Office of Research and Development

U.S. Environmental Protection Agency

MULTI-YEAR PLAN for

SAFE PESTICIDES/ SAFE PRODUCTS FY 2003-FY 2009[1]

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Not Yet Externally Peer Reviewed

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[1]*ORD Multi-Year Planning Committee Members: Andy Avel and Gregory Sayles, NRMRL; Val Garcia and Ross Highsmith, NERL; Karen Hammerstrom, NCEA; Chris Saint, NCER; Sally Darney, Mike Devito, Kevin Crofton, Jack Fowle, and Gilman Veith, NHEERL*

The Office of Research and Development's (ORD) multi-year plans (MYPs) present ORD's proposed research (assuming constant funding) in a variety of areas over the next 5-8 years. The MYPs serve three principal purposes: to describe where our research programs are going, to present the significant outputs of the research, and to communicate our research plans within ORD and with others. Multi-year planning permits ORD to consider the strategic directions of the Agency and how research can evolve to best contribute to the Agency's mission of protecting human health and the environment.

MYPs are considered to be "living documents." ORD intends to update the MYPs on a regular basis to reflect the current state of the science, resource availability, and Agency priorities. ORD will update or modify future performance information contained within this planning document as needed. These documents will also be submitted for external peer review.

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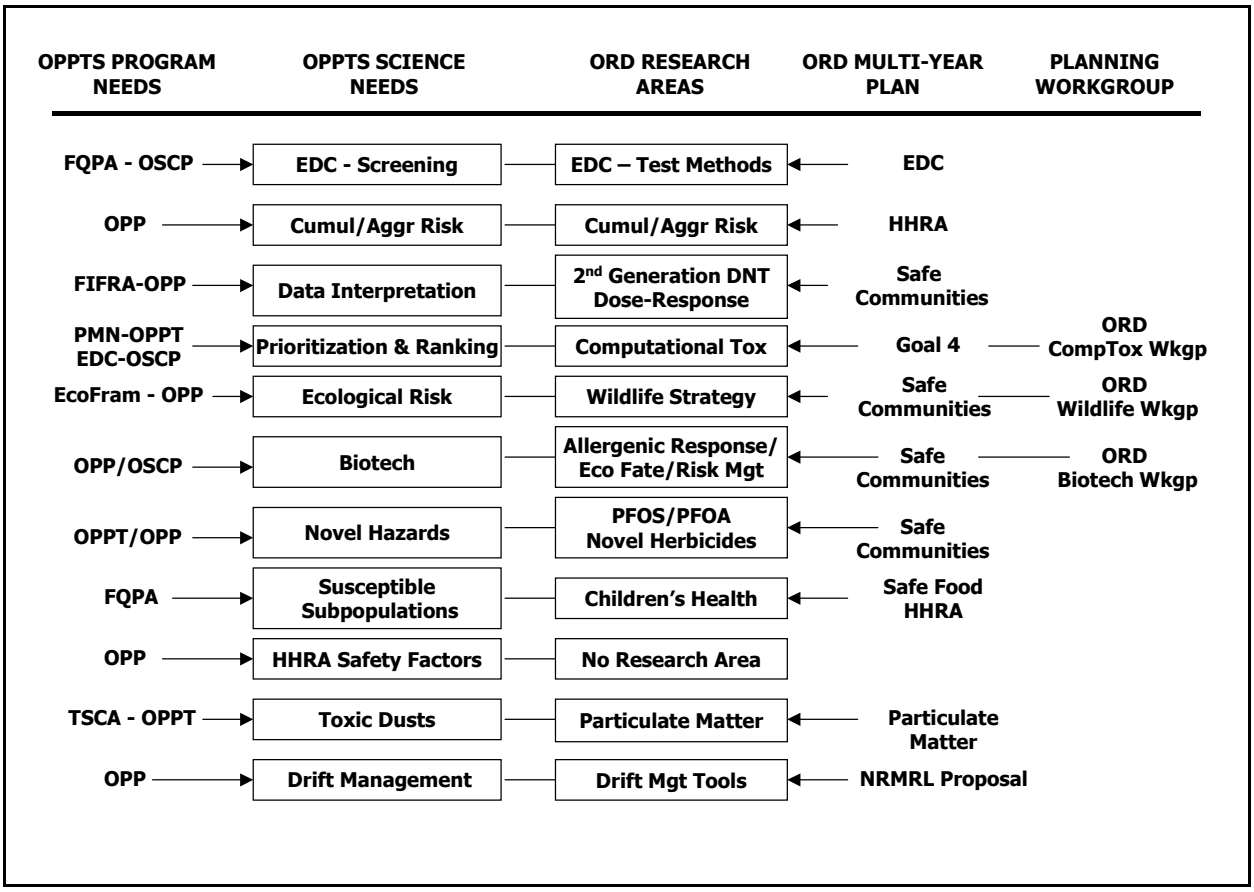
A. INTRODUCTION

This multi-year plan for research associated with EPA objectives for safe pesticides/safe products addresses the need for new scientific information required in the new EPA Goal 4 entitled "Healthy People, Communities and Ecosystems". The scope of the safe pesticides/safe products Multi-Year Plan (MYP) is intended to span the breadth of the regulatory authorities of the Office of Prevention, Pesticides and Toxic Substances (OPPTS). Because OPPTS plays a leading role in regulatory risk assessment in EPA, many of the research needs require very large research efforts which are intrinsic to the agency business of environmental protection and often solve similar problems faced by other EPA offices. Some of the scientific needs of OPPTS, therefore, have been consolidated into individual ORD research programs to facilitate the long-term planning. For the highest priority research issues, ORD has developed separate research strategies and multi-year plans. Noteworthy examples are the MYPs for Safe Food, Endocrine Disrupting Chemicals, Mercury, Human Health Risk Assessment, and Homeland Security. Therefore, this safe pesticides/safe products MYP is intended to identify additional science issues important to OPPTS, including the effects of other pesticides and toxic substances, ecological assessments in addition to human health assessments, and plant incorporated protectants. This MYP directs the reader to companion ORD plans for critical OPPTS science needs that have been consolidated into other ORD MYPs and presents the strategic focus of the research to be completed by safe pesticides/safe products resources. A schedule for meeting the safe pesticides/safe products objectives is included.

The ORD Science Council commissioned the development of research strategies for all major ORD programs prior to the full implementation of the Government Performance and Results Act (GPRA) in EPA. As the ORD programs have been aligned under the GPRA structure, research being coordinated by the Goal 4 Research Coordination Team maintained a rigorous plan to attain the safe pesticides/safe products objectives but the program lacked an overarching strategic plan like similar to many other large research efforts. To provide that strategic direction, the ORD Science Council initiated a series of meetings with the senior leadership of OPPTS to identify the major scientific impediments in the OPPTS regulatory programs. Subsequently, a crosswalk between the strategic OPPTS needs and all of ORD multi-year plans led to the identification of major areas which were not addressed by other MYPs and where safe pesticides/safe products resources for research should be focused. Those research areas are nested in the appropriate long-term research goals of the safe pesticides/safe products Multi-Year Plan as illustrated in Figure 1.

ORD has committed approximately $17 million annually to implement the research specifically aligned to safe pesticides/safe products. These resources are intended to complement even larger core research efforts found in Goal 4 which also addresses many OPPTS needs as well as other problem-driven research efforts for OPPTS regulatory programs in Safe Food. An outline of the science needs in OPPTS is presented in the Research Framework in Figure 1 along with an indication of how ORD has aligned and consolidated research efforts to respond to these needs.



B. BACKGROUND

The science questions to be addressed in the safe pesticides/safe products Multi-Year Plan are derived from the programmatic needs for new scientific approaches and understanding that are found in the risk assessment/risk management within OPPTS. As shown in the Research Framework, there are a number of high priority science needs in OPPTS programs which represent such fundamental and complex scientific challenges that ORD has committed core research efforts to the problems. As examples, Pollution Prevention comprising a major part of the OPPTS organizational title and mission and research to support pollution prevention enjoys an entire Multi-Year Plan in ORD under Goal 4. The scientific gaps in our capability to assess cumulative and aggregate risks, susceptible sub-populations amongst human or other vulnerable species, and stochastic exposure scenarios as well as to screen chemicals for their potential to disrupt the endocrine systems all comprise additional core ORD research efforts under the Endocrine Disruptor Multi-Year Plan. Each is described in detail in these separate Multi-Year Plans. Special research needs required to adequately protect the health of our children are being addressed in the Safe Food Multi-Year Plan. The scientific gaps pertaining to the toxic effects of respirable dusts are being addressed by a comprehensive particulate matter Multi-Year Plan under Clean Air.

An important purpose of the strategic discussions within the senior leadership was to identify among the wide array of scientific needs for safe pesticides/safe products those needs that can be adequately addressed by other existing research programs and thereby excluded from the safe pesticides/safe products Multi-Year Plan. Reducing redundancy of research efforts is an important first step in the strategic use of Goal 4 resources. The next step in the MYP development was to reach consensus with respect to the science needs that are the most important obstacles in reaching the Safe Community objectives. Four large, long-term science needs have been identified and structured as long-term research goals for ORD. The first goal is to build on the decades of test method development for assessing the risks of chemicals and to develop genomic methods for prioritization of regulatory data requirements and to facilitate the interpretation of submitted data in risk assessments. The second goal is to develop the scientific underpinning necessary to transform ecological risk assessments to a more realistic, probabilistic basis where effects can be judged by their impacts at the population level. The third goal is to develop new approaches to facilitate OPPTS outreach efforts to local communities with respect to preventing or reducing non-chemical risks in our communities. Finally, OPPTS is faced with chemicals and chemical classes that have novel properties and potential hazards for which conventional assessments may be inadequate. The fourth long-term goal for ORD in this MYP will be to provide the scientific understanding of two large, economically important classes of novel agents including the high potency herbicides and perflourinated industrial esters.

C. LONG-TERM GOALS

As described above, four major OPPTS research needs were identified to form the basis of the Long-Term Goals (LTGs) for multi-year planning for safe pesticides/safe products. The safe pesticides/safe products LTGs are:

1. ...to provide EPA with predictive tools for prioritization and enhanced interpretation of exposure, hazard identification and dose-response information;

> This objective shifts the emphasis of research from developing new test methods for hazard identification and dose-response assessment to one of enhancing the usefulness and interpretation of submitted data.

2. ...to create the scientific foundation for probabilistic risk assessment methods to protect natural populations of birds, fish and other wildlife;

> This objective responds concisely with the recommendations of ECOFRAM for developing probabilistic wildlife risk assessments for cumulative effects of habitat loss and use of pesticides.

3. ...to provide OPPTS with the scientific underpinnings for guidance to prevent or reduce risks of human environments within communities, homes, workplaces;

This objective creates research on important potentially non-chemical risks in human environments with emphasis on genetically modified food and other products.

4. ...to provide OPPTS with strategic scientific information and advice concerning novel or newly discovered hazards.

This objective bring ORD experts to bear on scientific uncertainties that are associated with regulatory issues requiring about five years to find a general solution to a specialized class of hazards.

A brief summary of the science issues and the research program objectives makes up the body of this plan. The timeline for delivery of research products can be found at the end of this multi-year plan.

LTG 1. To provide EPA with predictive tools for prioritization of testing requirements and enhanced interpretation of exposure, hazard identification and dose-response information

Protecting human health and the environment from harmful agents carries the challenge of developing the capability for assessing hundreds of possible hazardous effects for tens-of-thousands of important commercial chemicals. Establishing strategic priorities to focus available laboratory testing resources on those chemicals posing the greatest potential risks is essential to EPA in minimizing environmental risks from harmful agents. Over the last three decades, ORD has developed for EPA an extensive arsenal of test methods needed in all aspects of regulatory risk assessment. ORD will continue in safe pesticides/safe products Multi-Year Plan to refine many of these methods and to reduce the uncertainty with respect to interpreting the results of tests in EPA decisions. However, in the safe pesticides/safe products Multi-Year Plan, ORD will also address the greater challenge of developing the science necessary for EPA to know when and how to apply those test methods to gain greatest insight into the potential risks of a specific chemical.

1.1 Enhancing the Developmental Neurotoxicity Testing Guidelines

The Developmental Neurotoxicity Testing (DNT) guidelines were promulgated in 1991 in response to the need for regulatory screening for developmental neurotoxicity. A recent data call-in issued by the Office of Pesticide Programs for developmental neurotoxicity testing of a number of organophosphorous pesticides has refocused attention on the DNT guidelines including several major uncertainties in the methods. Challenges to the current DNT guidelines are that the tests are not sensitive enough and produce a too many of false positives; that structures/functions such as social behavior, neurochemistry or changes in senescence should be included; and that the current methods for assessing cognitive and sensory dysfunction are inadequate. Also, a protocol is needed for mechanistically-based predictive methods including biochemical markers.

