OFFICE OF INSPECTOR GENERAL

Catalyst for Improving the Environment

Evaluation Report

Opportunities to Improve Data Quality and Children's Health through the Food Quality Protection Act

Report No. 2006-P-00009

January 10, 2006

Report Contributors: Jerri Dorsey
Alice Fong
Montira Pongsiri

Abbreviations

CFR	Code of Federal Regulations
EPA	Environmental Protection Agency
DHHS	Department of Health and Human Services
FFDCA	Federal Food, Drug, and Cosmetic Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FQPA	Food Quality Protection Act
OIG	Office of Inspector General
OMB	Office of Management and Budget
OPP	Office of Pesticide Programs
OPPTS	Office of Prevention, Pesticides, and Toxic Substances
ORD	Office of Research and Development
STAR	Science to Achieve Results
USDA	U.S. Department of Agriculture

Glossary: *A glossary of the technical terms used in this report is in Appendix A.*

Cover Photos: The Food Quality Protection Act emphasizes the need to protect children from pesticides (EPA photos).

U.S. Environmental Protection Agency
Office of Inspector General

2006-P-00009
January 10, 2006

At a Glance

Catalyst for Improving the Environment

Why We Did This Review

We sought to determine the impact of the 1996 Food Quality Protection Act (FQPA) on the need of the Environmental Protection Agency (EPA) for scientific data on how pesticides impact children's health. We evaluated whether EPA enacted guidelines and procedures, and addressed new aggregate exposure and cumulative risk assessment efforts. We also sought opportunities for improvement.

Background

FQPA changed the way EPA regulates pesticides, including the introduction of aggregate exposure and cumulative risk assessments. FQPA required the Office of Pesticide Programs (OPP) to take into account children's unique patterns of exposure and vulnerability regarding pesticides. Additional data needs were identified to achieve the Act's mandates.

For further information, contact our Office of Congressional and Public Liaison at (202) 566-2391.

To view the full report, click on the following link:

www.epa.gov/oig/reports/2006/20060110-2006-P-00009.pdf

Opportunities to Improve Data Quality and Children's Health through the Food Quality Protection Act

What We Found

To meet the requirements of FQPA, EPA instituted numerous data requirements designed to provide infants and children with better protection against the health risks of pesticides. FQPA established a single, health-based standard that eliminated discrepancies, and emphasized infants and children.

FQPA resulted in the revision of many regulations, guidelines, and procedures. OPP made substantial changes to the aggregate risk assessment process, which considers multiple routes and pathways of exposure for a particular pesticide, to acquire more and better data on children's exposure. OPP also took steps to collect data on the cumulative effects of pesticides sharing a common mechanism of toxicity, which represent the combined risks to children from a group of pesticides.

Significant challenges nonetheless remain. EPA's required testing does not include sufficient evaluation of behavior, learning, or memory in developing animals. There is no standard evaluation procedure for interpreting results from developmental neurotoxicity tests (involving substances that damage a developing nervous system, including the brain). OPP has requested data on developmental neurotoxicity for certain pesticides, but to date no summaries have been released or conclusions drawn. OPP is unable to collect sufficient data on aggregate risk due to time and cost constraints and relies on other agencies for data. Specific opportunities for improvement involve finalizing Science Policy papers, assessing alternative testing strategies, using logic models, and developing a multi-year strategic plan.

What We Recommend

We made recommendations to EPA for improving data collection. EPA should develop a standard evaluation procedure, evaluate certain testing methods, and take steps to reduce uncertainties. EPA can take various steps to improve its aggregate exposure and cumulative risk assessments, including updating databases and expanding partnerships with other Federal organizations. EPA can also take steps to enhance accountability, act on Science Policy papers, try alternative testing strategies, and develop an overarching logic model and long-term strategic plan. The Agency concurred with many of our recommendations but expressed concern with certain issues raised.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
INSPECTOR GENERAL

January 10, 2006

MEMORANDUM

SUBJECT: Opportunities to Improve Data Quality and Children's Health through the Food Quality Protection Act
Report No. 2006-P-00009

FROM: Jeffrey K. Harris /s/
Director for Program Evaluation, Cross-Media Issues

TO: Susan Hazen
Acting Assistant Administrator,
Office of Prevention, Pesticides, and Toxic Substances

This is the final report on the subject review conducted by the Office of Inspector General (OIG) of the U.S. Environmental Protection Agency (EPA). This report contains findings that describe the problems the OIG identified and corrective actions the OIG recommends. This report represents the opinion of the OIG and the findings contained in this report do not necessarily represent the final EPA position. Final determinations on matters in the report will be made by EPA managers in accordance with established resolution procedures.

Action Required

In accordance with EPA Manual 2750, you are required to provide a written response to this report within 90 days of the date of this report. You should include a corrective actions plan for agreed upon actions, including milestone dates. We have no objections to the further release of this report to the public. For your convenience, this report will be available at http://www.epa.gov/oig/.

If you or your staff have any questions, please contact me at (202) 566-0831 or Jerri Dorsey, Assignment Manager, at (919) 541-3601.

cc: George Gray, Assistant Administrator, Office of Research and Development
Jim Jones, Director, Office of Pesticide Programs

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Chapter 1
Introduction

Purpose

We performed this review to examine the impact of the Food Quality Protection Act of 1996 (FQPA) on the Environmental Protection Agency's (EPA's) need for scientific data and predictive tools, particularly in relation to children's health. This report is the second in a series of three reports on FQPA's impact on EPA regarding children's health. We specifically sought in this review to determine:

- What data requirements were required by FQPA;
- Whether testing guidelines, requirements, and evaluation procedures allow EPA's Office of Pesticide Programs (OPP) to determine the potential adverse effects of pesticide exposure on the developing nervous system;
- What challenges OPP overcame and what opportunities exist for OPP to acquire better pesticide exposure data to aggregate risks;
- What challenges exist and what opportunities are available for OPP to improve cumulative risk assessments; and
- What opportunities exist to better manage pesticide health risk for children.

Background

The FQPA of 1996 established a single, health-based standard that eliminated discrepancies from the past. The Act requires that standards for agricultural pesticides be set at levels that protect the health of infants and children. The FQPA altered the way OPP regulates pesticides. OPP must now ensure that the pesticide residue limits in food (or tolerances) are at safe levels, and that there is a reasonable certainty of no harmful developmental effects[1] for children before a pesticide can be registered.

The mission of OPP, within the Office of Prevention, Pesticides, and Toxic Substances (OPPTS), is to protect human health and safeguard the environment from unreasonable adverse effects resulting from the use of pesticides. OPP is to ensure that pesticides are regulated fairly and efficiently while reducing pesticide risks, especially for infants and children. The role of EPA's Office of Research

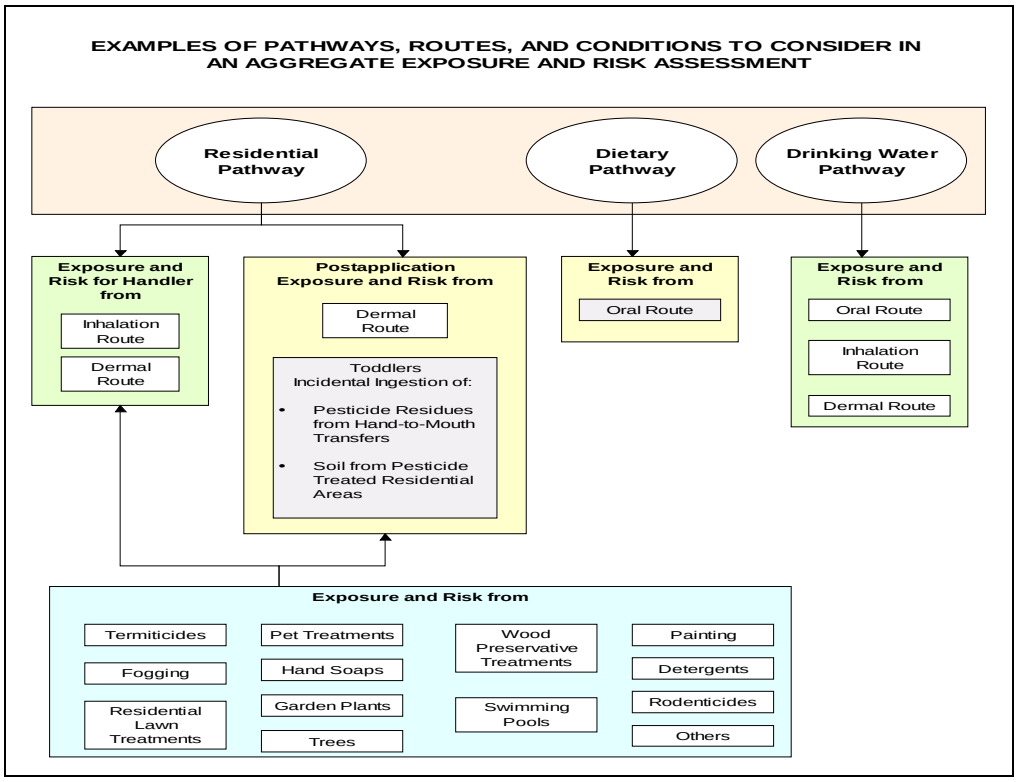
[1] Development effects are adverse effects such as altered growth, structural abnormality, functional deficiency, or death observed in a developing organism.

and Development (ORD), as the principal research arm of EPA, is to provide the critical science for environmental decision-making through its problem-driven and core research projects. In support of OPP/OPPTS, ORD provides scientific tools that can be used to characterize, assess, and manage risks in implementing the FQPA requirements. FQPA emphasized the need for three types of information for pesticide regulatory decision making:

- Developmental toxicity data (the adverse effect pesticide exposure will have during prenatal development and after birth);
- Aggregate exposure risk data (all routes and pathways of exposure) for a pesticide; and
- Cumulative risk data for pesticides with common mechanisms of toxicity.

Prior to FQPA's enactment, OPP treated exposures to pesticides from different pathways as independent events. The pathway represents the physical course a pesticide takes from the source to the person (such as through food or residential use pesticides). In reality, exposures to pesticides do not occur as single, isolated events, but as a series of sequential or concurrent events. As a result of FQPA, exposures from food, drinking water, and residential uses of a single pesticide are combined when completing an aggregate risk assessment (see Figure 1.1).

Figure 1.1[2]: Pathways, Routes, and Conditions in Aggregate Risk Assessment



[2] Source: US EPA, Nov 28, 2001. General Principles for Performing Aggregate Exposure and Risk Assessments.

OPP performs an aggregate exposure risk assessment for each chemical in the common mechanism group before undertaking a cumulative risk assessment on pesticides sharing a common mechanism of toxicity. The aggregate exposure risk assessment process includes identifying significant contributors to risk and estimating risk using probabilistic modeling (determining distribution of possible values). In assessing cumulative risks, OPP evaluates the potential for people to be exposed to more than one pesticide at a time from a group of pesticides with an identified common mechanism of toxicity. The objective is to appropriately match and combine estimates of pesticide exposures in a way that considers factors associated with exposure (i.e., time, region, and age groups). The potential for concurrent exposure to multiple chemicals by multiple pathways (including food; drinking water; and exposure to air, soil, grass, and indoor surfaces) would be included in the cumulative risk assessment.

Scope and Methodology

We performed our evaluation generally in accordance with *Government Auditing Standards*, issued by the Comptroller General of the United States. Our review focused on existing data and interviews. We did not examine internal controls. Our field work occurred between July 2004 and July 2005. We generally covered events from 1993, when the National Research Council released a report, entitled *Pesticides in the Diets of Infants and Children*, which had many recommendations that were incorporated into the FQPA of 1996.

This is the second in a series of three reports on FQPA's impact on EPA regarding children's health. The first report, *Changes Needed to Improve Public Confidence in EPA's Implementation of the Food Quality Protection Act (2006-P-00003)*, was published October 19, 2005. A third report is planned to address the measures and indicators for measuring progress in implementing the FQPA.

Further details on our scope and methodology are in Appendix B.

Results of Review

FQPA resulted in the revision of many regulations, guidelines, and procedures related to protecting infants and children from the health risks of pesticides. To meet the requirements of FQPA, EPA instituted numerous data requirements that should provide better protection. Additionally, EPA took steps to develop science policies, develop methods and tools, and collect required data on aggregate exposure and cumulative risk. Nonetheless, significant data gaps remain. Data collected from developmental neurotoxicity tests need to have summaries released and conclusions drawn. EPA needs to collect more data on aggregate exposure risk and apply better methods to collect data on and assess cumulative risk. Opportunities for improvement involve system accountability, finalizing Science Policy papers, assessing alternative testing strategies, using logic models, and

developing a multi-year strategic plan. We made various recommendations to EPA for improving data collection.

The Agency concurred with many of our recommendations. However, the Agency expressed concern that the report focused on issues that are "minor and relatively insignificant within the overall scope of FQPA implementation," "characterized incorrectly," or "outside the control of the Agency." Also, the Agency stated that "OPP had already identified and begun working on many of the issues discussed" in this report. We summarized the Agency's response and provided our comments on the response at the end of each chapter that contained recommendations. The full text of EPA's response is in Appendix C. Appendix D provides the full text of our comments on the Agency's response.

Chapter 2
FQPA Inspired Numerous EPA Data Requirements

To implement the requirements of FQPA, EPA had to institute numerous data requirements. FQPA established a single, health-based standard and requires that allowable residue levels for food use pesticides be protective of the health of infants and children. EPA data requirement changes involved emergency suspension procedures, data collection activities, registration renewal, and tolerance reevaluation. FQPA requires EPA to perform risk assessments differently, in that it must now assess aggregate and cumulative risks of pesticides instead of just the risks for one pesticide and one medium at a time. EPA must consider all non-occupational sources of exposure, including drinking water, and exposure to other pesticides. Such additional steps should provide improved data and potentially result in better protection against pesticides for infants and children.

National Research Council Report Emphasized Need for Better Data

Many of the provisions in the 1996 FQPA originated from recommendations made in a 1993 National Research Council report, *Pesticides in the Diets of Infants and Children.* This report brought attention to how better data on dietary exposure to pesticide residues should be combined with improved information on the potentially harmful effects of pesticides on infants and children. The report emphasized the need for testing procedures and that "testing must be performed during the developmental period in appropriate animal models, and the adverse effects that may become evident must be monitored over a lifetime."

The National Research Council called for the development of new risk assessment methods that would incorporate better data on children's exposure to pesticides during fetal development, infancy, and childhood. Furthermore, it recommended the use of exposure distributions, expansion of exposure assessment to consider exposure to multiple chemicals with multiple routes of exposure, and the development of pharmacokinetic models (for determining and quantifying the time or absorption, distribution, biotransformation, and excretion of pollutants) that could incorporate the unique physiological features of developing children.

FQPA Resulted in Numerous Key Changes

According to EPA, FQPA provides a more consistent pesticide regulatory scheme by amending the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug, and Cosmetic Act (FFDCA). Primary authority for pesticide regulation at EPA is through FIFRA and FFDCA:

- Under FIFRA, EPA registers pesticides for use in the United States and prescribes labeling and other regulatory requirements.

- Under FFDCA, EPA establishes tolerances for pesticide residues in food, both domestic and imported. A tolerance is the maximum level of pesticide residue allowed in or on human food and animal feed. These tolerances are enforced by the Food and Drug Administration for most foods and by the U.S. Department of Agriculture for meat, poultry, and some egg products.

The following outlines many of the requirements and amendments to FIFRA and FFDCA resulting from FQPA, as interpreted by EPA:

Table 2.1: Key Changes and Additions for Pesticide Regulations Due to FQPA

FIFRA
Permits emergency suspension of a pesticide without simultaneously issuing a notice of intent to cancel.
Prescribes data collection activities to ensure health of infants and children: • Collection of adequate data on food consumption patterns of infants and children. • Improved data collection on occurrence of pesticide residues in foods most likely consumed by infants and children. • Evaluation of pesticide usage information and improved information gathering.
Requires registration review and renewal, once every 15 years.
Establishes special provision for minor use pesticides, including public health pesticides.
Links tolerance reassessment to reregistration.
Establishes special provisions for antimicrobial pesticide registration.
Establishes mandate for continuing expedited consideration of application for pesticides meeting one or more criteria for reduced risk pesticides.[3]
Establishes a Scientific Advisory Board to assist in the scientific peer reviews conducted by the FIFRA Scientific Advisory Panel.
FFDCA
Delinks pesticides from Delaney clause and places all pesticide authority in FFDCA.
Establishes standard for establishing a tolerance based on whether tolerance is "safe," defined as "a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information."
Defines types of exposure to be aggregated for risk assessment purposes.
Requires consideration of cumulative effects of pesticides having common mechanism of toxicity.
Requires tolerance reassessment in three phases – review 33 percent within 3 years of FQPA enactment; a second 33 percent within 6 years; and the remaining number within 10 years.
Specifies an additional 10-fold margin of safety for infants and children for threshold effects.[4]
Requires development of an estrogenic substances screening program.
Requires development and distribution of consumer information on pesticide risks and benefits.

[3] This provision was overtaken by the 2004 Pesticide Registration Improvement Act, which establishes specific timeframes for reduced risk pesticides.

[4] Threshold effects are those effects considered to have exposure doses at some identifiable level which are likely to be without appreciable risk of deleterious consequences.

Various Registration Data Required

The 1993 National Research Council report brought attention to the uncertainty about childhood exposure and toxicity at different stages of development. Under FQPA, EPA must ensure that the pesticide residue limits in food tolerances are at safe levels, and that there is a reasonable certainty of no harmful developmental effects for children before a pesticide can be registered. Pesticide registration is dependent upon the fulfillment of a series of data requirements. The number and types of studies to be conducted vary with the intrinsic chemistry, anticipated inherent toxicity, and proposed use pattern of the pesticide. Pesticides of conventional chemistry proposed for use on agricultural commodities generally require the greatest amount of information, whereas those for non-food use generally require less.

Title 40 of the Code of Federal Regulations (CFR) Part 158 presents the regulatory roadmap specifying the types and amounts of data needed by EPA to decide whether to approve an application for a new or amended registration or reregistration under FIFRA. The data requirements specified in Part 158 cover areas such as product chemistry, toxicology for human health and domestic animals, wildlife and aquatic toxicology, nontarget insects, environmental fate, aerial drift evaluation, reentry protection, plant protection, product performance, residue chemistry for food uses, and biochemical and microbial pesticides. The type of data required is dependent on the product's proposed pattern of use, the results of earlier studies, and other circumstances.

Chapter 3
OPP Lacks Consistent Data on the Developing Nervous System to Determine Potential Adverse Effects

OPP's testing and evaluation procedures need improvement to better determine the potential adverse effects of pesticide exposure on the developing nervous system. EPA's current required toxicity testing does not include evaluation of behavior, learning, or memory in developing animals until triggered by predefined effect conditions in other required toxicity studies. Also, there is no standard evaluation procedure for interpreting results of such tests. OPP had requested data on developmental neurotoxicity (involving substances that damage a developing nervous systems, including the brain) for certain pesticides in 1999, but to date no summary has been released or conclusions drawn from the data. Also, data requirements for pesticide registrants have not been comprehensively revised since 1984; although EPA published proposed changes in March 2005, EPA was awaiting public comments prior to amending the proposed rule or promulgating a final rule. In the proposed changes, developmental neurotoxicity data tests are proposed to only be "conditionally required."

Assessing Developmental Neurotoxicity Important

One of the conclusions in the National Research Council report was that the toxicity testing strategies used by regulatory agencies were inadequate for assessing toxicity to a number of organ systems, including neurodevelopmental processes. The report indicated that pesticide exposures may disrupt the normal development of a child's brain and nervous system, and recommended regulatory agencies such as EPA revise published guidelines on testing as new information is obtained.

Pesticide chemicals can easily enter the brain of fetuses and young children because the blood-brain barrier is not fully developed. In the developing brain, billions of cells must form, move to their positions, and establish precise connections with other cells. If cells in an infant's brain are destroyed, or connections between brain cells fail or send false signals to the developing reproductive organs, nervous system or reproductive dysfunction may result that can persist throughout life.

ORD's human health research has characterized the differential response of younger animals to the neurotoxic effects of cholinesterase inhibiting pesticides (cholinesterase is one of many important enzymes needed for the proper functioning of the nervous systems of both humans and animals). ORD's

research indicated that when younger animals are more sensitive to these chemicals, they are also less efficient in detoxifying the pesticides. According to ORD, this information has been used by OPP to limit the use of selected pesticides, and helped form the basis for the data call-in process to collect comparative sensitivity data for all registered organophosphate pesticides (a group of pesticides that act to inhibit acetylocholinesterase enzymes, which result in dysfunction in the nervous system). Through this data call-in process, OPP seeks data from appropriate pesticide manufacturers. OPP issues a data call-in when there is no existing, reliable information to characterize a pesticide's risk or exposure, or otherwise complete a risk assessment. OPP implemented the data call-in process for the cholinesterase-inhibiting organophosphates based on known neurotoxicity concerns.

In an Overview[5] that provided the basis for evaluating the Human Health Research Program at the Agency, ORD indicated that EPA had resolved a variety of groundbreaking policy and scientific issues in conducting the organophosphate pesticides cumulative risk assessment. However, to protect the health of children, ORD strongly recommended that OPP change its approach to require a developmental neurotoxicity study for pesticide registration, and that in the absence of this study, OPP should consider applying the traditional uncertainty factor.

