

The Role of IR-4 in the Herbicide Registration Process for Specialty Food Crops

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The Interregional Research Project Number 4 (IR-4) Specialty Food Crops Program is a publicly-funded program initiated in 1963 to develop and submit regulatory data to support registration of pest control products for specialty crops. In the early to mid 1990s, nearly 45% of the IR-4 residue projects supported new herbicide registrations for fruits and vegetables with the other 55% devoted to fungicides, insecticides, and nematocides. In 2005, the number of residue projects conducted by IR-4 to support herbicide fruit and vegetable registrations was less than 30%. The three main factors that have contributed to this decline are: fewer herbicides available for registration; product liability concerns; and an increased focus on new, safer, and Reduced Risk Pesticides for insect and disease control. It has been a number of years since a new herbicide has been developed for a major crop that could be extended to specialty food crops. Many of the current IR-4 herbicide projects are with products that have been on the market for 20 or more years. Product liability is a concern because of the high value of many specialty crops relative to the potential market opportunity. In many cases, the registrant requires product performance data before IR-4 can proceed with a residue project. With limited funds for developing these data, many new projects never proceed to the regulatory stage. Although registrants can seek indemnification for some of these uses, it is a complicated often state-specific process. IR-4 has been successful in a number of areas, including the registration of a large numbers of uses through reduced data extrapolations for products such as glyphosate and carfentrazone-ethyl. Additionally, IR-4 submitted the first successful petition establishing an exemption of tolerance for a conventional herbicide (imazamox). Future IR-4 initiatives include collaboration with industry, growers, and academia to develop new herbicide technologies such as plant breeding or transgenic crops and generation of appropriate data to extend those products to specialty food crops. IR-4 will also assist in registering products that can be used on crops that have been selected (or developed through biotechnological approaches) to be tolerant to existing herbicides. Registrants should strongly consider developing herbicides for specialty food crops, with IR-4's assistance, as a means to expand markets and also as a means to extend data protection of their products, as allowed under the Food Quality Protection Act.

Nomenclature: Carfentrazone-ethyl; glyphosate; imazamox.

Key words: Codex, EPA, European Union, OECD, reduced data extrapolations, transgenic crops, triazine, minor crops, minor uses.

The IR-4 Program (Interregional Research Project Number 4) is a publicly-funded program that develops regulatory data to register pest control products for specialty crop growers or minor uses (uses that were not of economic importance to chemical manufacturers, generally grown on less than 300,000 acres). The program started rather modestly in 1963 with a grant from the land grant university agriculture experiment station directors to address the concerns of specialty crop growers concerning the lack of products to control pests. The need for pesticide products was important because the crop protection industry could not develop products for specialty food crops due to the cost involved in developing residue data for small acreage crops. The program was initially organized in cooperation with state university researchers and laboratories under registration requirements overseen by the United States Department of Agriculture (USDA). Regulatory requirements were increased in the early 1970s, when the U.S. Environmental Protection Agency (EPA) took over the registration of pesticides. Additional USDA funding was provided by the Cooperative State Research, Extension and Education Service (CSREES) in 1975 and the Agriculture Research Service (ARS) in 1976.

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Today, the program is supported by funds appropriated by the president and congress and then administered by USDA–CSREES to IR-4 Headquarters and the regional offices. This funding partnership between the state land grant university system and the USDA has flourished in the past 30 yr and has become a model for intergovernmental cooperation. Other key partners in this process are the specialty crop growers, the crop protection industry, and the regulating agencies (mainly the EPA, although California's Department of Pesticide Regulation [CDPR] has become an important component in recent years). The regulatory partnerships have extended beyond U.S. borders to North American Free Trade Agreement (NAFTA) countries, especially Canada's Pest Management Regulatory Agency (PMRA) in cooperation with Agriculture and Agri-Food Canada (AAFC).

IR-4 has had a positive relationship with the EPA for its 30 plus years of existence and worked with them to pioneer crop residue groupings (Anonymous 2004), representative crops, and other initiatives that have enhanced specialty crop registrations in the United States. However, after the passage of the Food Quality Protection Act (FQPA), it was apparent that IR-4 and the EPA needed to work much more closely together to address concerns about the loss of older products and support the registration of newer technologies that could serve as lower risk replacements (Baron and Kunkel 1998). This partnership was a strategy that has helped to register many Reduced Risk products rapidly on a large numbers of specialty food crops.

