Synthesis Report of Research from EPA's Science to Achieve Results (STAR) Grant Program:

Feasibility of Estimating Pesticide Exposure and Dose in Children Using Biological Measurements

December 2006

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The research described in this document has been funded wholly by the United States Environmental Protection Agency (EPA) under the Science to Achieve Results (STAR) grants program. The information does not necessarily reflect the views of the Agency and no official endorsement should be inferred. Mention of trade names or commercial products does not constitute endorsement or recommendation by EPA for use. The information presented in this synthesis report is intended to provide the reader with insights about the progress and scientific achievements of STAR research grants. The report lists the grantees whose research is discussed, and it also indicates where more detailed peer-reviewed scientific data can be found. This report is not sufficiently detailed nor is it intended to be used directly for environmental assessments or decision-making. Readers with these interests should instead consult the peer reviewed publications produced by the STAR grants and conduct necessary data quality evaluations as required for their assessments.

Executive Summary

This report provides a brief overview of research funded by 12 grants issued through the Environmental Protection Agency's (EPA) Science to Achieve Results (STAR) program. These grants were all aimed at advancing the state of knowledge concerning children's exposures to pesticides and the potential adverse effects of these exposures. Children's pesticide exposures are a major concern to EPA because of extensive evidence that children may be more vulnerable to the effects of pesticide exposures than adults and because children's exposures to pesticides may be greater than those of adults under typical use scenarios. The grants reviewed in this report address three related topics:

- Development of improved biomarkers of children's pesticide exposure,
- Studies of the basis for children's vulnerability to pesticides, and
- Development of improved information relating to the nature and magnitude of children's pesticide exposures.

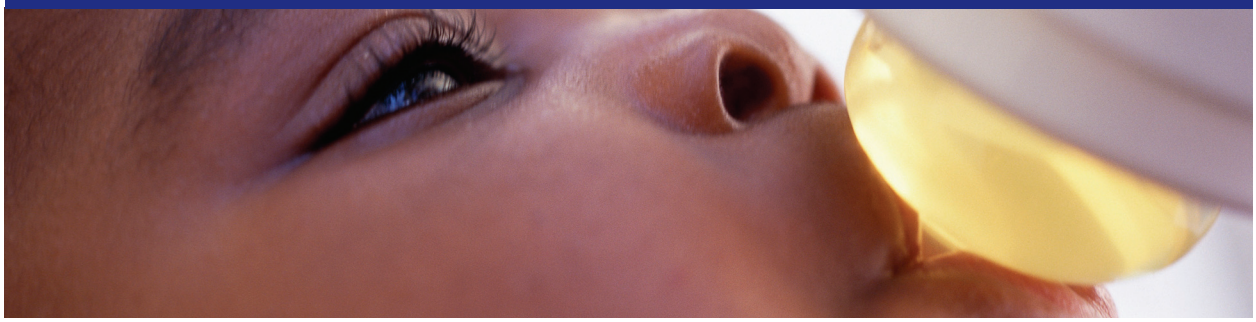
Biomarkers are physiological or biochemical measurements that can be used to estimate pesticide exposures and body burdens, which indicate the amounts of pesticides remaining in the body. Three of the grants reviewed in this document investigated the development of less invasive biomarkers (analyses of saliva, hair, meconium) that can provide rapid, reliable indications of children's, infants', and fetal exposures to commonly used pesticides, and have related these biomarkers to indices of early neurological development.

A second group of grants attempted to determine the most important factors explaining why children are often disproportionately exposed to pesticides. These studies have confirmed the ubiquity of children's exposure to household pesticide residues, provided insights into the reasons for high variability of exposures in children, and confirmed the importance of specific behaviors (mouthing in infants and toddlers) associated with children's exposures.

Finally, three of the grants set out to develop detailed estimates of pesticide exposures for specific groups of children. These studies evaluated differences in exposures between urban, rural, and agricultural communities, and the effects of ethnicity, socioeconomic factors, and household conditions on the magnitude of exposures. One of the grants funded research that compared children's and adults' exposures to support evaluations of the differences in risks between adults and children exposed to pesticides in similar settings.

Research under these grants has added greatly to the available data on children's pesticide exposure patterns and potential risks, confirmed the usefulness of biomarkers of pesticide exposure, and identified major methodological and data gaps in risk assessment for children exposed to pesticides.

1. Background



1.1 History and Objectives of STAR Grants Related to Children's Pesticide Exposures

As part of its mission to improve public health and increase the reliability with which risks to the public health are identified and measured, the Office of Research and Development (ORD) at the Environmental Protection Agency (EPA) funds extramural research through the Science to Achieve Results (STAR) program. The STAR program is managed by the ORD's National Center for Environmental Research (NCER) and provides grants and fellowships mainly to academic researchers to address research goals under ORD's *Human Health Research Strategy* (EPA, 2003) and the *Human Health Multi-Year Plan* (EPA, 2003). These documents, and the research goals, are updated regularly.

A major focus of ORD's research in the last decade has been to improve the quality of risk assessments for children. In addition, the Agency has been supporting the development of improved methods for measuring and estimating children's exposure to pesticides and other common environmental contaminants. Recent research has provided extensive evidence that children may be more vulnerable to the effects of pesticide exposures than adults. Children may absorb, metabolize, and react to pesticides differently than adults because of differences in physiology associated with specific stages of development. In addition, children's behavior patterns differ from adults—they spend more time in contact with potentially contaminated media such as soil and house dust. Thus, they may receive higher exposures and doses than adults in the same exposure setting. Exposure to pesticides may begin before birth, and the effects of prenatal exposure are poorly understood. Currently available models and data are not always adequate to assess children's exposures to pesticides or to estimate the risks associated with these exposures.

In addition, passage of the Food Quality Protection Act (FQPA) of 1996 requires EPA to specifically and quantitatively consider the special vulnerability of children in decisions related to pesticide tolerance setting. This has provided additional incentive for EPA to improve methods for characterizing children's exposure to pesticides, how children metabolize pesticides and other chemicals, and how the differences between children's and adults' responses to pesticide exposure translate into differences in health risks.

1.2 Research Covered by This Report

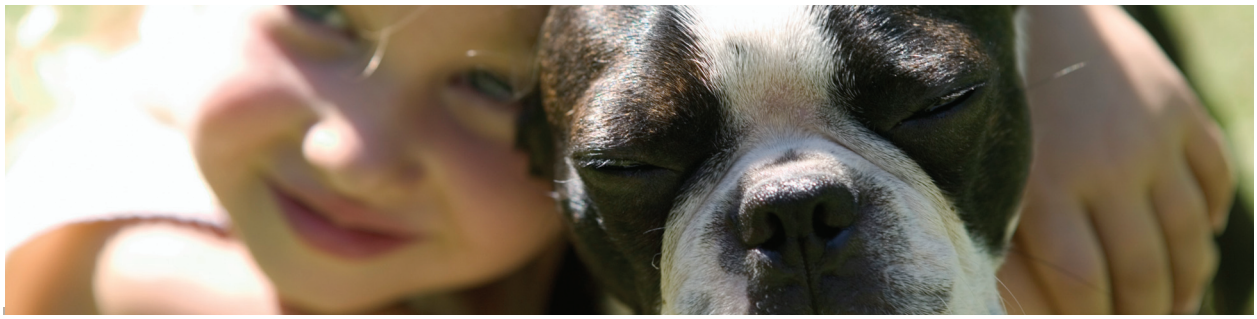
To address these concerns, EPA has issued Requests for Applications (RFAs) in three major topic areas related to children's pesticide exposures, as summarized in table 1:

- Development of improved biomarkers of children's pesticide exposure,
- Studies of the basis for children's vulnerability to pesticides, and
- Development of improved information relating to the nature and magnitude of children's pesticide exposure.

This report provides a brief overview of 12 grants funded under the STAR program in these three general areas. The projects listed in table 1 were initiated between 1996 and 2001. Progress in research under these grants, and important research results, are described in section 2 of this report. Where projects have not been completed, progress through 2005 is summarized. Section 3 briefly discusses how the individual grants have contributed to the fulfillment of seven specific ORD research goals specified in the *Human Health Research Strategy* and the *Human Health Multi-Year Plan.*

