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Human Health
RESEARCH CONTRIBUTIONS REPORT


U.S. Environmental Protection Agency
Office of Research and Development

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Washington, DC 20460

Notice

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Contents

Introduction

The mission of the U.S. Environmental Protection Agency (EPA) is clear—to protect human health and the environment. Since its formation in 1970, EPA has made great progress in making the environment cleaner and safer. However, today's remaining environmental issues are much more complicated than those 20-30 years ago. Scientific advances and technological developments, as well as a better understanding of factors that pose risks to humans, have generated new concerns about environmental hazards and how best to protect human health. More than ever, there is a need to look to the future, anticipate potential threats to human health, and establish scientifically defensible approaches for addressing them.

Sound science is needed for EPA to determine and assess environmental problems that are the most threatening to human health and our quality of life. In that regard, EPA's Office of Research and Development (ORD) maintains several problem-driven research programs that address specific, short-term research gaps identified by EPA's Program and Regional Offices (e.g., research on drinking water, water quality, global change, air, and safe pesticides/safe products). EPA also supports two research programs, the Human Health Research Program (HHRP) and the Ecological Research Program, that provide relevant research to support problem-driven research efforts. HHRP provides an understanding of fundamental processes which underlie environmentally related health problems and develops principles that are broadly applicable to a variety of real-world environmental problems. The ultimate objective of the HHRP is to provide the scientific foundation for regulatory decision-making.

This Research Contributions Report is intended to provide general background material about the HHRP and to document significant milestones accomplished by the program over the last five years. The Overview section describes the HHRP in the context of the overall research effort in ORD and delineates the four main themes covered by the HHRP—research on biological mechanisms, cumulative risk, susceptible subpopulations, and tools for evaluating risk management decisions. The Research Contributions section describes 11 major accomplishments of the program. This research consists of multi-disciplinary, integrated efforts to address significant research gaps facing EPA risk assessors and risk managers. The Summary of Progress section that follows describes other accomplishments that represent important products produced by the HHRP. The Future Directions section of this document builds on the program's accomplishments and describes the projected direction of the research program for the next five years.

Overview of the Human Health Research Program

EPA's Human Health Research Program (HHRP) in the Office of Research and Development (ORD) uniquely integrates many environmental science disciplines to build a strong foundation for risk assessment and improve understanding of toxic chemical exposure and health effects. The multidisciplinary program coordinates fundamental research to fill gaps in scientific knowledge that will ultimately improve assessment of public health risks and solve environmental problems.

The program is organized around four main themes to address areas of research needed to advance risk assessment capabilities. They are:

- **BIOLOGICAL (MECHANISTIC) RESEARCH**: To understand underlying biological processes triggered when people are exposed to environmental contaminants

- **CUMULATIVE RISK RESEARCH**: To evaluate what happens when we are exposed to the many chemical mixtures in our environment

- **SUSCEPTIBLE SUBPOPULATION RESEARCH**: To protect the aging population, children, and those with chronic diseases by providing new insights into how pollutants may affect their health

- **TOOLS FOR EVALUATING RISK MANAGEMENT DECISIONS**: To develop measurement tools and biological indicators needed to assess the impact of regulatory decisions on public health

We contribute to other research areas and programs in ORD by providing broad and generic information that will help to improve understanding of many environmental problems now and in the future. For example, in order to develop approaches to conduct risk assessments of mixtures of pesticides based on mode of action, as required by the Food Quality Protection Act, it is necessary to have some knowledge of the mode of action, i.e., how a contaminant interacts with the body. Our research makes significant contributions to the pesticide research program by providing fundamental knowledge about potential modes of action that can be used for studying cumulative risk.

Our research focuses on developing a more systematic understanding of the physical, chemical, or biological processes that underlie how humans can be affected by environmental agents. We develop broadly applicable research tools for analyzing and using information in science-based decision making. Thus we can generate data that can be used to support EPA's risk assessments. The research is strategically organized and planned to provide the methods, tools, and data for addressing risk assessment needs.