Developmental Neurotoxicity Testing Issues

While developmental neurotoxicity tests have helped to characterize risks to young animals, particularly effects on learning/memory, auditory response, motor activity, and neuropathology, external and internal stakeholders have raised concerns regarding this test data. Industry representatives have said that developmental neurotoxicity study results are difficult to interpret and expensive to conduct. Public health and children's advocates expressed concerns about EPA being slow in its review of the developmental neurotoxicity data call-in studies and that the review results were not publicly available. OPP scientists reported that call-in data are inconclusive because there is great variability among the various sets of developmental neurotoxicity data and uncertainty in laboratory conditions.

On August 6, 1999, EPA published in the Federal Register[6] that it was requiring registrants of neurotoxic pesticides to conduct acute, subchronic, and developmental neurotoxicity studies and submit the results to EPA via the data call-in process. As of March 11, 2005, a total of 50 developmental neurotoxicity studies have been received for review by OPP. However, to date, no summary has been released or conclusions drawn from the data.

[5] From page 27 of "Section 007 Overview" in the ORD CD containing the briefing book and poster abstracts provided to the Board of Scientific Counselors for Review of ORD's Human Health Research Program on February 28, 2005, to March 2, 2005 in Research Triangle Park, North Carolina.
[6] 64 Federal Register 42945

We found that EPA lacks a Standard Evaluation Procedure for developmental neurotoxicity studies, even though the final Standard Evaluation Procedures for developmental toxicity and a draft procedure for reproductive toxicity are now available. OPP scientists reported that interpreting developmental motor activity is relatively easy, but interpreting learning and memory tests from the developmental neurotoxicity data call-in information is difficult, because such tests are more qualitative in nature and not sensitive enough to determine if there is a cause and effect. However, developmental neurotoxicity tests have helped to characterize risks to young animals, particularly effects on learning/memory, auditory response, and motor activity.

Weaknesses in Toxicity Testing Guidelines

Non-EPA scientists reported in literature[7] published post-FQPA on the insufficiency of current testing requirements for assuring children's safety from most food-use pesticides. Examples of the weaknesses noted are:

- EPA's core testing has included no requirement for specific testing of developmental neurotoxicity in developing animals and immunotoxicity in adult or developing animals.
- EPA's core testing includes no adequate assessment of the effect of toxicity on the function of developing animals (possibly apart from reproduction) involving behavior, learning, or memory.
- All but two core toxicity tests EPA required for food-use pesticides are performed in adult animals, including the only test of metabolism.
- EPA requires no data on pharmacokinetics (rate of absorption and distribution of toxin in the body) or pharmacodynamics (sequence of events in the cell leading to a toxic response) of the pesticide in developing animals, and its risk assessments include no such information.
- The exposure period recommended by EPA's developmental neurotoxicity guidance may be too short to reflect the entire vulnerable period of brain development in children, and statistical procedures to define the minimal number of animals in a test group are lacking.

A 2002 EPA review by a technical panel[8] also identified numerous gaps in testing guidelines, and the panel suggested that the Agency develop alternative strategies

[7] Claudio L. et al. 1999. Assessment of the US Environmental Protection Agency Methods for Identification of Hazards to Developing Organisms, Part II: The Developmental Toxicity Testing Guideline. *American Journal of Industrial Medicine* 35:554-563. Schettler, T et al. January 2001. In Harm's Way: Toxic Threats to Child Development. *Greater Boston Physicians for Social Responsibility/Clean Water Fund*. Slotkin, TA. 2004. Guidelines for Developmental Neurotoxicity and Their Impact on Organophosphate Pesticides: A Personal View from an Academic Perspective. *Neurotoxicology* 25: 631-640. Wallinga, D. April 1998. Putting Children First: Making Pesticide Levels in Food Safer for Infants & Children. *Natural Resources Defense Council*.

[8] US EPA. December 2002. Review of the Reference Dose and Reference Concentration Processes. Risk Assessment Forum, EPA/630/8-02/002F.

and guidance to allow more targeted testing. The panel indicated that current testing protocols do not provide information collected at different life stages – that is, comparison of effects of exposure during infancy, adulthood, or old age. We believe the case of Chlorpyrifos[9] demonstrates this point and the intrinsic incompleteness of scientific evidence in the existing regulatory test guidelines. For example, as scientists probed deeper into the activity of this organophosphate pesticide in the laboratory, they found previously unknown effects on the development and function of the brain and nervous system in embryos, fetuses, and young animals (including possible serotoninergic[10] and dopaminergic[11] effects).[12]

When assessing risk of developmental neurotoxicity, EPA may need to identify more sensitive endpoints, or indicators, accompanied by the analytical methods to test for them. Cholinesterase inhibition is currently the driving endpoint for organophosphate pesticides, but there is concern in the scientific community that this parameter alone may not be enough to assess the consequences of exposure for some pesticides. This raises the issue of how EPA can begin to evaluate the many different pesticides with potentially overlapping but different mechanisms and outcomes. It has been suggested in literature that using an in vitro approach, or lower organisms, might enable a high-throughput screening for developmental neurotoxicants.[13] Proposed model systems include neural cell cultures, invertebrate (such as sea urchin), and non-mammalian systems (like the zebrafish).

See Appendix E for further details on issues related to toxicity testing.

Proposals Made for Changes to Testing Requirements

The data requirements for pesticide registrants in 40 CFR Part 158 have not been comprehensively revised since 1984. Other than some minor changes and additions in the "Maxi-Regs" final rule[14] published on May 4, 1988, relative to

[9] See Chapter 4, section on Substantial Changes Made in Aggregate Risk Assessment.
[10] Serotoninergic effect: The serotoninergic system is known to modulate mood, emotion, sleep, and appetite and thus is implicated in the control of numerous behavioral and physiological functions.
[11] Dopaminergic effect: Neurons or brain cells in the mid-brain produce dopamine which is a neurotransmitter that controls movement and balance and is essential to the proper functioning of the central nervous system.
[12] Slotkin, TA. 2006. Developmental Neurotoxicity of Organophosphates: A Case Study of Chlorpyrifos. In: *Toxicity of Organophosphate and Carbamate Pesticides*. RC Gupta, Elsevier: (In press). Aldridge, JE et al. 2005. Developmental Exposure to Terbutaline and Chlorpyrifos: Pharmacotherapy of Preterm Labor and an Environmental Neurotoxicant Converge on Serotonergic Systems in Neonatoal Rat Brain Regions. *Toxicology and Applied Pharmacology* 203: 132-144. Qiao D et al. 2003. Fetal Chlorpyrifos Exposure: Adverse Effects on Brain Cell Development and Cholinergic Biomarkers Emerge Postnatally and Continue into Adolescence and Adulthood. *Environmental Health Perspective* 111:536-544.
[13] Slotkin, TA. 2004. Guidelines for Developmental Neurotoxicity and Their Impact on Organophosphate Pesticides: a Personal View from an Academic Perspective. *NeuroToxicology* 25: 631-640. Slotkin, TA. 2004. Cholinergic Systems in Brain Development and Disruption by Neurotoxicants: Nicotine, Environmental Tobacco Smoke, Organophosphates. *Toxicology and Applied Pharmacology* 198: 132-151.
[14] 53 Federal Register 15951

data formatting and flagging of certain toxicology studies, the requirements have remained unchanged.

On March 11, 2005, EPA published proposed changes to the data requirements regulation.[15] OPP established a docket for this action, which includes the proposed rule revisions, background and supporting documents, and comments filed by outside individuals. The Agency was awaiting public comments prior to either amending the proposed rule or promulgating a final rule. Public comments were due June 9, 2005, but the deadline was extended to September 7, 2005.

Although 40 CFR Part 158 has remained virtually unchanged, there have been major changes in the testing guidelines[16] and de facto data requirements imposed by the Agency. Since 1984, EPA has issued additional test guidelines, first under the old Pesticide Assessment Guidelines, then as the OPPTS Harmonized Guidelines.[17] However, Part 158 has never been revised to reflect these additions and changes. The new proposed rule attempts to codify the changes and make new additions, changes, and revisions.

EPA proposed adding new requirements for developmental neurotoxicity test data to the toxicity testing battery as part of the chemical registration process. The original documents submitted to Office of Management and Budget (OMB) for review indicate that current studies do not include an in-depth assessment of the nervous system, and that the proposed developmental neurotoxicity study would evaluate "functional and behavioral deficiencies, as well as structural alterations to the nervous system, that may result from pesticide exposure that occurs *in utero* and/or during early postnatal life."

However, in the proposed rule for which OMB completed its review on February 28, 2005, developmental neurotoxicity studies were changed to "conditionally required," meaning that they would only be required under certain conditions. Notes in the revision of the proposed requirements indicated the change was a response to questioning by OMB. In a letter dated March 14, 2005, OMB expressed its concerns on the increasing amount of resources devoted to pesticide registration and the amount of data required to support a new registration. OMB asked EPA to provide a specific plan on how the Agency will improve its current toxicity testing data requirement for chemical registration, including considering the International Life Sciences Institute's approach to testing pesticides. According to OMB, the plan should contain information on critical actions, target timelines (including the timing of the Part 158 final rule for conventional

[15] 70 Federal Register 12276

[16] According to EPA, guidelines only provide suggested protocols which a registrant can follow to meet data requirements posed in Part 158. Guidelines are not enforceable as they are not codified.

[17] These guidelines were issued in 1998. They include measures of gross morphology in the brain; tests for evidence of deficits in neurobehavioral functions (for example, auditory startle, habituation, associative learning and memory, and monitoring of motor activity); and measurement of surrogate biomarkers specific to certain classes of neurotoxic chemicals, such as the use of plasma cholinesterase inhibition as a biomarker for organophosphate pesticide developmental neurotoxicity.

pesticides), and stakeholders' engagement in the process. EPA briefed OMB on October 6, 2005, about its Integrative Toxicology Testing Strategy, but had not responded in writing to OMB.

Recommendations

We recommend that the Acting Assistant Administrator for Prevention, Pesticides, and Toxic Substances:

3-1 Develop a Standard Evaluation Procedure to assess results of developmental neurotoxicity testing. Within this Procedure, incorporate a discussion on the developmental neurotoxicity data call-in results and address which indicator, or combination of indicators, is considered most sensitive and meaningful for assessing developmental neurotoxicity from exposures during critical windows of development.

3-2 Evaluate the utility of using alternative toxicity testing methods to evaluate developmental neurotoxicity. For example, assess whether relying on primary work in cell culture, invertebrate, or non-mammalian species, followed by more targeted examinations of specific processes in mammalian species, may benefit the assessment of developmental neurotoxicity and improve testing efficiency.

3-3 Implement the recommendations made by National Research Council in its report to reduce uncertainty in neurodevelopment effects of exposure during critical windows of development by:

- ensuring that developmental neurotoxicity tests are conducted on developing animals in addition to young adult animals;
- assuring that developmental neurotoxicity test information is collected at different life stages and that there is comparison of effects of exposure during infancy, adulthood, or old age; and
- revising the developmental neurotoxicity testing guidelines to better assess risks of chemical exposure during the critical period of rapid human brain development.

Agency Response and OIG Evaluation

The Agency agreed with Recommendation 3-1 and said that a formal internal Standard Evaluation Procedure is expected to be completed in 2006. The Agency also explained that "OPP is currently involved in the final stages of an ILSI [International Life Sciences Institute] project which is developing approaches to evaluating/interpreting" different sensitive parameters to address issues of sensitivity and meaningfulness of the developmental neurotoxicity data.

The Agency agreed with the principle of Recommendation 3-2 but disagreed with

the recommendation as drafted, citing the lack of well accepted methods for testing. While we acknowledge the complexity of the issue, we encourage the Agency to review the research in the area. We have modified Recommendation 3-2 to offer the Agency flexibility in its evaluation of new strategies for detection of developmental neurotoxicant actions of suspected pesticides.

The Agency offered no statement of agreement or disagreement for Recommendation 3-3 but claimed that most recommendations listed have been appropriately addressed. It stated that the "current developmental neurotoxicity test guideline includes testing during the major phases of development (i.e., during early lactation and around the time of weaning) as well as in young adults." The Agency acknowledged that "there is no current test guideline in which exposure occurs continuously from conception through old age" but that required studies assess neurotoxicity at a variety of lifestages spanning the full life span. Also, the Agency acknowledged that its current developmental neurotoxicity test guideline recommends exposures up to post-natal day 10, that an extended exposure period up to post-natal day 21 would be incorporated into the next guideline revision, and that during the organophosphate developmental neurotoxicity data call-in in 1999 it recommended manufacturers to dose animals up to post-natal day 21. It mentioned that it has not yet developed the developmental immunotoxicity testing guideline, although it has proposed requiring the adult immunotoxicity test data for pesticide registration.

The full text of the Agency's response is in Appendix C, and our detailed comments on that response are in Appendix D.

Chapter 4
OPP Made Substantial Changes to Address Aggregate Risk, but Challenges Remain

OPP has made substantial changes to the aggregate risk assessment process to acquire more and better data on children's exposure to pesticides, but challenges remain. Aggregate exposure risk assessments, as required by FQPA, specify that all routes and pathways of exposure for a given pesticide be considered when assessing risk. Although OPP has taken various actions, data are needed to understand pesticide levels based on crop cycles, and more effort is needed to consider food consumption information. Sufficient data are not always collected because of time and cost constraints, and because EPA is often dependent on other agencies for data. Without adequate and timely information to perform aggregate exposure risk assessments, there will be uncertainty surrounding pesticide licensing decisions and how pesticides impact children's health.

Substantial Changes Made in Aggregate Risk Assessment

Since FQPA's passage, EPA has made progress in acquiring exposure data from young children and developing tools to use such data. Besides updating its pesticide testing guidelines to include animal study data on reproductive and developmental effects, EPA developed methods and generated laboratory data that had an impact on the risk assessment of the pesticides methyl parathion, chlorpyrifos, and diazinon. As a result, EPA cancelled the use of methyl parathion on all fruits and many vegetables, eliminated the manufacturing of chlorpyrifos for nearly all residential uses, and eliminated all indoor and garden uses of diazinon as well as uses on about 20 different food crops. Also, EPA:

- Identified and prioritized aggregate exposure data needs for other tolerance reassessments and determinations.
- Conducted and funded research to develop biomarkers[18] for pesticides and collect data on children's residential pesticide exposures, physical activity patterns, and food handling practices.
- Collaborated with the Agricultural Research Service of the U.S. Department of Agriculture (USDA) to collect additional food consumption data from children in USDA's Continuing Survey of Food Intakes by Individual, and to generate a Food Commodity Intake Database from the survey data.
- Collaborated with USDA's Agricultural Marketing Service to obtain additional pesticide residue data for children's foods.

[18] Biomarkers are substances in blood, other body fluids, or tissues that can be used to indicate exposure to chemicals or diseases.

- Refined its drinking water assessment approach, and initiated research to collect available data on pesticides in drinking water and effects of drinking water treatment on degradation products toxicity.
- Developed predictive methods for pesticide dermal and inhalation determinations and exposure dose estimations.

Data on Children's Nondietary Pesticide Exposure Limited

FQPA requires EPA to consider all nonoccupational exposures from a single pesticide when conducting aggregate risk assessment. Figure 4.1 illustrates some nondietary routes of exposure and related data that are needed to assess risks. Several computer models have been developed and are being used for exposure and risk assessments. Such probabilistic models enable risk assessors to answer questions about the sources, pathways, and factors that contribute to aggregate exposures and risks.

Children engage in behaviors and consumption that can increase their risk of pesticide exposures compared to adults. They eat more food, drink more water, and breathe more air than adults on a body-weight basis. Further, the risk to children is increased because they are generally lower to the ground than adults, and they often engage in hand-to-mouth behavior that further adds to oral pesticide exposure. Literature[19] indicates that data on children's exposures and the factors that affect their exposures are limited and generally not adequate to assess children's exposures to a wide array of chemicals in their homes and other environments. Both OPP and ORD scientists agree that better data on infants' and toddlers' physical activity patterns would improve aggregate risk assessments. Elements still missing on nondietary exposure as identified by the scientific community and ORD include:

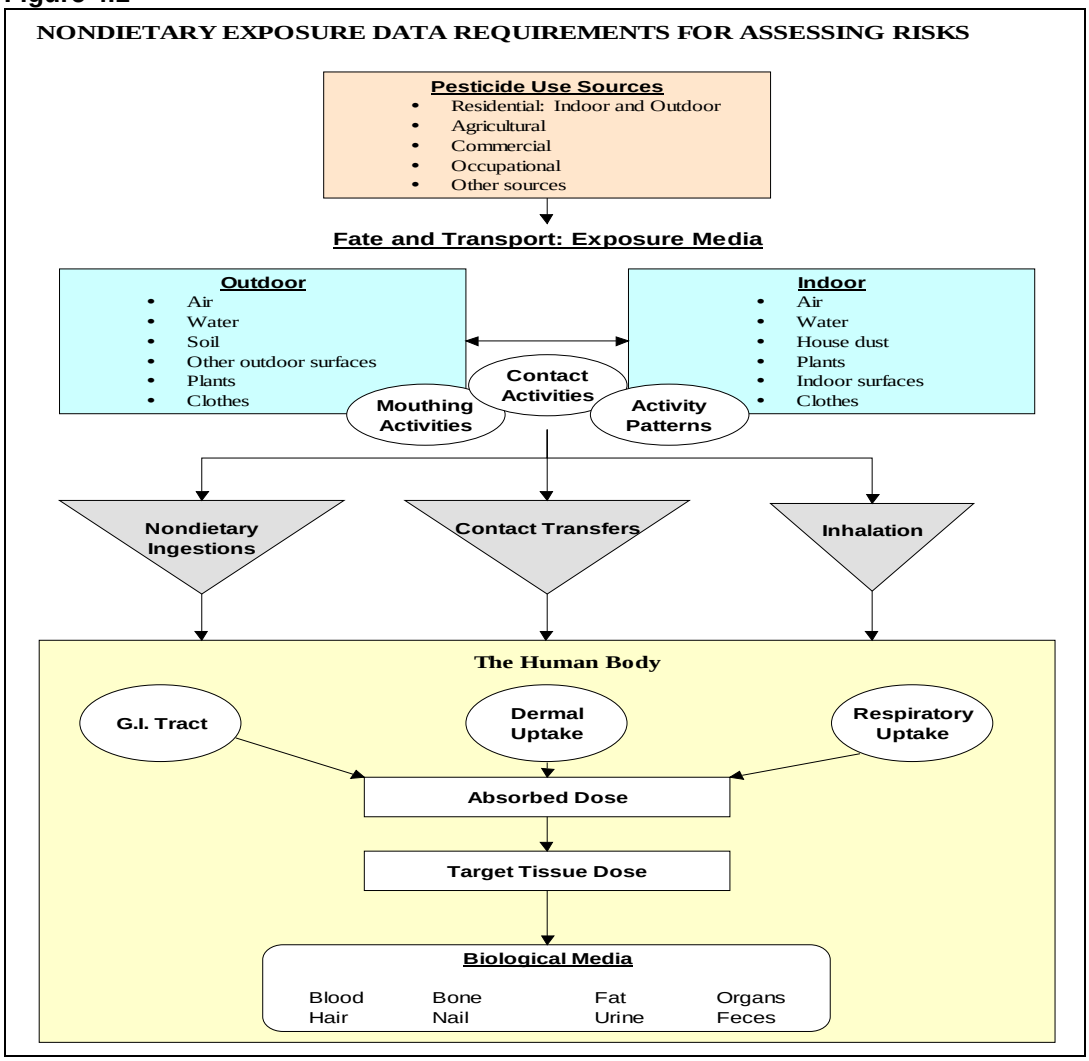
- An understanding of the most important pathways of exposure for young children.
- Approaches for evaluating exposure for critical pathways, such as dermal and indirect ingestion exposure.
- Protocols for generating the exposure data.
- Approaches for determining the exposure factor and data on fate-and-transport (how a pesticide is applied and then moves in the environment).

[19] Daston, G et al. February 2004. A Framework for Assessing Risks to Children from Exposure to Environmental Agents. *Environmental Health Perspectives* 112(2): 238-256. Gitterman, BA and CF Bearer. October 2001. A Developmental Approach to Pediatric Environmental Health. *Pediatric Clinics of North America* 48(5): 1071-83. Goldman, L et al. April 2004. Environmental Pediatrics and Its Impact on Government Health Policy. *Pediatrics* 113(4): 1146-1157. Landrigan, PJ. October 2001. Children's Environmental Health. *Pediatric Clinics of North America* 48(5): 1319-1330. Moya, J et al. April 2004. Children's Behavior and Physiology and How It Affects Exposure to Environmental Contaminants. *Pediatrics* 113(4): 996-1006. Weiss, B et al. April 2004. Pesticides. *Pediatrics* 113(4): 1030-1036.

To meet these needs, priority research needs include:

- Pesticide use patterns.
- Spatial and temporal distribution of pesticides in residential dwellings (movement of pesticide chemicals across space and time).
- Dermal uptake (pesticides entering through the skin from touching surfaces).
- Nondietary/indirect ingestion (swallowing substances through such nondietary means as hand-to-mouth activity or swallowing swimming pool water).
- Oral exposure assessments (how often children lick but not eat food, bite a toy, eat dirt, etc.) which include children's food handling practices.