ORD will evaluate the data currently being submitted to EPA from registrants with respect to variability, reliability, and sensitivity to positive control chemicals. For example, the morphometric measurement of brain size has been criticized as being too variable to a useful endpoint. A second issue concerns the utility of positive control data required of all testing laboratories to show proficiency with the methods required in the DNT. Output from these reviews will include new or revised guidance documents for data requirements, standardized protocols and data evaluation, for use both within and outside the Agency.

ORD will develop the necessary testing batteries that are specifically targeted to major categories of developmental neurotoxicants, such as the major classes of insecticides. These more targeted batteries will be more sensitive to the neurotoxicological effects as well as more

cost-efficient. The greater efficiency will come from predictive biomarkers tailored to high priority classes of conventional pesticides. In particular, the assessment of organophosphorous pesticides requires biomarkers of effect correlative to adversity, especially for cumulative risk estimates. A second issue is that a biomarker similar to cholinesterase inhibition is not available for most of other important classes of pesticides such as the pyrethroids and neonicotinoids. Both classes or pesticides have neurotoxic mechanisms-of-action, and both have a time line for cumulative risk assessments that are far enough in the future to allow basic research efforts to result in productive outputs. The research effort within NTD will focus on developing predictive biomarkers of effect that are based on key events in the toxicological pathway. Possibilities include mode-of-action endpoints (e.g., pyrethroids and neuronal excitation) and receptor binding affinities (e.g., neonicotinoids and nicotinic receptors).

Another critical refinement of the testing protocols to improve the interpretation involves the histopathological methods required by the DNT. Morphological assessments at two ages, one early assessment at postnatal day (PND11) and another at study termination (~young adult) are currently required. A critical unanswered question is what ages of assessment are adequate detect alterations in nervous system structure. The objective of this research is to provide guidance on the proper procedures and times-of-assessment for potential neuropathic chemicals. Finally, ORD will develop a revised testing protocol which includes biomarkers of key events in the developing nervous system. The use of these biomarkers would help to establish a linkage between exposure and endpoints of concern aiding predictions of effect and extrapolation (low dose effects, long-term toxicity, and species differences). Particularly promising is the research on *in vitro* methods using cell cultures and endpoints for cell differentiation, proliferation, migration, synaptogenesis, myelination, and apoptosis. Recent technological advances in genomics and/or proteomics to identify patterns of gene expression characteristic to neurological development will be used.

A problem-directed research program has been developed that focuses on four key issues related to improving the interpretation, reliability and use of the Developmental Neurotoxicity Testing Guideline:

(1) Criticisms from outside the Agency that the DNT guideline is not a useful screening tool.

A key issue inhibiting OPPTS' ability to use the DNT guideline stems from heterogeneous criticism. While some argue that the tests are insensitive, others argue that the tests suffer from a high rate of false positives. There have been calls to include assessments of structures/functions not currently included, such as social behavior, neurochemistry or changes in senescence. It has been stated that the current methods for assessing cognitive and sensory dysfunction are inadequate and insensitive. The agreed upon research need is to develop a unbiased evaluation the data currently being submitted to EPA from registrants in order to evaluate the overall quality and diagnostic value of the procedures. Parameters such as variability, reliability, and sensitivity to positive control compounds will be evaluated across studies and laboratories conducting the tests.

(2) Targeted test methods for screening chemical classes with defined mechanisms/modes-of-action

The current DNT Guideline was devised for the testing of unknowns. A current problem in requiring the use of this Guideline is that for many classes of pesticides the mechanism/mode-of action in the nervous system is known. Concerns have been raised for chemicals with known mechanisms/modes use of a potentially inaccurate or insensitive testing method. The agreed upon research need is to develop testing batteries that are specifically targeted to major categories of developmental neurotoxicants, such as the major classes of insecticides. These more targeted batteries should be both more sensitive to the major neurotoxicological consequences of exposure, but also more efficient to run because there would be less emphasis on detecting non-specific actions.

(3) Age of histopathological assessments during development.

There is a critical need to refine the histopathological methods which are required by the DNT Guideline. Morphological assessments at two ages, one early assessment at postnatal day (PND11) and another at study termination (~young adult) are currently required. An important unanswered question is what ages of assessment are adequate detect alterations in nervous system structure. The agreed upon research need is methods to assess the effects of known developmental neuropathic xenobiotics at different stages of development. The goal of this research is to provide guidance as to proper procedures and times-of-assessment for potential neuropathic chemicals.

(4) High throughput in vitro screening methods for developmental neurotoxicity

A critical long-term need is the development of in vitro screening methods for developmental neurotoxicity. While the current DNT guideline may be defensible for very high volume, high exposure chemicals, there is no way in which this in vivo testing battery can be used on the thousands of chemicals that pose potential risk to the developing nervous system. The agreed upon research needs are to develop an *in vitro* testing battery using cell cultures and/or genomic and proteomic technologies that will allow screening for the major neurodevelopmental processes that are adversely impacted by environmental contaminants (such as: differentiation, proliferation, migration, synaptogenesis, myelination, and apoptosis); a testing strategy to validate the *in vitro* test methods; and guidance for the use and interpretation of data from these methods in a risk assessment context.

1.2 Assessing Risks to the Developing Immune System

There is no standardized laboratory animal testing approach to assess the potential toxicity of chemicals to the developing immune system. The goal of this research is to apply a panel of *in vivo*, *ex vivo* and *in vitro* assays to determine whether the developing (i.e., prenatal, neonatal and/or post-weaning/juvenile periods of development) immune system of the rat exhibits increased susceptibility to immunosuppressive chemicals compared to the adult. The

assays employed include, but are not limited, to the following: cell-mediated delayed-type hypersensitivity response; humoral antibody response; innate natural killer cell activity; flow cytometric phenotype analysis; and cytokine message profiles. This research will employ a known immunosuppressive agent to accomplish the following: 1) determine the effective dose that produces immunosuppression in rats treated during the stages of development identified above; 2) determine whether chemical exposure during these developmental stages suppresses immune function at comparable or lower doses than adult exposure; and 3) identify the critical developmental windows during which chemical exposure produces immediate and/or persistent immunosuppression. This research will aid in the determination of whether the developing immune system exhibits greater susceptibility to chemical perturbation compared to that of the fully mature immune system. As such, it will provide OPPTS with important information relative to the potential increased susceptibility of the developing immune system to perinatal pesticide exposure, as well as to identify the more sensitive and predictive immune function endpoints for assessment of developmental immunotoxicity.

1.3 Enhancing the Interpretation of Reproductive Function

The harmonized Health Effects Test Guidelines OPPTS 870.3800 Reproduction and Fertility Effects (1997) improved the process of hazard identification by supplementing fertility end points with more specific tests of reproductive function such as sperm measures (numbers, motility, morphology) in males and estrous cyclicity in females. An advantage of these more specific tests for risk assessment is that they have human correlates (semen analysis and menstrual regularity). Furthermore, as potential risks to human reproduction have come to the public's attention, numerous epidemiology and occupational health studies have been launched, and these are providing data on the same outcomes in humans. Indeed, EPA's Reproductive and Developmental Risk Assessment Guidelines specify that human data should be used for risk assessment when it is available. Nevertheless, interpretation of the human data is complicated by several fundamental differences between rodents and humans. For example, most rodent sperm are motile and normal in shape, whereas a minority of human sperm meet these criteria. This makes direct comparisons inappropriate. Likewise, human menstrual cycles include a luteal phase whereas rodent cycles do not. Therefore, research is needed with respect to interpreting changes in measures of human reproductive health as they relate to companion test data obtained in rodents.

Furthermore, new tests have been and continue to be developed for assessing specific aspects of human gametes. For example, a plethora of new tests are available to assess the genomic integrity of human sperm (DNA, chromatin and chromosome damage) and these are being included in epidemiology studies, the results of which need to be interpreted by OPPTS. However, data on these outcomes is rarely available from test species as these tests are not required. Also, human ovarian tissue and oocytes are becoming increasingly available for research from in vitro fertilization programs. This makes it possible to conduct in vitro assessments of human ovarian function as bio-indicators of the endocrine support of oocyte maturation and pregnancy maintenance. Parallel studies can be conducted with rodent ovarian tissues to evaluate effects of in vivo or in vitro exposures. Again, research is needed to understand species differences and interpret these in vitro-derived data.

Finally, novel molecular sperm biomarkers under development in RTD and elsewhere, such as RNA profiles in sperm and specific sperm proteins associated with fertility (e.g. SP22), may prove to be more sensitive indicators of adverse effects than currently specified outcomes. Thus, research is needed to demonstrate the utility of such new biomarkers in humans and rodents. Taken together, the research under this LTG will enhance interpretation of hazard identification and dose response data obtained in human studies and facilitate the use of new endpoints for reproductive effects in humans and rodents, so that such data can be used in the risk assessment process. Specifically, research will include:

• Application of new tests for genomic integrity in *human* semen studies to determine their value as predictors of adverse effects relative to routine measures of sperm quality.

• Evaluation of RNA profiles in rodent and human sperm to determine whether they echo adverse effects in the testis and male reproductive tract such that human sperm may be considered sentinels for adverse testicular effects.

• Application of proteomics in rodent and human semen to characterize new sperm biomarkers and demonstrate their use in human studies.

• Evaluation of in vitro follicle and corpus luteum cultures in rodents to determine their usefulness in ascertaining modes and mechanisms of female reproductive toxicity and abnormal pregnancy outcomes.

1.4 Prioritization and Ranking

Prioritization and ranking of chemicals of concern has been a historical problem in EPA because the ordering of concerns must be accomplished without measured data, especially if the prioritization is linked to testing requirements under EPA authorities. This problem is highlighted by the EPA responsibility to screen chemical inventories for endocrine disruptors. Even when the chemical inventory is narrowed to 6,000 chemicals, the cost of testing requirements is large. In FY02, ORD redirected $4M of the safe pesticides/safe products program to address the need for new methods of ranking and setting risk-based priorities for untested chemicals, hopefully with an adjunct benefit of making the use of animal testing more optimal.

These gaps in our ability to estimate risk assessment endpoints well enough to set risk-based priorities are the result of a lack of understanding of mechanisms of toxicity as well as a lack of methods to model the complex behavior of chemicals. To overcome these gaps, ORD has initiated a Computational Toxicology Research Program as part of the redirected safe pesticides/safe products research program. This program will use new genomics technology to unravel the toxicity mechanisms of important chemicals so that QSAR models can be developed for mechanism of developmental and reproductive impairment. In FY04, the Computational Toxicology program will be expanded and aligned with other ORD core research programs in Goal 8 in an effort to also develop a better understanding of molecular initiating events that

underlie the adverse outcomes important to EPA risk assessments, models to simulate metabolic activation of chemicals, and genomic biomarkers to improve species extrapolation, interpretation of bioassay results and biomonitoring.

The integration of virtual and high-throughput screening methods, however, has many applications to regulatory program activities across OPPTS, and an ongoing research need exists under safe pesticides/safe products in making the interpretation of data more efficient. Virtual screening methods have been recently been categorized as *in silico* methods, but are centered around a 40-year history of the development of quantitative structure-activity relationships (QSAR) to quantify chemical structure in relevant terms. The endocrine disruptor challenge under FQPA represents only one aspect of the prioritization problem in that a large group of chemicals must be screened for a designated (albeit, complex) hazard. This problem is analogous to the PMN review process where missing data must estimated from chemical structure; however, the PMN process is more complex in that many types of chemical hazards and numerous environmental fate issues must be assessed in addition to endocrine disrupting potential.

Perhaps less obvious is the importance of virtual screening methods such as the technology used in PMN review to improving the interpretation of submitted data and the prioritization of testing requirements under FIFRA. Methods of estimating important parameters for exposure and effects assessment, whether directly from chemical structure or from extrapolation from data on analogue structures, form the only risk-based foundation for setting priorities before testing is completed. Moreover, having a rigorous list of hypotheses on chemical behavior before attempting to interpret extensive compilations of laboratory and field data adds efficiency to the review process.

As a compliment to the Computational Toxicology Research Program in Goal 8, the safe pesticides/safe products MYP will retain a modest effort focused on the challenge of tailoring ranking and prioritization methods to specific OPPTS regulatory authorities. Examples of this research include:

- Pollution Prevention: High Volume Challenge to Reduce PBT Chemicals. ORD will work with OPPT on the evolution of the web-based PBT Profiler for ranking industrial chemicals and provide improved methods for defining persistence, bioaccumulative and toxic chemicals.

- PMN Review: Assessment of New Chemicals. ORD will continue to develop QSAR methods to estimate important chronic health and ecological effects endpoints as well as exposure endpoints.

- FIFRA: Pesticide Registration/Reregistration. ORD will work with OPP on methods for formulating strategic testing requirements for classes of pesticides based on toxicity mechanisms.