One example was the addition of 206 glyphosate tolerances (Maximum Residue Limits, also called MRLs) in 2000 that were obtained as part of an innovative regulatory approach (Anonymous 2000). Since 2001, IR-4 has provided data to support nearly half of the new pesticide tolerances approved by the EPA. More recently, IR-4 has utilized electronic tolerance petition submissions as a means of gaining additional review efficiencies at EPA. Since 2006, essentially all of IR-4's tolerance petitions were being submitted electronically.

The IR-4 Program conducts about 100 food-use residue studies (crop-chemical combinations) involving approximately 700 field trials each year. This includes 50 to 70 field trials conducted jointly with the Pest Management Centre of AAFC for a number of cooperative projects with Canada. The EPA requires that residue studies be conducted and documented following exacting procedures as outlined in the Good Laboratory Practice (GLP) Standards (Anonymous 2004). In order to conduct this research, IR-4 has established 31 field research centers at strategic locations throughout the United States in cooperation with land grant universities and the USDA-ARS. IR-4 also has a network of three ARS, four regional, and two satellite analytical laboratories located at land grant universities that conduct research to determine the amount of residues remaining in harvested crop samples from the field trials. All data from IR-4-sponsored studies are transferred from the field sites and/or analytical laboratories to the IR-4 Headquarters where the study directors critically review the data and summarize it in the format required for submission to the EPA. As required by GLP, all aspects of the studies are monitored by a Quality Assurance Unit. The petitions are also reviewed by the cooperating agricultural products company, and, once complete, submitted to the EPA for scientific review and tolerance (MRL) setting.

The California Department of Pesticide Regulation (CDPR) conducted one chemistry evaluation of an IR-4 tolerance petition (report) for EPA in 2001; this partnership expanded dramatically in 2002 with 30 IR-4 petitions, which comprised 10% of the entire EPA workload or 20% of the total IR-4 food-use submissions. This work-share program was the major factor allowing IR-4 to double its contribution to the EPA's Work Plan from 2000 to 2002. The CDPR management and scientists have maintained this rate of accomplishment from 2002 to 2004 in spite of severe state budget restrictions. In 2005, CDPR increased its review to nearly 50 IR-4 petitions, another significant increase, and now reviews nearly 40% of the petitions submitted to the EPA by IR-4 annually.

Canada has cooperated with IR-4 in joint residue programs since 1996, initially through funding provided by the Canadian Horticultural Council (CHC). In May 2002, the Canadian government announced funding for the Pesticide Risk Reduction and Minor Use, a joint AAFC and PMRA effort. This program represented a major financial commitment that dedicated over \$79 million CN over a 6-yr period (\$58.5 million CN to AAFC and \$20.8 million CN to PMRA were devoted to minor uses [specialty crops]). The AAFC Minor Use Program is known as The Pest Management Centre (PMC) and has a staff of 25 who oversee nine

test sites or field research centers across Canada where efficacy (a Canadian but not U.S. submission requirement) and field GLP residue studies are conducted to support product registrations on specialty crops.

International Harmonization

North American Free Trade Agreement (NAFTA). Over the past several years through the NAFTA agreement, regulators from Canada, Mexico, and the United States have made work sharing a way of doing business. These governmental regulatory agencies have shared the work required for the review of pesticide petitions, and have implemented efforts to streamline registration procedures and eliminate redundant regulatory requirements. This cooperation improves the working relationships among Canada, Mexico, and the United States, and allows more rapid pesticide regulatory decisions. Additionally, these efforts minimize trade barriers and facilitate the free flow of trade in agricultural goods across borders to ensure the sound sustainable management of pest control products. Canada and the United States have developed a coordinated joint review process for specialty food crop registrations, where stakeholder needs are identified and supportive data are generated by Canada's AAFC Minor Use Program and USDA's IR-4 Program. These data are submitted to both agencies simultaneously. At the initiation of a minor crop review, the EPA and PMRA act to identify the lead country that will conduct the review for a given project, including the complete chemistry, dietary, and other required reviews. Once those reviews are complete, the reports are peer reviewed by the companion agency and the registration is approved in both countries at approximately the same time with harmonized MRLs. The review and approval process for the specialty use joint reviews is expected to take as little as 8 mo compared to the standard 15-mo EPA review timeline.