Figure 4.1[20]



[20] OIG staff developed this figure based on EPA's documents on exposure data requirements.

According to OPP and ORD officials, longitudinal consumption and activity data are important for the assurance that short-term measurements relate to long-term exposures and the validation of various modeled assumptions in the probabilistic exposure models used by OPP. ORD scientists designed and implemented small pilot field studies to capture exposure data and work out methods for two larger children's health and pesticide exposure longitudinal studies (across a string of time rather than a "snapshot" at a given time), but these projects have encountered delays. The National Children's Study will examine the effects of environmental influences on the health and development of more than 100,000 children across the United States, following them from before birth until age 21. The long term support for the National Children's Study[21] is still under debate.[22] Meanwhile, the Children's Health and Environmental Exposure Research Study (CHEERS), designed to study how children are exposed to household-use pesticides, was cancelled by EPA on April 8, 2005.

EPA Relies on Public and Private Sources of Dietary Exposure Data, and More Needed

Collecting national food consumption data is costly and complex, and EPA relies on other Federal agencies for such data. FQPA contains specific provisions for cooperative activities between EPA and USDA. USDA provides data on food consumption, food commodity, and pesticide residue through such databases as the Food Commodity Intake Database. However, there are various data gaps in the collection of food consumption data for infants and children. Some food consumption monitoring activities and gaps are discussed below; more details are in Appendix F.

Since 1999, USDA integrated its food intake survey with another large survey known as the National Health and Nutrition Examination Survey, which is conducted by the Department of Health and Human Services (DHHS). However, OPP has not incorporated the new consumption data into its risk assessment work, but it reported planning to do so in 2006.

In 2002, Gerber Products Company conducted its latest Feeding Infants and Toddlers Study, which surveyed 3,022 children from 4 to 24 months of age. This study is the most comprehensive, largest, and nationally representative study on food consumption for this age group. Additionally, USDA's School Lunch and Head Start programs may be other worthwhile avenues for collecting data on young children.

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[21] The National Children's Study is led by a consortium of Federal agency partners: DHHS, National Institutes of Health, Centers for Disease Control and Prevention, and EPA. The Web site for additional information on the study is http://nationalchildrensstudy.gov.

[22] Kehn, BM. 2005. Children's Health Study Closer to Launch: Lack of Funding Could Cause Delays. *JAMA* 294: 2154.

FQPA requires that drinking water be considered as a pesticide exposure pathway in human health risk assessment. Preliminary data suggest conventional water treatment processes do not appear to remove most pesticides, and chemical water softening and disinfection processes may cause chemical transformation of some pesticides into toxic by-products. Because the regulated communities are responsible for generating the necessary data for pesticide risk assessments, standard testing protocols and strategies for evaluating water treatment effects on pesticide removal and transformation need to be developed and provided to pesticide manufacturers. ORD's research shows that water treatment processes are highly variable among community water systems.

The main data sources for dietary residues data are from monitoring studies conducted by the Pesticide Data Program at the USDA Agricultural Marketing Service and field studies of residues on commodities in their raw state at the farm. Also, the Food and Drug Administration within DHHS maintains both regulatory and incidence/level monitoring on particular commodity/pesticide combinations and carries out its market basket survey known as the Total Diet Study. USDA's Pesticide Data Program has generated extensive pesticide residue data on over 50 foods out of hundreds of key foods eaten daily in the United States, and many of the foods not tested may be important in the diets of infants and children.

EPA's National Human Milk Monitoring Program studies, done in the 1970s to evaluate the extent of human milk contamination with organochlorine and other pesticides, are the most recent nationwide studies on breast milk. Since mother's milk is a staple food for many newborns, and lactation is one major route of elimination of endogenous and exogenous substances, knowledge of concentration of pesticides in breast milk would reduce uncertainty and yield better aggregate risk assessments.

Recommendations

We recommend that the Acting Assistant Administrator for Prevention, Pesticides, and Toxic Substances:

4-1 Update the dietary exposure databases used in probabilistic models for risk assessments as soon as the food consumption data from the 2003-2004 National Health and Nutrition Examination Survey become available in 2006. EPA should also update the Food Commodity Intake Database with the latest food consumption survey data, and if possible use data such as the Gerber Products Company's Feeding Infants and Toddlers Study.

4-2 Continue collaborating with USDA and with assessing whether there are additional foods consumed frequently by children that should be included by USDA in its Pesticide Data Program testing based on consumption results reported from the National Health and Nutrition Examination Survey.

4-3 Expand its partnerships with USDA and DHHS to further reduce uncertainty in aggregate risk assessments and

- develop the methodologies for collecting longitudinal food intake and physical activity information from children, and utilize such methodologies
  - to validate modeled assumptions in the probabilistic exposure models used by OPP,
  - to improve the current tools for estimating longitudinal exposures, and
  - to better understand timing or patterns of exposure;
- collect more current data on pesticide concentration in human breast milk among lactating women;
- evaluate dietary and nondietary exposures among children at schools and day cares; and
- continue to conduct research to characterize effects of dietary and nondietary exposures of pesticides on children's cognitive functions and performance.

Agency Response and OIG Evaluation

The Agency generally agreed with the OIG recommendations in Chapter 4 and the overall message of updating its food consumption databases, developing methodology for collecting longitudinal food intake and physical activity information from children, surveying human breast milk, and collaborating with its Federal partners to acquire more and better dietary and nondietary exposure data. However, the Agency commented that implementation of Recommendation 4-1 should wait until later in 2006, when it expects the release of "the first full set of 2-day data" from the 2003-2004 National Health and Nutrition Examining Surveys. We modified Recommendation 4-1 to meet the Agency's need for "sufficient data to provide a database comparable to USDA's Continuing Survey of Food Intakes by Individuals (CSFII) currently used by OPP."

In addressing our recommendation on assessing whether additional foods should be analyzed for pesticides by the USDA, the Agency responded that the "recommendation does not adequately take into account that sampling budgets are finite and that infrequently sampling a broader swath of foods with less frequency may not yield improved or more accurate dietary risk assessments." Also, EPA commented that "the methodology for collecting longitudinal data is extremely difficult," that longitudinal data are "extremely expensive and difficult to obtain," and that "long-term, intra-individual eating patterns through extensive consumer surveys does not appear sufficiently promising, at this time, to justify further pursuit of methodology development."

We recognize that resource limitations constrain each agency's research efforts in measuring residual and dietary consumption patterns. However, in the area of dietary pesticide exposure, EPA has a major responsibility because it sets the tolerances and registers the pesticide chemical use on food.

The full text of the Agency's response is in Appendix C, and our detailed comments on that response are in Appendix D.

Chapter 5
OPP Moving to Assess Cumulative Risk, but Complexities and Concerns Remain

EPA has initiated steps to perform cumulative risk assessments for pesticides, and more action is needed. FQPA had directed EPA to include in its assessment of pesticide safety the risks associated with the cumulative effects of chemicals. Conducting cumulative pesticide exposure risk assessments is complex because children are continuously exposed to mixtures of low-dose pesticide chemicals through many sources and routes. Organophosphate pesticides were the first class of pesticides that OPP evaluated, but OPP does not expect to publish the final cumulative risk assessment until later in 2006. ORD and OPP scientists have identified the need for better methods and more sensitive tests to estimate the amount of chemicals in humans. Concerns about adverse effects of chronic low-dose, concurrent exposures continue.

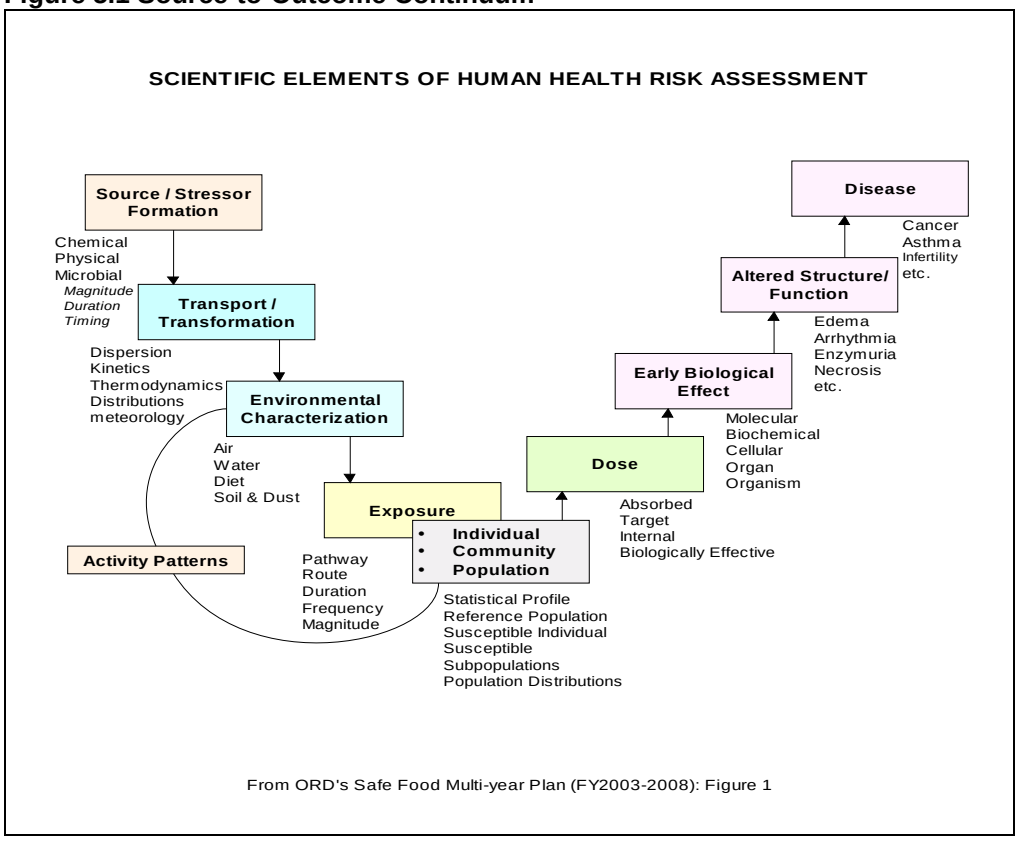
Many Factors Impact on Assessing Cumulative Risk

Both ORD and OPP recognize that questions related to assessing cumulative risk and evaluating risks to children are complex. Such assessments require an integrated approach to understand the linkages along a continuum, from source to exposure, and dose to adverse outcomes or disease. In a recent ORD Human Health Research review, ORD scientists indicated that improved tools (methods, data, models, risk assessment guidance, and toxicity testing methods and protocols) are needed to assess cumulative risks. These tools need to look at children's exposure to different pesticides with the same mechanism of toxicity, through the air, water, soil, and dust; from eating and drinking; and from touching and hand-to-mouth activities. EPA is currently designing and collaborating in research studies to fill gaps. To understand the linkages along this continuum, research is needed on:

- the effects of concurrent exposure to pesticides and other chemicals with like mechanisms of action;
- the nature of chemical (especially pesticide) interaction in producing a toxic response;
- the methods by which cumulative risk to chemicals (especially pesticides) with common mechanisms of action may be assessed; and
- when and how concurrent, low-dose effects experienced during stages of development could result in an adverse effect over the course of a person's lifetime.

Figure 5.1 shows the complex scientific steps and the data necessary for human health risk assessments. The challenge in such assessments begins with knowing the chemical source, its concentration in the environment, the media carrying the chemical, activities contributing to the actual human exposure, the dose that results from exposure, and the biological and other impacts on a person.

Figure 5.1 Source-to-Outcome Continuum



From ORD's Safe Food Multi-year Plan (FY2003-2008): Figure 1

New Science Needed to Measure Effects of Concurrent Exposures

Exposure to multiple pesticides in homes, schools, public areas, food, and drinking water is a routine part of life for children. Concerns about adverse effects of chronic low-dose, concurrent exposures on children continue to surface. Factors that complicate the evaluation of effects of chronic low-dose, concurrent pesticide exposures include:

- difficulties in measuring actual exposure levels;
- length of time between exposure and appearance of symptoms;
- the diversity of the symptoms; and
- the nature of exposures experienced in the environment over time.

Research confirms the need to perform more sensitive tests to measure effects of chemical exposure. Application of such sensitive techniques as biomonitoring methods and neuroimaging technology may be needed to detect significant, subtle sub-symptomatic, and below-pesticide poisoning health effects.[23] Based on findings by an EPA technical panel,[24] OPP's current testing methods used for assessments of reproductive toxicity and developmental toxicity should be revisited to determine whether changes are needed regarding animal-model selection and the end points being measured.

Models, Computer Tools Can Enhance Cumulative Risk Assessments

ORD and OPP scientists have identified the need for better methods of estimating internal doses in target tissues to determine cumulative risk assessments. According to OPP, since real-world data to characterize risk of human exposure often cannot be collected, it relies on computer models and other computer simulation tools to assess and predict cumulative risks from pesticide exposures.

ORD researchers have developed a physiologically-based pharmacokinetic model called the Exposure-Related Dose-Estimating Model (ERDEM). It simulates the human organism and its ability to absorb, metabolize, store, and eliminate chemicals. Pharmacokinetic describes a process to determine and quantify the time course of distribution, biotransformation, and excretion of pollutants. This model has been used by EPA risk assessors to simulate the reaction of multiple pesticides. Discussions are now underway on how this model can be interfaced with ORD's probabilistic human exposure and dose simulation model, SHEDS (Stochastic Human Exposure and Dose Simulation pesticides exposure model), to provide enhanced dose estimates.

Computational toxicology can provide tools that OPP can use to assess differences and similarities between children's and adults' responses to chronic, concurrent low-dose pesticide exposures. According to ORD, computational toxicology uses computing approaches to link chemical transformation and metabolism, exposure indicators, dose metrics, toxicity pathways, systems biology, and modeling programs. This approach can improve testing efficiency and reduce uncertainties in such areas as genomics (how an individual's genes interact with each other and the environment); literature suggests that genetics can play an important role in how different people are affected by pesticides. ORD has developed a new Computational Toxicology Program that uses computational chemistry, genomics, bioinformatics, and systems biology to:

- improve understanding of the linkages in the continuum between the source of a chemical in the environment and adverse outcomes;
- develop approaches for prioritizing chemicals for screening and testing; and

[23] Such effects may include those resulting from chronic low-dose, concurrent exposures.
[24] US EPA. Review of the Reference Dose and Reference Concentration Processes. Risk Assessment Forum, EPA/630/8-02/002F, December 2002.

- produce better methods and predictive models to assess risk.

OPP is awaiting products from ORD's Computational Toxicology Program to improve the pesticide regulatory program by incorporating bioinformatics, genomics, and toxicogenomics in its work. Computational toxicology may be the new scientific tool that could bring interdisciplinary work (e.g., public and environmental health, agricultural sciences) and data (e.g., human exposure information, chemical structure, fate and transport information) on a broader ecological and biological context for OPP. OPP's Health Effects Division plans to build a team of multi-disciplinary experts with diverse background to meet future work demands from computational toxicology.

Recommendations

We recommend that the Acting Assistant Administrator for Prevention, Pesticides, and Toxic Substances:

5-1 Follow through with ORD to finalize the integration of probabilistic modeling outputs with physiologically based pharmacokinetic modeling to better address cumulative risk from concurrent exposure to pesticides and other chemicals with like mechanisms of action.

5-2 Continue to execute plans and strategies on how computational toxicology outputs from ORD's Computational Toxicology Program will integrate into OPP's regulatory process; monitor, assess and document progress.

Agency Response and OIG Evaluation

The Agency agreed with Recommendation 5-2, but indicated that OPP's past and continuing actions fully address Recommendation 5-1. The Agency also commented that the "draft report does not recognize" additional on-going efforts by EPA to link probabilistic exposure models with physiologically-based pharmacokinetic models. While we agree with the spirit of outsourcing software development for probabilistic models or funding external researchers to seed research and develop the next generation of environmental scientists, we do take the position that the Agency should fully utilize the expertise of ORD scientists to develop exposure estimate models (including physiologically-based pharmacokinetic modeling) for its core work. We maintain our position for Recommendation 5-1 that OPP needs to coordinate its probabilistic efforts with ORD. The full text of the Agency's response is in Appendix C, and our detailed comments on that response are in Appendix D.

Chapter 6
Opportunities Exist to Better Manage FQPA Implementation

Since 1996, both OPP and ORD have generated a number of FQPA-related scientific outputs; however, there are additional opportunities to better manage health risk for children and reduce uncertainty in pesticide decisions. Specifically, OPP can:

- Take action on finalizing science policy papers.
- Continue working with organizations to assess alternative testing strategies.
- Use logic models to guide efforts.
- Develop a multi-year strategic plan to support goals.

These efforts should result in improved data and better protection against pesticide exposures for infants and children.

OPP Science Policy Papers Not All Finalized

The implementation of FQPA required OPP to revisit some of its existing policies related to the determination and regulation of dietary risk, and raised a number of new issues for which policies needed to be created. Since 1996, OPP has developed and refined nine science policy areas[25] identified as key to implementing the FQPA. These activities were done in collaboration with other Agency offices and programs, and with external stakeholders from industry, environmental groups, and other interested entities. We found that a number of the papers in the nine science policy areas are still in draft format. OPP officials said they consider these draft papers as operating documents that they will update as new information becomes available. Papers in draft form, as shown on EPA's Web site as of August 2005, are shown in Figure 6.1.

[25] The nine policy areas are: FQPA 10-Fold Safety Factor; Dietary Exposure and Risk Assessment; Threshold of Regulation; Drinking Water Exposure; Residential Exposure; Aggregate Exposure and Risk Assessment; Cumulative Risk Assessment for Pesticides with a Common Mechanism of Toxicity; Cholinesterase Inhibition End Point; and Use and Usage Information.

Figure 6.1: Science Policy Areas Identified as Key to Implementing FQPA but Papers Still in Draft

Key Science Policy Areas	Science Policy Papers Still in Draft
FQPA 10-Fold Safety Factor	- Standard Operating Procedures (SOPs) for Use of the FQPA Factor
Dietary Exposure and Risk Assessment	- Guidance for the Submission of Probabilistic Human Health Exposure Assessments to the Office of Pesticide Programs - Use of the Pesticide Data Program (PDP) in Acute Dietary Assessments (not accessible via the Web site)
Drinking Water Exposure	- Drinking Water Screening Level Assessment, Part A: Guidance for Use of the Index Reservoir in Drinking Water Exposure Assessments - Standard Operating Procedure for Incorporating Screening-Level Estimates of Drinking Water Exposure in Aggregate Risk Assessments - Water Treatment Effects on Pesticide Removal and Transformation
Residential Exposure	- Standard Operating Procedures (SOPs) for Residential Exposure Assessment - Framework for Assessing Non-occupational / Non-dietary (Residential) Exposure to Pesticides
Cumulative Risk Assessment for Pesticides with a Common Mechanism of Toxicity	- Application of the 10X safety Factor in Cumulative Risk Assessment.

EPA Needs to Continue Pursuing Alternative Testing Efforts

EPA is working with external scientific organizations to assess alternatives to the current pesticide data requirements: the International Life Sciences Institute and the National Academy of Sciences.

EPA started discussions with the Health and Environmental Sciences Institute at the International Life Sciences Institute on alternative testing strategies in 2001, and created a cooperative agreement to work with the Agricultural Chemical Safety Assessment Technical Committee under these groups. ORD and OPP scientists are members on the three task forces that prepared a proposal for a new testing strategy and three white papers for publication. Under the new strategy being designed by the Institute, the following data could be used to inform a more targeted testing approach in the design of studies or to support waiving specific toxicology tests:

- Data on toxicity and dose-response;

- Mechanism or mode of action of the chemical;
- Pharmacokinetic data;
- Data on age-related sensitivity or susceptibility to chemical exposure; and
- Information on potential or actual exposure to humans.