• OPPTS: Probabilistic Risk Assessment for Wildlife: Goal 2 of this MYP outlines a coordinated effort in ORD to develop the scientific basis for wildlife risk assessments. A significant part of that research is the estimation of missing data and the QSAR methods will be serve to fill this important need.

LTG 2. To create the scientific foundation for probabilistic risk assessment methods to protect natural populations of birds, fish and other wildlife

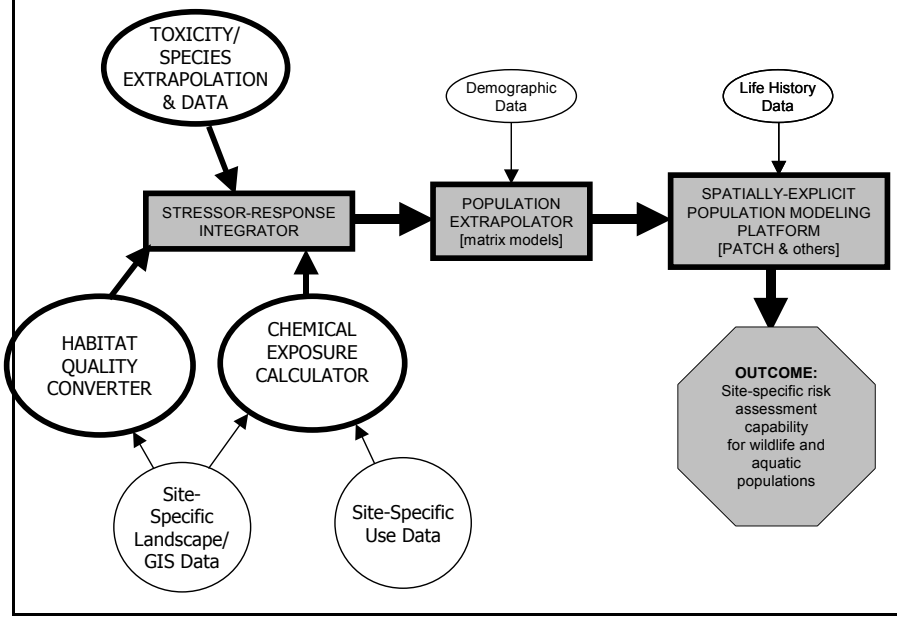
The Office of Pesticide Programs is leading the way in expanding ecological risk assessments to provide probabilistic expressions of risk to fish and wildlife populations. The goal of the ORD wildlife research is to develop scientifically valid approaches for assessing risks to wildlife populations from multiple stressors. This requires a means of mathematically integrating dose-response and habitat suitability relationships as well as computer platform for site-specific, spatially-explicit population modeling. Four key components of research include:

- extrapolation among wildlife species and exposure scenarios of concern
- population biology to improve population dynamics in spatially-explicit habitats
- models for assessing the relative risk of chemical and non-chemical stressors
- models to define geographical regions/spatial scales for risk assessments

Research within these four components will be coordinated using the conceptual framework illustrated below (Figure 2) so that present gaps and uncertainties can be reduced systematically as ORD build this new Geographic Information System (GIS)-driven approach for spatially explicit population models in ecological risk assessment.

In 1996, the Scientific Advisory Panel for the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) reaffirmed the utility of the ecological assessment process followed by the Environmental Fate and Effects Division (EFED) within the Office of Pesticide Programs (OPP). However , the Panel also offered a number of suggestions for improvement. Foremost among the Panel's recommendations was to move beyond the current single-point deterministic assessment approach and develop the tools and methodologies necessary for a probabilistic assessment of risk. As a follow-up to this and other reviews, the Ecological Committee on FIFRA Risk Assessment Methods (ECOFRAM) was formed by OPP to develop specific recommendations for revising the assessment process. In response to ECOFRAM, ORD developed a Wildlife Research Strategy that employs a tiered approach where a series of wildlife risk assessments are arrayed from most general and broadly based (screening level) to most realistic, accurate and situation-specific (definitive level) with the sustainability of wildlife populations as the assessment endpoint of concern throughout all tiers. The appropriate final tier for a wildlife risk assessment is based on a risk management

Figure 2. Wildlife Risk Assessment Framework



analysis that weighs risk assessment uncertainties against the context of the management decision and the costs associated with a 'wrong' decision compared to the costs of gathering and employing increasingly realistic and accurate data and models.

In reviewing wildlife risk assessments and criteria development, four steps were identified that are critical to completing effects and exposure characterizations. The first step involves the spatial and temporal characterization of stressors; e.g., contaminant exposure, habitat suitability, and introduced species, that may adversely impact the wildlife population of concern. Based on the results of step one, quantitative chemical dose-response relationships and habitat-response relationships at the individual level are developed in step two (e.g., relationships to fecundity and life-stage specific probability of survival). In step three, these demographic rates are used in population models to generate outputs describing population growth rates or other appropriate population-level endpoints. Finally, in step four, these relationships are 'inserted' back into the landscape to determine cumulative population dynamics across the landscape and assess effects due to chemical exposure as well as other forms of habitat disturbance. Wildlife populations are impacted by many stressors other than pesticides or contaminants that result directly or indirectly from human activities (e.g., habitat loss and alterations, introduced species, hunting pressure). The sensitivity of a population to a given contaminant, as well as the ecological significance of a contaminant effect, are influenced by these other stressors. The level of accuracy and realism required for these four steps varies with risk assessment and management needs.

Because neither stressors nor wildlife populations are distributed uniformly within the environment, the interplay between spatial and temporal heterogeneity in wildlife population structure and spatial and temporal patterns of stressors is a major factor controlling the severity of effects on wildlife populations. Thus, a critical feature of this research is development of probabilistic models that deal explicitly with the spatial distribution of population and stressors over time. These models will be designed for application to real landscapes, by interfacing with geographical information systems (GIS).

To meet the long-term goal of developing tools for spatially-explicit, population-level wildlife risk assessments, ORD will focus on four major research objectives:

(a) develop mechanistically-based approaches for extrapolating toxicological data across wildlife species, media, and individual-level response endpoints

Research will emphasize approaches for extrapolating toxicity data to a broader array of species, environmental media, and response endpoints (in particular, the endpoints required as input to population response models).Work will continue on the refinement of the Interspecies Correlation Estimations (ICE) program. Several areas within the model have been identified for further development including 1) identification and expansion of appropriate surrogate species; 2) increased representation of non-pesticide industrial organic and inorganic chemicals; 3) increased representation of metals; 4) improvement in taxonomic classification schemes; and 5) model expansion and modification integrating novel (example: genomic/proteomic) endpoints. These efforts will specifically addresses the stated APG under LTG 2: "Provide methods for extrapolation chemical toxicity data across species which can support assessment of risks to aquatic life and aquatic-dependent wildlife for chemicals with limited data."

(b) develop spatially-explicit, probabilistic exposure models for wildlife

Exposure estimates will be refined and placed in spatially-explicit and probabilistic frameworks with the same temporospatial scales used by effects modeling. Research activities are needed for the creation of screening models to characterize chemical persistence from molecular structure, algorithms for determining environmental transformation pathways and reaction kinetics, and probabilistic exposure models integrating chemical, biological, climatological, and geographic knowledge into an integrated computerized system for supporting risk assessment and analysis.

Possible pesticide use scenarios can be enhanced with information from spray drift research performed to advance our understanding and ability to project the magnitude, duration, frequency, and underlying causes for the atmospheric transport, fate, and deposition of synthetic organic chemicals. Additional spray drift research is needed to investigate multiple scales (near-field, meso-scale and far-field) as well as multiple paths suspected of being critical factors to pesticide exposure. Mechanistically-based QSAR models to categorize chemical reactivity and estimate rate constants for both microbial and chemically-mediated transformations are needed to identify toxic chemicals that are persistent and/or transformed to more toxic reaction products.

The integration of food web bioaccumulation and physiologically-based toxicokinetic models is needed to yield a more robust, integrated approach to chemical bioaccumulation, metabolism, and food chain contamination.

(c) develop approaches for predicting population-level responses to stressors and for identifying the responses at the individual level that have the greatest influence on population-level responses

This objective develops methods to extrapolate from individual level responses up to the population. Development and application of population response models will be the primary approach and organizing structure. NERL's Pesticide Root Zone Model (PRZM), the world-wide workhorse of ecological risk assessment will be modernized and enhanced. PRZM 3.12ß upgrades include (1) adding multiple curve numbers, (2) utilization of EXAMS' methodology with daughter products, (3) correction of an irrigation bug, and (4) support EXPRESS (PRZM/EXAMS GUI). A PRZM computational kernel and a windows interface will be created. The computational kernel (translated to Fortran 95) will have groundwater capabilities, improvements to PRZM infiltration algorithms (unchanged since 1982), Penman-Monteith ET0, sorption kinetics or "aging", Freundlich soil sorption isotherms, and soil moisture effects on biodegradation. A probabilistic exposure modeling system for small watersheds will be developed by integrating PRZM, EXAMS, and AgDISP codes currently in use by OPPTS. The system will include national-scale climatological and physiographic databases tailored to system requirements, in a GUI designed to facilitate scenario development and production of problem-specific output graphics and analyses. User manuals will be delivered and the system will be refined in its algorithmic content and output capabilities via exposure studies at watershed and regional scales delivered. These targeted laboratory and field studies will be designed to evaluate model outputs, key assumptions and model parameters, and potential population-level compensatory mechanisms. Analyses also will be conducted to identify responses at the individual level that have the greatest influence on population-level responses for a variety of species with differing life-history strategies.

(d) develop approaches for evaluating the relative risks from chemical and non-chemical stressors on spatially structured wildlife populations across large areas or regions.

This objective introduces issues associated with the spatial and temporal heterogeneity of populations and stressors, and extends the analyses under the previous two Objectives to applications in real landscapes. Because different stressors tend to be distributed differently in the landscape, this approach will address the interactive effects of contaminants, habitat alteration, and introduced species on wildlife populations. Models and analyses will be designed both to assess risks from multiple stressors and to evaluate the relative effectiveness of alternative management strategies. The basic GIS and population modeling platform is in development under the Ecosystem Protection Research MYP (Goal 8) so as to serve the needs of all EPA Program and Regional Offices. Under the safe pesticides/safe products MYP, research is focused on the relative risk assessments for bird populations exposed to toxic chemicals and landscape disturbances within the natural range of the species. Birds are the class of vertebrate

wildlife of principal concern due to their higher susceptibility as compared to mammals to past and current generations of pesticide chemicals, their high visibility, and high public concern. Programs such as the Breeding Bird Survey conducted by the USGS and the multisectorial program Partners in Flight provide a high level of public input and scrutiny to monitoring bird populations and biodiversity.

LTG 3. To provide OPPTS with the scientific underpinnings for guidance to prevent or reduce risks of human environments within communities, homes, workplaces

OPPTS has made great strides in reaching out to communities to provide important information for achieving safe pesticides/safe products as well as in engaging industries, citizens and communities with respect to the goals of environmental protection. While many of these activities would obviously involve toxic chemicals, safe pesticides/safe products also require information and guidance on non-chemical risks. To support OPPTS efforts, research is needed to support risk assessments in communities, homes, workplaces, and at other specific sites. Risk assessments that focus on a defined population in a community are often referred to as community-based or population-based assessments. At EPA they are also called cumulative risk assessments, where "cumulative" is used in a broad sense to refer to risks from exposure to multiple chemicals and non-chemical stressors in a defined population at a specific location.

Combining different types of stressors (e.g., chemical and non-chemical) can be a problem. Certain stressors cannot be evaluated using existing methods, and little attention has been given to how to combine different types of stressors. Research is needed on risks of non-chemical stressors, how exposure to non-chemical stressors affects risks of chemical stressors, and methods for conducting population-based cumulative risk assessments. This section discusses research related to non-chemical stressors and cumulative risk that can be supported by the resources in the current safe pesticides/safe products base program over the next several years. Additional research in this area is described below in the section entitled "Potential Research Initiative" in Appendix E . For the near-term, this Long-Term Goal will focus on the risk of genetically modified products.

3.1 Evaluating Potential Risks Associated with Biotechnology Products

Biotechnology presents a wealth of opportunities to improve crop productivity, nutritional value and ability to resist pests and other stresses. However, there are potential risks to human health and ecological systems that need to be evaluated so that these products can be properly regulated. Currently, EPA regulates biotechnology products which are pesticides (either produced by plants or by microorganisms) and non-pesticidal substances produced by microorganisms. In the near future, it is anticipated that EPA will also regulate nonpesticidal products produced by plants, including pharmaceuticals and industrial chemicals.

