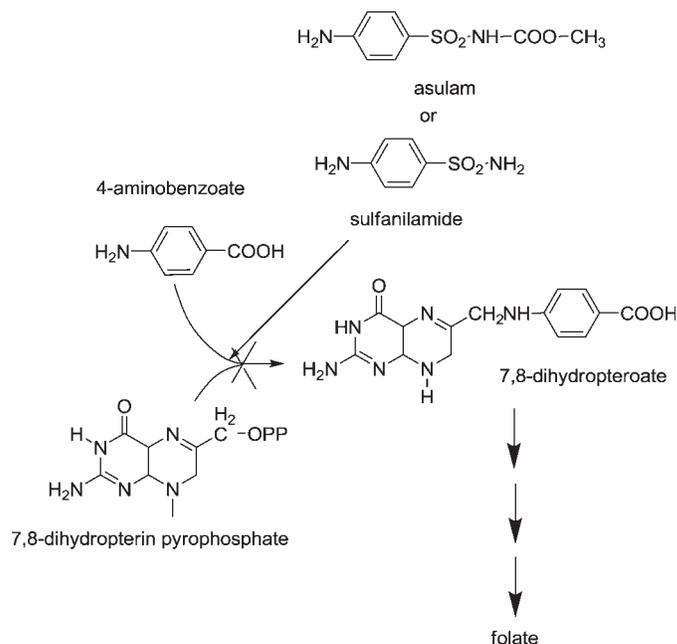


Figure 2. Effects of asulam and sulfanilamide on the folate pathway.

the same organism (Bajsa et al. 2007). Although Roberts et al. (2002) suggested that glyphosate or other inhibitors of the shikimate pathway might be good antimalarial drugs, this seems improbable considering its weak activity and that no other good, effective inhibitors of the shikimate pathway have been found. They also found glyphosate to be weakly active (50% inhibition concentration ca. 3 mM) against another apicomplexan disease organism, *Toxoplasma gondii*. The authors point out that glyphosate has extremely low mammalian toxicity, so it would probably be a safe pharmaceutical.

Aryloxyphenoxypropionate herbicides that inhibit acetyl coenzyme A (acetyl-CoA) carboxylase (ACCase) are much more effective against *T. gondii* than glyphosate (Figure 3) (Zuther et al. 1999). Cyclohexanedione ACCase-inhibiting herbicides were inactive. The active compounds were not toxic to human foreskin fibroblasts (Figure 3). ACCase of this apicomplexan is localized in the plastid (Jelenska et al. 2001).

Dinitroaniline herbicides are perhaps the most studied herbicides for potential use as pharmaceuticals. Trifluralin and oryzalin are active against *P. falciparum* (Bell 1998; Fennell et al. 2006). Fennell et al. (2006) also found amiprofos-methyl, another herbicidal mitotic inhibitor, to be active against *P. falciparum*. The malaria organism life cycle is complicated, moving through several stages. The typical bioassay only looks at activity on one of these stages, so that it would be easy to miss a life stage-specific activity or inhibition of the transition from one life stage to another.

Both trifluralin and oryzalin are active against *T. gondii* (Stokkermans et al. 1996). The selectivity factor between *T. gondii* and human cells was about 1000 \times , suggesting a high level of safety at therapeutic doses. The effect is apparently due to its interference with microtubule formation, which is its known target site in plants (Kaidoh et al. 1995). *Cryptosporidium parvum*, an apicomplexan human parasite without genes in its plastid, is also sensitive to both trifluralin and oryzalin (Benbow et al. 1998). Several nonapicomplexan protozoan parasites are sensitive to trifluralin, including