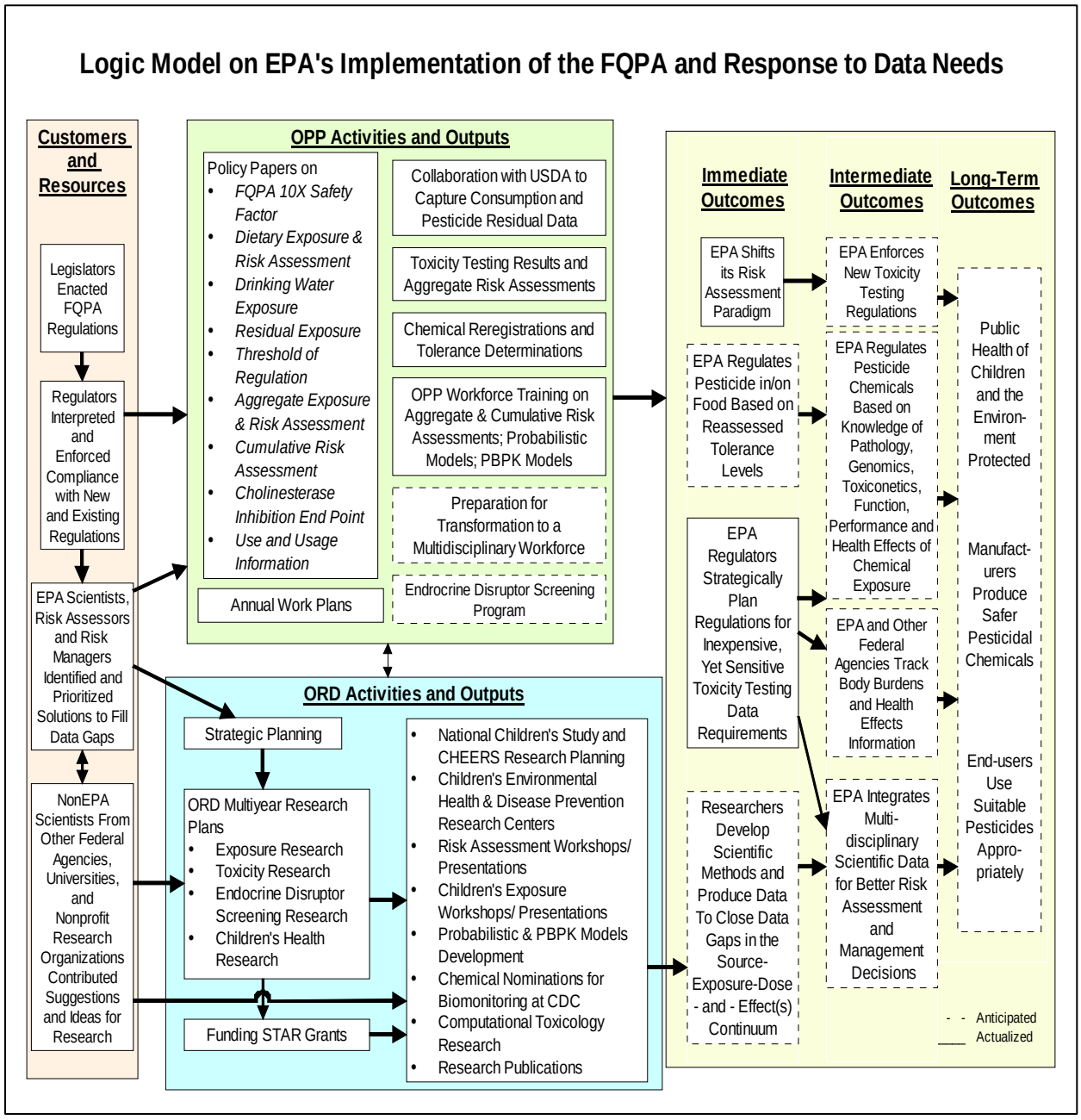
The National Academy of Sciences project is a two-part study funded by EPA to advance current approaches to toxicity testing to meet regulatory data needs. Part 1 of the study was designed to provide a report reviewing selected aspects of several relevant reports provided by EPA and others on toxicity testing and assessment. Part 2 is to be funded separately at EPA's option, and is to present a long-range vision and strategic plan for advancing the practices of toxicity testing and human health assessment for environmental contaminants. If funded, the second report is anticipated for fall 2006.

Logic Models Could Better Guide Efforts

OPP has not developed a logic model as part of the strategic planning process. Program logic models represent the logic underlying a program's design. They can indicate how various components are expected to interact, the products or services they produce, and how they generate the desired results. Significantly, a logic model distinguishes between outputs (the specific tasks performed) and outcomes (the actual results).

Figure 6.2 provides a logic model we produced that could assist EPA in gathering the scientific data needed to implement FQPA. We have described in the logic model our findings on EPA's response to the scientific data needed for implementation of the FQPA. This logic model distinguishes between tasks performed by OPP and ORD. Operations managers within OPP should focus on the production of high quality outputs in the model we produced, but managers who are concerned with overall FQPA implementation must look beyond outputs to outcomes. In our model, outputs are valuable because they lead to benefits. The long-term outcomes in the model are examples of how these ultimate criteria can be used to gauge EPA's effectiveness in implementing FQPA.

Figure 6.2[26]



Multi-year Strategic Plan Can Support Goals

We found OPP has not developed a multi-year strategic plan that would enable it to more efficiently achieve FQPA requirements and the ultimate goal of preventing the exposure of children to pesticides. OPP has divisional annual work plans that focus on annual work outputs, but no overarching, program-wide

[26] OIG staff developed this figure based on data collected during this evaluation.

strategic plan with immediate, intermediate, and long-term goals and expected outcomes. According to OPP, FQPA's mandate of registration renewal every 15 years is expanding OPP's work plans to encompass long-term strategic planning. Among the annual work plans that we reviewed, only the Fiscal Year 2004 plan from the Health Effects Division described short-term, intermediate, and long-term strategic projects. However, nearly all projects in this plan were labeled as "high priority," with limited personnel resources designated. To more efficiently plan its FQPA-required work and the resources needed to accomplish that work, OPP should develop a multi-year strategic plan.

Recommendations

We recommend that the Acting Assistant Administrator for Prevention, Pesticides, and Toxic Substances:

6-1 Either finalize all of the Science Policy issue papers, or change the word "draft" to "operational" and schedule annual updates.

6-2 Sustain the development of an alternative testing strategy, ensuring that risks are assessed across the entire life cycle of development.

6-3 Develop an overarching logic model and long-term strategic plan across divisions to identify and link immediate work outputs to outcomes.

Agency Response and OIG Evaluation

The Agency agreed with all recommendations in this chapter. However, it commented that the OIG report mischaracterized the status of some of its science policy papers and that, specifically, Figure 6.1 fails to list three other draft policy papers. We made modifications to Figure 6.1 based on comments provided by the Agency. However, we have concerns over the "Science Policy Issues & Guidance Documents" Web site being unclear, out-of-date, and misleading. Additionally, we noted that there are four science policy papers posted on the Web page for which OPP plans to issue Federal Register Notices announcing their withdrawal. It is our opinion that managing the currency of science policy papers and Web sites should be an Agency priority. We believe the Agency's Web site is a tool that can be used to demonstrate how OPP applies sound science to reduce uncertainty in its regulatory decisions. The full text of the Agency's response is in Appendix C, and our detailed comments on that response are in Appendix D.

Appendix A

Glossary of Terms

Aggregate Exposure: The combined exposure of an individual or defined population to a specific agent or stressor via relevant routes, pathways, and source.

Aggregate Risk: The risk resulting from aggregate exposure to a single agent or stressor.

Cholinesterase: One of many important enzymes needed for the proper functioning of the nervous systems of both humans and animals.

Common Mechanism of Toxicity: When two or more pesticide chemicals or other substances cause a common toxic effect(s) by the same, or essentially the same, sequence of major biochemical events (for example, a mode of action).

Computational Toxicology: The application of mathematical and computer models to better understand the mechanisms through which a given chemical or exposure induces harm and predicts adverse effects.

Concurrent Exposure: Potential human exposure by all relevant pathways, durations, and routes that allow one chemical to add to the exposure of another chemical such that the total risk is an estimate of the sum of the exposures to the individual chemicals.

Cumulative Risk: The combined risks from aggregate exposures to multiple agents or stressors. Cumulative risk is the risk of a common toxic effect associated with concurrent exposure by all relevant pathways and routes of exposure to a group of chemicals that share a common mechanism of toxicity.

Data Call-ins: A process through which EPA seeks data from appropriate pesticide manufacturers.

Deterministic Model: A model that contains no random elements. The model provides a point estimate of exposure, assuming that a typical child eats an assumed mass of food per day with a given concentration of a pesticide residue.

Developmental Neurotoxicity: Involving substances that damage a developing nervous system, including the brain.

Developmental Toxicity: Adverse effects on the developing organism that may result from exposure prior to conception (either parent), during prenatal development, or postnatally until the time of sexual maturation. The major manifestations of developmental toxicity include death of the developing organism, structural abnormality, altered growth, and functional deficiency.

Dose: The amount of a substance available for interactions with metabolic processes or biologically significant receptors after crossing the outer boundary of an organism.

Endpoint: An observable or measurable biological event or chemical concentration (e.g., metabolite concentration in a target tissue) used as an index of an effect of a chemical exposure.

Mechanism of Action: The complete sequence of biological events that must occur to produce a toxic effect.

Pathway of Exposure: The physical course a pesticide takes from the source to the person exposed (e.g., through food or drinking water consumption or residential pesticide uses).

Pharmacodynamics: The determination and quantification of the sequence of events at the cellular and molecular levels leading to a toxic response to an environmental agent (also called toxicodynamics).

Pharmacokinetics: The determination and quantification of the time course of absorption, distribution, biotransformation, and excretion of pollutants (also called toxicokinetics).

Physiologically-Based Pharmacokinetic Model: A model that estimates the dose to a target tissue or organ by taking into account the rate of absorption into the body, distribution between target organs and tissues, metabolism, and excretion.

Probabilistic Model: A system whose output is a distribution of possible values; the model considers the range of estimates and provides a probability distribution of exposures.

Risk: The probability of adverse effects resulting from exposure to an environmental agent or mixture of agents.

Risk Assessment: The evaluation of scientific information on the hazardous properties of environmental agents (hazard characterization), the dose-response relationship (dose-response assessment), and the extent of human exposure to those agents (exposure assessment).

Route of Exposure: The way a chemical enters an organism after contact (e.g., ingestion, inhalation, or dermal absorption).

Statistical Significance: The probability that a result is not likely to be due to chance alone. By convention, a difference between two groups is usually considered statistically significant if chance could explain it only 5 percent of the time or less.

Subchronic Exposure: Exposure to a substance spanning approximately 10 percent of the lifetime of an organism.

Tolerance: The maximum level of pesticide residue allowed in or on human food and animal feed.

Toxicology: The study of harmful interactions between chemical, physical, or biological agents and biological systems.

Appendix B

Details on Scope and Methodology

During our evaluation, we conducted a literature review on FQPA and the potential health outcomes of prenatal and childhood exposures to pesticides. We reviewed documents pertinent to risk assessment prepared by EPA and other Federal agencies. We examined dietary assessment methods and examined food consumption databases, pesticide residue data sources, and probabilistic models to better understand how such data integrate in risk assessments performed by OPP. We reviewed the annual work plans prepared by OPP and the multi-year research plans by ORD. We collected data to:

- Report the types of scientific tools and data needed to meet the regulatory challenges posed by FQPA;
- Identify and evaluate OPP's existing toxicity testing strategy and tools;
- Assess and report the types of dietary and nondietary exposure data OPP has and needs for aggregating risks to establish tolerances that protect children;
- Identify challenges and assess new science, technology, and research that could enhance OPP's strategy to assess cumulative pesticide exposure risks; and
- Identify and recommend strategies to assure successful implementation of the FQPA.

We reviewed EPA's infrastructure and Human Health Research Strategies to determine ORD's role in supplying scientific data and tools for OPP's pesticide regulatory work. We attended ORD's Human Health Research Program review meetings and public sessions on proposed revisions to 40 CFR Part 158. Furthermore, we interviewed various administrators, science policy directors, scientists, and risk assessors from various EPA offices, as well as experts from other Federal agencies and outside organizations, to capture expert viewpoints, clarify our interpretations, and confirm our findings (see below). We visited various offices in Washington, DC, and Research Triangle Park, North Carolina.

Organizations for Experts Reviewed

EPA	• Office of Pesticide Programs • Office of Prevention, Pesticides, and Toxic Substances • Office of Research and Development • Office of Children's Health Protection
Other Federal Agencies	• Department of Agriculture • Department of Health and Human Services • Office of Management and Budget
Nongovernmental Sources	• Environmental health scientists, toxicologists, and epidemiologists • Pediatricians/physicians • Environmental law professors from universities • Children's Environmental Health and Disease Prevention Research Centers • Environmental health groups

Appendix C

Response from the Agency

October 17, 2005

MEMORANDUM

SUBJECT: Draft Evaluation Report: Opportunities to Improve Data Quality and Children's Health through the Food Quality Protection Act

FROM: Jim Jones /s/
Director, Office of Pesticide Programs

TO: Jeffrey K. Harris
Director for Program Evaluation, Cross Media
Office of Inspector General

Thank you for the opportunity to comment on the draft report, dated September 1, 2005, by the Office of Inspector General on EPA's Implementation of the Food Quality Protection Act (FQPA). The Office of Pesticide Programs (OPP) appreciates the Office of Inspector General's review of OPP's implementation of FQPA.

I. Introduction to OPP's Response to OIG's Report

The EPA's OIG draft report "Opportunities to Improve Data Quality and Children's Health through the Food Quality Protection Act" focuses upon the following issues: (1) What data requirements were required by FQPA; (2) Whether testing guidelines, requirements, and evaluation procedures allow EPA's OPP to determine the potential adverse effects of pesticide exposure on the developing nervous system; (3) What challenges did OPP overcome and what opportunities exist for OPP to acquire better pesticide exposure data to aggregate risks; (4) What challenges exist and what opportunities are available for OPP to improve cumulative risk assessments; and (5) What opportunities exist to better manage pesticide health risks for children. The OIG's specific recommendations and OPP's comments on the draft report and the recommendations are below.

Overall, the OIG draft report confirms OPP's many accomplishments to implement FQPA mandates to strengthen the human health protections for infants and children:

1. The draft report notes that OPP developed, issued and implemented a vast number of key science policies and regulations, improving our ability to assess risks.

2. The draft report recognizes that OPP has successfully incorporated into its pesticide risk assessment procedures new cutting-edge methodologies and tools, including aggregate exposure and cumulative risk assessment.

3. The draft report corroborates OPP's risk management priorities (focusing on high risk pesticides such as organophosphates) and acknowledges the improved public health outcomes that have resulted from OPP's risk management decisions (such as the cancellation of certain chlorpyrifos products due to risks to children).

4. The draft report highlights forward-looking steps that both OPP and OIG believe are important, exemplified by the ongoing National Academy of Sciences (NAS) and International Life Sciences Institute (ILSI) work on improved approaches to human health risk assessment, which incorporates more targeted testing and computational toxicology to refine and reduce animal testing.

See OIG Comment in Appendix D, Note 1

However, OPP believes that the draft report is uneven, and sometimes misleading, in its evaluation of its progress in implementing the provisions of FQPA. The draft report glosses over significant scientific accomplishments of the past nine years (i.e., since 1996 when FQPA was enacted). It then tends to focus on issues that are 1) minor and relatively insignificant within the overall scope of FQPA implementation, 2) characterized incorrectly, or 3) outside the control of the Agency.

See OIG Comment in Appendix D, Note 2

Likewise, while the draft report recognizes potential opportunities for collaboration between OPP and ORD and other organizations, it generally fails to acknowledge that such collaboration has been on-going for years, and provides little indication of the significant scientific gains that have been realized through these efforts. The following comments are provided to clarify the specific issues, and suggestions are made in order to add balance to the report and provide emphasis on opportunities and challenges that remain for continued implementation of FQPA.

See OIG Comment in Appendix D, Note 1

Of the thirteen (13) recommendations provided by the OIG in their draft report, OPP agrees with eight of them because, in fact, we are already implementing most of them (i.e., six of the eight are already implemented by OPP). OPP appreciates the OIG validating its current work processes. OPP believes, however, that the final report would be more complete and balanced by acknowledging that OPP had already identified and begun working on many of the issues discussed in the draft. On the other hand, OPP disagrees with five of the recommendations mainly because we feel, at this time, these recommendations have been made either prematurely or with little practical or scientific basis.

II. Chapter 1 – Introduction to the Report

The first chapter of the report provides background on the scope and methodology of the report and on FIFRA and FQPA generally, and also includes a brief summary of the results of the OIG's review. This summary acknowledges that to meet the requirements of FQPA "EPA instituted numerous data requirements that should provide better protection. Additionally, EPA took steps to develop science policies, develop methods and tools, and collect required data on aggregate and cumulative risk." However the summary concludes with "significant data gaps remain" and summarizes the report's general recommendations concerning collecting and using data. While we work actively to improve the databases supporting our decisions, we generally disagree with the draft report's unsupported, sweeping conclusion that "significant data gaps remain."

See OIG Comment in Appendix D, Note 3

One specific technical correction we would like to draw your attention to is on page 3, lines 5-7 of the draft report. The definition/explanation of cumulative exposure is incorrect. It states "Cumulative risk information for a given common toxic effect is calculated separately for each exposure route and duration and then combined." It is not the toxic effect, or adverse outcome, that defines the ability to group chemicals for a cumulative assessment; rather, it is a common mechanism of toxicity (per OPP's peer-reviewed guidance on this topic).

See OIG Comment in Appendix D, Note 4

III. Chapter 2 – FQPA Inspired Numerous EPA Data Requirements

Chapter 2 of the report highlights the FQPA inspired changes to data requirements. FQPA established a single, health-based standard and requires that allowable residue levels for food use pesticides be protective of the health of infants and children. Chapter 2 includes a table outlining key requirements and amendments to FIFRA and FFDCA resulting from FQPA, as interpreted by EPA.

We would like to draw your attention to the following technical corrections:

1. Page 5: Table 2.1

Table 2.1 describes selected FQPA statutory changes; however, it misstates some of the changes. We have prepared a substitute table that accurately reflects the FQPA changes, and have added citations to the appropriate sections of the statutes.

See OIG Comment in Appendix D, Note 4

Table 2.1 Key Changes and Additions for Pesticide Regulations Due to FQPA

FIFRA
▪ Permits emergency suspension of a pesticide without simultaneously issuing a notice of intent to cancel. – FIFRA sec. 6(c)(3). ▪ Requires Registration Review, with a goal of once every 15 years – FIFRA sec. 3(g). ▪ Establishes special provisions for minor use pesticides, including public health pesticides – FIFRA sec. 3 and sec. 4. ▪ Links tolerance reassessment to reregistration – FIFRA sec. 4(g). ▪ Establishes special provisions for antimicrobial pesticide registration – FIFRA sec. 3(h). ▪ Establishes mandate for continuing expedited consideration of application for pesticides meeting one or more criteria for reduced risk pesticides – FIFRA sec. 3(c)(10). However, this provision was overtaken by 2004 Pesticide Registration Improvement Act (PRIA), which establishes specific timeframes for reduced risk pesticides. ▪ Establishes Science Review Board to assist in scientific peer-reviews conducted by the FIFRA Scientific Advisory Panel – FIFRA sec. 25(d)(2).
FFDCA Sec. 408
▪ Delinks pesticides from the Delaney clause (FFDCA sec. 409) which prohibited establishment of tolerances for carcinogens, by placing all pesticide authority in FFDCA sec. 408. ▪ Establishes standard for establishing a tolerance based on whether tolerance is "safe", defined as "a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information." ▪ Defines types of exposures to be aggregated for risk assessment purposes. ▪ Requires consideration of cumulative effects of pesticides having common mechanism of toxicity. ▪ Requires tolerance reassessment on phased schedule: 33% within 3 years of enactment; a second 33% within 6 years; and the remaining number within 10 years of enactment. ▪ Creates a presumption in favor of applying an additional 10-fold margin of safety for infants and children for threshold effects. ▪ Requires development of an estrogenic substances screening program. ▪ Requires development and distribution of consumer information on pesticide risks and benefits.
FQPA sec. 301-305
Prescribes data collection activities to ensure the health of infants and children: ▪ Collection of adequate data on food consumption patterns of infants and children. ▪ Improved data collection on occurrence of pesticide residues in foods most likely to be consumed by infants and children. ▪ Evaluation of pesticide usage information and improved information gathering.

2. Page 6: First paragraph, lines 3-5

The statement that FQPA requires "that there is a reasonable certainty of no harmful developmental effects for children" is incorrect. FQPA does not limit the assessment or consideration of adverse effects to only those that are considered "developmental." The correct safety standard is "…that there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information."

See OIG Comment in Appendix D, Note 5

3. Page 6: Second paragraph, lines 5-6

The precise text of the CFR uses "domestic animals" (not "terrestrial mammals")

IV. Chapter 3 – OPP Lacks Consistent Data on the Developing Nervous System to Determine Potential Adverse Effects

Chapter 3 provides an overview of the importance of developmental neurotoxicity data and the concerns which have been raised by stakeholders concerning conducting developmental neurotoxicity tests such as the expense of conducting such tests and the difficulty in interpreting the results. Below are some specific comments we have on this chapter.

Recommendation 3-1: Develop a Standard Evaluation Procedure to assess results of developmental neurotoxicity testing.

OPP agrees with this recommendation and has been actively addressing it over the past few years and expects to have a final Standard Evaluation Procedure (SEP) in 2006.

Over the past few years, a standard Data Evaluation Review format was developed which harmonized with Health Canada's Pesticide Management Regulatory Agency (PMRA) and included detailed guidance on the summary/reporting, evaluation, and interpretation of all endpoints typically reported in a Developmental Neurotoxicity (DNT) study.

In the summer of 2004, OPP directed resources to the assessment of 29 unreviewed DNT studies by having the OPP's DNT Committee assemble a package of references and guidance that was provided to all OPP toxicologists responsible for reviewing the studies. A special two-day training session was held to ensure that all toxicologists would be familiar with the documented evaluation procedure.

See OIG Comment in Appendix D, Note 6

Now that these reviews have been completed, the informal guidance package is being used as the nucleus of a more formal, internal Standard Evaluation Procedure (SEP) that is expected to be completed in 2006.

Finally, there is an on-going International Life Sciences Institute (ILSI)/Risk Science Institute (RSI) project on DNT data interpretation (including OPP and ORD staff experts in DNT testing and evaluation) that is addressing DNT methodology and performance, variability, positive control data, and statistical data analysis; the results of these efforts will be published in the near future.