From a human health perspective, a major focus is on the potential toxicity and allergenicity associated with biotechnology derived foods. Potential adverse effects can be from intended modifications (i.e. from the pesticidal substance) or from unintended effects resulting from production of a unexpected substance from the insertion of the new genetic material into the host genome. To date, the products approved by EPA for use in human food have all been

proteins that degrade rapidly, so no chronic effects would be anticipated. This approach has been accepted by the FIFRA Scientific Advisory Panel. However, some members of the public have raised issues about long term exposure to eating foods containing these proteins. It is well accepted that the genetic material itself will not cause and acute or chronic toxic effects and has been exempted from tolerance.

From an ecological perspective the regulation of biotechnology products is focused on cases where there is little prior experience with the new trait and host combination; a transformed organism may persist and perhaps replicate in the environment without human intervention; genetic exchange is possible between a transformed organism and unaltered organisms; or the trait confers an advantage to the transformed organism over native species in a given environment. Additional concerns about rapid evolution of resistance in targeted pest species; potential risk to nontarget invertebrates; and alterations in terrestrial or aquatic food chains also have been raised.

The goal of the biotechnology research program is to provide the scientific information needed to assess and manage the risks of biotechnology by providing the tools needed to generate information about biotechnology products and by generating the knowledge needed to understand the nature and magnitude of potential risks and benefits resulting from the use of biotechnology products in commerce and the means to prevent or control such risks. The research program will focus on five key issues:

(a) potential allergenicity of proteins introduced into the food supply by gene transfer;

The key issue inhibiting OPPTS' ability to evaluate the potential allergenicity of proteins introduced into the food supply by gene transfer is that there are no valid models for predicting dietary allergenicity and the long-term effects from consuming crops containing PIPs and other biotechnology products. EPA and FDA are currently using several screening assays designed to compare new substances to the properties of known dietary allergens, but this approach is not useful for those substances that do not pass the screening criteria. The research need is to develop an understanding of the basis for human sensitization to dietary allergens to help develop methods to assess dietary allergenicity and to apply such methods to monitor human populations exposed to genetically modified foods for increased allergenicity.

(b) potential ecological effects and impacts from the use of biotechnology products on non-target species;

There is not an agreed upon set of questions that need to be asked about the possible impacts of PIPs on non-target species. In addition to potential direct toxicity to the insects, concerns have been raised that PIPs are so effective at controlling insect pests that bird populations might be adversely impacted because of a lack of food. Conflicting data indicates that the number of song birds is increasing in areas where Bt cotton adoption is high. The research need includes baseline and monitoring studies to assess the structure and dynamics of populations of beneficial insects, insect pests, and other insects such as butterflies in and around crops grown using conventional, organic, and biotechnology pest management tools.

Further, there are still no standardized, validated, affordable assays for assessing exposure and effects on non-target species. This is a significant gap in our understanding of the potential for unintended consequences and methods to evaluate the scale over which biologically meaningful exposures to non-target species may occur and the vectors (e.g., pollen, insect movement, predation) that mediate this exposure are needed. Specifically this research will:

•develop an understanding of the mechanisms that lead to adverse effects in non-target species (e.g., honeybees) as a basis to develop standardized, validated, affordable assay for testing for effects on important species

•develop an understanding of the impacts of metabolism in genetically altered plants as a basis to assess risk and to develop methods for testing genetically altered plants for such changes (Increasingly, transgenic plants are being developed with altered metabolic or signaling pathways, and such constructs may have secondary effects on plant physiology due to pleiotropy or epistasis)

(c) escape of altered plants to the natural environment and likelihood and impact of gene transfer;

The ability of some crops to transfer introduced genes through hybridization to wild and/or weedy relatives can make assessment for effects on non-target organisms very difficult. There is one report, in *Arabidopsis thaliana* which does not normally outcross, in which a transgenic plant "showed a dramatically increased ability to donate pollen to nearby wildtype mothers compared with *Arabidopsis thaliana* mutants expressing the same mutant allele as the transgenic plants" . The research needed includes an exploration of factors influencing gene transfer rates, particularly in highly selfing plants, to provide a basis for better assessments; and the development of methods to evaluate the persistence/maintenance of transgenes in plants and microorganisms to help evaluate the exposure to those gene products and an evaluation of whether environmental conditions or common stressors influence this process.

(d) effects of altered plants on development of pesticides resistance in the target species; and

Laboratory and small scale field testing have been the basis for evaluating the likely safety of biotechnology products, but long term, extensive monitoring has not been conducted to determine whether the effects predicted in such assessments actually occur in the field. The research objectives are to:

• develop models to estimate likelihood of insect resistance development that incorporate detailed biological information for pest species, including gene flow and mating patterns in the wild, geographic and chromosomal distribution of resistance alleles, and their additive and nonadditive effects on resistance under selective pressures in the field, and..

• perform monitoring studies of gene transfer, the development of resistance to PIPS and impacts on non-target species (as noted in 2b) to allow field validation of conclusions

regarding transgenic plants with new pesticide traits, including recommendations to prevent development of insect resistance to support or to refine assessments.

• strategies for identifying the key risks of concern and effective risk management technologies to mitigate these key risks when the monitoring studies indicate unintended adverse consequences.

The effectiveness of strategies for identifying the key risks of concern and effective risk management technologies to mitigate these key risks when the monitoring studies indicate unintended adverse consequences has not been adequately evaluated. Extensive work is needed to improve strategies for identifying the key risks of concern and effective risk management technologies to mitigate these key risks when the monitoring studies indicate unintended adverse consequences; and to explore the application of socio-economic methods such as benefit-cost analysis and life cycle analysis to better understand issues related to the public acceptance of genetically altered products and to evaluate whether the genetic alterations produce new organisms that are not substantially equivalent to currently existing ones

By FY 2008, this research will result in improved capability to assess the risks of allergenicity from genetically altered food; it will improve EPA's capability to assess the ecological risks associated with genetically modified organisms; and, it will produce tools for use by EPA and others to understand and better manage gene transfer and resistance. Program performance will be evident when the research products are used by the OPPTS in the registration and re-registration process, both in hazard identification and risk assessment and in setting risk management requirements for registration; there is general acceptance of these methods by other regulatory agencies; and there is greater public acceptance of EPA's approach to regulating these genetically modified crops.

3.2 Molecular Exposure Diagnostics

The advent of genomics technologies has produced a quantum leap in ORD's capabilities and capacity to rapidly assess exposures, better relate the exposures to health effects, and thus assess risks. Genomics is also allowing the coordinated development of several diagnostic indicators using patterns of expression of multiple genes. Molecular Expousre Diagnostics research, a program directly related to ORD's Computational Toxicology research program, is needed to develop new sensitive subcellular indicators of exposure to specific pesticides. Molecular biological advances demonstrated in the human health sciences are now ripe for application in environmental studies. Measurements using indicators developed through research will reveal to what extent pesticides in the water column are bioavailable to aquatic organisms even in the presence of mixtures. Predictions made by pesticide fate and transport models should be extended beyond issues of chemical speciation and concentration to include comparative biological exposure assessments. Linkages between the first response (exposure) of aquatic organisms and effects and outcome will then be enabled.

Initial research will be focused on the development of indicators using the change in expression of one gene to detect bioavailable estrogens, PAHs or metals. The development of

these screening-level tools for chemical transformation processes is needed to categorize the reactivity of chemicals as high, medium, or low by defining windows of reactivity and determining the environmental conditions under which these processes occur. The development of simulators for critical metabolic processes (e.g., transformation pathways and thermodynamic constants), will ultimately provide the user with the metabolic pathways based on chemical structure. Future research will focus on the development and real-world application of indicators for exposures to pesticides and toxics (including mixtures), developing core molecular genetic resources (fast gene discovery and aquatic organism microarrays) and sex steroid specific indicators of exposure that are linked to effects, and developing genomics research links chemical transformation pathways with toxicity pathways in computational toxicology.

3.3 Transport and fate of pesticides in Drinking Water Distribution Systems

An area of critical concern to OPPTS and the Office of Water is the ultimate product that results and is available for exposure to the environment and public when a pesticide or toxic chemical enters a drinking water distribution system. Drinking water treatment often has a large effect on pesticides and toxic chemicals that occur in source waters; and both OPP and OPPT have articulated their high priority need to incorporate these effects into chemical risk assessments. The Food Quality Protection Act (FQPA) requires the Office of Pesticide Programs (OPP) to consider all anticipated dietary exposures when conducting risk assessments for pesticides. Drinking water (DW) is considered a potential route of exposure because many DW sources contain detectable levels of pesticides and toxics. However, the majority of the U.S. population consumes treated DW. It is anticipated that DW treatment will: a) partially remove some chemicals, b) transform some chemicals (perhaps to more-toxic byproducts), and c) have virtually no effect on some chemicals. Unfortunately, very little data has been collected, and very little mechanistic information is available, on the effects of DW treatment processes on pesticides (or on any chemicals for that matter).

OPP has announced a policy to systematically consider DW treatment effects on pesticides for FQPA risk assessments. For this policy to make risk assessments significantly more certain, pesticide-specific information on DW treatment effects is needed. Also, reliable tools to extrapolate effects across chemical classes is required. These needs, which have been articulated by OPP, are driving this research. Without the type of information and tools that ORD will provide, OPP will have to assume that DW treatment has no effect on a pesticide or toxic chemical. This may be overly- or under-conservative, depending on the pesticide or toxic chemical, and the treatment conditions.

Research needs include the examination of the fate and transport of current use and proposed pesticides and toxics, and their byproducts in the drinking water pipeline. Research is needed to examine how drinking water treatment processes impact pesticides and toxics, what by-products are produced, the chemical and physical parameters of these byproducts, and their fate. Research will be implemented to develop chemical-specific information on the effects of water treatment for OPPTS identified high-priority pollutants, provide physicochemical parameters for transformation products, and develop predictive models for forecasting treatment effects that cross chemical class and treatment conditions.

A step-wise research approach will be implemented that includes: (1) Measuring chemical transformation rates and products for disinfection and water softening processes ; (2) Determining physicochemical properties of transformation products formed from DW treatment; (3) Determining physicochemical properties of transformation products formed from DW treatment; (4) Determining physicochemical properties of transformation products formed from DW treatment; (5) Investigating the influence of chemical speciation on DW treatment effects of organic chemicals; (6) Developing models for removal and transformation of chemicals during the DW treatment process. The resulting data, models, and enhanced scientific understanding regarding forecasting the fate of key classes of pesticides and toxics chemicals in the drinking water treatment process will be used by the risk managers to ensure that drinking water treatment processes are minimizing potential exposures to highly toxic chemicals and their metabolites.

3.4 Spray Drift

ORD will continue to serve as the lead Agency for characterizing community risks associated with the large-scale application of agricultural pesticides. ORD coordinates and integrated Spray Drift research program addressing key OPPTS, Regional Office and industry high priority science needs. NERL's program will expand it's current near field exposure modeling research focus towards a regional perspective. NRMRL, serving as ORD's lead in collaboration with the Spray Drift Task Force, will focus its research on developing and validating improved engineering and risk management approaches to reducing risks associated with the application of agricultural pesticides.

NERL Spray Drift Exposure Assessment and Modeling. OPP's Environmental Fate and Effects Division and Health Effects Division, along with the Regions and States have consistently listed as a high priority need an integrated community level drift exposure modeling capability to assess community risk in areas of intensive agriculture. This modeling capability needs to fully incorporate factors that reflect the inherent conflicts between agricultural production, human habitation and ecological resources. ORD's Spray Drift Exposure Research Program is designed to address these needs by advancing our understanding and ability to project the magnitude, duration, frequency, and underlying causes for the atmospheric transport and deposition of synthetic organic chemicals. Building on its successful production of a validated near-field model of drift from aerial application of pesticides, ORD's research will produce:

- supplemental ground-spray and orchard-blast algorithms for the near field (<1 km)
- source-term models for revolatilization and wind-borne contaminated dust
- meso-scale (1 - 30 km) models for the transport and deposition of re-mobilized chemicals
- models that link near and meso-scale exposure models to far-field (regional) transport models to assess regional impacts

A model linking near-field off-site drift algorithms to a model for evaluating transport out to approximately 30 km (meso-scale) will be tested, refined, and applied in an example assessment. Ground and orchard spray sources algorithms will be developed and incorporated into the meso-scale drift platform. Mechanistically-based source terms for these two application types will be developed and evaluated. Secondary drift algorithms – revolatilization and wind-blown dusts – will be evaluated, refined and incorporated into the meso-scale drift platform. The algorithms will be initially developed and tested based on data and process descriptions available in the literature. Field test data will be developed to test the meso-scale drift platform from multiple source primary drift processes. The field study design will be completed in 2005 and a model/data comparison report will be generated in 2007. A screening-level monitoring effort will be conducted to provide a preliminary assessments of the extent and magnitude of Long Range Atmospheric Transport (LRAT) of pesticides and other contaminants. A workshop will be held to evaluate the current state of the science regarding LRAT. Knowledge gaps that preclude an accurate assessment of the extent, magnitude, and impact of LRAT by OPPTS and other concerned Offices (e.g., OIA, OA, AMD) will be identified, and a draft strategy to address gaps and provide a preliminary assessment of extent and magnitude will be developed. Research will be conducted to upgrade ORD's spray drift exposure models to incorporate the recommended long range exposure modeling needs.