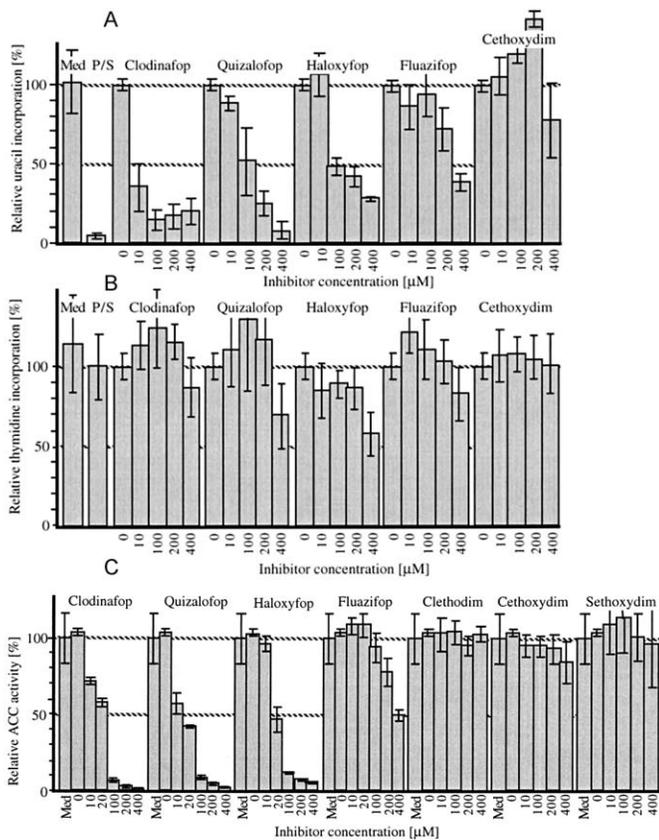


Figure 3. Inhibition of *Toxoplasma gondii* growth by herbicides. (A) Inhibition of *T. gondii* growth measured by [³H]uracil incorporation after 2 d of culture in the presence of herbicide. (B) Effect of herbicides on growth of human foreskin fibroblasts measured by [³H]thymidine incorporation after 2 d of culture in the presence of inhibitor. Med, medium without inhibitor or dimethyl sulfoxide (DMSO). PyS, pyrimethamine plus sulfadiazine. (C) Inhibition of *T. gondii* acetyl coenzyme A carboxylase (ACCase) activity by herbicides. Med, activity in medium without inhibitor or DMSO, 100%. Reproduced from Zuther et al. 1999, courtesy of the U.S. National Academy of Sciences.

trypanosomal diseases such as caused by *Leishmania* spp. and *Trypanosoma cruzi* (Chan and Fong 1990; Chan et al. 1993; Traub-Cseko et al. 2001). *Leishmania* spp. were much more sensitive to the herbicide than were human macrophages (Chan and Fong 2000). An example of the effects of this herbicide on cutaneous leishmaniasis lesions in mice is provided in Figure 4. Chan et al. (1993) stated “Trifluralin is a promising lead drug for several related, prevalent tropical diseases: leishmaniasis, trypanosomiasis of animals, and, possibly, African trypanosomiasis in humans.” In their review Fennell et al. (2008) concluded that the most promising immediate avenues for discovery and design for protozoal parasites are compounds based on antimetabolic herbicides.

Plants, apicomplexans, and some pathogenic bacteria have the nonmevalonic acid isoprenoid pathway in common. In plants, this plastid-localized pathway generates phytol for chlorophyll synthesis, as well as carotenoids and other plastid-generated terpenes. Clomazone is the only known herbicide to target an early enzyme in this pathway, after being metabolized to the active 5-hydroxy form. It inhibits deoxyxylulose 5-phosphate synthase (DXP synthase) (Mueller et al. 2000). Several papers (Lichtenthaler et al. 2000; Rodriguez-Concepcion 2004; Singh et al. 2007; Testa and Brown 2003) have pointed out that enzymes in this pathway are excellent targets for both herbicides and a wide array of

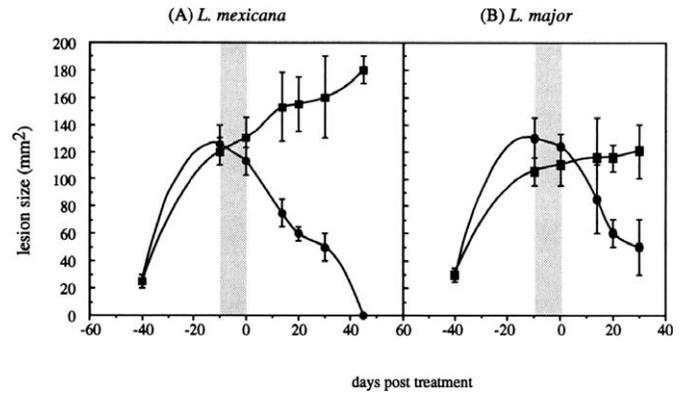


Figure 4. Trifluralin effects on the size of the cutaneous leishmaniasis lesions. Mice were infected subcutaneously with *Leishmania mexicana* (A) and *L. major* (B) promastigotes for 50 d to obtain lesions (day -60 to -10). Then, 15 of the animals were treated with trifluralin topical ointment twice a day for 10 d (■), and 10 of the animals were treated with the carrier alone (●) (day -10 to 0). The lesion size was measured at the indicated intervals—i.e., at the end of treatment, at days 14, 20, and 30 posttreatment for *L. major* and, in addition, day 45 for *L. mexicana*. Reproduced from Chan et al. 1993, courtesy of the U.S. National Academy of Sciences.