<u>Recommendation 3-2</u>: Evaluate whether relying on primary work in cell culture, invertebrate, or non-mammalian models, followed by more targeted examinations of specific processes in mammalian models, may benefit the assessments of developmental neurotoxicity and improve testing efficiency.

See OIG Comment in Appendix D, Note 7

Since there was no discussion of this strategy in the draft report (it is mentioned in passing at the top of page 10), the basis for this recommendation is unclear. OPP actively supports the development of test methods that do not use (or use fewer) animals (i.e., in vivo testing) to assess the potential toxicity of a pesticide. To our knowledge, however, there are no well-accepted methods of the types listed in the recommendation (i.e., in vitro, invertebrate, or non-mammalian models), that have been shown to have clear linkages to adverse functional outcomes for toxicity to developing nervous system in mammals. Consequently, while OPP agrees with the principle behind the recommendation, OPP disagrees with this recommendation, as drafted.

See OIG Comment in Appendix D, Note 7

OPP is currently working with ORD/National Health and Environmental Effects Research Laboratory (NHEERL)/Neurotoxicology Division on several research projects relevant to this recommendation:

- Development of a high throughput screening battery (primarily using cell culture techniques) focused on detecting chemicals likely to be developmentally neurotoxic; and

- A proposal to evaluate the utility of considering molecular markers for some classes of neurotoxic pesticide chemicals, to determine whether such markers could be more sensitive/equivalently sensitive than the current DNT guideline for detecting adverse effects on the developing nervous system.

Finally, EPA (both OPP and ORD) have been part of the steering committee for an upcoming symposium to look at alternative ways to perform DNT-type studies. The TestSmart Developmental Neurotoxicity (DNT) Test symposium, sponsored by the Johns Hopkins University, the National Institute of Environmental Health Sciences (NIEHS), and others, will be held March 13 - 15, 2006 to discuss the DNT and alternative methods. More information is available at: http://caat.jhsph.edu/dnt/.

See OIG Comment in Appendix D, Note 8

<u>Recommendation 3-3</u>: Evaluate which indicator, or combination of indicators, is most sensitive and meaningful for assessing developmental neurotoxicity consequences of exposure during critical windows of development.

OPP agrees generally with this recommendation and we are addressing it as part of the Standard Evaluation Procedure (SEP) for Developmental Neurotoxicity (DNT) tests. DNT studies involve dosing pregnant animals (generally rats) during gestation, allowing them to deliver their pups, and continuing dosing the mothers during the lactation period (up to 21 days after birth). In many cases, the pups are dosed directly beginning a few days after birth up to weaning (approximately 21 days after birth). This exposure period generally encompasses the critical windows of development of the rodent brain.

See OIG Comment in Appendix D, Note 9

Based on a review of dozens of DNT studies, OPP believes that it is unlikely that a single 'most sensitive' parameter would be found. During the course of the experiment, pups are examined daily (clinical observations) and are also tested at various time points for the following indicators of developing nervous system functions: auditory startle habituation, functional observations, motor activity, learning and memory, and brain pathology (brain weight, neuropathology and brain morphometric measurements). Part of evaluating a DNT study is understanding that each of these parameters is important and needs to be assessed in a "weight-of-the-evidence" approach. Different chemicals with different modes of action are likely to affect different functional systems. OPP is currently involved in the final stages of an ILSI project which is developing approaches to evaluating/interpreting these different parameters which will help address the issue of the sensitivity/meaningfulness of DNT data.

See OIG Comment in Appendix D, Note 9

<u>Recommendation 3-4</u>: Implement the recommendations made by National Research Council in its report to reduce uncertainty in neurodevelopment effects of exposure during critical windows of development by:

a) **ensuring that developmental neurotoxicity tests are conducted on developing animals in addition to young adult animals;**

b) **assuring that developmental neurotoxicity test information is collected at different life stages and that there is comparison of effects of exposure during infancy, adulthood, or old age; and**

c) **revising the developmental neurotoxicity testing guidelines to better assess risks of chemical exposure during the critical period of rapid human brain development.**

OPP takes the National Research Council's (NRC's) report seriously and believes that most of the recommendations listed by the OIG already have been appropriately addressed, as summarized below.

a) With respect to bullet "a", the current Developmental Neurotoxicity (DNT) test guideline includes testing during the major phases of development (i.e., during early lactation and around the time of weaning) as well as in young adults (around post-natal day (PND) 60). Thus, testing according to the current guideline addresses this recommendation.

See OIG Comment in Appendix D, Note 10

b) With respect to bullet "b", while there is no current test guideline in which exposure occurs continuously from conception through old age, required studies assess neurotoxicity at a variety of lifestages spanning the full life span. The DNT and subchronic neurotoxicity guidelines assess neurotoxicity during development/early life and adulthood, respectively. Neurotoxicity-related parameters are assessed about half-way (approximately one year) into the current two-year chronic rat study guideline. OPP is currently part of discussions to address a variety of endpoints in a lifestage approach to toxicity testing underway through the International Life Sciences Institute (ILSI)/Health Environmental Sciences Institute (HESI) project identified in our response to Recommendation 6-2.

See OIG Comment in Appendix D, Note 10

c) With respect to bullet "c", the current (1998) DNT test guideline recommends exposures up to post-natal day (PND) 10; however, since the organophosphate DNT data call-in in 1999, OPP has recommended investigators dose up to PND 21. The latest OECD draft guideline also includes exposure through PND 21. This longer exposure period will be incorporated into the next guideline revision/OECD harmonization. The text of the report (p. 9, 5th bullet) should be revised to reflect OPP's practice.

See OIG Comment in Appendix D, Note 11

<u>Other OPP Comments for Chapter 3</u>

Page 7, section title: "Assessing Developmental Neurotoxicity Important"

The title should be revised to clearly articulate the topic of the following section. We suggest the title simply be "Assessing Developmental Neurotoxicity."

Page 8, line 3 of Developmental Neurotoxicity Testing Issues section

In addition to the neurobehavioral tests cited, it is important to include "neuropathology," which is assessed in the DNT study.

Page 8, line 8 of the same paragraph:

OPP suggests that the text be changed to read as follows, "Data received through the data call-in were difficult to interpret because of: (1) significant variability seen in some data sets of developmental neurotoxicity data; (2) differences in studies conducted across laboratories; and (3) incomplete reporting of methods and results in some study reports."

Page 9, first paragraph in the "Weaknesses in Toxicity Testing Guidelines" section.

OPP suggests deleting the first four words of the first sentence (i.e., "Independent scientists reported in") and start the sentence with "Literature reports…...". The reason for this is because the four articles referenced were not all written by "independent scientists." Two of the articles were from peer-reviewed journals; the other two articles were from Non-Governmental Organizations.

Page 9, bullets under "Weaknesses in Toxicity Testing Guidelines"

The first bullet in this section states that there is no requirement for immunotoxicity testing, either in adult or developing animals. While this is true, it fails to address the fact that the adult immunotoxicity testing guideline was first finalized in 1998, and that OPP proposed in March 2005 (in the revisions to 40 CFR Part 158) that this test be required for pesticide registration. A developmental immunotoxicity (DIT) testing guideline has not yet been developed; however, OPP and ORD scientists have participated in three public workshops on this topic which resulted in peer-reviewed published proceedings (2001 ILSI/HESI workshop, Holsapple, 2002; 2002 National Institute of Environmental Health Sciences (NIEHS)/ National Institute for Occupational Safety and Health (NIOSH) workshop, Luster et al, 2004; & 2003 ILSI/HESI roundtable, Hosapple et al., 2005) and are in the process of drafting a DIT guideline and background document.

See OIG Comment in Appendix D, Note 12

Page 10, 2nd paragraph in the section "Proposals Made…": "The Agency is awaiting public comments prior to either amending or promulgating the proposed rule."

OPP recommends that the sentence be revised to read: "The Agency will consider public comments prior to promulgating a final rule." The wording about promulgation needs to be corrected. Only final rules are "promulgated."

Page 10, 3rd paragraph in the section "Proposals Made…"

OPP suggests that this paragraph should include a specific statement that says the Guidelines are not part of Part 158, nor are they proposed to be incorporated into Part 158. The Guidelines provide protocols that can be used to satisfy the data requirements but they are not the only protocols that can be used. This is critical because as written it sounds like the Guidelines are regulatory in nature.

Page 10, last paragraph, 1st sentence: "However, in the proposed rule released on February 28, 2005, developmental neurotoxicity studies were changed to "conditionally required," meaning that they would only be required under certain conditions."

OPP believes that the OIG text is unclear. OPP believes that the sentence is referring to the end of the Office of Management and Budget (OMB) review of the draft proposed rule. The proposed rule was publicly released as a Notice for Proposed Rulemaking (NPRM) in the Federal Register on March 11, 2005 (70 FR 12276). OPP suggests that the sentence be revised

as follows: "However, in the proposed rule that completed OMB review on February 28, 2005…."

p. 10, last paragraph, discussion on the Part 158 (conventional pesticides rulemaking) proposed rule

EPA is proposing to conditionally require DNT studies for all neurotoxic pesticides and for pesticides that meet other criteria indicating a potential for toxicity to the developing nervous system, based upon a weight-of-evidence evaluation of the toxicological database. The first two sentences give the misleading impression that OPP changed the substance and scope of the proposed Developmental Neurotoxicity Test (DNT) requirement based on questioning by OMB. In actuality, the draft proposed rule was clarified in response to OMB questions, but neither the substance nor the scope of the proposed DNT required was altered. We recommend deletion or revision of this discussion.

See OIG Comment in Appendix D, Note 13

In the draft proposed rule submitted to OMB, a DNT was "Required" and the notes denoted the limited instances when the test would be necessary. The preamble of the draft proposed rule also mentioned the weight-of-evidence approach, without an extensive discussion of the approach. After discussions with OMB to clarify the criteria associated with the requirement to conduct a DNT study, OPP realized that the rule should describe the DNT study as "conditionally required" to reflect the limited conditions when the data requirement would be imposed. Accordingly, OPP developed a more extensive discussion of its weight-of-evidence approach in the preamble to the proposed rule; expanded one of the notes to include the weight-of-evidence approach; and changed the "Required" to "Conditionally Required" to better reflect the frequency that EPA would impose the requirement. Thus, the change was elicited by OMB's request for clarification but the substance of the requirement was not changed.

Page 11: "EPA had not responded to OMB as of August 30, 2005."

Since response can include conversations, this sentence should be changed to read: "EPA had not submitted a plan to OMB as of August 30, 2005."

V. Chapter 4 – OPP Made Substantial Changes to Overcome Aggregate Risk Challenges, but Challenges Remain

Recommendation 4-1: Update its dietary exposure databases used in probabilistic models for risk assessments. EPA should use the dietary consumption data compiled from the DHHS's National Health and Nutrition Examination Survey, update the Food Commodity Intake Data Base with the latest food consumption survey data, and if possible use data such as the Gerber Products Company's Feeding Infants and Toddlers Study.

While OPP is indeed moving toward using dietary consumption data compiled from the DHHS' National Health and Nutrition Examination Survey (NHANES) survey and updating the Food Commodity Intake Database (FCID), we believe implementation of this recommendation should

wait until 2006 when we expect NHANES to release sufficient data to provide a database comparable to the USDA's Continuing Survey of Food Intakes by Individuals (CSFII) currently used by OPP. Therefore, while OPP generally agrees with updating our food consumption database to reflect the NHANES data, we believe the OIG recommendation, as drafted, is premature. In fact, EPA has been planning to update the food consumption database since the NHANES effort began, and we intend to move beyond our current exploratory analysis of the NHANES dietary consumption data after the first full set of 2-day consumption data for 2003-2004 is released in 2006.

See OIG Comment in Appendix D, Note 14

With respect to the DHHS' NHANES survey, we note that only the 1999-2000 and 2001-2002 data have been released so far and full survey integration between the NHANES and USDA CSFII methods only began with the NHANES 2002 data. We further note that DHHS offers several cautions about combining these data sets and it released publicly only part of the data due to confidentiality concerns. In addition, different interview systems/ methodologies were used between the 1999-2000 data, the 2001 data, and the 2002 data. For these reasons and others, OPP has so far only conducted initial exploratory analyses on these data while anticipating the release of the next set of data.

This next set of data, consisting of the 2003-2004 dietary consumption data, will be the first complete, integrated 2-day dietary consumption data set released by the NHANES program. This is expected to be made publicly available in 2006. OPP will begin examining this data closely upon its release, particularly for kids' foods and for comparison with the 1998 Supplemental Children's Survey. We expect differences to be minimal for the fresh (raw) commodities which we have generally found to contribute most to pesticide dietary burden.

Furthermore, as suggested by the OIG, we intend to update the FCID to incorporate new (generally processed) foods that have come onto the market since the earlier USDA survey and are being reported in new food consumption surveys. We are beginning to plan for updating this database, but the majority of this work will not occur until after the work associated with meeting the August 2006 FQPA tolerance reassessment deadline is completed.

Several years ago, OPP decided that practical considerations prevented the use of the Gerber Feeding Infants and Toddlers Study (FITS), which is a survey of the eating habits and nutrient intakes of more than 3,000 infants and young children, conducted during the five-month period from March-July 2002. A study summary was published as a supplement to FITS in the January, 2004 issue of the Journal of the American Dietetic Association. Foods are reported in this survey on an "as eaten" basis. OPP contacted the Gerber Company several years ago to obtain this data; however, Gerber provided only limited data quantity and format. Specifically, the data was provided to us in a voluminous hardcopy (not electronic) form and the data were expressed on a food form rather than a commodity form basis. Recipes (aka 100 gram files) were proprietary and not provided for translating the foods (e.g., baby food applesauce) to its component raw agricultural commodities (e.g., apples, sugar, etc.) on which our pesticide residue data and exposure assessments are based.

See OIG Comment in Appendix D, Note 15

Given the nature of and issues associated with the FITS data, the fact that the FITS survey was conducted only four years after the USDA-conducted 1998 Supplemental Children's Survey associated with the CSFII, OPP's active involvement in the early stages of the replacement NHANES dietary survey, and the reasonably comparable size of the CSFII survey for the subpopulation of interest, OPP decided then and continues to believe that resources were more appropriately invested in working jointly and cooperatively with other U.S. government agencies toward a large scale, nationally-representative NHANES dietary survey.

Recommendation 4-2: Continue to collaborate with USDA to develop the methodology for collecting longitudinal food intake and physical activity information from children.

EPA recognizes that data from a longitudinal dietary consumption survey could provide a better basis for estimating longer-term dietary risk than the food consumption databases now available. However, the methodology for collecting longitudinal data is extremely difficult. It requires that individuals track and record their consumption of food and beverages with respect to the identity of each food, the amount consumed, and (generally, to be most useful) the time at which it is eaten. While this might be possible and feasible over shorter periods of time (e.g., one or two weeks), it becomes very difficult to collect reliable, accurate information over the longer periods of time (months or years) which are of particular interest to OPP. Over extended periods of time, difficulties understandably arise with respect to differential drop-out rates and adequacy/accuracy of recorded eating occasions. Also, the very process of continually recording eating patterns over an extended period of time is thought to potentially change those eating patterns. Longitudinal food consumption data is also extremely expensive and difficult to obtain. While there is general and widespread interest and support among a multitude of governmental agencies and others with respect to general eating patterns and eating patterns over shorter terms, there is less interest in collecting information on detailed eating patterns over extended periods of time. Considering these issues, gathering extensive data on long-term, intra-individual eating patterns through extensive consumer surveys does not appear sufficiently promising, at this time, to justify further pursuit of methodology development.

See OIG Comment in Appendix D, Note 16

As discussed in the response to Recommendation 4-4, we are pursuing alternative approaches to improving our estimation of longer term dietary risk, including the statistical modeling techniques and simulations which have developed under collaborative efforts with consulting firms and science research organizations. Our efforts also include monitoring the work of the National Cancer Institute (NCI) in this area.

Recommendation 4-3: Assess which additional foods frequently consumed by children should be included by USDA in its Pesticide Data Program testing.

OPP believes that its current practice fully addresses this recommendation and that no change is warranted. To the extent this recommendation concludes that EPA and the USDA's Agriculture Marketing Service (AMS) have failed to consider appropriately which

See OIG Comment in Appendix D, Note 17

food commodities should be included in the Pesticide Data Program (PDP) monitoring (and with what frequency), we disagree. OPP also believes that this recommendation does not adequately take into account that sampling budgets are finite and that infrequently sampling a broader swath of foods with less frequency may not yield improved or more accurate dietary risk assessments.

OPP has an extensive and ongoing relationship with USDA with respect to determining which foods are included in USDA's PDP program. As stated in PDP's annual summary reports:

> "AMS works closely with the US EPA to select commodities and pesticides for PDP testing. Commodities selected are those most often consumed by U.S. consumers, with emphasis on foods consumed by infants and children."[1]

See OIG Comment in Appendix D, Note 18

We disagree strongly with the OIG statement that USDA's PDP program has generated extensive residue data on over, "50 foods out of hundreds of key foods eaten in the U.S." but that, "many of the foods not tested [by PDP] may be important in the diets of infants and children." This statement incorrectly implies that EPA may be underestimating kids' exposure because EPA is "missing" many important foods consumed by children. The sampled PDP commodities for children 1-2 years old directly or indirectly represent approximately 90% of children's diets. Moreover, EPA does include in its risk assessments a contribution from consumption of foods not tested in the PDP. For those foods, EPA uses field trial residue data. While these data tend to overestimate potential exposure, they rarely represent a significant part of the total exposure.

Determining which foods to sample and not to sample should be (and is) based on careful consideration of food consumption patterns, residue levels, and frequency of pesticide detections. Professional judgment, grounded in extensive experience performing dietary exposure assessment, should guide the choice of foods that collectively are likely to account for the greatest amount of exposure. It would be unwise, given finite sampling resources, to design the PDP survey program so that a greater number of commodities representing a high cumulative (total) percentage of the diet are sampled. This is particularly true if this means important high consumption children's commodities such as apples, oranges, grapes, or potatoes would be sampled less frequently (i.e., at longer intervals) or with less intensity. In general, we attempt to sample high consumption foods for 2-3 consecutive years at a time and at an interval which does not exceed 4-5 years.

<u>Recommendation 4-4</u>: Expand its partnerships with USDA and DHHS to collect data on:

- **longitudinal food consumption information;**
- **pesticide concentration in human breast milk among lactating women, through the National Health and Nutrition Examining Survey and/or USDA's WIC Program**

[1] Pesticide Data Program: Annual Summary Calendar Year 2003 United States. Department of Agriculture, Agricultural Marketing Service, Science and Technology Programs. February 2005. http://www.ams.usda.gov/science/pdp/Summary2003.pdf

(Special Supplemental Nutrition Program for Women, Infants, and Children);

- **dietary exposures among children at schools and day cares (perhaps through the USDA's School Lunch and/or Head-Start programs); and**
- **effects of dietary and nondietary exposures of pesticide on children's cognitive functions and performance.**

With respect to the first bullet, while the OIG report presents no analysis or discussion of this issue in the main body of its text, EPA agrees that understanding longitudinal dietary consumption is important. OPP believes our actions have fully addressed this recommendation. We have communicated our interest in longitudinal consumption information to DHHS. However, due to cost and various logistical considerations, they (i.e., the designers of the NHANES study) are not able to provide dietary recall information for more than two (2) days. We understand and agree with that position; we do not think it is realistic to extend the number of days of consumer reporting.

See OIG Comment in Appendix D, Note 16

OPP currently relies on the USDA's Continuing Survey of Food Intakes by Individuals (CSFII). This survey is being replaced by DHHS's National Health and Nutritional Examination Survey (NHANES) which is its successor survey. Both surveys are large, complex, multi-stage cross-sectional surveys of 2-day consumption patterns and are designed to be representative of the U.S. population. These surveys serve a variety of interests and customers of which EPA is only one of many.

As noted in our response to Recommendation 4-2, we agree that understanding longitudinal patterns in food consumption is important. To that end, here are some current activities that we have participated in with USDA and DHHS:

- EPA has made attempts to statistically simulate this data in its dietary exposure assessments in as realistic a manner as possible. In addition, a variety of software developers (DEEM, CARES, and LifeLine) have incorporated longitudinal consumption patterns into their software. This, however, is not based on actual longitudinal consumption data, but rather on statistical "matching" and other criteria which attempt to simulate, on an individual-by-individual basis, consumption patterns over the long term (e.g., seasonal or yearly). This methodology has been presented to the SAP for two of the models (CARES and LifeLine). OPP is beginning to incorporate this information into its risk assessments.

See OIG Comment in Appendix D, Note 16

  → In particular, EPA's Office of Research and Development (ORD) is attempting to gather longitudinal data on eating and activity patterns through its STAR (Science to Achieve Results) grant program and OPP has been closely involved in these activities. OPP has participated extensively on the ORD review panels which recommend funding priorities for these kinds of studies. For example, OPP was actively involved in the review of proposals

See OIG Comment in Appendix D, Note 19

for ORD's STAR grant project entitled "Aggregate Exposure Assessment for Pesticides: Longitudinal Case Studies." These grants were awarded several years ago and amounted to several million dollars. These grants funded a variety of innovative small-scale pilot studies collecting (many times simultaneously for the same individual) information on both food consumption and physical activity. Many novel methodologies for collecting this information were proposed which were designed to minimize study participant effort and tedium. These methodologies hold promise for the future.