For example, to prioritize pesticides and drinking water contaminants for screening and testing, it is necessary to identify the chemicals of greatest concern to public health. Human health researchers have contributed in a strategic way to this hazard identification effort. They have identified biological effects or endpoints that can be incorporated into computational models for predicting hazards, and they have identified key toxicity pathways for use in physiologically based pharmacodynamic models that can be used to predict adverse human health effects.

Projects are based on ORD's annual planning process, which involves input and prioritization of research by the Agency's Program and Regional Office risk assessors, risk managers and other stakeholders. A multi-year plan for human health research charts the course for the program over the next seven years to provide significant outputs needed by EPA to make decisions on protecting the public health. The multi-year plan for fiscal years 2006-2013 is responsive to the needs identified by EPA to advance risk assessment and address environmental problems. www.epa.gov/osp/myp/HH%20MYP%20Final.pdf

The research program is evaluated through extensive independent expert review by EPA's Board of Scientific Counselors (BOSC). This evaluation assesses the development and application of new human health research knowledge, as well as the relevance, quality, and scientific leadership of the program. In 2005, the BOSC Subcommittee for Human Health found that the Human Health Research Program is of high quality, appropriately focused, multidisciplinary, displayed good stakeholder participation, informed risk assessments, and achieved the goal of reducing uncertainty (www.epa.gov/osp/bosc). The BOSC Subcommittee recommended greater involvement of stakeholders in the planning and prioritization process, better articulation of the overall goals of the program, and development of a framework for research on tools for evaluating risk management decisions. We have successfully integrated these practices into our research program.

To fulfill the mandate to protect human health, EPA uses a process known as risk assessment to identify and characterize environmentally related health problems. This process is an integral component of environmental decision making under regulatory statutes such as the Clear Air Act (1970), the Toxic Substances Control Act (1976), the Safe Drinking Water Act

There are many uncertainties associated with the assessment of human health risk due to data limitations and the complex relationship between source, exposure, and biological response to environmental agents.

(1996), the Federal Insecticide, Fungicide and Rodenticide Act (1996), and the Food Quality Protection Act (1996). HHRP is designed to strengthen and advance this risk assessment process.

Biological Research

There are many uncertainties associated with the assessment of human health risk due to data limitations and the complex relationship between source, exposure, and biological response to environmental agents. Specific knowledge gaps have been articulated by the scientific community (NRC, 1994; SAB, 1995; Presidential/Congressional Commission on Risk Assessment and Risk Management, 1997) and EPA risk assessors and risk managers (U.S. EPA, 2005).

For example, data on the biological response to environmental agents is often gathered from laboratory animals under entirely different sets of exposure conditions than humans may experience. Therefore, extrapolating from laboratory animals or cell culture systems to humans in assessing risk can be uncertain. In the case of atrazine, a widely used herbicide, HHRP science addressed this uncertainty, improving the risk assessment. The research demonstrated that carcinogenic effects in animals are not relevant to humans and that humans are more likely to experience non-carcinogenic effects such as developmental and reproductive dysfunction because of the mode of action of atrazine.

Data available to risk assessors may be based on studies that used moderate-to-high concentrations. Because most real-world exposures occur at lower concentrations, risk assessors must extrapolate from these higher-dose studies to lower doses “real-world” exposure scenarios, which can be problematic. Risk assessors and managers need to understand better the linkages between environmental exposures and how the chemicals are handled once they get into the body, as well as how chemicals act on a target site and the subsequent health effects. For example, in the risk assessment for arsenic, dose-response information from ORD was used to support the default risk assessment model (linear model) for carcinogenic agents.

Cumulative Risk Research

In the past, evaluation of human health risk has focused on a single chemical or single exposure pathway, e.g., by inhalation only. However, most humans are exposed to many environmental contaminants via multiple pathways and routes. Such combinations could result in unexpected aggregate or cumulative effects. The combined risk from such exposures may be greater or less than what would typically be predicted from data on individual chemicals with single routes of exposure (U.S. EPA, 2000). Furthermore, it is now clear that people are exposed to many stressors— chemical and non-chemical—and risk assessors and risk managers often are confronted with assessing risks in populations residing in specific geographical locations. HHRP research established a common mode of action for the chlorotriazine class of pesticides, and this information was used to support the default assumption of additivity—the interaction of chemicals with one another—in the cumulative risk assessment for this class of compounds.