This research will be planned and implemented through an integrated and collaborative program among ORD, OPPTS, our Federal partners (USDA FS and ARS, DOD, etc.), and industry. Evaluated models will be provided to the Agency for improved community risk assessments.

Risk Management of Pesticide Drift. Risk management of pesticide drift is the employment of methods to maximize pesticide application to the target while minimizing other pathways of fate of the pesticide. Barriers to implementing innovative technologies to minimize drift appear to exist including technical barriers to development of pesticide application equipment that lower drift, barriers to validation of the capability of application technologies to lower drift, and regulatory barriers to the use of innovative technology. This research area will identify these barriers and identify risk management research needs to lower these barriers. Future work, if additional resources become available, will include research to relieve these barriers.

3.5 Toxic Molds and Asthma Triggers in Indoor Air

Protecting indoor human environments from toxic agents is a special concern for OPPTS and OAR, as well as Regional Offices and state and local governments. Over the past decade, research efforts have focused on methods to detect indoor emission sources, models to estimate exposure, tobacco smoke and particle air cleaners. Effects research has been limited to a small number of toxic contaminants. Current research on the risks of indoor air are found in the PM Strategy and the Children's Health Research Strategy. While these other research efforts address toxic chemicals and particulate matter, the strategic focus of Safe Communites research on indoor air quality is that of toxic molds.

State-of-the-art microarray technology is needed to assess human exposures to toxic molds and other microbiologicals. Genomic approaches for examining the role of fungal exposures and health need to be examined and a set of indicator molecules and/or methods for exposure developed and evaluated in selected microenvironments is needed. The results of this research should produce a set of diagnostic tools to confirm exposures to molds. These tools can then be employed within the National Children's Study to evaluate all environmental influences on children's health.

3.6 Evaluation of Commercial Coatings to Minimize the Potential for Dermal Arsenic Exposures on the Surfaces of Pressure-Treated Wood

Chromated copper arsenate (CCA) is a chemical wood preservative injected under high pressures to protect wood from decay and insect damage. In one formulation, CCA contains a mixture of 46.9% CrO3, 17.4% CuO, and 35.7% As2O5. In February 2002, the manufacturers of CCA- treated wood asked the U.S. EPA to remove the registration of CCA for residential use including playground equipment, decks, and landscape timbers. The CCA-treated wood manufacturers are phasing out production and use of CCA in favor of alternative chemicals and processes. They intend total conversion (for residential uses) by December 31, 2003. Of concern is the possible dermal exposure of children to the arsenic (As) contained within the CCA- treated wood that has been used for playground equipment, decks, and outdoor furniture. There is currently little data available on efficacy of sealants and coatings to minimize dermal exposure. Thus, there is an immediate need to identify and evaluate commercial coatings that can reduce or prevent exposure to arsenic from CCA treated wood.

Objectives of this research are: (1) to identify commercially available coatings that are suitable for application to CCA- treated wood used in outdoor environments, and (2) to evaluate several commercially available coating systems for their ability to mitigate dermal exposures by prevention of As on the surface of CCA-treated wood.

LTG 4. To provide OPPTS with strategic scientific information and advice concerning novel or newly discovered hazards

The development of research strategies and multi-year plans in ORD serves to keep research activities focused on the frontiers that cause the greatest uncertainties in risk assessment and risk management. In designing the strategic framework for the Safe Communites Multi-Year Plan, it became clear that the broad spectrum of regulatory responsibilities in OPPTS presented special problems for research planning. While there was general agreement that ORD should focus more resources on fewer and more central research needs of the many OPPTS programs, there was also the concern over having all available resources committed to plans and not being free to respond to special problems that arise. To avoid having Safe Communites become a collection of small technical assistance projects, ORD and OPPTS agreed that the strategic framework would include one long-term goal for research on novel hazards, but that the definition of novel hazard will be limited to chemicals which pose unique problems in risk assessments and represent a large class of similar chemicals which are likely to cause similar problems in the future. Under this strategy, ORD can respond to the issues of novel hazards over longer periods with assurance that the research will be useful for many other chemicals in the future. Two immediate priorities for OPPTS was the class of perfluorinated surfactants (OPPT) that have anomalous behavior in risk assessment models and the new generation of herbicides (OPP) that have novel toxicity mechanisms giving rise to extreme potency.

4.1 High Potency Herbicides

Low-dose, high-potency herbicides are defined as those herbicides with a maximum label application rate of 0.5 pounds of active ingredient per acre. Several classes of chemicals fall into this category, including the acetolactate synthase (ALSase) inhibitor herbicides, imidazolinones, sulfonylureas, triazolophyrimidine sulfonamides, isoxaflutoles, and pyrimidyl thio-benzoates. Chlorsulfuron, an ALSase inhibitor, was the first commercial product of this type, first marketed in 1981. There is evidence for a wide variation in response of various plant species to these chemicals (about 3 orders of magnitude), making it difficult to extrapolate potential risk from the current suite of plant test species. Given the increasing use of these types of herbicides, the FIFRA Science Advisory Panel (2001) recommended restructuring the Tier II risk assessment process to expand the number of species tested and the endpoints evaluated.

The existing plant test protocols required prior to the registration of pesticides were developed in the early 80's under FIFRA regulations by the OPPTS. Three tests for terrestrial plants were required: 1) seed germination, 2) seedling emergence and 3) vegetative vigor. A field test is mentioned in the regulations but has rarely been implemented and when performed it has been criticized for insufficient replication, lack of protocols and poor design. A major problem with the present test guideline is the lack of information on pesticide effects on plant reproduction. Current testing is limited to a very small portion of a plant's life cycle, that does not include reproduction.

These and other uncertainties in current test methods identified by OPP's Science Advisory Panel (2001) can be addressed through research focusing on the following questions:

- are greenhouse test results predictive of field test results?
- how does the response of a seedling compare to a mature plant?
- what bearing does inhibition of seedling growth have on the survival and eventual growth (yield) of a plant?
- can results from experiments on one species be extrapolated to another?
- is it possible to extrapolate from individual species tests to communities?

The objective of the research proposed below is to determine the short and long term effects of pesticides on non-target plants, plant communities and their associated biota including and wildlife. A revised set of protocols (seedling emergence, vegetative vigor and reproduction/developmental) for terrestrial plants will be developed utilizing a new set of species. Test species will be selected by agro-ecoregions within the United States. When a new pesticide is proposed for use, it should be tested against plants from the agro-ecoregions in which it is most likely to be released. Species selected will meet one or more of the following criteria: 1) a dominant native plant, 2) a dominant cultivated species, 3) an important food or shelter plant for wildlife, or 4) a rare or endangered species of the ecoregion. Candidate plant species also will be evaluated for their ability to be cultured and their sensitivity to various pesticides. Field tests will be developed using multiple species, modified for each region. End points will include production (yield), reproduction and species interactions. Test scenarios will include existing vegetation surrounding test plots such as field margins, as well as more structured designs where mixtures of plants are seeded/planted in various relative densities and proportions. This will provide information on changes in species composition and system dynamics, along with the more traditional endpoints of phytotoxicity or death**.** This information will be used to develop guidelines for revised field tests and for assessments of impacts of pesticides on quality of plant communities for wildlife.

Because of the difficulty of setting up a comprehensive monitoring system to detect off-target incidents across the US, a system for localized and/or regional field monitoring will be developed using a GIS (geographical information system) approach. Potential trouble spots will be identified by overlay maps that will include (but not limited to): current herbicide use patterns, anticipated herbicide use patterns, climate (especially wind speed), crops, soils types, natural vegetation, endangered plant species, water resources and wildlife ranges.

Risks from pesticides to ecologically and economically important plant resources will be determined at the regional and landscape level. Information generated regarding potential hazards of low-dose, high-potency herbicides to nontarget plant species needs to be combined with estimates of potential exposure in order to define the risk from use of existing or proposed substances. Given the geographically focused nature of plant species distributions, cropping

practices, and herbicide use, a spatially explicit framework is being developed that allows for probabilistic risk determination. The impact of pesticide drift is dependent upon the sensitivity of the non-target species at the time of exposure and the magnitude of the pesticide exposure. At regional spatial scales, pesticide drift problems are most likely to occur in agricultural regions that have two or more dominant crop species, moderate-sized farms and are subject to high winds (> 10 mph). Exposure varies with distance from the field margin, and can be estimated using current models (e.g., AgDRIFT 2.0). The research will develop several case studies to identify and prioritize potentially important uncertainties, and identify the actions needed to address gaps in the knowledge base.

4.2 PFOS and related organic fluorochemicals

A host of organic fluorochemicals increasingly are being used for a variety of household and industrial applications. These include the surfactant coatings for fabrics and paper products, fire-fighting foams, electronic etching baths and insecticides. Concern for the potential toxicological risk of these types of chemicals had been minimal until recent documentation of the extensive distribution and persistence in both humans and wildlife of perfluorooctane sulfonate (PFOS), the primary degradation product of a widely-used class of sulfonyl-based fluorochemicals primarily manufactured by 3M. There is some recent information, mostly derived from rodent and monkey studies, concerning the potential developmental, reproductive and systemic toxicity of PFOS. In particular, certain aspects of perinatal development appear to be quite sensitive to the effects of PFOS. While PFOS has been withdrawn from the commercial market by 3M in 2000, the product is still readily available from other oversea manufacturers. More importantly, alternative chemicals such as perfluorooctanoic acid (PFOA), or re-formulation of PFOS with shorter carbon chain (such as C6) products have emerged in the commercial market. At present, little to no information is available concerning the environmental distribution and adverse health effect potentials of these substituting organic fluorochemicals.

Because of its unique chemical properties (strong C-F bond for stability, involatility, hydrophobicity and lipophobicity), the organic fluorochemicals represent a novel class of environmental contaminant that are quite distinguishable from the classical persistent organic pollutants (POP). In order to provide OPPTS with a sound scientific basis for potential regulatory action on this class of chemicals, research efforts have been initiated by RTD of NHEERL, and co-ordinated with RAD/OPPT. Because of the known pervasive distribution and persistent nature of PFOS, this chemical will be examined as a prototype for the class of organic fluorochemicals. As we gain a better understanding of this particular chemical, investigation will be extended to other related compounds such as PFOA and shorter carbon chains of the perfluoro-sulfonates and carboxylates to determine if certain characteristics are common to this class of chemicals. This objectives of this research are:

- to characterize the reproductive and developmental toxicity of PFOS in laboratory rodent models, and to provide a dose-response profile for each of the significant findings.

• to ascertain whether the toxic effects are dependent on the windows of exposure during development. This issue is of particular importance because of the high exposure potentials for infants and children.

• to construct a pharmacokinetic (PK) model for PFOS, in collaboration and 3M Company for use in future applications extended to other related fluorochemicals. In addition, because the body burden of PFOS is known in various human and wildlife populations, a margin of exposure (MOE) can be estimated based on the toxicity data derived from laboratory animal studies.

• to elucidate the modes and/or mechanisms of actions for PFOS that are related to its toxic effects; an understanding of these mechanistic properties will be critical to hazard identification and risk assessment of this novel class of chemicals as a whole

• to compare the reproductive and developmental toxicity among the various perfluorinated organic chemicals (such as PFOS, PFOA, PFHS (C6), PFBS (C4)), using relevant endpoints derived from the PFOS studies.

• to evaluate the usefulness of genomic and proteomic techniques to identify the mechanisms of PFOS toxicity and the applicability of these experimental tools to screen for common features/indicators of toxicity among the various perfluorinated organic chemicals.

Compared to information derived from laboratory animals models, even less is known about the toxicity of the organic fluorochemicals in wildlife. This is of particular concern given the relatively high concentrations of PFOS that have been reported in mammals, birds and fish from locations throughout the world. Exacerbating this lack of information is the fact that the actual toxic mode/mechanism of action (MOA) of PFOS is unknown, so extrapolation of effects from rodent studies to wildlife of concern is uncertain. Further complicating assessment of the ecological risk of fluorinated chemicals in general and PFOS, in particular, are their unique physicochemical properties. For example, historically-used models, developed primarily for nonionic organic chemicals, are of limited utility with respect to predicting the distribution and effects of these chemicals either in the environment, or within individual animals. In addition, existing test methods with aquatic species may not suffice for evaluating fluorinated chemicals in terms of traditional approaches for chemical delivery.