- We note that we have pursued alternate routes toward obtaining or incorporating this information into our risk assessments. One approach is through the ORD STAR grant program which recently award grants for specifically looking at longitudinal patterns of exposure. Specifically, EPA's ORD sought grant proposals that described studies for assessing pesticide exposure that incorporate estimates of temporal and inter-individual variability and attempt to effectively include and address many exposure issues using longitudinal studies. These are naturally long-term studies and OPP will remain involved and looks forward to receiving this data when it becomes available.

See OIG Comment in Appendix D, Note 19

- ORD is exploring the possibility of working with other Federal partners to collect longitudinal food consumption data. In September, 2005, NERL sponsored "EPA's Workshop on Analysis of Children's Measurements Data" that included discussions of the major sources of children's exposures to pesticides, and approaches to analyze existing data. Information from this workshop may be used in future discussions with other agencies.

- Additional work on the issue of longitudinal consumption is being performed by the National Cancer Institute (NCI) and others who are attempting to merge two types of data to develop better estimates of long-term consumption. Specifically, they are combining 24-hour dietary recall information (e.g., "What did you eat today?") with food frequency information (e.g., "How many times in the last 90 days did you consume peas?"). By merging these two kinds of data sets, it should be possible to develop better estimates of long-term dietary consumption on an individual-by-individual basis.

See OIG Comment in Appendix D, Note 16

EPA will remain active in its pursuit of data to support longitudinal consumption estimates. However, as discussed in our response to Recommendation 4-2, we recognize that obtaining actual, longitudinal consumption data from a large, representative survey is an extremely costly undertaking for which there are inadequate funds and insufficient widespread or general interest. EPA will work with ORD, various software vendors, and others to make the best and most cost-effective use of available data and most appropriate use of appropriate simulation methods.

With regards to the second bullet in this recommendation (collecting data on pesticide concentrations in human breast milk among lactating women), OPP acknowledges that for certain chemicals – particularly stable, highly lipophilic chemicals (i.e., persistent

bioaccumulative and toxic chemicals) like the organochlorine pesticides – with specific physical-chemical characteristics, availability of exposure information from breast milk provides additional characterization of the dietary exposure to nursing infants. Fortunately, the vast majority of currently approved pesticide chemicals do not exhibit these physical chemical characteristics, and are not expected to be found in significant amounts in human breast milk, and EPA has breast milk data for most or all of the chemicals that have such characteristics. In the event that OPP identifies a chemical for which it thought breast milk might be a significant source of exposure, but for which it lacked adequate data, OPP could address the situation using the FQPA Children's Safety Factor provision that directs EPA to retain an additional 10X margin of safety when it has uncertainty about the exposures experienced by infants or children.

See OIG Comment in Appendix D, Note 20

OPP is not opposed to working with USDA and DHHS to collect data on pesticide residues in human breast milk but overall, OPP does not believe this should be a high priority item for the majority of pesticide chemicals as discussed below. In most cases it would be more valuable to have monitoring data on infant's and children's foods which are directly treated with pesticide, and therefore have a higher potential to lead to infant's and children's exposure (e.g., apples/apple sauce/apple juice). (Also, because animal feeds frequently have significantly higher residues than human foods, residues in cow's milk would be expected to be greater than those in human breast milk. In these cases, risks associated with cow's milk consumption would likely be greater than risks associated with breast milk consumption, and could be captured in infant's risks assessments.)

See OIG Comment in Appendix D, Note 20

Finally, OPP notes that collection and analysis of useful breast milk biomonitoring is very complicated. Care must be taken in choosing the population to be sampled, the pesticide chemicals to be monitored, and in developing other aspects of the sampling protocol. For example, since the composition of human milk changes within a feeding, over the course of a day, and over the course of lactation, the exact timing and method of sampling can influence measured levels. Quantitative use of these data in a risk assessment will also be complicated by these factors.

See OIG Comment in Appendix D, Note 21

With regards to the third bullet in this recommendation (collecting data on dietary exposures among children at schools and day cares), the current CSFII and NHANES dietary survey collection methodology considers and includes food consumption at schools and daycare centers. Consumption amounts and items are already included in the CSFII and NHANES surveys.

See OIG Comment in Appendix D, Note 22

With regards to the fourth bullet in this recommendation (effects of dietary and non-dietary exposures of pesticide on children's cognitive functions and performance), OPP has worked, and will continue to work, closely with USDA on a number of dietary exposure issues relevant to children's food consumption (see our responses to Recommendations 4-2, 4-3, and the first three bullets for 4-4).

In addition, children's non-dietary exposures to pesticides have been a focus of an intense ORD research effort (http://www.epa.gov/heasdweb/children/children.htm). It is not clear to us whether the USDA or DHHS has any research/activities in this area, but we would be happy to collaborate if such opportunities were made available.

See OIG Comment in Appendix D, Notes 14 and 16

Finally, the effects of pesticide exposure (dietary or non-dietary) on children's cognitive functions and performance is an important area that EPA, along with NIH from DHHS, strongly support and should be addressed in the development of the National Children's Study (cited as footnote 8 on page 14 of the OIG draft report). This study is designed to follow the lives of 100,000 children from gestation through 21 years of age to examine the effects of physical, chemical, biological, and psychosocial environmental influences on health and development. Although the OIG draft report notes that the long-term support for this longitudinal study is "under debate", six study centers were chosen and recently awarded contracts on September 29, 2005 to begin work on this important project (http://www.nationalchildrensstudy.gov/). In addition, the EPA/NIEHS children's research centers at UC Berkeley and University of Washington are conducting epidemiologic studies comparing aggregate pesticide exposures with neurobehavioral and cognitive development in birth cohorts living in agricultural communities in the Salinas (CA) and Yakima (WA) valleys.

Other Comments for Chapter 4

Page 12, paragraph 1, lines 3-5 (2nd sentence)

OPP suggests that the sentence be revised to read as follows: "Aggregate risk assessments, which are required by FQPA, specify that all routes and pathways of exposure for a given pesticide be considered when assessing risk."

Page 12, paragraph 1, lines 9-11 (last sentence)

OPP suggests that the sentence be revised to read as follows: "Without sufficient information to perform highly refined and meaningful aggregate risk assessment, there will be uncertainty…."

Page 12, lines 13-14 (2nd paragraph, 2nd sentence)

OPP suggests that the sentence be revised to read as follows: "Besides updating its pesticide testing guideline to improve and expand animal study data on reproductive and developmental effects, EPA developed methods…."

Page 13, line 6 in paragraph starting with "Children engage...."

OPP suggests that any and all citation(s) supporting the statement "Literature indicates…" should be included in the text or as a footnote.

Page 13, bullets on missing elements and research needs

This text should acknowledge that all of these identified needs are the subject of on-going collaborative research efforts by ORD.

Page 15, 3rd paragraph, line 3 (paragraph starting with "In 2002, Gerber Products….")

OPP suggests that the sentence be revised to read as follows: "This is the most comprehensive, largest, and nationally representative study on food consumption for this age group,…"

VI. Chapter 5 – OPP Moving to Assess Cumulative Risk but Complexities and Concerns Remain

<u>Recommendation 5-1</u>: Coordinate efforts with ORD to finalize the integration of probabilistic modeling outputs with physiologically based pharmacokinetic modeling to better address cumulative risk from concurrent exposure to pesticides and other chemicals with like mechanisms of action.

OPP believes that its past and continuing actions fully address this recommendation. Chapter 5 of the OIG draft recognizes that ORD has begun discussions of linking two of their models. One of these models, ERDEM (Exposure Related Dose Estimated Model), is a physiologically-based pharmacokinetic (PBPK) model. The other model, SHEDS (Stochastic Human Exposure and Dose Simulation), is a probabilistic exposure model. OPP acknowledges that PBPK models are powerful risk assessment tools that can incorporate the dynamic nature of environmental exposure, internal dose, toxic effect, and recovery. OPP and ORD have been collaborating for several years on many efforts to develop PBPK models for a variety of chemicals (e.g., carbaryl, malathion, and pyrethroids). Furthermore, OPP will continue to encourage efforts to link probabilistic exposure models with PBPK models. The OIG draft report does not recognize these additional on-going efforts by EPA to link probabilistic exposure models with PBPK models. For example, the LifeLine Group, under contract with OPP, developed a white paper entitled "Designing Exposure Models that Support PBPK/PBPD Models of Cumulative Risk" which was reviewed by the FIFRA Scientific Advisory Panel (SAP) in December 2004. This paper highlights issues regarding linkage between probabilistic exposure models and PBPK models. The FIFRA SAP's report can be found at http://www.epa.gov/scipoly/sap/index.html.

See OIG Comment in Appendix D, Note 23

In addition, with funding from an EPA STAR grant, the University of Washington is conducting a concordance analysis of probabilistic aggregate exposure assessment and biomarkers of exposure. The overall objectives of this study are to examine the accuracy of current pesticide exposure assessment models, and to demonstrate a novel method for the development and evaluation of such models. Researchers have proposed to conduct second order probabilistic assessments of aggregate pesticide exposures in three existing data sets, characterize the variability of biological exposure measures, and evaluate the concordance of these two exposure assessment approaches. This novel analytical approach will produce new methods for determining the validity of exposure and risk estimates.

See OIG Comment in Appendix D, Note 19

With funding from an EPA STAR grant, researchers at Battelle are developing a physiologically based pharmacokinetic/ pharmacodynamic (PBPK/PD) model to quantitate biomarkers of exposure to organophosphate pesticides. The project entails development and validation of a PBPK/PD model for chlorpyrifos to quantitate biomarkers of dosimetry and pharmacodynamic (PD) response (i.e., acetylcholinesterase (AChE) inhibition) in young rats and children.

Recommendation 5-2: Develop specific plans on how computational toxicology outputs from ORD's Computational Toxicology Program will integrate into OPP's regulatory process, and implement such a transformation.

OPP agrees with this recommendation and believes its past and continuing activities fully address this recommendation. A strategic plan for developing and implementing advances in computational toxicology research in the context of pesticide and industrial chemical regulatory frameworks was developed and endorsed by OPPTS and ORD Office and Laboratory/Center Directors in 2004. This strategic plan for developing an integrative, or intelligent, risk assessment paradigm complements related efforts by the National Academy of Sciences (NAS), the European Union (EU), and the Organization for Economic Co-operation and Development (OECD). The strategic view considers the development of ORD products with the associated implementation of new OPPTS risk assessment methods as part of the current Agency goals, programs and planning processes. The plan outlines includes activities and outcomes in the short- to long-term. OPP has already begun collaborations with ORD's National Center for Computational Toxicology (ORD-NCCT) to improve risk assessment methodologies. For example, the dose-response modeling used in the Preliminary Cumulative Risk Assessment for the N-methyl carbamate pesticides (August, 2005) was performed by the NCCT. This work was reviewed by the FIFRA Scientific Advisory Panel (SAP) in August, 2005. OPP and ORD, including NCCT, continue to work collaboratively to develop research plans to develop and apply new technologies which will meet the needs of the regulatory program. OPP notes that the outputs of the Computational Toxicology Program will likely apply not only to cumulative risk assessment (the topic of Chapter 5) but also single chemical assessments.

Other Comments for Chapter 5

Page 19, paragraph 1, line 4 (paragraph beginning with "Research confirms the need…")

OPP requests clarification on what the following phrase means: "…below pesticide poisoning health effects." Is this intended to refer to "low-dose effects"?

Page 20, paragraph 1, lines 7-10 (sentence beginning with "For EPA scientists to use…")

We do not believe that this is a sentence. OPP suggests revisions to the sentence: "For EPA scientists to use the data and products from the Computational Toxicology Program, interdisciplinary backgrounds in such areas as biostatistics, molecular biology, metabolism, systems biology, computational chemistry, toxicology, and bioinformatics will be required."

VII. Chapter 6 – Opportunities Exist to Better Manage FQPA Implementation

<u>Recommendation 6-1</u>: Either finalize all of the Science Policy issue papers, or change the word "draft" to "operational" and schedule annual updates.

OPP generally agrees with this recommendation. However, OPP notes that the OIG report fails to recognize the extent of OPP's progress in completing science policy papers, contains a number of errors, and contains no explanation for its recommendation. Moreover, the report does not analyze the impact of leaving the documents in "draft" form or the priority that EPA should give to finalizing the documents.

The draft OIG report recommends that EPA finalize the "FQPA science policy papers" that were only issued in "draft" form and never revised. Although the OIG indicates there are twelve (12) papers, in fact there are only nine such papers. The OIG report purports to identify in Figure 6.1 twelve (12) science policy papers that "are still in draft format," based on "EPA's website as of August 2005." It neglects to say OPP finalized 16 major science policies. While Figure 6.1 correctly identifies six science policy papers never issued in "revised" form, Figure 6.1 mischaracterizes the status of others:

See OIG Comment in Appendix D, Note 24

- It lists as "draft" two papers that were revised: "User's Guide to Available EPA Information on Assessing Dietary (Food) Exposure to Pesticides" and "Science Policy 5: Estimating the Drinking Water Component of a Dietary Exposure Assessment."

- It lists two papers twice, giving the impression there are four "draft" papers when there are only two: "Standard Operating Procedures (SOPs) for Residential Exposure Assessment" and "Framework for Assessing Non-occupational / Non-dietary (Residential) Exposure to Pesticides."

- It lists two documents that are not FQPA Science Policies: "Draft Toxicology Data Requirements for Assessing Risks of Pesticide Exposure to Children's Health" and "Draft Exposure Data Requirements for Assessing Risks of Pesticide Exposure to Children's Health." These two documents are actually appendices to a revised science policy document titled "Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment." OPP will update its website to make the status of these two papers clearer.

The OIG report fails to list three papers that EPA has issued only in "draft" form: "Standard Operating Procedures (SOPs) for Use of the FQPA Factor"; "Use of the Pesticide Data Program (PDP) in Acute Dietary Assessments"; and "Water Treatment Effects on Pesticide Removal and Transformation."

Changing Figure 6.1 to correct these errors would result in the listing of nine science policy papers that OPP has issued in draft form but never finalized. See the Table below.

OPP generally agrees with the recommendation and intends to finalize some, but not all, of the science policy papers that remain in "draft" form. See the Table below. OPP, however, does not regard these actions as a high priority because:

See OIG Comment in Appendix D, Note 24

- OPP is subject to statutory and court-ordered deadlines to complete regulatory decision-making that will require significant resources, leaving limited resources to address this activity; and

- External stakeholders have not asked OPP to finalize these science policy papers.

OPP Science Policy Papers that have not been issued in revised form	**Proposed OPP Action**
1. "Standard Operating Procedures (SOPs) for Residential Exposure Assessment"	OPP is planning to finalize this paper.
2. "Application of the 10X Safety Factor in Cumulative Risk Assessment"	OPP is planning to finalize this paper.
3. "Framework for Assessing Non-occupational / Non-dietary (Residential) Exposure to Pesticides"	OPP is planning to finalize this paper.
4. "Drinking Water Screening Level Assessment"	OPP is planning to issue a Federal Register Notice announcing that it has withdrawn this paper because it refers to a method of estimating potential drinking water exposure that OPP no longer uses.
5. "Standard Operating Procedure for Incorporating Screening-Level Estimates of Drinking Water Exposure in Aggregate Risk Assessments"	OPP is planning to issue a Federal Register Notice announcing that it has withdrawn this paper because it refers to a method of estimating potential drinking water exposure that OPP no longer uses.
6. "Guidance for the Submission of Probabilistic Human Health Exposure Assessments to the Office of Pesticide Programs"	OPP is planning to issue a Federal Register Notice announcing that it has withdrawn this paper because the guidance is generic, has been superseded by a number of more specific policy documents, and is adequately covered in other finalized Agency documents.
7. "Standard Operating Procedures (SOPs) for Use of the FQPA Factor"	OPP is planning to finalize this paper.
8. "Use of the Pesticide Data Program (PDP) in Acute Dietary Assessments"	OPP is planning to issue a Federal Register Notice announcing that it has withdrawn this paper because the paper refers to a method of estimating potential exposure through food that OPP no longer uses. OPP will review additional data to determine whether it needs to issue a new science policy paper to explain its general approach in this area.
9. "Water Treatment Effects on Pesticide Removal and Transformation."	OPP is planning to finalize this paper.

Recommendation 6-2: Sustain the development of an alternative testing strategy, ensuring that risks are assessed across the entire life cycle of development.

OPP agrees with this recommendation. OPP scientists, together with other EPA colleagues, have engaged in a number of activities on different fronts to improve the toxicology testing paradigm for environmental chemicals, including pesticides. First, EPA conducted a review and published a Risk Assessment Forum report in 2000 on the current reference dose and reference concentration (RfD/RfC) processes, in particular with respect to how well children and other potentially susceptible subpopulations are protected. One of the objectives of this EPA activity was to consider new scientific issues that have become more important and of greater concern in risk assessment, and to raise issues that should be explored or developed further for application in the RfD/RfC process.

Second, OPP scientists participated in an effort sponsored by the International Life Sciences Institute (ILSI)/Health Environmental Sciences Institute (HESI) to design a better testing paradigm for pesticide chemicals. This ILSI effort examined whether: 1) life-stages (i.e., infancy, pre-adolescence, adolescence, reproductive stage, post-reproductive stage, elderly) are adequately assessed by the current battery of studies; 2) scientific evidence exists that certain life-stages may be comparatively more susceptible to the effects of exogenous chemicals; 3) altered susceptibility in a life-stage is general or specific. The goal of this analysis is to identify a hierarchy of study types, endpoints and triggers that might be used in a decision tree to guide appropriate testing to determine the safety of a pesticide. This new testing proposal will be published by early 2006.

Lastly, EPA sponsored a National Academy of Sciences (NAS) study to review evolving regulatory needs, current toxicity testing guidelines, emerging science and new tools (e.g., -omics, transgenics, bioinformatics, computational toxicology, in vitro testing, alternatives to animal testing) and develop a strategy that incorporates more complex information (e.g., toxicokinetics, mechanisms of action, systems biology) into improving human health risk assessment. The NAS report is anticipated 2007. OPP will consider all of these activities, as well as its own computational toxicology program, as it moves forward in developing a hypothesis driven paradigm that uses resources more efficiently and improves the assessment of human health.

Recommendation 6-3: Develop an overarching logic model and long-term strategic plan across divisions to identify and link immediate work outputs to outcomes.

The recommendation that OPP use logic model (e.g., the logic model provided in the draft OIG report) to guide efforts is a good idea and in reviewing this section, we interpret that the OIG is trying to connect "opportunities to improve data quality" data with performance accountability. The draft report appears to suggest is that it could be beneficial to develop strong performance measures that would "pass muster" in an Office of Management and Budget (OMB) Program Assessment Rating Tool (PART) review. Developing such a logic model could aid in the development of a strategic plan.

Other Comments for Chapter 6

Page 23, "Logic Models…" section, paragraph 1, last sentence

OPP suggests the following revision: "Significantly, a logic model distinguishes between outputs (the specific tasks performed) and outcomes (the actual results)."

OPP's comments for the Appendices

Appendix C: Toxicity Testing Issues

Page 29, Table of developmental tests for effects on offspring

The table states that offspring are not evaluated in the developmental guideline. This is incorrect; the test is focused on fetal development. While it is true that there are no post-natal tests and no functional tests in this guideline, the fetus evaluation is an evaluation of the offspring.

See OIG Comment in Appendix D, Note 25

Page 30, first paragraph, line 4

Behavior and functional tests are sensitive…….

Page 30, last paragraph

OPP believes that the discussion is too specific and thus out of place in a discussion of general toxicity testing requirements.

Page 33

OPP recommends that the OIG consider the relevance of the ERDEM (Exposure Related Dose Estimating Model).

OIG's Comments on Agency's Response

1. We disagree with the Agency's statements that our report is "uneven" and "sometimes misleading." We conducted this review to examine the impact of the Food Quality Protection Act of 1996 on the Agency's need for scientific data and predictive tools, particularly in relation to children's health. As an independent office within EPA, we presented information based on facts uncovered and evidence found. In helping the Agency identify where it needs more and better scientific data and tools in its implementation of FQPA, we have strived to serve as a catalyst for protecting children's health, improving the environment, and increasing the Agency's accountability.

   Additionally, we disagree with the Agency's statements about this report "glossing over significant scientific accomplishments of the past nine years." In this report, we have outlined the Agency's major scientific accomplishments since 1996. For example, we have discussed how the Agency made substantial changes to the aggregate exposure risk assessment process, eliminated usage of some pesticides like chlorpyrifos and diazinon, and initiated steps to perform cumulative risk assessments for pesticides. We have described the contributions of ORD in assuring that the Agency meets the scientific challenges posed by FQPA. We have highlighted in our logic model a list of OPP's and ORD's scientific activities and outputs. Finally, we have mentioned how OPP worked with ORD, external scientific organizations, and its Federal partners to acquire more and better data on children's exposure to pesticides.

2. We disagree with the Agency's statement that this "report tends to focus on issues that 1) are minor and relatively insignificant within the overall scope of FQPA implementation, 2) characterized incorrectly, or 3) outside the control of the Agency." The findings we have presented in this report are based on facts and evidence we have uncovered during our review. We agree with the Agency that EPA depends on others for much of the data it uses in risk assessments. However, it is our opinion that the Agency has the responsibility to identify and make known the quantity and quality of data needed for its risk assessments.