infectious disease organisms that have this pathway. Almost all of the effort has been focused on enzyme immediately after DXP synthase (DXP reductoisomerase), rather than the clomazone target.

Compounds belonging to various herbicide chemical classes have been studied for potential pharmaceutical uses against infectious diseases. For example, triazines are effective against malaria (March et al. 1976). Acetolactate synthase in the tuberculosis bacterium has been targeted with putative sulfonyleurea and imidazolinone drugs (Zohar et al. 2003).

Pharmaceuticals for Noninfectious Diseases

Herbicides have also been reported to have pharmaceutical activity against several nontransmittable diseases (Table 2). In some cases, the herbicide targets the same enzyme as the pharmaceutical. For example, NTBC and triketone herbicides such as mesotrione (Figure 1) both target the enzyme HPPD, although the enzyme has very different functions in plants and humans (Figure 5). NTBC is used to treat type I hereditary tyrosinemia (Al-Dhalimy et al. 2002), preventing buildup of toxic fumarylacetoacetate by blocking HPPD in patients lacking sufficient fumarylacetoacetate hydrolase. HPPD inhibitors have also been patented for treatment of depression or drug withdrawal symptoms (Travis and Posner 2008).

Endothall and its natural product analogue cantharidin (Spanish fly) have been studied as anticancer drugs (Liu and Chen 2009; Thiery et al. 1999). Endothall conjugated with the natural product illudin M has better specificity toward tumor cells than illudin M alone (Schobert et al. 2008). Endothall has been used in the study of the role of protein phosphatases in diabetes-associated atherosclerosis (Campbell et al. 2008).

ACCase-binding herbicides are poor inhibitors of mammalian ACCase (Shaner 2004). However, the CoA esters of the grass herbicides diclofop, haloxyfop, and fluazifop are potent inhibitors of rat liver ACCase (Kemal and Casida 1992). The binding site is stereoselective for the *R* form, the herbicidally active enantiomer. The CoA esters of the anti-inflammatory drugs ibuprofen and fenoprofen also strongly

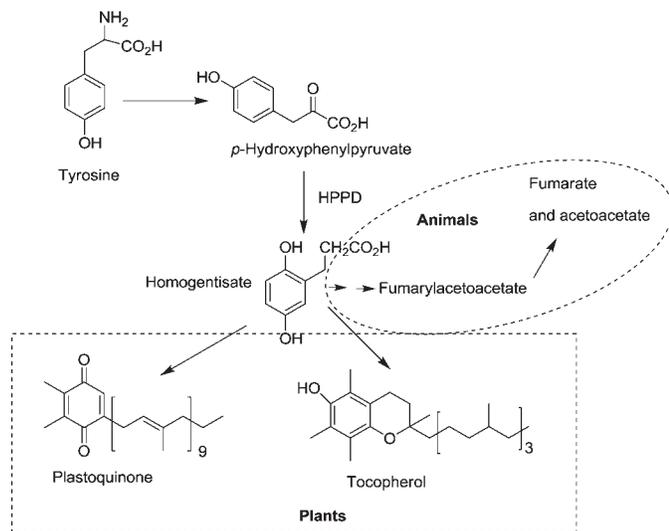


Figure 5. Role of *p*-hydroxyphenylpyruvate dioxigenase (HPPD) in plants and animals.

inhibit this carboxylase. These results suggest that some of the biological effects of these herbicides and anti-inflammatory drugs in animals may be due to the inhibition of ACCase. ACCase has also been implicated in obesity and cancer (Diacovich et al. 2004), so it would be interesting to see if CoA esters of aryloxyphenoxy herbicides would be effective against these diseases. Cyclohexanedione herbicides apparently are good enough mammalian ACCase inhibitors to be considered as potential antiobesity drugs (Haselkorn and Gornicki 2006).