To complement the ongoing and planned research with PFOS and related chemicals being conducted at RTD, parallel studies to develop techniques for assessing the ecological risk of these perfluorinated organic chemicals will be undertaken at MED. Similar to the tack taken by RTD, PFOS will be examined as the prototypical representative of this class of compounds. A critical aspect of the research conducted at MED will be identification of biological models (species, life stages, endpoints) that effectively reflect both conditions of the greatest sensitivity to PFOS, and result in data of utility for predicting population-level effects. This work will examine reproduction and development in a small fish model(s) (fathead minnow, medaka,

zebrafish) and development in amphibians (*Xenopus*, native North American ranids). Toxicology studies will be conducted with careful attention to dosimetry issues (uptake, metabolism, distribution) to enhance development of credible exposure approaches, as well as support derivation of models suitable for extrapolation across species. Characterization of dosimetry under controlled conditions will be complemented with hypothesis-driven analyses of key environmental samples to facilitate extrapolation from the laboratory to the field. Attempts will also be made to gain insights as to toxic MOA of PFOS through the use of DNA microarrays currently under development at MED for amphibians. An understanding of MOA would not only enhance extrapolation of effects across species, but could also could directly support the development of *in vivo* endpoints and/or *in vitro* systems that could be utilized to obtain data for structure-activity relationship (SAR) models suitable for hazard identification.

Improved methods and protocols are needed for identifying the presence and extent of the potential exposures of these new chemicals to humans and the environment. The Regions, States, and Tribes require assistance in the application of these methods to diagnose, assess, and mitigate current and emerging exposure issues. Activities include:

Techniques for PFOS/PFOA and other emerging polymers. Mechanistically -based models to categorize chemical reactivity and estimate rate constants for both microbial and chemically-mediated transformations will help to identify toxic chemicals that are persistent and/or transformed to more toxic reaction products. Technical support will provide fate data for agreed upon chemicals of interest (e.g., developing fate data for perfluorinated compounds such as perfluorooctane sulfonate (PFOS) and carboxylate (PFOA)).

D. DESCRIPTION OF THE FLOW DIAGRAMS, APGS AND APMs

This section of the Multi-Year Plan provides a summary of the resources needed to complete the research, a listing of the annual performance goals and measures for each LTG, and a brief description of the critical paths for the research in the form of a flow diagram.

RESOURCE PROJECTIONS TO COMPLETE THE MYP

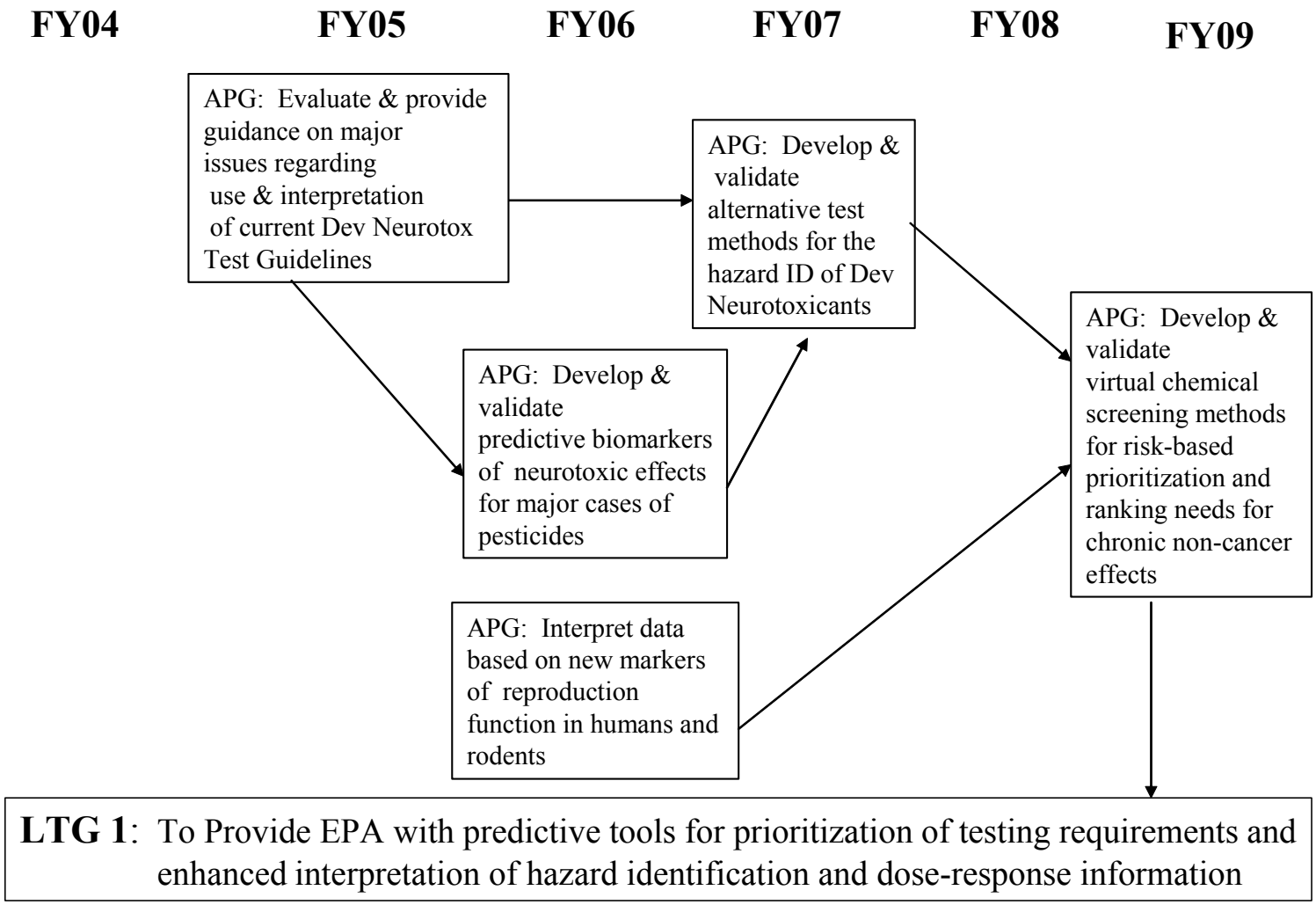
Long-Term Goal	Emphasis from 2003 through 2009
1	Level through 2009
2	Level through 2005 and then increasing
3	Increase through 2006 and then level
4	Level through 2008 and then decreasing

LTG 1: To provide EPA with predictive tools for prioritization of testing requirements and enhanced interpretation of hazard identification and dose-response information

ANNUAL PERFORMANCE GOALS, MEASURES, AND MILESTONES		YEAR	LAB/ CENTER
APG:	**Evaluate and provide guidance on major issues regarding the use and interpretation of the current Developmental Neurotoxicity Test guidelines**	**FY 05**	
APM	Report on the results from a workshop on the current state of knowledge of test methods for developmental neurotoxicity and develop a long-range research plan	04	NHEERL
APM	Provide an evaluation of the relevance, use and interpretation of positive control data in developmental toxicology studies	04	NHEERL
APM	Provide an evaluation of the appropriate age(s) of assessment of neuropathology as it applies to the Developmental Neurotoxicity Test guidelines	05	NHEERL
APG:	**Develop and validate predictive biomarkers of neurotoxic effects for major classes of pesticides**	**FY 06**	
APM	Provide a guidance document on predictive alternatives to the Developmental Neurotoxicity Guideline testing for thyroid active compound	04	NHEERL
APM	Report on predictive biomarkers of effect for pyrethroid insecticides	05	NHEERL
APM	Provide a draft revision for the Developmental Neurotoxicity Test guidelines that includes predictive biomarkers	06	NHEERL

APG:	**Interpret data based on new markers of reproductive function in humans and rodents**	**FY 06**	
APM	Evaluate and provide guidance on utility of new tests for genomic integrity of human sperm relative to routine sperm measures	04	NHEERL
APM	Demonstrate ability of in vitro tests of follicular steroidogenesis to reveal modes/mechanisms of pesticides and toxic substances that affect female reproduction	05	NHEERL
APM	Report on the usefulness of sperm RNA profiles and sperm protein biomarkers for detecting subtle changes in testicular or epididymal function	06	NHEERL
APM	Develop protocols and provide guidance to predict long term consequences of early exposures that result in low fetal/birth weight	06	NHEERL
APG:	**Develop and validate alternative test methods for the hazard identification of developmental neurotoxicants**	**FY 07**	
APM	Report on a predictive in vitro model for estimating the potential for age-dependent toxicity of cholinesterase-inhibiting organophosphate pesticides	04	NHEERL
APM	Initial report on the development of predictive methods to examine the effect of pesticide mixtures acting on neuronal ion channels	05	NHEERL
APM	Provide validated predictive in vitro test methods for major neurodevelopmental processes, including neuronal differentiation and apoptosis	06	NHEERL
APM	Provide validated predictive in vitro test methods for major neurodevelopmental processes, including axonal growth and synaptogenesis	07	NHEERL
APM	Provide validated predictive methods to examine the effect of pesticide mixtures acting on neuronal ion channels	07	NHEERL
APG:	**Develop and validate virtual chemical screening methods for risk-based prioritization and ranking needs for chronic non-cancer effects**	**FY 09**	
APM	Provide library of QSAR models for developmental and reproductive toxic effects for use PMN review and pollution prevention	04	NHEERL
APM	Deliver a computerized algorithm for identification of industrial chemicals and pesticides that have activated metabolites	05	NHEERL
APM	Report on the development of a systematic approach for the identification of strategic testing sequences for pesticides	06	NHEERL
APM	Report on the integration of virtual and high-throughput screening methods for setting risk assessment priorities	07	NHEERL
APM	Report on the use of QSAR as a hazard identification method for chemicals causing developmental and reproductive impairment	08	NHEERL

Figure 3. LTG 1 Research Path

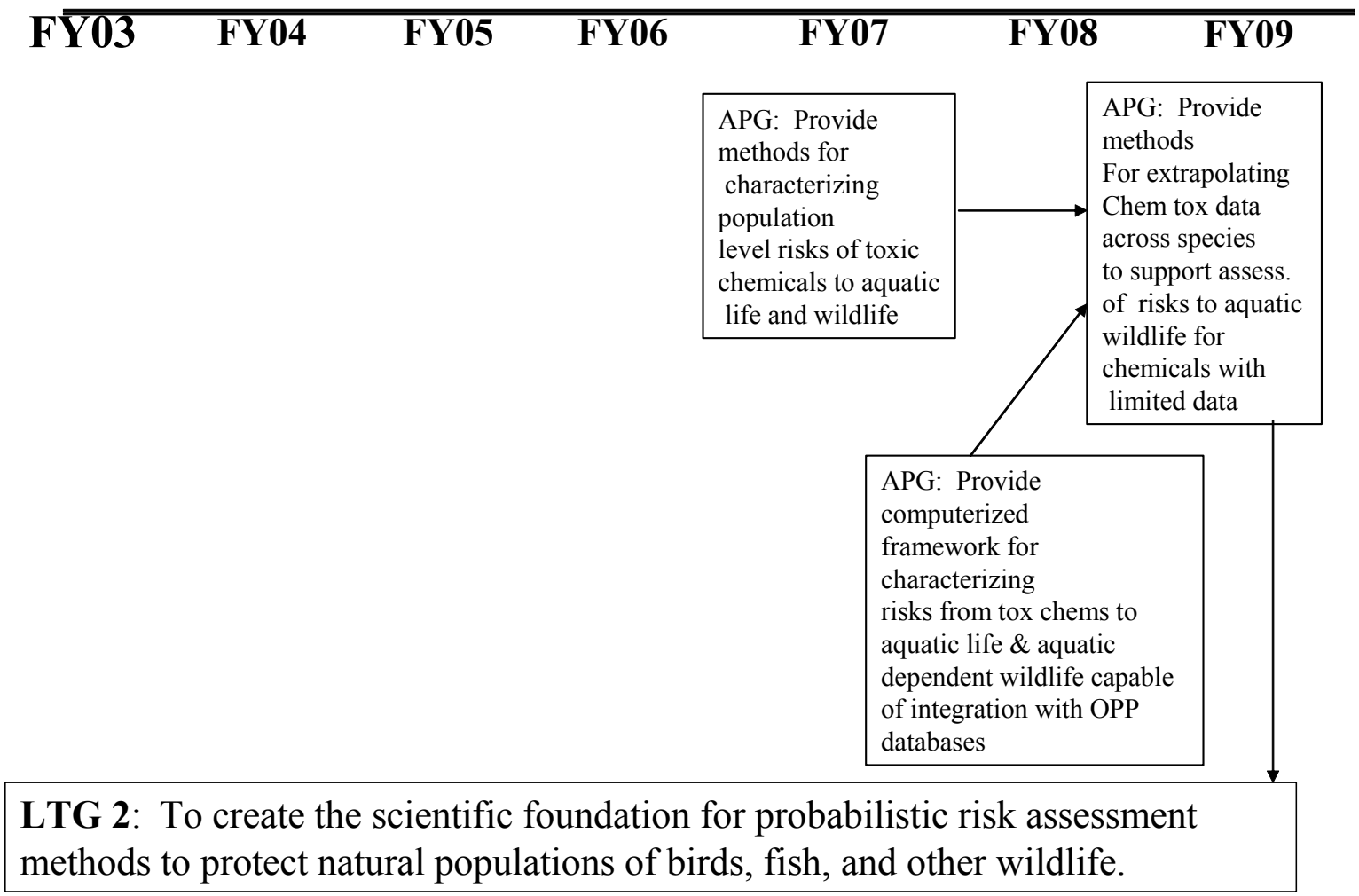


LTG 2: To create the scientific foundation for probabilistic risk assessment methods to protect natural populations of birds, fish and other wildlife