   In the next few paragraphs we have outlined why issues like acquiring developmental neurotoxicity and additional exposure data are important. We have also discussed how these issues are neither minor nor insignificant within the overall scope of FQPA implementation.

   - *Acquiring developmental neurotoxicity test data is neither a minor nor insignificant issue:* Prediction of neurotoxic effects is a key feature in the toxicological profile of chemicals. It is our opinion that the Agency may be vulnerable to legal challenges to the 10X additional FQPA safety factor if it does not consistently require developmental neurotoxicity testing of chemicals. Congress acknowledged that protecting the developing nervous system from toxic insult is important[27] when it unanimously passed

[27] 21 U.S.C. §346a (b)(2)(C)(i)(II)

FQPA. We believe it was not a minor or insignificant issue when the Agency had to eliminate the manufacturing of chlorpyrifos for nearly all residential usage. The driving force behind this change in regulatory policy was the recognition that chlorpyrifos exerts untoward effects on the developing nervous system.[28] Scientists and public health researchers[29] have further confirmed that this pesticide interferes with brain development and children's growth. The lessons learned from chlorpryifos are that the developing brain is highly vulnerable and that a common pesticide can interfere with a child's brain development.[30]

We believe EPA has the responsibility to guide the development of alternative developmental neurotoxicity testing protocols which yield cost-effective, efficient data for pesticide regulation and children's health decisions. Beyond having optimal, cost-effective testing of developmental neurotoxicity for chemicals, we believe EPA can demonstrate its commitment to protecting children by ensuring that such data are collected across life stages beginning at critical windows of development (e.g., pre-natal).

- *Acquiring more and better dietary and nondietary exposure data for use in its risk assessments is an EPA responsibility*: We recognize the Agency depends on its Federal partners for national dietary exposure data. We also recognize that resource limitations constrain the Agency's research efforts in measuring residual and dietary consumption patterns. We acknowledge the problem of managing pesticide residue in food lies within a much larger food safety monitoring arena in which EPA is a minor player. However, in the area of dietary pesticide exposure data, we believe the Agency has a major responsibility because it sets the tolerances and registers the pesticide chemical use on food. Likewise, for nondietary pesticide exposure, because EPA registers the pesticide chemicals use in homes, schools, public areas, and gardens, it has the responsibility to acquire residential and nonoccupational pesticide exposure data. Thus, it is our opinion that EPA should assess the scale of monitoring required to know and manage the mixture of pesticides dispersed into our food and water supplies and our environment.

3. Our review focused on existing data and interviews. During our evaluation, we conducted a literature review on FQPA and the potential health outcomes of prenatal and childhood exposures to pesticides. We reviewed documents pertinent to risk assessment prepared by

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[28] Slotkin, TA. 1999. Developmental Cholinotoxicants: Nicotine and Chlorpyrifos. *Environmental Health Perspective* 107 (suppl 1), 71-80. Slotkin, TA. 2004b. Cholinergic Systems in Brain Development and Disruption by Neurotoxicants: Nicotine, Environmental Tobacco Smoke, Organophosphates. *Toxicology and Applied Pharmacology* 198, 132-151.

[29] Needham, LL. 2005. Assessing Exposure to Organophosphorus Pesticides by Biomonitoring in Epidemiologic Studies of Birth Outcomes. *Environmental Health Perspective* 113:494-498. Berkowitz, GS et al. 2004. In Utero Pesticide Exposure, Maternal Paraoxonase Activity, and Head Circumference. *Environmental Health Perspective* 112:388-391. Eskenazi, B et al. 2004 Association of in Utero Organophopshate Pesticide Exposure and Fetal Growth and Length of Gestation in an Agricultural Population. *Environmental Health Perspective* 112:116-1124. Whyatt, RM et al. 2004. Prenatal Insecticide Exposures and Birth Weight and Length among an Urban Minority Cohort. *Environmental Health Perspective* 112:1125-1132.

[30] Slotkin, TA. 2006. Developmental Neurotoxicity of Organophosphates: A Case Study of Chlorpyrifos. In: Toxicity of Organophosphate and Carbamate Pesticides. RC Gupta, Elsevier: in press. Colborn, T. Online 7 September 2005. A Case for Revisiting the Safety of Pesticides: A Closer Look at Neurodevelopment. *Environmental Health Perspectives*, available at http://dx.doi.org.

EPA and other Federal agencies. We examined dietary assessment methods and examined food consumption databases, pesticide residue data sources, and probabilistic models to better understand how such data integrate in risk assessments performed by OPP. We reviewed the annual work plans prepared by OPP and the multi-year research plans by ORD. Furthermore, we interviewed current and past administrators, science policy directors, scientists, and risk assessors from EPA offices, as well as experts from other Federal agencies and outside organizations, to capture expert viewpoints, clarify our interpretations, and confirm our findings.

Based on our field work, examples of the types of data gaps we have uncovered include:

- The Agency has not published a summary of its findings from the developmental neurotoxicity data submitted after the 1999 Data Call-ins.
- The Agency needs alternative developmental neurotoxicity testing models that are targeted, efficient, and cost-effective.
- The Agency requires no developmental immunotoxicity testing data on food-use pesticides.
- The Agency has no review of existing pesticide residual data from the Food and Drug Administration, U.S. Department of Agriculture, and State residue monitoring programs in terms of their reliability in describing the exposure of fetuses, infants, and other children to potentially toxic pesticides. Also, it has no public, user-friendly national residue database derived from data collected by these governmental partners.
- The Agency lacks protocols for generating exposure data.
- Data on non-dietary routes of exposure to pesticides are limited; missing data includes exposure through pesticide use in homes and schools, as well as pesticide levels in air, soil, surface water, or rainwater.
- The Agency needs additional scientific tools and data to provide an understanding of the most important pathway(s) of exposure for young children.
- The Agency needs data on fate-and-transport and approaches for determining and verifying the exposure factor.
- The Agency requires no data on pharmacokinetics or pharmacodynamics of pesticides in developing animals, and its risk assessments include no such information.
- The Agency has not required chemicals to undergo endocrine disruption screening and has little data on a pesticide's potential to disrupt the endocrine (hormonal) system. However, EPA has a planned Endocrine Disruptor Screening Program in a validation phase.
- The Agency requires no testing and has little test data to assess the interactive effects of multiple chemicals or of chronic low-dose multiple chemicals.

We maintain our position that more scientific tools and better data are still needed to help the Agency meet its regulatory challenges posed by FQPA.

4. We recognize the legal and sensitive nature of using terminology specific to the Agency's science policy language. We have considered the Agency suggestions for technical or editorial changes and made minor editorial changes throughout the report to minimize

confusion for the Agency and our stakeholders. In the case of the Agency's comment on the usage of the term "toxic effect" versus "common mechanism of toxicity," we substituted the existing sentence with two new sentences to provide clearer discussion on that subject matter. Likewise, we edited Table 2.1 for the purpose of clarity.

5. We acknowledge that the Agency's suggestion of quoting FQPA statutory language would be beneficial. However, we reject the Agency's view that our statement is incorrect. FQPA charges the Agency to employ a new standard for establishing pesticide tolerances and articulates a strong policy of protecting infants and children from *reproductive and developmental hazards*. In establishing tolerances, EPA must assess risks to infants and children on the basis of available information concerning consumption patterns among infants and children, special susceptibility of infants and children, and cumulative effects of exposures to infants and children.[31] More importantly, "in the case of threshold effects," the Act specifies that the Agency must apply an additional "*ten-fold margin of safety*" to take into account "***potential pre- and postnatal toxicity*** and ***completeness of the data with respect to exposure and toxicity to infants and children***."[32] The Agency may use a different additional margin of safety, but "only if, on the basis of reliable data, such margin will be safe for infants and children."[33]

6. We believe expediting the completion of any remaining work from the developmental neurotoxicity studies since the 1999 Data Call-ins is a demonstration of accountability. Our opinion is that the Agency owes stakeholders a written summary of the findings and conclusions from the developmental neurotoxicity data submitted by the manufacturers after the 1999 Data Call-ins.

7. We did not elaborate on the details of the alternative developmental neurotoxicity testing methods in the draft report. However, during our field work we discussed alternative developmental neurotoxicity testing methods with OPP and ORD representatives. ORD scientists have mentioned their efforts in developing a high throughput screening battery focused on detecting chemicals likely to be developmentally neurotoxic. Also, we have suggested to OPP staff present at our exit briefing to consider usage of cell culture, invertebrate, or non-mammalian models for primary testing prior to more targeted examinations of developmental neurotoxicity. We have referred them to the research at Duke University and one specific manuscript[34] which contained suggestions for alternative models with high throughput (e.g., rat embryo cultures, neurotypic and gliotypic cells, zebrafish embryos, and/or sea urchin embryos). In this final report, we have expanded our discussion and provided references suggesting possible strategies. We encourage OPP to review the references we have passed along and consider Recommendation 3-2.

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[31] 21 U.S.C. §346a (b)(2)(C) (1994 & Supp. IV 1988).

[32] 21 U.S.C. §346a (b)(2)(C)(ii)(II) (emphasis added) and as reference on page A-1 in EPA's Science Policy paper, *Determination of the Appropriate FQPA Safety Factor(S) in Tolerance Assessment,* OPP, USEPA,Washington, DC, February 28, 2002.

[33] *Id*.

[34] Slotkin, TA. 2004. Guidelines for Developmental Neurotoxicity and Their Impact on Organophosphate Pesticides: a Personal View from an Academic Perspective. *Neurotoxicology* 25, 631-640.

8. We believe when the Agency engages its staff in learning events like the TestSmart Developmental Neurotoxicity Test symposium sponsored by the Johns Hopkins University and its partners, it demonstrates commitment to children's health and continuous regulatory performance improvements.

9. The Agency commented that it is addressing the evaluation of sensitive and meaningful indicators as part of the Standard Evaluation Procedure for Developmental Neurotoxicity tests. We have modified Recommendation 3-1 to include information on sensitive and meaningful developmental neurotoxicity indicators and deleted the issue as a stand-alone recommendation.

   Our recommendation suggests the Agency evaluate "which indicator, ***or combination of indicators***, is most sensitive and meaningful for assessing developmental neurotoxicity consequences of exposure during critical windows of development." Hence, we are not in disagreement that a single, most sensitive parameter might be unlikely for assessing developmental neurotoxicity consequences. Risk assessment of a developmental toxicant requires careful consideration of the end point of toxicity, the dose-response relationship, and the relevance of the animal model to humans. Improvements in analytical laboratory equipment and testing procedures have made it easier to detect pesticides and their metabolites (breakdown products) at very low concentrations in animal and almost all human tissue. However, some of the endpoints used in the laboratory to detect functional impairment of the brain and nervous system are measured at the biochemical, gene, cell, and physiological levels, requiring high tech instrumentation to quantify. Emerging fields, such as medical imaging, nanotechnology, and sensor technology are beginning to generate insight on effects of pesticide exposure on brain cell damage.[35] We encourage the Agency follow the findings in these areas of research.

10. We disagree with the Agency that it ensures developmental neurotoxicity tests are conducted on developing animals in addition to young adult animals. First, the Agency only "conditionally required" developmental neurotoxicity tests; the trigger for nervous system toxicity testing hinges on results from other, less specific, toxicological testing that generally does not involve the nervous system. Second, the current developmental neurotoxicity tests do not assess toxicant-induced alterations in the developing nervous system of fetuses and the embryos.

    The current developmental neurotoxicity test guideline *suggests* neuropathology with morphometry of several brain regions *on postnatal* day 11 and at termination of study, observation of offspring for motor activity "*on postnatal* days 13, 17, 21, and 60 (±2 days)," auditory startle response habituation and pre-pulse inhibition, and "a test of associative learning and memory" "conducted around the time of weaning and around day 60." However, morphologic and histopathologic assessment of toxicant-induced alterations in the developing nervous system for human health risk assessment requires an understanding of corresponding timeframes for the critical events in nervous system development of the rat and human. Additionally, such morphologic and histopathologic assessments require careful

[35] Research Advisory Committee on Gulf War Veterans' Illnesses. September, 2004 Scientific Progress in Understanding Gulf War Veterans' Illnesses: Report and Recommendations.

qualitative and quantitative evaluations, including such basic methods as determination of brain weight and dimensions as well as the more complex approaches of linear, areal, or stereologic measurements of brain sections.

11. We fear the loss of public confidence in EPA's commitment to protect infants and children from developmental hazards when the Agency allows 6 years to elapse before it revises the developmental neurotoxicity test guideline. However, we confirm that in 1999, when EPA issued a Data Call-In for neurotoxicity testing of a list of organophosphate insecticides, the exposure period was extended from gestation day 6 through post-natal day 10 to gestation day 6 through post-natal day 21.

12. We do not disagree that EPA has an adult immunotoxicity testing guideline and proposed in March 2005 that immunotoxicity testing be required for pesticide registration. However, as the Agency states, it currently has no requirement for immunotoxicity testing in adult or developing animals. Furthermore, it has not developed a developmental immunotoxicity testing guideline in the 9 years since FQPA was passed. Unlike adults, a child's immune system is a protective mechanism still in development. Pesticides may interfere with the maturation of immune cells during childhood and cause abnormal development of the immune system. Abnormalities of the immune system could potentially lead to allergies, asthma, and autoimmune disease or increased susceptibility to infections. We encourage the Agency to expedite the completion of a developmental immunotoxicity testing guideline.

13. In its own response the Agency stated, "OPP realized that the rule should describe the DNT [developmental neurotoxicity test] study as 'conditionally required' to reflect **the limited conditions when the data requirement would be imposed**." Our concern is with "**the limited conditions"** under which such data would be required. While it is true that "neither the substance nor the scope of the proposed DNT [developmental neurotoxicity test] required was altered," the Agency changed the condition under which it requires developmental neurotoxicity testing. As stated previously, by labeling the developmental neurotoxicity testing as "conditionally required," the Agency is in fact saying it will only recommend this kind of testing after certain conditions (triggers) have been met. Non-EPA scientists have criticized the Agency for using triggers that are inadequate or not enforced. Also, a former EPA neurotoxicologist had been cited[36] to point out that the triggers for recommending a developmental neurotoxicity study in some cases depend on information best obtained from the developmental neurotoxicity study itself. It is our opinion that the Agency takes seriously the lessons learned from chlorpyrifos and accepts the weight of scientific evidence that points to how exposure to common pesticides can damage the developing brain.

14. We disagree with the Agency that Recommendation 4-1 is premature. However, we have modified the recommendation to ensure that the Agency updates its food consumption data in 2006 when USDA and DHHS release the 2003 and 2004 food intake survey data sets. We believe that after the 1998 children's consumption survey activity, the Agency neglected to communicate to its Federal partners OPP's continuous need for children-specific consumption data. We agree that OPP's and ORD's expertise is not in dietary assessment

[36] Schettler, T et al. January 2001. "In Harm's Way: Toxic Threats to Child Development" *Greater Boston Physicians for Social Responsibility/Clean Water Fund, page 111*.

methodology. We also recognize that Agency depends on its Federal partners for national dietary exposure data and that the National Health and Nutrition Examination Survey used different interview systems/methodologies between the 1999-2000/2001 data and the 2002 data. For these reasons, we organized a meeting during our field work for Agency representatives to meet with dietary assessment methodology experts from USDA's Agricultural Research Service. We invited the Agricultural Research Service National Program Research Leader for Human Nutrition and her staff to this meeting. In their presentations, these scientists discussed the Agricultural Research Service's role in developing the dietary methodologies used in the National Health and Nutrition Examination Survey and in handling the analysis of the survey's dietary data. Our hope was that the Agency officials would seize this opportunity to dialogue about it needs to utilize the various years of the survey when methodologies are different and to communicate its need to link consumption, commodity, and pesticide residual data more efficiently. We encourage the Agency to communicate with the dietary methodology experts at the Agricultural Research Service about the feasibility of using the dietary consumption data from the National Health and Nutrition Examination Survey after the 1999 USDA/DHHS integration.

15. The Agency mentioned that "practical considerations prevented the use of the Gerber Feeding Infants and Toddlers Study." It further commented that it decided "resources were more appropriately invested in working jointly and cooperatively with other US government agencies…." We do not disagree with this thinking; however, we would like to point out for OPP that if it is serious about using the Gerber study's data, it needs to dialogue with Gerber during the survey planning phase, not when the results have been compiled for Gerber's needs. Also, the Agency's response alludes to Feeding Infants and Toddlers Study data from older studies, perhaps before the release of Gerber's most recent study. Since Gerber conducts the Feeding Infants and Toddlers Study at least once every 5 to 10 years, the Agency might consider communicating its interest in acquiring data from the next study now.

16. The Agency recognized the importance of correlating or validating model-predicted exposures with "real world" measures from longitudinal studies, especially, since for humans, food consumption and pesticide usage patterns do vary across weeks in a month and seasons within a year. We believe the choice of data sets for food intake, pesticide residues, chemical use, and toxicity as presented in probabilistic models can have dramatic effects on exposure and risk estimates. Also, while OPP utilizes pesticide exposure models (like Lifeline, CARES, DEEM-Calendex) to predict long-term dietary exposure risk, such risks are estimates and could easily be above or below real world levels.

    After reviewing the Agency comments on longitudinal consumption data, we consolidated our recommendations on developing methodology for collecting longitudinal consumption data with the recommendation to collect such data. In so doing, we also renumbered the other recommendations accordingly. We agree with the Agency that it has neither the expertise to develop the methodology for collecting longitudinal consumption data nor the resources/funding to collect and analyze longitudinal food and activity exposure information. Therefore, as stated in note #14, during our field work we organized a meeting for Agency representatives to meet with dietary assessment methodology experts from USDA's Agricultural Research Service. At the meeting, the Agricultural Research Service scientists

introduced research activities from their human nutrition research centers (two of which focus on children's health), highlighted the compact tools developed by the Agricultural Research Service's scientists for food intake and activity monitoring, and discussed the Agricultural Research Service's role in developing the dietary methodologies used in the National Health and Nutrition Examination Survey (including commenting on the Food Propensity Questionnaire) and in handling the analysis of the survey's dietary data. We encourage the Agency to dialogue with the experts at Agricultural Research Service about opportunities for collaborative research for more and better children's dietary and nondietary exposure data.

We are aware that the National Cancer Institute's Food Propensity Questionnaire was pilot tested in the National Health and Nutrition Examination Survey and was included in the survey starting in 2003. This data collection instrument is the National Cancer Institute's attempt to improve the method of assessing long-term average, or "usual dietary intake." The Food Propensity Questionnaire was designed to build on the strengths of both the 24-hour dietary recalls and Food Frequency Questionnaires. It is similar to the National Cancer Institute's Diet History Questionnaire but without portion size questions. Such an instrument is meant to supplement the 24-hour dietary recall methodology currently used in the National Health and Nutrition Examination Survey. We have learned the propensity method assumes that usual intake is a function of the propensity to consume (the probability that a person will eat a specific food or beverage on a given day over a designated time period) and the average amount consumed on a day when the food is actually eaten. Initial validation studies have shown the Food Propensity Questionnaire accurately measures propensity *as defined for this method* and that *combining the 24-hour dietary recall and the Food Frequency Questionnaire is a more efficient way to estimate* commonly eaten foods in the U.S. diet. However, this approach is still subject to error associated with self-reporting of intakes. We encourage the Agency to dialogue with the experts at the Agricultural Research Service about its need for more and better longitudinal dietary exposure data.

17. We disagree with the Agency that its current practice fully addresses Recommendation 4-2. During our review, the Agency provided no documentation and we found no evidence that it assessed Food and Drug Administration and USDA residual data in terms of their reliability in describing the exposure of fetuses, infants, and children (through adolescence) to pesticides consumed through domestic and/or imported foods, including ethnic foods. We recognize that resource limitations constrain the Agency's research efforts in measuring residual and dietary consumption patterns. Since OPP relies heavily on the use of models and assumptions to determine risk for setting pesticide tolerances, the choice of data sets for food intake, pesticide residues, chemical use, and toxicity as presented in models can have dramatic effects on exposure and risk estimates. Also, given evidence from recent studies demonstrating that a switch to organic diets significantly lowered children's dietary exposure to organophosphorus pesticides,[37] our recommendation is for the Agency to assess which additional foods frequently consumed by children (including adolescents) should be included

[37] Curl CL et al. 2003. Organophosphorus Pesticide Exposure of Urban and Suburban Pre-school Children with Organic and Conventional Diets. *Environmental Health Perspectives* 111:377-382. Lu C et al. Online September 1, 2005. Organic Diets Significantly Lower Children's Dietary Exposure to Organophosphorus Pesticides. Environmental Health Perspectives available at http://dx.doi.org.

in the Pesticide Data Program testing. We encourage the Agency to work closely with USDA and the Food and Drug Administration in this area.

18. The Agency stated that "the sampled PDP (Pesticide Data Program) commodities for children 1-2 years old directly or indirectly represent approximately 90% of children's diets." We require additional support to accept the claim that sampled commodity foods "for children 1-2 years old" would represent "90% of children's diets" when, according to the Agency (in its response to our prior report[38]), OPP evaluates pesticide risks for every pesticide in food for children including those between ages 3-5, 6-12, and 13-19. We recommend the Agency assess which additional foods (including ethnic foods) frequently consumed by children (through adolescence) should be included in the Pesticide Data Program testing. Furthermore, we believe it would be beneficial to assess the scale of monitoring required to know and manage the mixture of pesticides dispersed into the food and water supplies. We encourage the Agency to examine food intakes by children (through adolescence) from the National Health and Nutrition Examination Survey to assess whether additional foods should be analyzed.