OECD/Codex. The Organization for Economic Cooperation and Development (OECD) continues to examine ways to promote global joint reviews for new products, expansion of existing product labels, work share activities, and a number of other areas, in an effort to harmonize pesticide MRLs, or tolerances, to prevent trade barriers. The OECD has sponsored a workshop to advance work sharing internationally (January 2005, Washington, DC personal notes, no published reports to date). This workshop examined various national review procedures to identify specific barriers to work sharing and to develop recommendations to eliminate or reduce such barriers to promote time and resource savings. The workshop also sought to increase the experience and confidence of government evaluators and registrants in using dossiers and monographs developed for other countries and to identify the extent to which current review procedures and processes can be improved to facilitate work sharing. The main points developed through this workshop were to have common data requirements and guidelines and the standardization of MRLs on a global basis. The development of harmonized guidelines and terminology by the OECD is critical to the advancement of work sharing and harmoniza-

tion at the international level. Climate zones have been established for all of North America, extending from the tropical southern states of Mexico, through the United States (including Hawaii) and up to the northernmost regions of Canada; essentially all of the regions of the world can be represented by these 21 North American zones. Zones have also been established for the European Union as well. Interestingly, an OECD study indicated that climate zones might not be a major factor in pesticide residue variability (Harrison et al. 2002). The establishment of international crop climatic zones for pesticide residue research could greatly facilitate the development of residue data for both major and specialty crops, as well as prevent the expensive duplication of residue trials in various countries. Such crop residue zones could greatly reduce the overall cost of industry and government-sponsored programs, such as IR-4, to develop data globally.

Decline in Herbicide Development and Registrations.

Through the 1990s, there was a steady decrease in the development of new herbicides and this was especially true in the area of specialty crops. In the early to mid-1990s, nearly 45% of the IR-4 yearly pesticide residue projects supported new herbicide registrations and, by 2005, this number dropped to less than 30%. A number of factors have contributed to this decline, including fewer new herbicides available for registration and product liability concerns for high value crops by the registrants. In addition, the availability of many new insecticides and fungicides with reduced-risk regulatory profiles has driven much of the IR-4 research as a response to the FQPA.

During the late 1990s and early 2000s, industry increased resources in insecticide and to a lesser extent fungicide, discovery and development to address market opportunities. At the same time, a large amount of the major row crop acreage (mainly corn [*Zea mays* L. subsp. *mays*], cotton [*Gossypium* spp.], and soybean [*Glycine max* (L.) Merr.]) were planted to crops genetically-modified for herbicide resistance such as glyphosate-tolerant soybeans and glufosinate-tolerant corn. The few herbicides that were developed during this period had a very limited crop safety spectrum (cereal crops use only) with little or no utility in specialty food crops.

Product liability continues to be a major problem in extending or expanding herbicide uses to specialty crops where selectivity might not be as robust. Registrant's concern about financial vulnerability to losses from product liability should not be a surprise; a single complaint (lawsuit) can erase essentially the total profit realized from a single registration. Although many specialty crop growers realize that a crop might incur some injury as a result of using a herbicide developed for a different crop or application, most realize that the potential risk of injury is worth the benefits in weed control compared to the cost of manual labor that can cost as much as \$2,000 per hectare for some crops (Mossler and Dunn 2005). When lawsuits are brought against product manufacturers for crop injury, more often than not it means that crop will be removed from the product label to avoid further liabilities. Some registrants have pursued indemnification for some specialty crop uses; however, at this time it cannot be done on the national label and is a complicated and

expensive process involving individual state registrations under Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) 24(c); this type of registration must be repeated separately in every state of interest. Many registrants have developed their own methods to administer indemnification for their products. Usually, it is a form provided at the point of purchase that must be signed by the grower; however, some registrants have now started using web-based forms where the grower agrees to waive the liability for a product. The question of label wording (i.e., this product might cause some injury) has been discussed several times over the years; however, providing such wording on federal labels remains problematic. Although registrants understand that they are liable for product performance on those crops the product was originally designed for, the liability associated with marginal crop tolerance is one problem that needs to be resolved before additional herbicide labels can be expanded to include specialty crops.

It has been a number of years since a new herbicide that has been developed for a major crop could also be extended to specialty crops. Nearly all of the products currently being used for specialty crops were initially selected and developed for use in major crop markets. They made their way to specialty crops through the efforts of the researchers that found creative methods to use these herbicides in specialty crops. This often requires altered application methods or timings for the materials to work in specialty crop situations while resulting in little or no crop injury. For example, S-metolachlor is registered on a number of specialty crops as Dual Magnum® but it must be either directed to row middles (cucurbit crops) or applied after the crop has emerged to reduce potential crop injury. The applications can often miss already emerged weeds or weeds directly in the crop row, thus requiring expensive manual labor to remove weeds.