APG:	**Provide methods for characterizing population-level risks of toxic chemicals to aquatic life and wildlife**	**FY 07**	
APM	Provide basic deterministic population models for key species of aquatic organisms	03	NHEERL
APM	Develop a framework for use of diagnostic indicators, bioassays, and spatially-explicit matrix population models to assess current and future effects of pesticides on avian populations	03	NHEERL
APM	Literature based verification and performance evaluation of demographic modeling approaches	03	NHEERL
APM	Provide basic stochastic population models for key bird species, along with guidance and support in the application of the models to assess population-level risks of pesticides	04	NHEERL
APM	Refined stochastic population models for key bird species and appropriate guidance and support in model application	05	NHEERL
APM	Refined stochastic population models for key aquatic species and appropriate guidance and support in model application	06	NHEERL
APM	Verification of refined stochastic population models projections for key bird species	07	NHEERL
APG:	**Provide computerized framework for characterizing in a spatially-explicit manner risks from toxic chemicals to populations of aquatic life and terrestrial wildlife capable of integration with OPP databases**	**FY 08**	
APM	Ugrade metals and wildlife database in interspecies correlation estimations (ICE) model for acute toxicity	03	NHEERL
APM	Identification of appropriate surrogate test species for inclusion in ICE model to protect under-represented fish taxa	04	NHEERL
APM	Delivery of PATCH version with interfaces to distributed databases and population models	06	NHEERL
APM	PATCH II framework version (Windows) with generalized life history module, general stressor module, and GIS accessibility	08	NHEERL
APG:	**Provide methods for extrapolating chemical toxicity data across species which can support assessment of risks to aquatic life and aquatic-dependent wildlife for chemicals with limited data**	**FY 09**	
APM	Inclusion of appropriate surrogate test species in ICE model to protect under-represented fish taxa	05	NHEERL
APM	Provide OPPTS and the Regions with an upgraded PRZM for use in characterizing ecological risks	05	NERL

APM	Provide OPPTS and the Regions with a coupled AgDISP/PRZM/EXAMS registration modeling system and user's guide for characterizing ecological exposures and risks	06	NERL
APM	Establishment of a database for non-pesticide industrial organic chemicals for inclusion and refinement of interspecies correlation model	06	NERL
APM	Provide OPPTS with a revised EXAMS that includes algorithms for benthic boundary layer transport, sorption kinetics, and biolysis for risk assessment	07	NERL
APM	Establishment of a database for industrial inorganic chemicals for inclusion and refinement of interspecies correlation model	07	NHEERL
APM	Provide OPPTS with an upgraded ecological exposure assessment modeling tool and user's guide for probability risk assessment	08	NERL
APM	Report on incorporation of molecular endpoints into interspecies correlation models to improve extrapolation of chemical toxicity data across fish species	08	NHEERL

Figure 4. LTG 2 Research Path



LTG 3: To provide OPPTS with the scientific underpinnings for guidance to prevent or reduce risks of human environments within communities, homes, workplaces

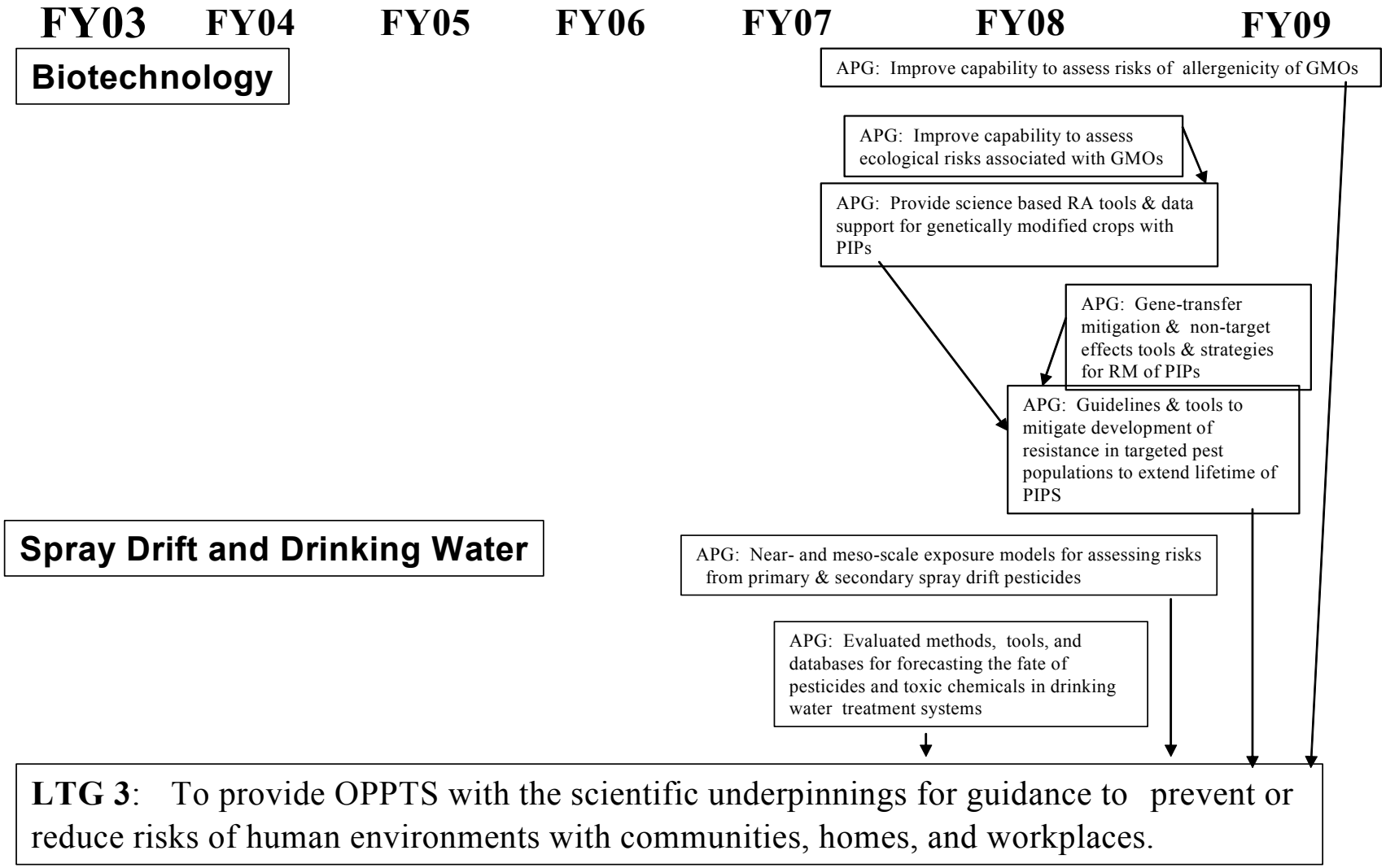
APG:	**Improved capability to assess the risks of allergenicity of GMOs**	**FY 08**	Lab/Center
APM	In joint with NIEHS and FDA assemble a panel of experts to examine the current state of knowledge, identify critical issues and research needs and publish these needs	03	NHEERL
APM	Develop models and methods for assessing potential allergenicity	05	NHEERL
APM	Demonstrate the vulnerability of newborns/ identify windows of vulnerability	08	NHEERL
APG:	**Improved capability to assess the ecologic risks associated with GMO**	**FY 08**	
APM	Quantitative measures for tracking transgenes in crop and non-crop plants	04	NHEERL
APM	Molecular methods (e.g., microarrays) applied to plant genomes for assessing genetic change and environmental stress	05	NHEERL
APM	Methods for estimating frequency of gene transfer from GM crops to non-crop plants	06	NHEERL
APM	Ecological consequences of movement of transgenes from GM crops to non-crop plants	07	NHEERL
APM	Probabilistic methods for assessing ecological risk of genetic transfer from GM crops	07	NHEERL
APG:	**To provide science based risk assessment tools and data support that ensure the comprehensive evaluation and long term safe use of genetically modified crops with plant incorporated protectants (PIPs).**	**FY 08**	
APM	FY03 APM - Review of the scientific literature on the use of genetic monitoring for long-term ecosystem surveillance, with special attention to its use in agroecosystems	03	NERL
APM	Report on the development and evaluation of a polymerase chain reaction-based “early warning” assay for adaptation by target pest populations	04	NERL
APM	Joint ORD/OPP workshop on the analysis of population genetics of invertebrates in agroecosystems	05	NERL
APM	Conference report on monitoring strategies to provide the most useful data for OPPTS risk assessments of the ecological impact of GM crops	05	NCEA
APM	External review draft of a report on a conceptual framework for assessing the ecosystem scale impacts of genetically modified crops to support OPPTS risk assessments	06	NCEA

APM	External review draft report outlining appropriate tools for monitoring resistance development to GM crops in the field and the use of target pest ecology to refine Insect Resistance Management strategies to support OPPTS ecological risk assessments of risk management techniques	06	NCEA
APM	Assessment of pest genetic architecture in order to inform optimized resistance management plans	06	NERL
APM	Report on the field comparison approach to risk-based monitoring for ecological impacts from genetically modified crops	07	NCEA
APM	Development and evaluation of a genetic monitoring program to assess long-term effects of PIPs on non-target organisms	07	NERL
APM	Report on the development and evaluation of a gene expression assay of non-target insect exposure to PIPs	07	NERL
APM	Report on impacts of Bt crops on agro-ecosystem functions as a risk assessment tool	08	NCEA
APM	Report on expert panel recommendations for a genetic monitoring program to assess long-term effects of PIPs on non-target organisms	08	NERL
APG:	**Establish and deliver for future use by Office of Pesticide Programs, EPA regions, state and local governmental agencies gene-transfer mitigation and non target effects tools and strategies to aid the management of environmental risks associated with PIP crops to help maintain the biological integrity of the environment**.	**FY 09**	
APM	Develop and deliver review of current practice for the management/ mitigation of gene transfer and non target effects from PIP crops and tools to assist risk management of adverse effects of PIP crops	04	NRMRL
APM	Develop and deliver for future use by EPA regions, state and local agencies preliminary methods for gene transfer detection and non target effects detection to assist the risk management of the potential adverse effects of PIP crops.	05	NRMRL
APM	Develop and deliver for future use by EPA regions, state and local agencies tools for gene transfer and non target effects management to assist the risk management of the potential adverse effects of PIP crops.	06	NRMRL
APM	Conduct and deliver for future use by EPA regions, state and local agencies preliminarily tested and validated tools for gene transfer and non target effects management to assist the risk management of the adverse effects of PIP crops.	07	NRMRL
APG:	**Establish and deliver for future use by Office of Pesticide Programs, EPA regions, state and local governmental agencies basic guidelines and tools to mitigate the development of resistance in targeted pest populations so as to extend the useful lifetime of PIP crops to minimize the use of chemical pesticides in agriculture**	**FY 09**	

APM	Develop and deliver survey of current practice in management tools for delaying the development of resistance to PIP crops in targeted insects including: modeling, remote sensing, and laboratory assays to help minimize pesticide use	04	NRMRL
APM	Conduct/deliver for future use by Office of Pesticide Programs, EPA regions, state and local agencies verified/validated resistance management models for delaying resistance to PIP crops in target insects minimizing pesticide use	05	NRMRL
APM	Establish/deliver for future use by Office of Pesticide Programs, EPA regions, state and local agencies principles for using remote sensing and GIS to detect pest infestation to delay insect resistance to PIP minimizing pesticide use	05	NRMRL
APM	Establish/deliver for future use by Office of Pesticide Programs, EPA regions, state and local agencies single laboratory standardization of lab assays to detect pest insect resistance to PIP crops to minimize pesticide use	05	NRMRL
APM	Develop/deliver for future use by Office of Pesticide Programs, EPA regions, state and local agencies data mining tools for models and methods to help manage and delay insect resistance to PIP crops to minimize pesticide use	06	NRMRL
APM	Establish/deliver for future use by Office of Pesticide Programs, EPA, state and local agencies proof of application of remote sensing & GIS to detect pest infestation to delay insect resistance in PIP crops minimizing pesticide use	06	NRMRL
APM	Develop/establish/deliver for future use by Office of Pesticide Programs, EPA, state and local agencies multilaboratory standardization of lab assays to detect pest insect resistance to PIP crops to minimize pesticide use	06	NRMRL
APM	Establish/deliver for future use by Office of Pesticide Programs, EPA, state and local agencies proof of practice for using remote sensing and GIS to detect pest infestation to delay insect resistance to PIP minimizing pesticide use	07	NRMRL
APG:	**Provide OPPTS information on the efficacy of commercial coatings to minimize dermal arsenic exposures on the surface of pressuree-treated wood**	04	
APM	Provide results from preliminary testing of sefvarl coatins	03	NRMRL
APM	Provide final results from chamber and field studies	03	NRMRL
APG:	**Determine barriers to the implementation of technologies that minimize drift of pesticides following application and identify appropriate risk management research**		
APM	Report on barriers to the implementation of technologies that minimize spray drift of pesticides	04	NRMRL