Table 1. STAR Grant Research Projects Reviewed in this Synthesis Report

Grant #	Project Title	Principal Investigator (PI)	Project Period
RFA: Biomarkers for the Assessment of Exposure and Toxicity in Children			
R828611	Biomarkers and Neurobehavioral Effects of Perinatal Exposure to Chlorpyrifos (CPF) and Other Organophosphate Insecticides	Wilkins	02/2001–02/2004 (extended to 02/2006)
R828608	Development of a Physiologically Based Pharmacokinetic/ Pharmacodynamic (PBPK-PD) Model to Quantitate Biomarkers of Exposure for Organophosphate Insecticides	Timchalk	01/2001–12/2003 (extended to 05/2005)
R828606	Saliva Biomonitoring for Organophosphorus Pesticide Exposures in Children	Fenske	09/2000–08/2003 (extended to 08/2005)
R828609	Measurement of Non-Persistent Pesticides in Postpartum Meconium as a Biomarker of Prenatal Exposure: A Validation Study	Whyatt	07/2000–06/2003 (extended to 06/2005)
R828610	Chlorotriazine Protein Binding: Biomarkers of Exposure and Susceptibility	Tessari (previously Andersen)	06/2000–05/2003 (extended to 05/2006)
RFA: Children's Vulnerability to Toxic Substances in the Environment			
R827440	Ingestion of Pesticides by Children in an Agricultural Community on the U.S./Mexico Border	Shalat	10/1999–09/2002 (extended to 03/2003)
R827444	Study of Exposure and Body Burden of Children of Different Ages to Pesticides in the Environment	Raymer	09/1999–08/2002
R827443	Vulnerability of Young Children to Organophosphate Pesticides and Selected Metals through Intermittent Exposures in Yuma County, Arizona	O'Rourke	05/1999–04/2002 (extended to 09/2004)
RFA: Exposure of Children to Pesticides			
R825169	Exposure of Children to Pesticides in Yuma County, Arizona	O'Rourke	10/1996–09/1999
R825283	Measuring and Apportioning Children's Exposure to Pesticides in Urban, Suburban, and Rural Communities	Sexton	10/1996–09/1999
R825170	Assessing Levels of Organophosphorus Insecticides Which Could Expose Children From Pets Treated with Flea Control Insecticides	Chambers	10/1996–09/1999
R825171	Total Organophosphorus (OP) Pesticide Exposure Among Children in Urban and Rural Environments	Fenske	09/1996–09/1999 (extended to 09/2000)



2. Summaries of Supported Research

This section provides brief summaries of the progress and findings of the twelve grants listed in table 1. Literature publications arising from the grants are listed in section 4, and detailed progress reports for each grant can be found on ORD NCER's Web site http://es.epa.gov/ncer/index.html.

2.1 Biomarkers of Pesticide Exposure

EPA released an RFA entitled "Biomarkers for the Assessment of Exposure and Toxicity in Children" in 2000. In 2000 and 2001, ORD awarded five grants to researchers investigating various aspects of biomarkers research. The RFA solicited research that would establish normative data for biomarkers, evaluate biomarker sensitivity in predicting exposure or health outcomes, and lead to the development of less invasive biomarkers.

Biomarkers and Neurobehavioral Effects of Perinatal Exposure to Chlorpyrifos (CPF) and Other Organophosphate (OP) Insecticides

This grant funded a large prospective longitudinal study of the relationships between biomarkers of exposure to common household pesticides (chlorpyrifos, diazinon, other OP pesticides, and synthetic pyrethroids) and indices of infant neurological development from birth through 2 years of age.

In spring 2005, mothers and children were still being recruited to reach a target sample of 176 low-risk pregnancies. The study involves an analysis of maternal urine and blood samples (at study entry and postpartum), infant urine samples (at or before 3 months, then every 7 months to 24 months), and infant blood samples (12 and 24 months) for pesticide biomarkers. Infant neurological development is being measured at 3, 12, and 24 months using the Bayley Scales of Infant Development 2nd Edition (BSID-II) and Child Development Index (CDI) tests. Urine and blood samples were originally to be analyzed for major metabolites of CPF and other OP pesticides, but the ban on household uses of CPF has caused a shift to synthetic pyrethroids. Therefore, the biological samples are also being analyzed for pyrethroid metabolites. In addition to biomonitoring, data are being gathered related to maternal exposure to cigarette smoke, ethnicity, socioeconomic status, parental intelligence, family structure, as well as clinical birth data.

PI:
Dr. John Wilkins,
Ohio State University

EPA GRANT NUMBER:
R828611

AMOUNT:
$1,126,423

DURATION:
February 2001 through February 2006

According to the PI's June 2005 progress report, 117 subjects were actively enrolled; 104 of these women have provided second urine specimens and completed questionnaires. The investigators collected 83 diaper urine samples from 2-month-old infants, 70 samples from 9-month-old infants, 46 samples from 16-month-old infants, and 29 samples from 23-month-old infants. The researchers also performed neurological testing (BSID-II) of 80 3-month-old infants and 21 24-month-old infants.

The researchers have analyzed and reviewed 198 maternal urine samples. In addition, approximately one-third of the 228 analyzed infant diaper urine samples have been reviewed. Organophosphates, pyrethroids, and cotinine (cigarette smoke) were detected in several of the 198 maternal urine samples analyzed. Final results are not yet available.

Development of a Physiologically Based Pharmacokinetic/Pharmacodynamic (PBPK-PD) Model to Quantitate Biomarkers of Exposure for Organophosphate Insecticides

The purpose of this research was to develop and validate an age-dependent PBPK-PD model for the OP pesticide CPF. The model was intended to include age-dependent changes in metabolism and pharmacodynamic response to facilitate quantitative biomonitoring of OP pesticides.

Research under this grant built on previous work by these authors on PBPK-PD modeling of OP pesticide responses in animals and humans. Researchers developed analytical

methods for quantifying CPF metabolites, investigated *in vivo* and *in vitro* mechanisms of CPF metabolism, and refined the PBPK-PD model to support the evaluation of noninvasive biomarkers of exposure.

PI:
Dr. Charles Timchalk, Battelle, Pacific Northwest Division

EPA GRANT NUMBER:
R828608

AMOUNT:
$733,174

DURATION:
January 2001 through May 2005

In the first year, grantees used their previously developed human PBPK-PD model to evaluate the effect of the known polymorphism of CPF oxonase (PON-1, a major detoxifying enzyme) on brain and plasma metabolite levels and plasma esterase inhibition (Timchalk et al., 2002). **They found that estimated brain concentrations of CPF-oxon were nearly equal for all three phenotypes (QQ, QR, and RR) at low single doses (~ 5 μg/kg). At higher doses (0.5–5.0 mg/kg) the brain oxon concentrations were significantly higher in the medium- (QR) and low-activity (QQ) phenotypes. They concluded that at low doses other detoxifying enzymes will likely prevent significant toxicity (as indicated by butylcholinesterase [BuChE] inhibition), but at higher doses, PON-1 polymorphism may contribute significantly to variations in human sensitivity to CPF exposure.**

Grantees also investigated the use of saliva cholinesterase levels as a possible biomarker for CPF exposures (Kousba et al., 2003). Experiments in rats showed that salivary esterase activity is predominantly (>95 percent) BuChE. Kinetic parameters for salivary esterase inhibition (active site concentration, Ki for CPF-oxon, and spontaneous reactivation rate) derived from the experiments were incorporated into the PBPK-PD model. The revised model was able to reproduce the time course of salivary BuChE inhibition in rats, supporting the potential use of saliva sampling as a noninvasive biomarker for acute CPF exposures (Timchalk et al., 2004).

Experiments were conducted to evaluate the role of intestinal metabolism in modifying the absorbed dose of CPF after ingestion exposure (Poet et al., 2003). Production of major CPF metabolites (CPF-oxon and trichlorpyridinol [TCPy]) by microsome preparations from rat hepatocytes and intestinal enterocytes was tracked using analytical methods developed for this study. Kinetic parameters (*Km, Vmax*) were measured for the major metabolic reactions (desulfurization and dearylization by cytochromes, hydrolysis by PON-1), and the overall metabolic capacities of the liver and intestine were compared. The authors concluded that first-pass metabolism (primarily detoxification) in the intestine may affect the systemic bioavailability and toxicity of CPF, especially at low doses.

The project results showed that the age-dependent rat model is quantitatively consistent with the general understanding of OP toxicity in younger versus older animals. The model suggested that neonatal rats are more sensitive to the high-dose acute effects of OP exposure; however, at low, environmentally relevant exposure levels, the neonatal rat model was not substantially more sensitive than adult rats.

Saliva Biomonitoring for Organophosphorus Pesticide Exposures in Children

PI:
Dr. Richard Fenske, University of Washington

EPA GRANT NUMBER:
R828606

AMOUNT:
$742,597

DURATION:
September 2000 through August 2005

The purpose of this study was to evaluate the feasibility of quantifying children's exposure to the OP pesticides diazinon and CPF, as well as a third pesticide from the synthetic pyrethroid family, permethrin, through saliva biomonitoring of pesticide levels.

Research performed under this grant included (1) measurement of diazinon concentrations in saliva after intravenous injection in rats, (2) evaluation of the effects of varying diazinon doses and salivary flow rate on diazinon excretion in saliva, (3) determination of the correlation between salivary and plasma concentrations, (4) measurements of CPF and diazinon concentrations in the saliva and urine of children in agricultural communities, and (5) development of a pharmacokinetic model for CPF and diazinon using salivary and urinary markers.

In the first part of the study, anesthetized rats were injected with various doses of diazinon. Time-course samples of plasma and saliva were obtained through 250 minutes after dosing. Concentrations of diazinon were determined using an enzyme-linked immunosorbent assay (ELISA). Statistical analyses of the data revealed that diazinon concentrations were consistently lower in saliva samples than in plasma samples, regardless of dose level, sampling time, or salivary flow rate. **The finding suggests that salivary excretion of diazinon is diffusion-limited, rather than transporter-mediated.**

A strong correlation was found between pesticide metabolite concentrations in saliva and plasma (Lu et al., 2003). Additional analysis revealed that the concentration of diazinon in saliva reflected the fraction of diazinon that did not bind to plasma proteins. This information allowed accurate prediction of the relative concentrations of diazinon in plasma and saliva, supporting the use of saliva biomonitoring as a noninvasive substitute for plasma sampling in the measurement of human diazinon exposures.