    We agree that determining which food to sample and not to sample requires careful consideration of food consumption patterns, residue levels, and frequency of pesticide detections. We also agree that the problem of managing pesticide residue in food lies within a much larger food safety monitoring arena in which EPA is a minor player. We understand the Agency is hampered in doing adequate aggregate exposure assessment both by the lack of data on individual routes of pesticide exposure and by a lack of biological monitoring data in infants and children. However, in the area of dietary pesticide exposure, we believe EPA has a major responsibility because it sets the tolerances and registers the pesticide chemical use on food. We encourage the Agency to solicit assistance from USDA (for example, the Agricultural Research Service and the Agricultural Marketing Service) and DHHS (for example, the Food and Drug Administration) when determining which additional foods to sample.

19. We agree that ORD has been a partner in funding and delivering research results pertinent to OPP's mission and needs. We have been informed that OPP is involved in drafting relevant Requests for Applications and participating in the internal relevancy review of grant applications. Also, we know OPP has requested more longitudinal data from ORD. We are aware of the extramural research program which the National Center for Environmental Research manages. We recognize that National Center for Environmental Research grants support both individual investigator research and multi-disciplinary research grants and centers. More specifically, the Science to Achieve Results (STAR) program is an extramural funding program within ORD and it has funded pertinent pesticide exposure and children's health projects. We know that the STAR program communicates grantees' research results to scientists in EPA and the public through Web sites, meetings, and publications. However, we learned during our evaluation from several sources that OPP risk assessors seldom included STAR grant project results into their risk assessments, do not routinely attend STAR program presentations or National Center for Environmental Research seminars, and

[38] EPA OIG. October 19, 2005. Changes Needed to Improve Public Confidence in EPA's Implementation of the Food Quality Protection Act. Report No. 2006-P-00003.

generally did not "participate extensively" in the ORD STAR program activities perhaps until recently. We encourage OPP to fully utilize relevant findings from the ORD STAR projects in its pesticide risk assessment work.

20. We agree with the Agency that it should continue to track pesticide residue in cow's milk. Nonetheless, the Agency's data on human breast milk have not kept pace with environmental effects. As the Agency concluded, "more recent information is needed on breast milk consumption and the incidence and duration of breastfeeding." [39] As a short-term solution we can accept the Agency's proposal to apply the FQPA Children's Safety Factor "in the event that OPP identifies a chemical for which it thought breast milk might be a significant source of exposure." However, we do not see this solution as adequate for risk assessments in the long term. In our opinion, up-to-date breast milk data should be considered when aggregating various sources of pesticide exposure among nursing infants.

21. In reviewing the Agency's comments on breast milk biomonitoring, we encourage the Agency to include in its research plans research to determine the rates of elimination kinetics for various classes of chemicals from the mother's body during lactation. Further, the Agency might consider partnering with the Centers for Disease Control and Prevention to identify human biomarkers of exposure, susceptibility, and effects to predict potential health risks associated with environmental chemicals to breast-fed and formula-fed infants and mothers.

22. We disagree with the Agency's view that it has adequate dietary exposure data through the Continuing Survey of Food Intake by Individuals and the National Health and Nutrition Examination Survey from schools and daycares. Throughout our evaluation, we were provided no evidence to illustrate that the Agency analyzed the Continuing Survey of Food Intake by Individuals dataset to confirm that it contains sufficient sample size to draw statistical conclusions about children's dietary exposure risk from school lunch programs and daycare centers. Also, we would need additional evidence to accept the Agency's view about the 2003-2004 NHANES dietary data providing adequate dietary exposure data on children from schools and daycares when the Agency has not updated its food consumption database since the NHANES effort began.

    We recommended the Agency expand its partnerships with USDA and DHHS and consider collecting data on dietary exposure at schools (elementary or secondary) and day cares so that the Agency increases its batch of children-specific data. A recent manuscript[40] reported several findings of concern about the risks of pesticide use in and around the nation's schools:

    - pesticide poisoning incidence rates among children increased significantly from 1998 to 2002;
    - drifting pesticides applied off site were responsible for 31 percent of reported poisonings; and

[39] US EPA. September 2002. Child-Specific Exposure Factors Handbook. National Center for Environmental Assessment, Office of Research and Development, Washington, D.C. EPA-600-P-00-002B. See page 1-22.
[40] Alarcon WA et al., July 27, 2005. Acute Illnesses Associated With Pesticide Exposure at Schools. *Journal of the American Medical Association*, Vol. 294, No. 4:455-465.

- insecticides and disinfectants were the pesticides most frequently at fault.

The authors noted that no Federal requirement limits pesticide exposures at childcare centers and elementary or secondary schools, and that their pesticide poisoning results "should be considered low estimates of the magnitude of the problem because many cases of pesticide poisoning are likely not reported to surveillance systems and poison control centers." Since simultaneous collections of nondietary exposure and biomonitoring data could be beneficial, we have modified our recommendation to include "nondietary exposure" data.

23. While we agree with the spirit of outsourcing software development for probabilistic models or funding external researchers to seed research and develop the next generation of environmental scientists, we do take the position that, prior to seeking external support, the Agency should fully utilize the expertise of ORD scientists to develop exposure estimate models (including Physiologically-Based Pharmacokinetic modeling) for its core work. ORD is the Agency's principal research arm; its role is to provide critical science and scientific products for environmental decision-making through its problem-driven and core research projects. We maintain our position that OPP coordinate efforts with ORD to finalize the integration of the Exposure-Related Dose-Estimating Model (ERDEM) with the Stochastic Human Exposure and Dose Simulation pesticides exposure model (SHEDS).

24. We appreciate the Agency's thoroughness in reviewing Figure 6.1. As a result, the figure was modified to reflect corrected information from the Agency. However, we have concerns over the "Science Policy Issues & Guidance Documents" Web site being unclear, out-of-date, and misleading. We noted that there are four science policy papers still posted on the "Science Policy Issues & Guidance Documents" Web page for which OPP plans to issue Federal Register Notices announcing their withdrawals. Although OPP is subject to statutory and court-ordered deadlines that require significant resources, we believe managing the currency of the science policy papers and associated Web site should be an Agency priority. We believe the Agency's Web site is a means to communicate EPA's FQPA implementation efforts and OPP's use of sound science to reduce uncertainty in its regulatory decisions

25. We included this table as an example of the types of toxicity testing data gaps cited by non-EPA scientists since the enactment of FQPA.

Appendix E

Toxicity Testing Issues

The following table contains examples of data gaps identified in the report *Putting Children First: Making Pesticide Levels in Food Safer for Infants and Children*, issued in April 1998 by the Natural Resources Defense Council. The complete table is on page 9 of that report.

Tests	Test includes *in utero* exposure	Test includes post–natal exposures	Tests for effects on offspring
Tests Required for Food–Use Pesticides			
Acute Tests: Oral toxicity (rat)	No	No	No
Dermal toxicity	No	No	No
Inhalation toxicity (rat)	No	No	No
Primary eye irritation (rabbit)	No	No	No
Primary dermal irritation	No	No	No
Dermal sensitization	No	No	No
Mutagenicity: Gene mutation[1]	N/A	N/A	N/A
Structural chromosomal abereration	No	No	Yes[2]
Subchronic: 90–day feeding (rodent & non–rodent)	No	No	No
Chronic: Feeding study (rodent & non–rodent)[3]	No	No[4]	No
Cancer: Carcinogenicity[3]	No[5]	No[5]	No
Metabolic: General metabolism tests	No	No	No
Developmental: Developmental toxicity (rat and rabbit)	Yes	No	No
Reproductive: Two–generation study (rat)	Yes	Yes	Yes
Significant Tests, Occasionally or Rarely Required			
Acute delayed neurotoxicity (hen)[6]	No	No	No
Developmental neurotoxicity study (rat)	Yes	Yes	Yes

[1] Most gene mutation tests are done on cell culture systems. Per 40 CFR Part 158, there may be other tests of genotoxicity done, but this determination is only made on a chemical-by-chemical basis.
[2] Second–generation offspring are tested only indirectly, by examining effects on sperm of exposed animals.
[3] The chronic feeding and carcinogenicity studies may be combined into one test using the same animals.
[4] Exposure is recommended to start immediately after weaning.
[5] Pre- and perinatal exposure of test animals may be required under certain conditions, according to guidelines, but is atypical.
[6] Only required for organophosphate or structurally related pesticides.

In a 2002 EPA review by an EPA technical panel, *Review of the Reference Dose and Reference Concentration Processes*,[41] the panel identified numerous data gaps in the testing guidelines. This panel suggested that the Agency develop alternative strategies and guidance to allow more targeted testing. The panel found study design and data collection gaps in life stages,

[41] Reference Dose/Reference Concentration Technical Panel, Risk Assessment Forum, EPA/630/8-02/002F, December 2002.

particularly in terms of the exposure periods in the current guideline testing protocols. The panel indicated that there is minimal evaluation of aged animals, especially after exposures that include early development. This panel pointed out that there is a lack of information on toxicokinetics (the determination and quantification of the time course of absorption, distribution, biotransformation, and excretion of chemicals), and that available data are generally limited to studies conducted of young adult animals. The panel found no guideline protocol for toxicokinetic evaluations during development or older age related to exposures and outcomes.

In the data requirements for pesticide registrants in 40 CFR Part 158, the Agency's required testing includes no evaluation of behavior, learning, or memory in developing animals. Learning and memory testing is part of the developmental neurotoxicity study, but requiring such a study is contingent upon predefined conditions or triggers. Behavior and functional tests are sensitive parameters that one would presume might be essential for assuring safety to infants and children and fulfilling the challenges posed by the FQPA. Also, although there is a developmental toxicity study and a two-generation reproductive study required in the testing, the Agency's own assessment of these two studies is that they "do not include an in-depth assessment of the development of the nervous system."[42] Also, the Agency's Science Advisory Panel acknowledged that these testing criteria "were not adequate for identifying every potential developmental neurotoxicant, supporting the Agency's concern about the criteria's limitations."

The current EPA guideline for developmental neurotoxicity study states that the "dosing period covers the period from day 6 of gestation through day 10 postnatally." According to literature, critical period of rapid human brain development is from the third trimester through the second year of life, which for mice or rats ranges during the first 21-28 days of life. The exposure period recommended by the guide may be too short to reflect the entire vulnerable period of brain development in children. Also, statistical procedures to define the minimal number of animals in a test group needed to give sufficient power to detect meaningful differences are lacking in the guide. Nonetheless, the current developmental neurotoxicity guideline is EPA's most sensitive validated means of examining unique endpoints that are not examined in other standard toxicity protocols. It enables the detection of effects in the offspring following pre- and/or postnatal exposure.

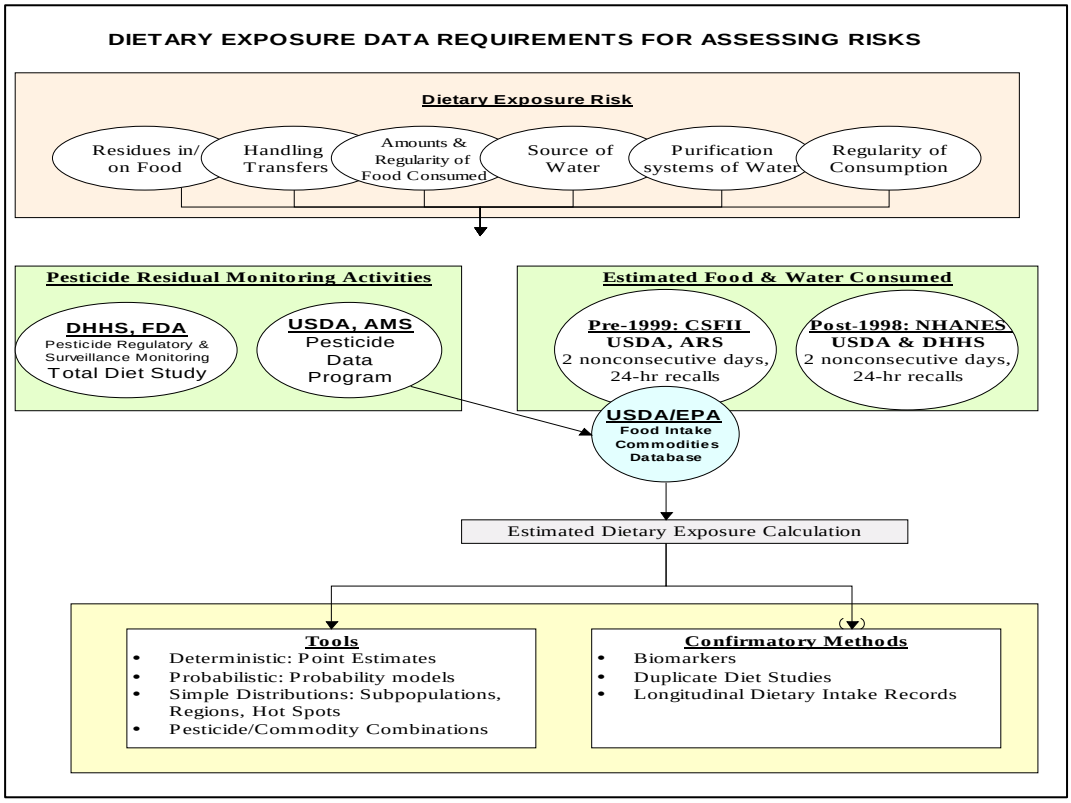
Finally, cholinesterase inhibition is the driving endpoint for organophosphate pesticides. Organophosphate pesticides were thought to affect brain development through their ability to elicit cholinesterase inhibition and cholinergic hyperstimulation. Cholinesterase inhibition can be detected in brain tissue, plasma, and red blood cells, but there is controversy over which form is the most sensitive method of measure and whether whole-brain cholinesterase assays could readily miss brain regional and sub-regional cholinesterase inhibition. Some researchers are concluding that cholinesterase inhibition alone is not enough to assess the consequences of exposure. Recent research shows that chlorpyrifos disrupted developmental neurotoxicity synthesis in the brain and synaptic signaling and function. This means chlorpyrifos has direct effects on cellular processes that are unique to brain development, and that these effects are mechanistically unrelated to inhibition of cholinesterase.

[42] 70 Federal Register 12275 (March 11 2005), page 122295; Docket Control ID OPP-2004-0387.

Appendix F

Data and Tools for Estimating Dietary Exposure

Collecting national food consumption data is costly and complex, and EPA relies on other Federal agencies for such data. FQPA contains specific provisions for cooperative activities between EPA and USDA. The figure[43] below illustrates some of the dietary exposure requirements for assessing risks, while the text that follows discusses various collection methods EPA relies upon to estimate dietary pesticide exposure risks.



AMS: Agricultural Marketing Services
ARS: Agricultural Research Services
CSFII: Continuing Survey of Food Intakes by Individuals
DHHS: Department of Health and Human Services
FDA: Food and Drug Administration
NHANES: National Health and Nutrition Examination Survey
USDA: U.S. Department of Agriculture

U.S. Food Consumption Data Collection Activities

"What We Eat in America from NHANES (National Health and Nutrition Examination Survey): The National Nutrition Monitoring and Related Research Act of 1990 provided the impetus for a coordinated effort to collect and report nutrition and health status data, and stimulate research to develop uniform methodologies, technologies, and procedures for national nutrition monitoring. In 1998, the National Center for Health Statistics of the Centers for

[43] OIG staff developed this figure based on data collected for this evaluation.

Disease Control and Prevention at DHHS and the Agricultural Research Services at USDA signed a memorandum of understanding to integrate the National Health and Nutrition Examination Survey and the Continuing Survey of Food Intakes by Individuals dietary data collection activities into an integrated survey. The Agricultural Research Services processes all dietary recall data collected and releases it under the title "*What We Eat in America from NHANES*."

Since 1999, the Continuing Survey of Food Intakes by Individuals was integrated with the National Health and Nutrition Examination Survey, which is a multistage, stratified area sample that is representative of the civilian noninstitutionalized population of the United States. Certain groups were over-sampled to allow for more precise estimates. Over-sampled groups include adolescents 12-19 years, persons 60-plus years, African Americans, Mexican Americans, low-income persons, and pregnant women.

"Nationwide Food Consumption Survey" and the "Continuing Survey of Food Intakes by Individuals": Prior to the passage of FQPA, food consumption surveys accepted by the EPA as sources for estimating food intake by individuals were from the USDA Nationwide Food Consumption Survey (1977-78) and the Continuing Survey of Food Intakes by Individuals (1989-91). These surveys were designed to provide nationally representative, multistage, stratified samples of U.S. adults, but infants, children, and certain demographic categories were under-surveyed. In 1998, after FQPA enactment, USDA and EPA collaborated to collect data specifically from children.

Food Commodity Intake Database: The Food Commodity Intake Database was generated by the USDA Agricultural Research Service for EPA from the data collected in Continuing Survey of Food Intakes by Individuals 1994-96, 1998.

U.S. Pesticide Residual Monitoring Programs

USDA Agriculture Marketing Service's Pesticide Data Program: This program concentrates its efforts in providing better pesticide residue data on foods most consumed by children. The program supplies continuing information on pesticide residues in fruits, vegetables, grains, dairy products, and meats. Food samples are collected by USDA's Agricultural Marketing Service immediately before commodities are shipped to grocery stores and supermarkets, and prepared by the laboratory as they typically would be for consumption.

Total Diet Study: This study, sometimes called the Market Basket Study, is an ongoing DHHS Food and Drug Administration program that determines levels of various contaminants and nutrients in foods. Since its inception in 1961, the study has grown to include analyses of radionuclides, residues of pesticides, industrial chemicals, toxic and nutritional elements, and folate. The number of different foods sampled in the study has increased from 82 food items when the study was initiated to about 280 foods in the current program. Three samples of four regional market baskets are collected each year from three cities per region. Study diets are derived from the national food consumption survey data and are generally compiled in conjunction with updates of the study's food list. In response to the FQPA, additional infant and

toddler foods were added to the study to provide more information on levels of pesticides and lead in the diets of young children.

Computerized Risk Assessment Computation Models

Pesticide exposure assessments can use models that are either deterministic, probabilistic, or both. Deterministic models provide a point estimate of exposure, assuming that a typical child eats an assumed mass of food per day with a given concentration of a pesticide residue. A probabilistic model considers the range of estimates and provides a probability distribution of exposures. It would calculate the range of mass of food and the range of food types eaten by a particular group of children of a certain age and gender. Whether EPA uses a deterministic or probabilistic approach, it will always be dependent on other Federal organizations for the large-scale human food consumption data needed in its risk assessment and the biomarker data from national biomonitoring studies to validate its modeling predictions.

OPP supports and encourages the development of freely available models and software tools that could be used to conduct such assessments. Besides the ORD SHEDS (Stochastic Human Exposure and Dose Simulation) pesticides exposure model, there are three other models developed for OPP risk assessment purposes. These probabilistic risk assessment models each project pesticide exposure for the U.S. population. However, they differ in their basic design in a number of ways. Details on the four models follow.

- **SHEDS (Stochastic Human Exposure and Dose Simulation)-PESTICIDES:** This is a physically-based stochastic model (one that involves a random variable) that quantifies exposure and dose of humans to multi-media, multi-pathway pollutants, and, in particular, aggregate exposures of children to pesticides. To date the model has focused on simulating aggregate exposures of children to pesticides. The model is being expanded to address cumulative exposures.

- **DEEM/CALENDEX (Dietary Exposure Evaluation Model/Calendar-Based Dietary and Non-dietary Aggregate and Cumulative Exposure Software System):** These are software systems developed and licensed by the private sector. The first provides a probabilistic assessment of dietary exposure/risk for the U.S. population or subsets. The second is an exposure assessment model that estimates aggregate pesticide exposures from multiple pathways as required by the FQPA.

- **LIFELINE Software for cumulative and aggregate exposure assessment Version 2.0:** This is an exposure model that produces exposure estimates using 1994-1998 Continuing Survey of Food Intake by Individuals and the USDA Food Commodity Intake Database to investigate pesticide residues in diet, tapwater, and residential environments.

- **CARES (Cumulative and Aggregate Risk Evaluation System):** This software consists of several modules, including a Population Generator; Dietary, Water, and Residential Modules; Aggregate and Cumulative Assessment Modules; and a Contribution and Sensitivity Analysis Module. The Population Generator is used outside of the system to generate a reference population of 100,000 individuals selected from 5,000,000 individuals who completed the long form of the 1990 U.S. Census.

Appendix G

Distribution

Office of the Administrator
Acting Assistant Administrator for Prevention, Pesticides, and Toxic Substances
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Acting Director, Office of Children's Health Protection
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Agency Followup Official (the CFO)
Agency Followup Coordinator
Audit Coordinator, Office of Prevention, Pesticides, and Toxic Substances
Audit Liaison, Office of Research and Development
Audit Liaison, Office of Pesticide Programs
General Counsel
Associate Administrator for Congressional and Intergovernmental Relations
Associate Administrator for Public Affairs
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