Prior to supporting an herbicide for a specialty crop, the registrant requires sufficient product performance and crop safety data in order to assess potential crop injury. Increasingly, the decline in financial support from manufacturers and limited public funds, including those for IR-4 support, are restricting development of this important crop safety data. This fact has made the development of herbicides for specialty crops even more difficult. Because of the concerns about the future availability of weed management tools for vegetable crops, IR-4 sponsored a nationwide screening program on several new herbicides in cucurbit crops (cucumber [*Cucumis sativus* L. var. *sativus*], summer squash [*Cucurbita pepo* L.], cantaloupe [*Cucumis melo* L. subsp. *melo* var. *cantalupensis* Naudin], watermelon [*Citrullus lanatus* (Thunb.) Matsum. & Nakai var. *lanatus*], and pumpkin [*Cucurbita* spp.]), and spinach (*Spinacia oleracea* L.) to identify potential safe and effective herbicides. More recently, IR-4 sponsored a pilot program to evaluate herbicides on leafy vegetables to find new herbicides. Although some new leads resulted from these efforts, additional studies (and additional products) are needed to address the weed control needs of our growers (unpublished data).

Biotechnology. The initial opportunities identified for transgenic specialty crops were herbicide tolerance and insect resistance (Bradford et al. 2004). IR-4 sponsored research on

herbicide-resistant specialty crops was initiated after recognizing that the FQPA might have a negative impact on several key herbicides used in vegetable weed control due to regulatory concerns about toxicology and groundwater contamination. The other justification for using herbicide-tolerant crops was that the newer herbicides in the development pipeline for major crops were demonstrating even greater risk of crop injury on specialty crops, prompting companies to restrict or avoid their uses on vegetables due to product liability concerns.

The first IR-4 herbicide transgenic crop project came as a result of research conducted by Dr. Gordon Harvey at the University of Wisconsin, who was looking for alternatives to triazine herbicide use for sweet corn production in Wisconsin due to concerns about groundwater contamination (Flowers and Harvey 2000). Dr. Harvey conducted studies on glufosinate-tolerant (Liberty-Link®) sweet corn and demonstrated excellent weed control. This research led to an IR-4 initiated residue study in 1998, which supported FIFRA Section 18 emergency uses that were granted in Wisconsin, Minnesota, and Michigan in 1999 and 2000. This was an interesting situation because the commercial varieties developed had the Bt gene to protect against corn borer and corn earworm, two major sweet corn pests, linked with the glufosinate-tolerant gene. However, due to concerns expressed by sweet corn processors, no significant commercial acreages were planted in 2001 and 2002. IR-4 has completed a registration package for glufosinate-tolerant sweet corn and is now waiting for the registrant's approval before submitting it to the EPA for full registration.

The other IR-4 herbicide transgenic crop project was glyphosate-tolerant lettuce (*Lactuca* spp.). The program was a cooperative partnership effort between Seminis Vegetable Seeds (provided seeds and technology support), Monsanto (residue analysis and technical support), and IR-4 (field residue program, project management, and petition preparation/ submission). Grower groups, including the California Lettuce Board, expressed reservations about the program in 2000. This and other issues related to public concerns about crops developed through biotechnology led IR-4, Seminis, and Monsanto to put the project on hold until there was support from the growers and marketers. Effective weed control, with reduced hand weeding costs, were observed with the use of glyphosate in glyphosate-tolerant lettuce (Fennimore and Umeda 2003).

The future of IR-4 involvement in transgenic specialty crops remains uncertain and will depend on the needs of IR-4 stakeholders. The program will not divert existing federal and state funding to an expanded transgenic horticultural specialty crop program because current funding is just adequate to cover the existing core efforts, including fruit and vegetable residue programs, development of reduced risk chemistries, biopesticides, nursery crops, and methyl bromide alternatives. For IR-4 to take a more active role in transgenic crops there would be a need for additional funding from Congress or other sources (public or private). Enhanced effort in this area might only come about when consensus is reached, at least at the policy level in the USDA and the land grant system, that using herbicide-resistant crops is a cost-effective weed control

approach that does not pose an unacceptable risk to the environment or to consumers.