Data from animals dosed with CPF suggest that CPF is metabolized within minutes in blood, and therefore, it is not measurable in saliva.

Permethrin was selected as one of the chemicals to be measured in saliva using the ELISA assay; however, the ELISA assay for permethrin was not optimized for use in specimen samples. Additional research is being conducted to improve the permethrin ELISA assay.

The second part of the study, conducted in Nicaragua, assessed pesticide exposures for 7 corn farmers who used CPF, 10 banana plantation workers who applied diazinon, and their children. The investigators conducted urine, blood, and saliva sampling. Their analysis of the urine samples indicated exposure to CPF for the farmers, plantation workers, and children, but the saliva samples did not indicate exposure. This results from the rapid metabolism and clearance of CPF. This finding was consistent with the animal studies. The study identified two important exposure factors: proximity to spraying and spray mixture preparation in the home. The analysis detected exposure to diazinon among the applicators, but not among their children. **Diazinon concentrations in the workers' saliva were significantly correlated with the time-matched samples of their blood. Diazinon concentrations in saliva also corresponded with excretion of the primary urinary metabolite of diazinon in these applicators.**

The investigators suggested that saliva sampling is a promising monitoring method because it is noninvasive, and it measures pesticides rather than pesticide metabolites. The method may not be suitable for some compounds (e.g., CPF), and dehydration among the study subjects can adversely affect sample collection.

Measurement of Non-Persistent Pesticides in Postpartum Meconium as a Biomarker of Prenatal Exposure: A Validation Study

The purpose of this research was to validate a new noninvasive biomarker of prenatal exposure to OPs and other pesticides. The study design involved measuring the levels of a large number of pesticide residues in meconium samples from 100 infants born to African American or Dominican women from Manhattan and the Bronx, New York. Pesticide levels in meconium were compared with the results of continuous indoor and personal air monitoring during the final 2 months of pregnancy and with self-reported pesticide use (Whyatt et al., 2003).

The study included 102 mother-newborn pairs. Biologic samples were collected from the mother during pregnancy and from the mother and newborn at delivery and included: 253 repeat spot urine samples collected from the mothers during pregnancy; urine samples collected from the mothers (n=74) and newborns (n=69) after delivery; maternal blood (n=95) and umbilical cord blood (n=69) collected after delivery; and postpartum meconium (n=85).

Eleven insecticide metabolites were measured in meconium. Those detected most frequently were carbofuranphenol, 1-naphthol, 4-nitrophenol, 2-isopropoxyphenol, and TCPy. TCPy levels in meconium were correlated positively but not significantly with CPF in the indoor air samples and were correlated positively and significantly with TCPy levels in the prenatal maternal urine samples, both before and after adjusting for creatinine. TCPy in meconium also was correlated significantly with CPF levels in both the maternal blood and umbilical cord blood samples collected after delivery.

PI:
Dr. Robin Whyatt,
Columbia University,
Mailman School of Public Health

EPA GRANT NUMBER:
R828609

AMOUNT:
$744,866

DURATION:
July 2000 through June 2005

CPF, diazinon, and propoxur were frequently detected in continuous air sampling results from 102 women between the week 32 of pregnancy and delivery (at 40–42 weeks). Levels of the individual pesticides were generally highly correlated (relatively constant) over time for individual women but varied greatly among individuals, with a few women showing much higher exposures.

The results from this study indicate that meconium is a useful biomarker of fetal prenatal exposure to CPF. CPF, or its metabolite, TCPy, was the only compound that was consistently detected across all environment and biologic matrices in the current study. While only a weak correlation between CPF levels in indoor air samples and TCPy levels in meconium was observed, there was a consistent and highly observed correlation between TCPy levels in other biologic matrices and meconium. Thus, TCPy appears to provide a valu-

able internal dosimeter for CPF exposures during pregnancy.

Chlorotriazine Protein Binding: Biomarkers of Exposure and Susceptibility

The purpose of this research was to develop analytical methods to characterize the reactivity of chlorotriazines with hemoglobin protein, and evaluate whether binding to hair proteins can be used as a noninvasive biomarker of triazine exposure. The investigators proposed to develop an age-specific PBPK model to assess tissue concentrations of chlorotriazines and their metabolites over time and validate the model using animal and human data.

PI:
Dr. John Tessari
(previously Dr. Melvin Andersen),
Colorado State University

EPA GRANT NUMBER:
R828610

AMOUNT:
$710,617

DURATION:
June 2000 through May 2006

Atrazine (ATRA) is a high-volume pesticide that has been found in a number of drinking water supplies. Available biomarkers of exposure have been limited primarily to metabolites in urine, and the details of ATRA absorption, metabolism, and excretion were not well characterized before this work. A major achievement under this grant was the development of an analytical method capable of detecting low levels of ATRA and its metabolites in serum (Brzezicki et al., 2003). Previous efforts to study the pharmacokinetics of ATRA had been limited by the lack of a metabolite-specific method, and were primarily based on radiotracer data. The analytical method included cleanup, liquid-liquid extraction, and derivatization with methyl bromide/tetrabutylammonium chloride. The method demonstrated clean separation of ATRA and its major metabolites with a level of quantitation (LOQ) of 100 ng/ml for all species. It was validated using spiked serum samples as well as an *in vivo* metabolite analysis after single-dose administration to Sprague-Dawley rats.

The investigators also developed a detailed PBPK model for ATRA (McMullin et al., 2003) in adult rats. The model simulated the metabolism, transformation, and elimination of two major classes of metabolites, the chlorinated triazines and glutathione conjugates. Modeled processes included gastrointestinal absorption, metabolism by cytochrome P450 isozymes, conjugation by glutathione (GSH), and the binding of chlorotriazines to hemoglobin and serum proteins. Development of the model involved extensive research on chlorotriazine-globin binding rates and mechanisms. The PBPK model was validated against previous multiple-dose radiotracer studies of total ATRA metabolites and against data from a single-dose time course study in rats. The latter study used the previously developed analytical method to quantify ATRA and its metabolites in serum over time. The model was able to accurately fit both the single- and multiple-dose data. **The importance of chlorotriazine reactions with serum proteins was confirmed and the rate constants for hemoglobin and serum binding and elimination were estimated. The slow gastrointestinal absorption of ATRA, followed by rapid metabolism to 2-chloro-4,6-diamino-1,3,5-s-triazine (DACT) were confirmed as dominant features of ATRA pharmacokinetics.**

According to the PI's June 2005 progress report, the research team was investigating methods for pretreatment, digestion, and extraction of hair and the formation of other protein-atrazine adducts.

2.2 Children's Vulnerability to Toxic Substances

In 1999, EPA released the RFA "Children's Vulnerability to Toxic Substances in the Environment." This request focused on research that quantified children's exposure to chemicals by examining factors contributing to exposure, such as frequency, duration, activity patterns, temporal variation, and individual physiological differences. Development of predictive exposure models incorporating these factors were also encouraged and funded.

Ingestion of Pesticides by Children in an Agricultural Community on the U.S./Mexico Border

The purpose of this research was to evaluate children's exposure to OP pesticides in households within rural, agricultural communities along the U.S./Mexico border. The research attempts to determine the influence of hygiene practices and behavior patterns of children on pesticide dose level.

Research under this grant included (1) collection of environmental and urine samples and analysis for the presence of pesticides and pesticide residues, (2) statistical analyses to evaluate the associations between pesticide levels in environmental samples and pesticide body burdens, and (3) observation and analyses of children's mouthing behaviors.

PI:
Dr. Stuart Shalat, University
of Medicine and Dentistry
of New Jersey

EPA GRANT NUMBER:
R827440

AMOUNT:
$710,231

DURATION:
October 1999 through March 2003

Environmental sampling revealed detectable levels of pesticides in house dust in 75 percent of the 29 homes studied; however, no correlation was found between levels of pesticides in house dust and pesticide metabolite levels in urine. Half of the hand-wipe samples taken from the children in the study contained levels of pesticides above the detection limit. **There was a significant association between pesticide levels on children's hands and pesticide metabolite levels in urine. Researchers conjectured this relationship was associated with frequent hand-to-mouth behaviors.** Video recordings of the participants' behavior will be analyzed to help substantiate this hypothesis.

Dimethyl phosphate (DMP) and diethyl thiophosphate (DETP) were the most commonly detected metabolites that were found in 100 percent and 96 percent of the subjects, respectively. The pesticides methyl parathion and azinophos-methyl were detected in both hand and dust samples taken, consistent with the detection of its metabolite, DMP, in urine samples.

No association was found between hand surface area and the total amount of pesticides on children's hands. This result suggests that hand surface area may not be useful as a scaling factor in risk assessments. Age was inversely and significantly correlated with estimated dose levels, while gender was not found to be predictive of body burden.

All of the urine samples contained concentrations of at least one pesticide metabolite above the limit of detection. Ninety-five of those samples contained more than one metabolite above the detection limit (Shalat et al., 2003).

Study of Exposure and Body Burden of Children of Different Ages to Pesticides in the Environment

Grantees set out to evaluate whether children incur more frequent and higher exposures to pesticides than adults living in the same household. Secondary objectives included evaluating pediatric environmental exposure rates and dose distributions in relation to demographic variables.