Photodynamic therapy is used with certain types of cancer. The approach involves treatment of the patient with a photodynamic pigment that generates sufficient reactive oxygen species to kill cancer cells when exposed to a high-intensity focused beam of light. Attempts are made to localize the pigment and light of the proper wavelength in the tumor. Mammals contain protoporphyrinogen oxidase (PPO) involved in heme synthesis within mitochondria. This enzyme is also the target site for a major herbicide class. Mammalian PPO is sensitive to PPO-inhibiting herbicides, so that treatment with the herbicide causes the photodynamic compound protoporphyrin IX (Proto IX) to accumulate, just as it does in plants (Dayan and Duke 2003). Fingar et al. (1997) describe treatment of tumorous animals with a PPO inhibitor with a structure similar to several herbicides. Sufficient Proto IX accumulated in tumors for the use of photodynamic therapy. Results were similar to those with a conventional phytodynamic therapy dye.

Some triazine compounds are directly effective against cancer because of their cytotoxicity to cancer cells (e.g., Moreau et al. 2008; Saczewski and Bulakowska 2006). Triazines have been studied for inhibition of cholesterol synthesis (d'Atri et al. 1984) and treatment of cardiovascular disease (Kirchengast and Muentner 1999; Nettleton et al. 1974), ulcers (Nakashima et al. 1984), and Parkinson's disease (Vu et al. 2005).

Certain sulfonylureas are used in the treatment of type II diabetes (e.g., Turner et al. 1999). They stimulate insulin production. Some sulfonylureas are also anticancer drugs (Morré and Reust 1997). Bifenox, a protoporphyrinogen

Table 2. Examples of herbicides and herbicide chemistries that have been reported to have activity against nontransmittable diseases.

Pesticide (class)	Disease	Reference
Acetyl-CoA carboxylase inhibitors	Heart disease	Sung et al. 2003
	Obesity	
Endothall	Anti-inflammatory	Kemal et al. 1992
	Cancer	Schobert et al. 2008
Imidazolinones	Hypertension	Burnier and Brunner 2000
	Cancer	Fingar et al. 1997
Protoporphyrinogen oxidase inhibitors	Diabetes	Taha et al. 2008
	Cancer	Morré and Reust 2003
Sulfonylureas	Type II diabetes	Turner et al. 1999
	Cancer	Moreau et al. 2008
Triazines	Cancer	Saczewski and Bulakowska 2006
	Cardiovascular	Nettleton et al. 1974
		Kirchengast and Muentner 1999
	High cholesterol	d'Arti et al. 1984
	Parkinson's	Vu et al. 2005
	Ulcers	Nakashima et al. 1984
	Diuretic	Shah et al. 1968
	Tyrosinemia	Al-Dhalimy et al. 2002

oxidase inhibitor, was found to be a potent inhibitor of hormone-sensitive lipase (Taha et al. 2008). Inhibitors of this enzyme have potential in the treatment of diabetes. Some imidazolinone compounds are effective against hypertension through their effects as angiotensin II receptor antagonists (e.g., Burnier and Brunner 2000).

Final Thoughts

Tables 1 and 2 provide only a few examples of the many reported pharmaceutical activities of pesticides and vice versa. Conducting a comprehensive search for this scattered information is difficult, in that there are many herbicides and related compounds and a large number of disease organisms and medical conditions that can be treated with pharmaceuticals. The number of possible combination key word searches is astronomical. Furthermore, herbicides are often not identified by their generic names or as herbicides in the pharmaceutical literature. In some cases, the same compound has been proposed as both herbicidal and pharmaceutical products, although there are no commercial products of either. The microbial product hydantocidin is an example of this (Mandal et al. 2005; Sano et al. 1995). In this brief review, there is no room to report the many thousands of papers and patents on the potential pharmaceutical uses of herbicides or closely related compounds.

The use of a compound for one category (pesticide or pharmaceutical) would likely preclude it from use in the other for economic, public perception, and regulatory reasons. But, from a scientific standpoint there are clearly many parallels between pharmaceutical and herbicide chemistries and target sites, as well as approaches to discovery.

In closing, I would like to quote Delaney et al. (2006): "The potential for unanticipated side (pharmaceutical) activity is clearest with herbicides that also tend to have lead-like properties. The *Silent Spring* image of pesticides is an anachronism that serves to obscure the pharmaceutical potential lurking within agrochemical collections. An opportunity missed?"

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