APM	Report on risk management research needed to address barrier identified above	04	NRMRL
APG:	**Provide OPPTS and the Regions with evaluated Near- and Meso-scale exposure models for assessing risks from primary and secondary spray drift of pesticides**	**FY 08**	
APM	Provide OPPTS with a refined exposure model and associated user guide for assessing meso-scale pesticides drift	05	NERL
APM	Provide OPPTS with a field evaluated exposure model that can be used to assess risks associated with secondary volatilization and drift	07	NERL
APM	Provide OPPTS with one or more evaluated models that can be used to assess near- and meso-scale community risks associated with the use of agricultural pesticides	08	NERL
APG:	**Provide OPPTS with evaluated methods, tools, and databases for forecasting the fate of pesticides and toxic chemicals in drinking water treatment systems**	**FY 08**	
APM	Provide OPPTS and NRMRL with a report that identifies the transformation and estimates the physical chemical properties of transformation products due to chlorine disinfection and water softening for two pesticides	04	NERL
APM	Provide OPPTS and NRMRL with evaluated measurement protocols for two pesticides that can be used to assess community exposures to chemical-specific treatment effects	05	NERL
APM	Provide OPPTS and NRMRL with a report highlighting the effects of speciation and varying treatment conditions on the transformation of two pesticides in different water treatment systems that can used to develop risk mitigation strategies	06	NERL
APM	Provide OPPTS with a prototype modeling system for forecasting the fate of one or two classes of pesticides and industrial chemicals in the drinking water treatment process	07	NERL

SAFE COMMUNITIES

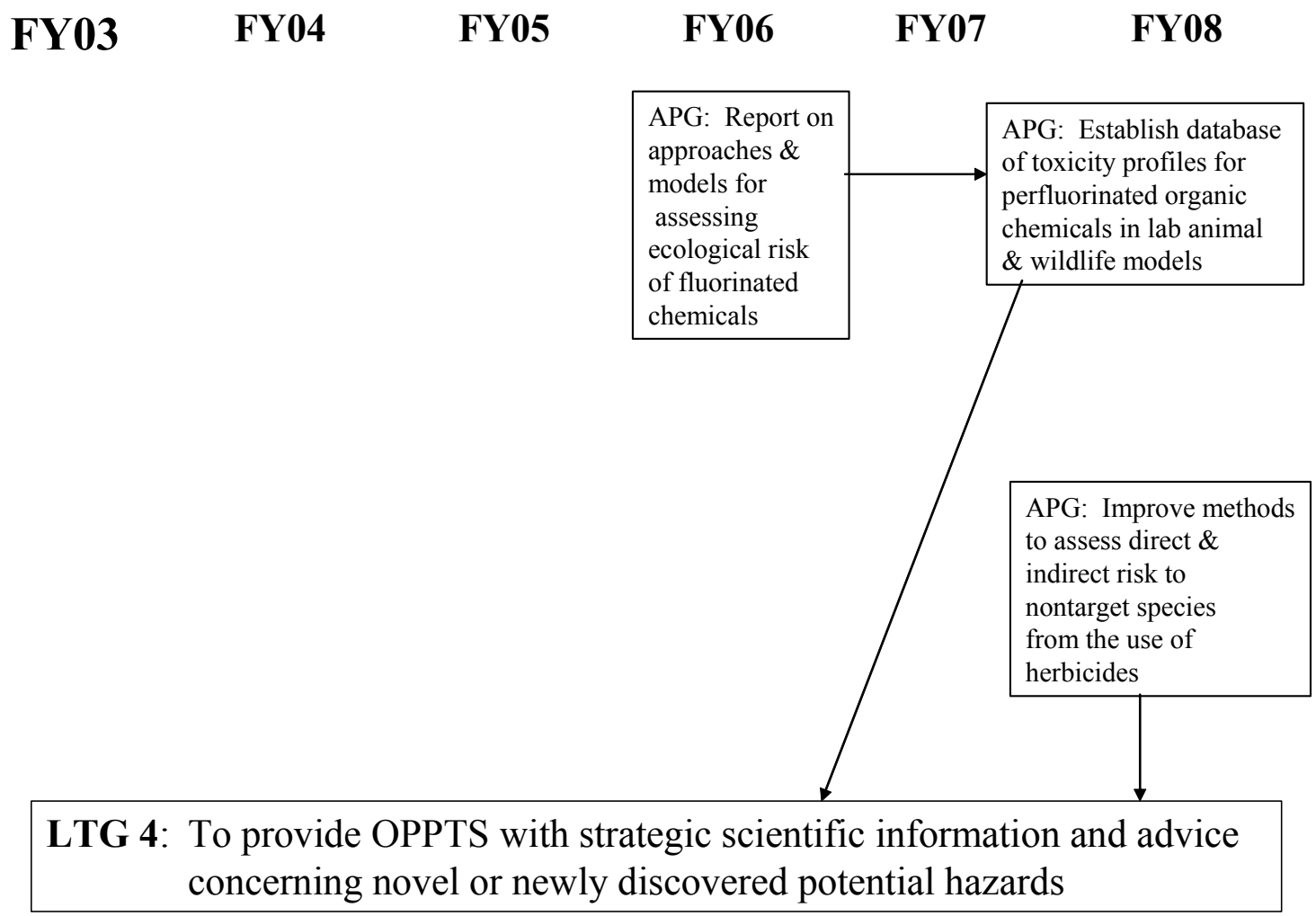


LTG 3: To provide OPPTS with the scientific underpinnings for guidance to prevent or reduce risks of human environments with communities, homes, and workplaces.

LTG 4: To provide OPPTS with strategic scientific information and advice concerning novel or newly discovered potential hazards

AAPG:	**Develop improved tools and models to assess and predict human health and ecological risk from exposure to commercial chemicals and mirroorganisms**	**FY 05**	
APM	Evaluate probabilistic risk assessment methods for herbicides	04	NHEERL
APG:	**Develop improved tools and models to assess and predict risks from exposure to perfluorinated organic chemicals**	**FY 06**	Lab/Center
APM	Report on approaches for assessing the ecological risk of fluorinated chemicals based on reproductive and developmental endpoints in small fish and amphibian models	04	NHEERL
APM	Provide an integrated model to assessing the risk of fluorinated chemicals	06	NHEERL
APG:	**To establish a database of toxicity profiles for various perfluorinated organic chemicals in laboratory animal and wildlife models, in order to facilitate the risk assessment of these chemicals**	**FY 08**	
APM	Research plan to coordinate research on per fluorinated organic chemicals among health and ecological laboratories, with inputs from OPPTS	03	NHEERL
APM	Characterization of reproductive and developmental toxicity of PFOS in laboratory rodent models (NHEERL)	04	NHEERL
APM	Deliver PK models for PFOS assessment to OPPT	05	NHEERL
APM	Evaluation of genomic and proteomic array techniques in identifying the mechanisms of PFOS toxicity and the potential use of these experimental tools in screening for toxicity induced by various perfluorinated organic chemicals	06	NHEERL
APM	Mechanistic characterization of PFOS developmental toxicity in laboratory rodent models	07	NHEERL
APM	Comparative toxicity profiles among various perfluorinated organic chemicals in laboratory animal models	08	NHEERL
APG:	**Improved methods to assess direct and indirect risk to nontarget species from use of herbicides**	**FY 08**	
APM	Guidelines for regional approach to selection of plant species for herbicide risk assessment	05	NHEERL
APM	Draft protocols for revised guidelines for vegetative vigor test with crops and selected native plants	05	NHEERL
APM	Draft protocols for new guidelines for reproductive/developmental endpoints with annual species	07	NHEERL
APM	Refined regional assessment tools for probabilistic assessments of risks to plants from herbicides based on GIS framework	08	NHEERL

Figure 6. LTG 4 Research Path



E. Unfunded Research Possibilities for safe pesticides/safe products

Possible Initiative for Community-Based Risk Assessment Research

Community-based risk assessments that consider the combined impacts of chemical and other stressors are growing in importance at EPA. Communities are coming to EPA with questions about health statistics within their regions, and how various sources of risk relate to those statistics. The composite health statistics for a community reflect the total risk associated with the genetic makeup of the community's individual members and the impact of all stressors in their environments, rather than just the "involuntary" risks that result from environmental pollution. Assessments of this type are often referred to as community-based or population-based. They start with the population and its individual members in a particular location and determine what chemicals, stressors, and other risk factors are affecting them. A population-based risk assessment considers the relationship between potential causes and adverse health impacts.

For example, in assessing risks associated with siting of an incinerator, industrial plant, or waste site, one might consider the possible impact of catastrophic releases and increased noise, dust, and traffic. In trying to answer questions related to high frequency of adverse health conditions related to indoor air exposures to chemicals, one might need to consider nutrition, presence of environmental tobacco smoke, and access to medical care. If EPA is to have a workable population-based risk assessment methodology, we must understand how other stressors interact with environmental agents to affect the overall risk.

Many of the stressors considered in a population-based assessment may fall outside EPA's regulatory purview. But these stressors often need to be assessed because they may interact with regulated stressors and affect risk. For example, poor nutrition may impact absorption of environmental agents in the G-I tract, increasing internal dose and risk. They may also need to be assessed in order to determine whether, for example, chemicals released from industrial plants, are the main sources of risks as opposed to other stressors in the environment that may not be within EPA's jurisdiction.

Several reports have highlighted the importance of understanding the accumulation of risks from multiple environmental stressors. These include the National Research Councils 1994 report Science and Judgment in Risk Assessment and the 1997 report by the Presidential/Congressional Commission on Risk Assessment and Risk Management entitled Risk Assessment and Risk Management in Regulatory Decision-Making. In addition, legislation such as the Food Quality Protection Act of 1996, has directed the Environmental Protection Agency to move beyond single chemical assessments and to focus, in part, on the cumulative effects of chemical exposures occurring simultaneously.

In response to the increasing focus on cumulative risk, several EPA programs have begun to explore cumulative approaches to risk assessment. The Office of Pesticide Programs has developed cumulative risk assessment guidance focused on implementing certain provisions of

FQPA and recently completed an assessment of risks from exposure to organophosphorus pesticides. The Office of Air Quality Planning and Standards is performing a national-scale cumulative assessment of human health risks posed by outdoor air exposures to a set of 33 priority urban air toxics. ORD has produced a draft dioxin reassessment that considers combined risks from exposure to dioxins, furans, and dioxin-like polychlorinated biphenyls. The EPA Science Policy Council has asked the Risk Assessment Forum to begin developing Agency-wide cumulative risk assessment guidance that builds from these ongoing activities. As a first step, a technical panel convened under the Risk Assessment Forum has developed a draft Framework for Cumulative Risk Assessment.

We propose to conduct research and develop risk assessment methods to support community-based risk assessment for human health and to develop tools to communicate risk information to communities and help communities understand and assess their environmental condition and risks. Some examples of the types of issues that must be addressed to develop our capability to conduct community-based assessments include:

- How the time sequence of exposures affects risks
- How the vulnerability of population and its members affects risk considering
  - Communities with susceptible members
  - Communities with special or heavy exposures
  - Differential preparedness to withstand toxic insult and differential ability to recover
    - Based on coping mechanisms of community and individual
    - Often considered in ecological assessments
    - Relevant to human health assessments in terms of impact of health care, health insurance, income, survival rates in community
- Stressor interactions, (e.g., Impact of noise on response to toxic chemical exposure)
- Joint assessment of chemical and non-chemical stressors
  - Common metrics
  - Ranking systems
  - Comparative risk assessment
  - Probabilistic risk assessment
- Interactions between environmental agent stressors and other factors
  - Current health status
  - Past exposure history
  - Economic status
  - Community property values
  - Lifestyle factors
  - Stress of living near waste site, incinerator, etc.
- Stresses on the ecological system that impact the human community