PI:
Dr. James Raymer,
Research Triangle Institute

EPA GRANT NUMBER:
R827444

AMOUNT:
$819,063

DURATION:
September 1999 through August 2002

Research under this grant builds on previous work of these authors on the National Human Exposure Assessment Study (NHEXAS) by using the same study population to examine exposures to CPF, diazinon, ATRA, and malathion (MDA). The research involved (1) developing a means of collecting infant urine samples, (2) collecting and analyzing environmental and urine samples, and (3) correlating observed behavioral and demographic data with measured exposures.

After encountering difficulties finding detectable levels of pesticide residues of target analytes to study in Rice and Goodhue Counties, Minnesota, grantees moved the study to Moore County in western Minnesota. Pesticide and pesticide metabolites were measured in indoor air, exhaled breath, domestic water, surface wipes, house dust, dermal rinses, and body suits.

Many pesticides and pesticide metabolites were found in the first morning urine samples from both children and adults. Estimates of mean exposures were dominated by a few highly exposed individuals. **Statistical analyses revealed significant differences between the metabolite levels present in the urine of children and adults. Specifically, the grantees determined that levels of the CPF metabolite TCPy in children's hydrolyzed urine samples were on average two times the levels detected in adults. Similarly, levels of ATRA and the diazinon metabolite 2-isopropyl-6-methyl-4-pyrimidinol (IMP) detected in nonhydrolyzed urine samples averaged to be two and seven times greater, respectively, in children than in adults. No other significant differences between adults' and children's pollutant exposure or body burdens were identified.**

There were significant differences in the levels of contaminants found in children's urine samples from differing age groups. Nonhydrolyzed urine sample analysis revealed that children birth to 3 years old excreted 16 times more of the diazinon metabolite IMP (mean=245 ng/ml) than children ages 4 to 12 (mean=14 ng/ml). Similarly, urine of the younger pediatric cohort contained more than twice as much CPF-oxon (mean=0.46 ng/ml), a major CPF metabolite, than that of the 4- to 12-year-old group (mean=0.17 ng/ml) on the third day of the study.

Conversely, the urine of children 4 to 12 years old contained significantly higher concentrations of TCPy and ATRA than that of children birth to 3 years old. Concentrations of ATRA in the nonhydrolyzed urine of children 4 to 12 (mean=0.076 ng/ml) were significantly higher than levels found in the younger group (mean=0.004 ng/ml) on the second day of the study. The following day, seven times the level of TCPy was found in the nonhydrolyzed

urine of children 4 to 12 years old (mean=0.54 ng/ml) than the urine of the younger children (mean=0.078 ng/ml).

Vulnerability of Young Children to Organophosphate Pesticides and Selected Metals through Intermittent Exposures in Yuma County, Arizona

The two major objectives of this effort were to evaluate the routes and amounts of OP pesticide and metal exposure among young children and identify activities that result in increased children's exposure to contaminants in the home.

Activities under this grant included (1) collection and analysis of samples of exposure media, (2) collection and analysis of pediatric urine samples, (3) collection and analysis of dermal hand-wipe samples, (4) administration of questionnaires about general household conditions and parental occupation, and (5) analyses of recorded activities and play areas of children to identify pesticide exposure pathways. Environmental samples were analyzed for nine OP pesticides (including CPF, diazinon, and MDA) and heavy metals; urine samples were also analyzed for OP metabolites.

PI:
Dr. Mary Kay O'Rourke,
University of Arizona

EPA GRANT NUMBER:
R827443

AMOUNT:
$712,313

DURATION:
May 1999 through September 2004

The results of household dust and pediatric urine samples of children living in agricultural communities were used as screening tools to identify potential participants with elevated pesticide exposure or risk of exposure. The recruited population of 217 was narrowed to 45 children who were then divided into low and high exposure groups matched by age and gender. The levels of metals in urine samples were generally low and showed no evidence of exposures above expected background levels. The investigators therefore abandoned their planned analyses of heavy metal exposures.

Preliminary results revealed a number of important behavior patterns that were associated with pesticide exposures. Children with the highest exposure levels were males who spent the greatest amount of time playing outdoors. Similarly, children who played extensively in laundry rooms and entry ways exhibited higher rates of pesticide metabolites in urine than those who did not play, or played less, in these areas.

Video analyses completed to date indicate that the number of hand-to-mouth, hand-to-food, and mouthing activities in a given time period are more accurate predictors of exposure than the time a child spends touching a contaminated item or surface. Repeated wipes from hands of the same child over a short time frame (hours) reflected the same concentration and loading value repeatedly. **This suggests that frequent hand washing does little to reduce children's exposures in the household if chemical contamination is readily accessible.**

Additional preliminary analyses appear to have identified a method for predicting exposure to contaminants using a urinary assay quantifying the presence of an endogenous metabolite.

2.3 Children's Exposure to Pesticides

EPA awarded four grants as a result of the RFA entitled "The Exposure of Children to Pesticides" that was released in 1996. This RFA requested research proposals that would enhance development of pediatric pesticide exposure assessment methods by characterizing the effect of age and behavioral factors on pesticide exposure. Additional research priorities set by this RFA included development of methods for assessing cumulative exposures from one or multiple pathways.

Exposure of Children to Pesticides in Yuma County, Arizona

The purpose of this study was to compare the OP pesticide exposure and exposure pathways in children living in agricultural communities to those living in nonagricultural communities in Arizona. Creatinine levels were used to normalize urinary biomarker data of the dialkylphosphates, which are common OP pesticide metabolites. Major study findings were reported in O'Rourke et al. (2000).

PI:
Mary Kay O'Rourke
University of Arizona

EPA GRANT NUMBER:
R825169

AMOUNT:
$596,039

DURATION:
October 1996 through September 1999

Communities in Arizona within 15 miles of the U.S./Mexico Border (46 percent from San Luis, 49 percent from Somerton, and 5 percent from Gadsden/Yuma) were selected from the NHEXAS, 1990 census tract, and the Arizona Border Survey (ABS), to create the Children's Exposure to Pesticide Survey (CPS) for this study. All children were Latino, most households were bilingual, 51 percent were male, and 49 percent were female. Spanish was the preferred language in 97 percent of the homes surveyed. Study subjects were recruited in two ways, a population-based probability design and from families enrolled

in services catering to children, with children that displayed bladder control (2 to 6 years old). A total of 154 children participated in the study (O'Rourke et al., 2000). Descriptive questions were submitted to each household and a two-visit screening was used to develop a 1-day record of typical activities and duration and a 1-day record of all food and beverages consumed. A first morning void urine sample and dust sample were taken during the screening stage as well. Urinary OP, OP metabolites, and creatinine were analyzed.

A total of 154 urine samples were collected with a mean urinary creatinine concentration of 0.90 g/L. The urinary creatinine data appeared to be lower than expected for the first bladder voiding. After questioning the families about their children's urinary behavior, 16 percent of the children were known to wet the bed and ~50 percent may have used the toilet in the night. Differences in seasonal creatinine excretions were observed when comparing autumn and spring (Mann-Whitney, P=0.038) and summer and autumn values (Mann-Whitney, P=0.041). Additional comparisons of the data to the larger data set from the 1996 National Health and Nutrition Examination (NHANES) III (DHHS, 1996) survey indicated racial differences, with African-American children having statistically higher creatinine values (mean=0.94 g/L; n=173; P=0.0000) as compared to Caucasian children (mean=0.78 g/L; n=285). Ethnic differences were observed with non-Hispanic children displaying a significant increase in creatinine (0.86 g/L; n=287; P=0.005) as compared to Hispanic children (mean=0.77 g/L; n=190).

Metabolites of OP pesticides, dialkylphosphates, were measured in the urine of 121 children who were 6 years or younger with valid creatine analyses. Thirty-three percent of the subjects had detectable levels of at least one metabolite, and many contained multiple metabolites. The dialkylphosphate distribution was as follows: 5 percent of the samples contained diethylphosphates (DEPs), 25 percent dimethylphosphates (DMPs), 26 percent dimethylphosphorothioates (DMTPs), and 3 percent dimethylphosphordithioates (DMDTP). Theoretical absorbed daily doses (ADDs) were calculated for three children that excreted the highest amount of biomarker, assuming that a single pesticide was metabolized and that all of the metabolite had cleared. CPF and diazinon are both used in the Yuma area and could be responsible for the DEP metabolites. At the highest DEP excretion, the ADD for diazinon was 126 times the permissible reference dose. DMP and DMTP are associated with methyl parathion metabolism, and the theoretical ADDs were 385 and 61 times the reference dose, respectively. **When examining aggregate exposure to OPs, floor dust appears to be the major medium through which young children are exposed (68.8 percent), followed by solid food (18.8 percent) and beverage (10.4 percent). Air and water (modeled from ABS and NHEXAS data) contribute less than 2 percent to the total aggregate exposure.**

Measuring and Apportioning Children's Exposure to Pesticides in Urban, Suburban, and Rural Communities

The purpose of this research grant was to determine children's actual exposure to pesticides, and to assess if current regulatory decisions (e.g., the Food Quality Protection Act of 1996) are either protective of children's health or cost effective. The study focused on collecting NHEXAS data for exposure to 4 primary pesticides (CPF, diazinon, MDA, and ATRA), 14 secondary pesticides, and 13 polyaromatic hydrocarbons (PAHs). The study was a part of NHEXAS.