The IR-4 has also been involved in the Specialty Crop Regulatory Initiative group that was formally established in January of 2005. The initial meetings have been organized by the Pew Initiative (Established by The Pew Charitable Trusts in 2001) and USDA to discuss plant biotechnology initiatives for specialty crops. In November of 2005, a proposal was developed for permanent funding to support biotechnology for specialty crops (Public Research and the Regulatory Consideration of Small-Market Biotechnology-Derived Crops, November 8 to 9, 2005, Riverdale, Maryland, sponsored by National Center for Food and Agricultural Policy, USDA, and Langston University). Proceedings are in preparation. Since that meeting, EPA has proposed that USDA-ARS pursue regulatory assistance of IR-4 to register their new plum pox-resistant plum with EPA's Biopesticide Pollution Prevention Division (BPPD). IR-4 has provided regulatory assistance on this as well as for other biopesticide regulatory work, including herbicide-tolerant specialty crops, on a case by case basis as directed by its stakeholders.

Herbicide-Tolerant Crops

For many of the same reasons that IR-4 participated in the transgenic projects, there should be consideration of developing herbicide-tolerant crops through the traditional selection process. There are a number of excellent products available which, if herbicide tolerance could be achieved, would provide many of the benefits noted for in the transgenic section, but without the concerns associated with biotech crops. These projects are a bit more complicated because they require participation from additional entities (the seed companies/breeders) and in some cases the seed company might be owned by a third party manufacturer. The potential for herbicide-tolerant specialty crops, developed by nontransgenic methods is great. However, cooperative partnerships will be key to making these programs successful.

Possible Market for Specialty Crop Herbicides

As noted earlier, there are many new insect and disease management tools being developed for vegetable crops that could serve as alternatives to the loss of existing crop protection chemicals; but this trend is not taking place in the weed management area. However, if the business model based on market potential were favorable, then the number of new herbicides for specialty crops would increase.

A Case Study for Developing Herbicide Markets for Specialty Crops. Specialty crops can provide significant markets domestically when a large number of crops can be added to the label. In addition, as global registrations become more common, a global registration for a product on a specialty crop could provide a large increase in market opportunities. The EPA has indicated that by 2007, nearly half of all of their reviews of new products will be linked to joint reviews with other countries, and in many cases a "global review" with more than three countries participating in the review process.

This case study considers global cabbage (*Brassica oleracea* L. var. *capitata* L.) production (Anonymous 2008) to see what potential herbicide market exist for that commodity. The United States cabbage production is approximately 40,500 hectares, and if one were pursuing a crop group label for cabbage, cauliflower (*Brassica oleracea* L. var. *botrytis* L.), broccoli (*Brassica oleracea* L. var. *italica* Plenck), and Brussels sprouts [*Brassica oleracea* L. var. *gemmifera* (DC.) Zenker], the market would likely exceed 100,000 hectares (2002 U.S. Census of Agriculture data). Granted, this is still a small market sales compared to the 25 million plus hectares domestically for each of corn, soybean, and wheat, but considering that grower profits are greater for specialty crops and the high price growers are paying for manual labor, the markets could be profitable in this area as well. Considering global markets can be even more profitable. Adding China could add another nearly 1.6 million hectares of cabbage, India an additional more than 200,000 hectares, and Russia another 200,000 hectares. In total, FAO reported 124 countries producing cabbage with a total of more than 3.0 million hectares in production. Again, if the product were registered on the crop group, it would be expected that the market would at least double and if the herbicide could be used on other specialty crops, there would be a significant increase in the potential market. As global regulatory communities continue to harmonize and share data, there soon could be the realization of global registrations without developing redundant regulatory data. Such a global registration would make specialty crop registrations substantially more cost effective and attainable.

As it has for over 40 yr, the IR-4 Specialty Crop Program continues to assist growers in gaining access to materials to control weeds and other pests so they can maintain high yields, produce quality commodities, and stay profitable in domestic and global markets. IR-4 realizes that weed control is a major issue for specialty crop growers and is ready to assist by helping register new herbicides, or registering products

that can be used on crops that have been selected (or through biotechnological or other means) to be tolerant to existing or new herbicides. With the rapid emergence in global regulatory harmonization, IR-4 can also assist registrants in finding new global markets for herbicides in specialty crops and reduce the cost of registration. Specifically, developing new products for specialty crops will be a key factor in finding solutions to meet the important needs of specialty crop growers.

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