PI:
Dr. Ken Sexton,
University of Minnesota

EPA GRANT NUMBER:
R825283

AMOUNT:
$745,572

DURATION:
October 1996 through September 1999

Children (102 children/families, 3 to 12 years old) were recruited from the urban Minneapolis/St. Paul area and rural Goodhue and Rice Counties. Analytical samples taken were as follows: 6-day integrated personal-indoor air; 4-day integrated food and beverages samples (duplicate diet); hand rinses; first morning urine voids; indoor and outdoor air; drinking water; surface wipes; and soils (Quackenboss et al., 2000). Questionnaire data were also collected, diary data of the child's activities were maintained, and a subset of children were videotaped to quantify children's hand-to-mouth activities.

Pesticide products were found in 97 percent of the homes with an 88 percent self-reported use (Adgate et al., 2000). The population-weighted mean numbers of products used and stored in a household in the prior year were 3.1 and 6.0, respectively. These results were at least twice the national averages reported in two previous major studies. However, no differences were observed between urban and rural communities, socioeconomic and/or racial/ethnic factors. CPF and its metabolites were the most commonly measured compounds found in the samples analyzed from personal air (95.0 percent), indoor air (91.5 percent), and dust samples (61.6 percent). Levels of MDA were detected in 54.1, 67.0, and 0.0 percent of these samples, respectively. Diazinon was detected in 64.1, 68.0, and 7.1 percent of personal air, indoor air, and house dust samples, respectively. ATRA, CPF, and diazinon were all detected in fewer than 16 percent

of outdoor air and soil samples. CPF was detected in 57 percent of food samples; detection frequencies for MDA, ATRA, and diazinon were 46, 8, and 3 percent, respectively (Sexton et al., 2003).

Hand-to-mouth behavior was the most observed exposure pathway in children. The 3- to 4-year-old children displayed the most frequent hand-to-mouth actions, however, the activity was also seen in older children at a lower frequency. There were few handwashings preceding food handling and consumption for all age groups with females washing their hands more frequently than males (Adgate et al., 2001 and Freeman et al., 2001).

ATRA, CPF, and MDA were detected in greater than 30 percent of the households in dust and hand washing samples. The median range of CPF and/or metabolites found in the dust samples were 0.07–0.42 ng/cm^2 (Lioy et al., 2000). CPF and/or metabolites were found in over 50 percent of the hand samples with a median amount of 0.03 ng/hand and a maximum of 2.14 ng/hand.

Urinary metabolites were analyzed from at least three first morning voids over a five day period in 90 children that were in households that reported frequent use of pesticides. Urinary pesticide metabolites (not adjusted for creatinine) percent detected were 96.6 percent CPF (6.9 μg/g or 59.0 μg/g, median and maximum, respectively), 46.6 percent MDA, and 4.4 percent ATRA; diazinon was not analyzed. Interchild variability (carbamates and related compounds [1-NAP], CPF and related compounds [TCPy], and MDA) indicated a larger sample size was needed to better assess exposure for the general population. **Intrachild average variability ranges were 1.3 times the weighted population mean for 1-NAP, 1.5 times the weighted population mean for MDA, and approximately equal the weighted population mean for TCPy suggesting single measurements are insufficient to characterize the relative magnitude of long-term exposure to the parent compound (Clayton et al., 2003).**

Assessing Levels of Organophosphorus Insecticides Which Could Expose Children From Pets Treated with Flea Control Insecticides

The objective of this project was to measure potential pesticide exposures to dog owners and their children from flea-dipped or collar-treated dogs. Major findings can be found in Boone et al. (2001).

The researchers recruited dogs from the general population. These dogs were treated with commercial, nonprescription flea control dips (CPF or phosmet) or collars (tetrachlorvinphos or CPF) and were rubbed on the midline back area for five minutes with a cotton glove. The glove was extracted and analyzed for pesticide residues. Pesticide residue samples were taken at 4 hours, and then at 7, 14, and 21 days after application. Collared animals were sampled from the neck area with and without the collar. The CPF-dipped animals were split into two groups (12 dogs/group) to assess if the pesticide accumulated over time; one group of dogs was shampooed before each reapplication; a second group was not bathed. Plasma butyrylcholinesterase and acetylcholinesterase activity were assayed in the dogs, and their owners' urine was analyzed for pesticide metabolites.

The transferable OP pesticide residues from the CPF and phosmet-dipped dogs were found to peak shortly after flea dip administration. CPF residues decreased by 87 percent after 1 week, 92 percent by week 2, and 97 percent by week 3, with similar residue attenuation in the phosmet-dipped dogs. There was no evidence of CPF accumulation from one dipping to the next in the nonshampooed dogs. Considerable individual variablity was observed; however, fur length was not considered a factor in the variability. Plasma butyrylcholinesterase activity in the nonshampooed CPF treated dogs was inhibited 50–75 percent throughout the study and acetylcholinesterase was inhibited by 11–18 percent, with no appreciable cholinesterase inhibition observed with the phosmet dipped or shampooed group of CPF-dipped dogs.

PI:
Dr. Janice Chambers,
Mississippi State University

EPA GRANT NUMBER:
R825170

AMOUNT:
$597,804

DURATION:
October 1996 through September 1999

The tetrachlorvinphos and CPF collars both yielded the least transferable residues from the backs of the dogs. The highest residues were found in the neck area when the tetrachlorvinphos collar was in place. The data suggest the pesticide does not migrate from the neck down the back. An appreciable degree of individual variation in the residues detected was observed with no correlation to fur length. There was negligible inhibition of the plasma cholinesterase in dogs with tetrachlorvinphos collars. In contrast, the CPF collar pesticide residues were considerably lower than those obtained with tetrachlorvinphos collars; however, the plasma cholinesterase activities in the dogs were inhibited about 60 percent compared to pretest activities throughout the sampling period.

Urine samples from the adults and children (aged 3 to 12 years) in the households with dogs that used collars indicated that TCPy levels increased when the collars were placed on the dogs. The magnitude of the increase in TCPy levels was highly variable

among both adults and children, and adjusting the TCPy levels for urinary creatinine concentrations did not significantly reduce the variability. Because of the high variability, the difference between precollar and postcollar TCPy levels in urine, while large for some individuals, was not statistically significant for the study group taken as a whole.

Total Organophosphorus Pesticide Exposure Among Children in Urban and Rural Environments

The primary objectives of the research conducted under this grant were to characterize the geographic, temporal, age-related, and gender-related variability in total OP pesticide exposure in children living in certain areas of Washington State and to determine the relative contributions of environmental sources to the children's total OP pesticide body burdens.

Two biologic monitoring experiments were conducted to measure pesticide metabolites in 2- to 5-year-old children's urine. Samples were analyzed for OP pesticide metabolites and six dialkylphosphates (DAP). The first study evaluated 110 children with sampling in the spring and fall, and the other involved 44 children from agricultural areas of Washington State whose urine was sampled monthly over 21 months. In addition to the first two efforts, the third field study was conducted to evaluate biomarkers in 13 children with higher potential OP pesticide exposure as judged based on behavioral surveys and residential location. Samples of inhaled air (24-hour), soil, house dust, drinking water, 24-hour duplicate diet, and 24-hour urine were analyzed. Another study measured DAP levels in urine from preschool children of urban and suburban communities that consumed a conventional diet or an organic diet.

In the first field study, no differences in DAP levels were observed when comparing values from spring and fall, urban or suburban communities, gender, age, family income, or housing type. Children whose parents reported pesticide use in the garden had significantly higher levels of dimethyl and diethyl DAPs in their urine (Lu et al., 2001). In the second field effort, a strong temporal trend in OP pesticide exposure was observed with DAP concentrations displaying an elevation in months when OP pesticides were sprayed. Boys had significantly higher DAP metabolite levels in their urine than did girls. No differences were found based on child age, parental occupation, or residential proximity to fields (Koch et al., 2002). The data were analyzed by a mixed-effects analysis of variance (ANOVA) model that compared the within- and between-child variance and standard deviation in urinary DMTP concentration during both the spray and nonspray months. The results of this analysis demonstrated that, regardless of time of year, the within-child component of variability is much greater than the between-child component for this population. **These results show that urinary DMTP concentration varied more from day-to-day than from child-to-child in this population.** In the third field effort, azinphosmethyl, CPF, malathion, methidathion, methyl parathion, and phosmet were detected in the food of these children. Azinphosmethyl (10 percent) was the compound found most frequently, particularly in foods or beverages containing apples or apple juice. No detections were found to be above legal tolerances for residues on produce. However, the acute population-adjusted reference dose (aPAD) for CPF of 1.7 mg/kg/day was exceeded by one child who consumed 10 cherry tomatoes that contained 30 ng/g azinphosmethyl and 350 ng/g CPF. This child's cumulative daily dose of CPF equivalents was estimated to be 2.5 mg/kg/day (Fenske et al., 2002). Diazinon and CPF were commonly detected in indoor air. Most housedust samples contained one or more OP pesticide. OP pesticides were virtually non-detectable in drinking water and soil. **Clear differences were noted in the exposure pathways for the rural agricultural children and Seattle metropolitan area children, with metabolite levels in suburban children being correlated with reported household pesticide use (Lu et al., 2004).**

PI:
Dr. Richard Fenske,
University of Washington

EPA GRANT NUMBER:
R825171

AMOUNT:
$600,145

DURATION:
September 1996 to September 2000

When four urine samples were collected from each child over the course of a 24-hour period, the data were highly variable, suggesting a single spot sample is not a reliable predictor of an individual child's exposure. First morning void samples were found to be the best predictors of total daily metabolite excretion (Griffith et al., submitted and Kissel et al., 2005). **In the fourth field study, children with organic diets were found to have significantly lower median dimethyl DAP levels than did children consuming conventional diets. No differences in occupational or household pesticide use were reported between the two groups (Curl et al., 2003).**

The researchers also developed a novel method for determination of OP pesticide concentrations in household and vehicle dust. This method used size exclusion chromatography (SEC) as a cleanup method for the analysis of organophosphorus pesticides diazinon, methyl parathion, CPF, MDA, phosmet, and azinphosmethyl (Moate et al., 1999).

3. Contributions to ORD Research Goals and State of Knowledge

3.1 Contributions to ORD Research Goals

All of the research contained in this report has helped to reduce uncertainties in risk assessment by providing better data on children's aggregate exposures and estimation of exposure factors, improving knowledge of children's pesticide exposure in agricultural communities, helping to identify principles for the use of scaling factors in risk assessment, and developing and validating biomarkers of exposure and dose. For convenience, grants are referred to in this section by the name of the first PI listed on the grant proposal. (Richard Fenske and Mary Kay O'Rourke were the PI on more than one grant; these grants are also referred to by number).

Four of the grants (**Fenske** 825171, **O'Rourke** 827443 and 825169, and **Sexton**) specifically involved measurements of aggregate pesticide exposures from multiple sources in different selected populations of children. **Fenske** looked at multipathway exposures in children in Washington State in relation to urban/rural residence, household and agricultural pesticide usage, versus parental and other household variables. Both of **O'Rourke's** grants evaluated pesticide exposures in predominantly Hispanic rural communities near the U.S./Mexico border in relation to pesticide levels in soil, house dust, and activity patterns. **Sexton** evaluated exposure patterns of children in urban and rural Minnesota communities. Multipathway aggregate exposures (air, soil, dust, diet, surfaces) were measured using urinary metabolites as biomarkers.

Shalat evaluated the factors contributing to children's ingestion exposures to OP pesticides, also in New Mexico. **O'Rourke** (825169) estimated OP exposures in children in Arizona, and evaluated the relative contributions of dermal and ingestion pathways to total exposure. **Whyatt's** analysis of meconium samples and maternal exposure levels will help characterize prenatal OP pesticide exposure patterns among minority infants in New York City. **Wilkens'** longitudinal study is examining maternal, prenatal, and postnatal biomarkers of exposuure that support analysis of aggregate exposures to OP and pyrethoid pesticides and may reveal age-related exposure differences. His work will also attempt to correlate biomarkers of exposure with impaired development in the exposed infants.

Along with **Sexton,** both **Shalat** and **O'Rourke** (827443) evaluated children's mouthing behaviors and found that they contributed significantly to aggregate exposures. **Raymer** evaluated levels of pesticide metabolites in urine from populations in rural Minnesota, finding that metabolite levels were much higher in children than in adults, and higher in younger children than in older children in similar exposure settings. **Chambers** developed a method for measuring the potential dermal exposures and doses in children and adult dog owners who use pesticide flea dips or collars and found that such exposures may contribute significantly to household pesticide exposures. These results are directly applicable to pesticide risk assessments.

Many of these grants provided information about children's exposures, body burdens and dose levels that could be used in conjunction with other data for comparison with adults' exposure patterns. **Raymer's** research specifically documented higher children's pesticide exposures and doses and higher exposures in younger children than in older children in similar exposure settings. **Wilkins** is engaged in a long-term study of maternal, prenatal, and postnatal pesticide exposures and body burdens. **Whyatt's** study is also evaluating and comparing indices of maternal and prenatal exposure. Finally, the PBPK modeling efforts of **Timchalk** and **Tessari** provide frameworks that may ultimately be used to compare children and adult body burdens of CPF and ATRA, respectively. **Chambers** compared adults' and children's levels of urinary pesticide metabolites in households with CPF-collared dogs.

Research under many of the grants has indirectly provided information that could be used in development of scaling factors for risk assessment (that is, for adjusting between adults and children). Data from the research that evaluated relationships between children and adult exposures and body burdens (**Raymer, Whyatt**) may find direct application in risk assessments for pesticide exposures. Data being developed by **Wilkins** on indices of maternal and infant body burdens of pesticides might also be used. **Shalat** evaluated methods for evaluating dermal and ingestion exposures based on children's body (hand) size and behavior patterns, and **O'Rourke** (827443) investigated the behavior and physical determinants (including gender) of children's pesticide exposure patterns. In addition, the PBPK models developed by **Timchalk** and **Tessari** are intended to help elucidate relationships between adult and children's exposures, absorbed doses, and adverse effects.

Grants involving PBPK modeling helped to understand differences between children and adults. **Timchalk** and **Fenske** (828606) developed and/or refined PBPK models for OP pesticides to improve their applicability in human health risk assessments for adults and children. **Timchalk** developed analytical methods and conducted *in vivo* and *in vitro* experiments on CPF metabolism to improve a previously developed PBPK-PD model. Studies of enzyme polymorphism on CPF metabolism, and on the role of first-pass metabolism in the intestine on absorbed dose, were used to improve the ability of the model to replicate serum time-course data. In addition, the refined model was used to establish the utility of saliva esterase inhibition as a useful biomarker of CPF exposure.

Fenske (828606) used data from rat studies to develop a pharmacokinetic model for diazinon and its metabolites. The model confirmed the utility of saliva metabolite levels as indicators of exposure.

Tessari developed the first metabolite-specific PBPK model for ATRA. **Tessari's** model incorporates dealkylation by cytochrome P450 isozymes and glutathione conjugation, as well as binding to hemoglobin and serum proteins. The model is intended for use in evaluating hair protein adducts as biomarkers of exposure and as potential risk indicators. This model may help to better elucidate the as yet poorly understood pharmacodynamic mechanisms of ATRA and its metabolites in humans.

The five studies funded under the biomarkers RFA were specifically devoted to biomarker identification and validation, and all attempt to improve risk assessment through biomarker use, and to develop more convenient, less invasive biomarkers of exposure. **Wilkins** conducted a detailed evaluation of a wide range of maternal and neonatal biomarkers of pesticide exposure as predictors of infants' neurodevelopmental impairment. **Fenske** (828606) and **Timchalk** used animal experiments and PBPK modeling to evaluate the usefulness of diazinon metabolites and cholinesterase levels, respectively, in saliva as noninvasive indicators of pesticide exposures and risks. **Whyatt** evaluated the use of OP metabolite levels in meconium as a noninvasive indicator of prenatal pesticide exposures. The PBPK model developed by **Tessari** could be used in pesticide risk assessments and is also intended for use in validating hair protein adducts as a noninvasive biomarker of ATRA exposure. Five studies that measured children's exposures (**Raymer, Shalat, O'Rourke**—both grants, **Sexton,** and **Fenske** 825171) evaluated correlations between environmental samples, noninvasive personal exposure samples (hand rinses and wipes), and more conventional biomarkers (urine metabolite analyses). **Wilkins**, **Sexton**, **O'Rourke**—both grants, and **Fenske** (R825171) supported development and validation of urinary metabolites as biomarkers of exposure to pesticides.

In summary, these research grants contributed to our knowledge of children's pesticide exposures, including pathways, types of pesticides, and age-related differences. This research also helps us understand differences in exposure between children and adults. Finally, it has increased our understanding of children's pesticide exposures in agricultural communities.

This research will be beneficial for risk assessments, for models that help quantify biomarkers of exposure, and for the identification and validation of novel biomarkers.

3.2 Summary of Major Contributions to the State of Knowledge

All three of the RFAs resulted in research that contributed significantly to the state of knowledge related to children's pesticide exposures and risks. Major contributions include:

Biomarkers for the Assessment of Exposure and Toxicity in Children

- *Novel Biomarkers.* Three studies investigated novel, noninvasive biomarkers of children's exposure, including saliva (diazinon metabolites, and cholinesterase inhibition by CPF), meconium (third-trimester cumulative exposure to OP pesticides), and hair protein adducts (ATRA and metabolites).

- *PBPK Validation and Support of Biomarkers.* Some of the studies discussed above included the evaluation and validation of biomarkers as part of comprehensive PBPK frameworks that may be used in future risk assessments for children's exposure to pesticides. These studies also suggest mechanistic and methodological approaches for future validation of children's biomarkers of exposure.

Children's Vulnerability to Toxic Substances in the Environment

- *Ubiquity of Pesticide Contamination and Exposure.* **Studies under this RFA found uniformly high frequencies of pesticide contamination in household dust and surface wipes, confirming the ubiquity of household sources of children's pesticide exposure.** The frequency of detection of pesticide metabolites in urine approached 100 percent in some populations.

- *High Variability in Children's Pesticide Exposures.* Levels of household pesticide contamination and biomarkers of children's exposure were found to be highly variable among households and individuals, with most subjects experiencing low exposures, while a few were highly exposed. **The most highly exposed children were found to have received estimated pesticide doses that exceeded health-based criteria in two instances. These studies demonstrated the need to thoroughly characterize population exposures to avoid potentially hazardous exposures, even where most exposures are low.**

- *Importance of Mouthing and Other Behaviors.* Results of several studies established quantitatively what had been suspected but not conclusively established, that mouthing behavior in young children is an important factor in determining total household exposure to pesticides. **One study showed that this risk is not reduced by normal hygiene practices, a finding that has important implications for the design of strategies to reduce children's pesticide exposures.**

Exposure of Children to Pesticides

- *Estimation of Aggregate Exposures.* Grants under this RFA funded four major studies of cohorts of children in different areas of the country, in different ethnic groups, and in urban, rural, and agricultural areas.

- *Sources of Exposure.* The studies addressed the relative importance of different sources of exposures, behaviors that contributed to exposures, and socieconomic, parental, and household variables.

- *Relative Exposures of Children and Adults.* Two of the studies compared children's and adults' exposure patterns, exposure levels, and biomarkers of exposure in such a way that inferences can be drawn regarding potential risk differences by age.

In summary, the grants evaluated in this report have resulted in a number of important advances in the state of knowledge relating to children's pesticide exposures. Research under these grants has added greatly to the available data on children's pesticide exposure patterns and potential risks, the usefulness of biomarkers of pesticide exposure, and identified major methodological and data gaps in risk assessment for children's pesticide exposures.

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Appendix A. Cross-Walk of STAR Grant Contributions to ORD Research Goals and Specific Grant Contributions to These Goals

More detailed tabular summaries of the contributions of each grant to meeting EPA ORD's Annual Perfomance Goals (APGs) or Annual Performance Measures (APMs) in the areas of children's exposure and risk assessment are provided in this appendix. The first column of table A-1 below lists these seven major research goals. Each column of the table identifies with a star the grants whose research has contributed significantly to the achievement of these goals.

Table A-1. Cross-walk of STAR Grant Contributions to ORD Research Goals

	Biomarkers of Pesticide Exposure					Children's Vulnerability to Pesticides			Children's Exposure to Pesticides			
Research Objective, Human Health Multi-Year Plan	R828611 Wilkins	R828608 Timchalk	R828606 Fenske	R828609 Whyatt	R828610 Tessari	R827440 Shalat	R827444 Raymer	R827443 O'Rourke	R825169 O'Rourke	R825283 Sexton	R825170 Chambers	R825171 Fenske
APG 44. Provide better data on children's aggregate exposures and estimation of exposure factors	★			★		★	★	★	★	★	★	★
APM 188. Provide information supporting the comparison of children's and adult exposures and body burdens	★	★		★	★		★				★	
APM 187. Improve knowledge of children's pesticide exposure in agricultural communities						★	★	★	★	★		★
APG 45. Help identify principles for the use of scaling factors in risk assessment	★	★		★	★	★	★	★				
APM 182. Development of physiologically based pharmacokinetic/pharmacodynamic (PBPK) models to quantify biomarkers of exposures to organophosphate pesticides		★	★									
APM 376. Provide biomarkers and pharmocokinetic data that can be used in pesticide risk assessments under the Food Quality Protection Act	★	★	★	★	★	★	★	★	★	★		★
APM 206. Develop less invasive biomarkers for assessing children's exposures and risks	★	★	★	★	★		★	★	★	★		★

Research Objective, Human Health Multi-Year Plan	EPA Grant Number R828611 (Wilkins) Biomarkers and Neurobehavioral Effects of Perinatal Exposure to Chlorpyrifos and Other Organophosphate Insecticides
APG 44. Provide better data on children's aggregate exposures and estimation of exposure factors	The study will provide biomarkers that indicate maternal, prenatal, and early aggregate exposures to a range of commonly used household pesticides.
APM 188. Provide information supporting the comparison of children's and adult exposures and body burdens	Relative body burdens of household pesticides may be estimated from the study results.
APM 187. Improve knowledge of children's pesticide exposure in agricultural communities	N/A
APG 45. Help identify principles for the use of scaling factors in risk assessment	The study results may support estimates of scaling factors for use in estimating pre- and postnatal pesticide exposures.
APM 182. Development of physiologically based pharmacokinetic/pharmacodynamic (PBPK) models to quantify biomarkers of exposures to organophosphate pesticides	N/A
APM 376. Provide biomarkers and pharmocokinetic data that can be used in pesticide risk assessments under the Food Quality Protection Act	The study will provide information concerning the relationships between biomarkers of specific pesticide exposures and adverse effects on neurological development, which may be applied in children's risk assessments.
APM 206. Develop less invasive biomarkers for assessing children's exposures and risks	The study can provide validation data in support of urinary metabolite analysis as biomarkers of exposure in infants, particularly for synthetic pyrethroids.

Research Objective, Human Health Multi-Year Plan	EPA Grant Number R828608 (Timchalk) Development of a PBPK-PD Model to Quantitate Biomarkers of Exposure for Organophosphate Insecticides
APG 44. Provide better data on children's aggregate exposures and estimation of exposure factors	N/A
APM 188. Provide information supporting the comparison of children's and adult exposures and body burdens	Refined PBPK-PD model can be used to investigate differences in metabolism, adverse effects associated with age differences, enzyme polymorphisms.
APM 187. Improve knowledge of children's pesticide exposure in agricultural communities	N/A
APG 45. Help identify principles for the use of scaling factors in risk assessment	Refined PBPK-PD model can be used to investigate differences in metabolism, adverse effects associated with age differences, enzyme polymorphisms.
APM 182. Development of physiologically based pharmacokinetic/pharmacodynamic (PBPK) models to quantify biomarkers of exposures to organophosphate pesticides	Developed data and PBPK model supporting the use of metabolite and cholinesterase measurement in saliva as biomarkers of OP pesticide exposure.
APM 376. Provide biomarkers and pharmocokinetic data that can be used in pesticide risk assessments under the Food Quality Protection Act	Refined PBPK-PD model can be used in risk assessments for OP residues in foods as required under the FQPA.
APM 206. Develop less invasive biomarkers for assessing children's exposures and risks	Developed data supporting the use of metabolite and cholinesterase measurement in saliva as biomarkers of OP pesticide exposure.

Research Objective, Human Health Multi-Year Plan	EPA Grant Number: R828606 (Fenske) Saliva Biomonitoring for Organophosphorus Pesticide Exposures in Children
APG 44. Provide better data on children's aggregate exposures and estimation of exposure factors	N/A
APM 188. Provide information supporting the comparison of children's and adult exposures and body burdens	N/A
APM 187. Improve knowledge of children's pesticide exposure in agricultural communities	N/A
APG 45. Help identify principles for the use of scaling factors in risk assessment	N/A
APM 182. Development of physiologically based pharmacokinetic/pharmacodynamic (PBPK) models to quantify biomarkers of exposures to organophosphate pesticides	Developed exposure model using metabolites in saliva as biomarkers of pesticide exposure; could be integrated into PBPK model for estimation of exposures or target organ dose.
APM 376. Provide biomarkers and pharmocokinetic data that can be used in pesticide risk assessments under the Food Quality Protection Act	Developed pharmacokinetic data on OP pesticide diazinon. Developed data supporting the use of saliva as a biomonitoring of OP pesticide exposure.
APM 206. Develop less invasive biomarkers for assessing children's exposures and risks	Developed data supporting the use of metabolite measurement in saliva as a biomarker of risk for OP pesticide exposure.

Research Objective, Human Health Multi-Year Plan	EPA Grant Number: R828609 (Whyatt) Measurement of Non-Persistent Pesticides in Postpartum Meconium
APG 44. Provide better data on children's aggregate exposures and estimation of exposure factors	Will help demonstrate prenatal exposure patterns of minority infants to OP pesticides.
APM 188. Provide information supporting the comparison of children's and adult exposures and body burdens	Meconium analyses may turn out to be useful biomarkers of cumulative (time-integrated) exposures and body burdens during pregnancy.
APM 187. Improve knowledge of children's pesticide exposure in agricultural communities	N/A
APG 45. Help identify principles for the use of scaling factors in risk assessment	The results could ultimately be used to help evaluate age-specific (including prenatal) variations in exposure and body burden that could be used in risk assessment.
APM 182. Development of physiologically based pharmacokinetic/pharmacodynamic (PBPK) models to quantify biomarkers of exposures to organophosphate pesticides	N/A
APM 376. Provide biomarkers and pharmocokinetic data that can be used in pesticide risk assessments under the Food Quality Protection Act	Meconium levels may shed light on prenatal exposure levels that could be used in risk assessment under the FQPA.
APM 206. Develop less invasive biomarkers for assessing children's exposures and risks	Meconium could be a useful noninvasive biomarker of cumulative exposure to OP pesticides and other chemicals.

Research Objective, Human Health Multi-Year Plan	EPA Grant Number: R828610 (Tessari; Previously Andersen) Chlorotriazine Protein Binding: Biomarkers of Exposure and Susceptibility
APG 44. Provide better data on children's aggregate exposures and estimation of exposure factors	N/A
APM 188. Provide information supporting the comparison of children's and adult exposures and body burdens	Future development of the atrazine PBPK model could be used to evaluate age-specific differences in pharmacokinetics.
APM 187. Improve knowledge of children's pesticide exposure in agricultural communities	N/A
APG 45. Help identify principles for the use of scaling factors in risk assessment	Future development of the atrazine PBPK model could be used to evaluate age-specific differences in pharmacokinetics.
APM 182. Development of physiologically based pharmacokinetic/pharmacodynamic (PBPK) models to quantify biomarkers of exposures to organophosphate pesticides	N/A (Atrazine is not an OP)
APM 376. Provide biomarkers and pharmocokinetic data that can be used in pesticide risk assessments under the Food Quality Protection Act	The atrazine PBPK model could provide a framework for assessing potential children's sensitivity to atrazine exposure, as required under the FQPA.
APM 206. Develop less invasive biomarkers for assessing children's exposures and risks	Further development of the model will allow evaluation of the feasibility of using hair protein adducts as a noninvasive biomarker for quantifying atrazine exposures.

Research Objective, Human Health Multi-Year Plan	EPA Grant Number: R827440 (Shalat) Ingestion of Pesticides by Children in an Agricultural Community on the U.S./Mexico Border
APG 44. Provide better data on children's aggregate exposures and estimation of exposure factors	Quantified levels of household exposures and determined dose levels.
APM 188. Provide information supporting the comparison of children's and adult exposures and body burdens	N/A
APM 187. Improve knowledge of children's pesticide exposure in agricultural communities	Developed direct measurements of pesticide body burden and excretion rates in children living in rural areas.
APG 45. Help identify principles for the use of scaling factors in risk assessment	Data collected indicative of variations in pediatric pesticide exposures and body burdens between age groups.
APM 182. Development of physiologically based pharmacokinetic/pharmacodynamic (PBPK) models to quantify biomarkers of exposures to organophosphate pesticides	N/A
APM 376. Provide biomarkers and pharmocokinetic data that can be used in pesticide risk assessments under the Food Quality Protection Act	Refined estimates of children's exposures and doses of OP pesticide metabolites that can be used in risk assessments for pesticide residues in foods as required under the FQPA.
APM 206. Develop less invasive biomarkers for assessing children's exposures and risks	N/A

Research Objective, Human Health Multi-Year Plan	EPA Grant Number: R827444 (Raymer) Study of Exposure and Body Burden of Children of Different Ages to Pesticides in the Environment
APG 44. Provide better data on children's aggregate exposures and estimation of exposure factors	Quantified levels of household exposures to pesticides.
APM 188. Provide information supporting the comparison of children's and adult exposures and body burdens	Developed data establishing that children have higher body burdens of OP pesticide metabolites than adults.
APM 187. Improve knowledge of children's pesticide exposure in agricultural communities	Developed direct measurements of pesticide body burden and excretion rates in children living in rural areas.
APG 45. Help identify principles for the use of scaling factors in risk assessment	Data collected indicative of variations in pediatric pesticide exposures and body burdens between age groups.
APM 182. Development of physiologically based pharmacokinetic/pharmacodynamic (PBPK) models to quantify biomarkers of exposures to organophosphate pesticides	N/A
APM 376. Provide biomarkers and pharmocokinetic data that can be used in pesticide risk assessments under the Food Quality Protection Act	Refined estimates of children's exposures and doses of OP metabolites that can be used in risk assessments for pesticide residues in foods as required under the FQPA.
APM 206. Develop less invasive biomarkers for assessing children's exposures and risks	Developed new noninvasive method for evaluating infant dermal contact exposures (body suits). Study provides data to support urinary metabolite analysis as biomarkers of exposure in children.

Research Objective, Human Health Multi-Year Plan	EPA Grant Number: R827443 (O'Rourke) Vulnerability of Young Children to OP Pesticides and Metals through Intermittent Exposures in Yuma, County, AZ
APG 44. Provide better data on children's aggregate exposures and estimation of exposure factors	Quantified levels of household exposure factors and determined exposure levels of children.
APM 188. Provide information supporting the comparison of children's and adult exposures and body burdens	N/A
APM 187. Improve knowledge of children's pesticide exposure in agricultural communities	Developed direct measurements of pesticide residues in children living in agricultural areas.
APG 45. Help identify principles for the use of scaling factors in risk assessment	Data collected indicative of variations in pediatric pesticide exposures and body burdens between genders.
APM 182. Development of physiologically based pharmacokinetic/pharmacodynamic (PBPK) models to quantify biomarkers of exposures to organophosphate pesticides	N/A
APM 376. Provide biomarkers and pharmocokinetic data that can be used in pesticide risk assessments under the Food Quality Protection Act	Identified a urinary metabolite as a biomarker of exposure.
APM 206. Develop less invasive biomarkers for assessing children's exposures and risks	Developed data supporting the use of metabolite measurement in urine as a biomarker of risk for OP pesticide exposure.

Research Objective, Human Health Multi-Year Plan	EPA Grant Number: R825169 (O'Rourke) Exposure of Children to Pesticides in Yuma County, Arizona
APG 44. Provide better data on children's aggregate exposures and estimation of exposure factors	Quantified levels of pesticide exposure from dust, food, and beverages that were correlated with urine samples taken from children in Arizona from urban and agricultural areas.
APM 188. Provide information supporting the comparison of children's and adult exposures and body burdens	N/A
APM 187. Improve knowledge of children's pesticide exposure in agricultural communities	Agricultural migrant communities in Yuma, Arizona, were compared to urban area.
APG 45. Help identify principles for the use of scaling factors in risk assessment	N/A
APM 182. Development of physiologically based pharmacokinetic/pharmacodynamic (PBPK) models to quantify biomarkers of exposures to organophosphate pesticides	N/A
APM 376. Provide biomarkers and pharmocokinetic data that can be used in pesticide risk assessments under the Food Quality Protection Act	Data collected on urinary metabolites (DAPs) from children in Yuma, Arizona, from urban and agricultural areas.
APM 206. Develop less invasive biomarkers for assessing children's exposures and risks	Urinary samples normalized with creatinine. Study supports the use of urinary metabolites as biomarkers of exposure in children.

Research Objective, Human Health Multi-Year Plan	EPA Grant Number: R825283 (Sexton) Measuring and Apportioning Children's Exposure to Pesticides in Urban, Suburban, and Rural Communities
APG 44. Provide better data on children's aggregate exposures and estimation of exposure factors	Quantified levels of pesticide exposure from dust, hand washing, indoor and outdoor air, food, and beverages, which were correlated with OP metabolites from urine samples taken from children in Minnesota from urban and agricultural areas.
APM 188. Provide information supporting the comparison of children's and adult exposures and body burdens	N/A
APM 187. Improve knowledge of children's pesticide exposure in agricultural communities	Assessed rural/agricultural communities of Goodhue and Rice Counties for pesticide exposure and metabolism.
APG 45. Help identify principles for the use of scaling factors in risk assessment	N/A
APM 182. Development of physiologically based pharmacokinetic/pharmacodynamic (PBPK) models to quantify biomarkers of exposures to organophosphate pesticides	N/A
APM 376. Provide biomarkers and pharmocokinetic data that can be used in pesticide risk assessments under the Food Quality Protection Act	Dietary exposure assessed through analyzing food and beverage OP content and correlated with urinary metabolites (DAPs) for children in Minnesota from urban and agricultural areas.
APM 206. Develop less invasive biomarkers for assessing children's exposures and risks	Study provides data that support the use of urinary metabolites as biomarkers of exposure.

Research Objective, Human Health Multi-Year Plan	EPA Grant Number: 825170 (Chambers) Assessing Levels of Organophosphorus Insecticides Which Could Expose Children From Pets Treated with Flea Control Insecticides
APG 44. Provide better data on children's aggregate exposures and estimation of exposure factors	Quantified levels of pesticide exposure from dog flea controls.
APM 188. Provide information supporting the comparison of children's and adult exposures and body burdens	Compared urinary pesticide metabolites for chloropyrifos in households with chloropyrifos collared dogs.
APM 187. Improve knowledge of children's pesticide exposure in agricultural communities	N/A
APG 45. Help identify principles for the use of scaling factors in risk assessment	N/A
APM 182. Development of physiologically based pharmacokinetic/pharmacodynamic (PBPK) models to quantify biomarkers of exposures to organophosphate pesticides	N/A
APM 376. Provide biomarkers and pharmocokinetic data that can be used in pesticide risk assessments under the Food Quality Protection Act	N/A
APM 206. Develop less invasive biomarkers for assessing children's exposures and risks	N/A

Research Objective, Human Health Multi-Year Plan	EPA Grant Number R825171 (Fenske) Total Organophosphorus Pesticide Exposure among Children in Urban and Rural Environments
APG 44. Provide better data on children's aggregate exposures and estimation of exposure factors	Quantified levels of pesticide exposure from dust, personal air, drinking water, and food, which was correlated with urine samples.
APM 188. Provide information supporting the comparison of children's and adult exposures and body burdens	N/A
APM 187. Improve knowledge of children's pesticide exposure in agricultural communities	Assessed urban/agricultural communities of Washington State for pesticide exposure and metabolism.
APG 45. Help identify principles for the use of scaling factors in risk assessment	N/A
APM 182. Development of physiologically based pharmacokinetic/pharmacodynamic (PBPK) models to quantify biomarkers of exposures to organophosphate pesticides	N/A
APM 376. Provide biomarkers and pharmocokinetic data that can be used in pesticide risk assessments under the Food Quality Protection Act	Six dialkylphosphates were analyzed in children's urine from various ages, genders, time points, geographical areas, and from children who consumed different diets. Duplicate diets were analyzed for 15 OP pesticides.
APM 206. Develop less invasive biomarkers for assessing children's exposures and risks	Study can provide data to support urinary metabolite analysis as biomarkers of exposure in children.

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