Susceptible Subpopulation Research

Human variability in exposure and response to environmental agents is a key uncertainty in assessing human health risk. The Safe Drinking Water Act (1996) requires EPA to consider risks to groups within the general population that are identified as being at greater risk of adverse health effects, including children and older adults. Similarly, the Food Quality Protection Act (1996) contains special provisions for the consideration of risks of pesticide exposure in children. Risk assessors and risk managers need to know the scientific basis for identifying and protecting susceptible subpopulations in the evaluation of environmental agents for potential human health risk. HHRP research with laboratory animals found an increased sensitivity of younger animals to the toxic effects of chlorpyrifos, and this information was used to help support the application of a safety factor to protect children’s health.

Tools for Evaluating Risk Management Decisions

Ensuring that pollution control programs produce measurable benefits in human health is fundamental to the mission of EPA to protect human health and the environment (U.S. EPA, 2003). It is increasingly important to assess the effectiveness of EPA's tools, approaches, and indicators to demonstrate the success of its risk management decisions. However, current health status trends in the U.S. and tools to determine the impact of regulatory decisions on exposures to environmental stressors that lead to adverse health outcomes are not widely understood.

ORD has started to focus much of its research effort on the issue of evaluating risk management decisions. The objectives of research in this area are to develop and validate environmental public health tools, approaches, and indicators that can be used to reflect the actual impact of environmental decision making on public health and to help clarify the health benefits and financial costs associated with further incremental environmental improvements. EPA is supporting two demonstration projects designed to develop principles to verify the protective benefit of environmental decisions. One is assessing reductions in waterborne illness from Safe Drinking Water Act regulations and the other is evaluating the impact of a "Clean Air Initiative" on environmental indicators in children and the elderly.

Research Contributions

Research Leading the Way in Understanding Dioxin Risks Standards

ISSUE:

Dioxins are a byproduct of routine combustion processes such as the burning of household trash, commercial or industrial incineration, volcanic eruptions, and forest fires. They tend to accumulate in the fatty tissue of the animals we eat. Numerous studies have shown that human exposure to high levels of dioxins can produce serious adverse health effects. Even extremely small exposures may be problematic.

SCIENCE OBJECTIVE:

Researchers in the U.S. Environmental Protection Agency's Office of Research and Development are contributing to the assessment of dioxin contamination in several significant ways. First, they have introduced the concept of using what is known as steady state body burden as the primary measure of exposure. Traditionally, scientists might simply look at how much of a chemical was ingested or came into contact with someone's skin – what's called a daily dose. But because dioxins are so persistent, remaining in the environment and in the body for years, it is important to know what was eaten yesterday, last month, and even ten years ago, to produce the total amount that's in the body – the steady state body burden.

Human health research also supports a method of assessing exposure to mixtures of dioxins that is called the toxic equivalency (TEQ) approach. Essentially, this approach takes an integrative measure of the potency of each compound (the Toxic Equivalency Factor, or TEF) and multiplies it by the total exposure amount to assess risk. This method underscores the concept that risk assessment of chemicals not only involves a measurement of how much but also how dangerous.

Finally, the Agency has introduced the concept of human relevance in the study of dioxin contamination. This concept considers that the effects of dioxins are not unique to a particular species; they cause similar effects in most every species.

APPLICATION AND IMPACT:

Research is helping to guide the world's ability to assess dioxin contamination and reduce the potential for human exposure. For example, the method used to determine steady state body burden is now the widely accepted standard method for measuring dioxin contamination as well as all persistent chemicals. Similarly, the toxic equivalency factor approach is the international standard for assessing exposure to combinations of dioxins and is the accepted method for measuring all persistent chemicals that are structurally related, act in the same way, and cause the same effect. And finally, while there is some debate among scientists as to whether humans are as sensitive to dioxins as are other animals, HHRP's work has added to the evidence that people are indeed very sensitive to dioxin exposures.

In the United States, the potential human health risks associated with dioxin contamination has led to voluntary industry practices limiting the levels in certain consumer products. Major sources from 20 years ago have been largely eliminated.

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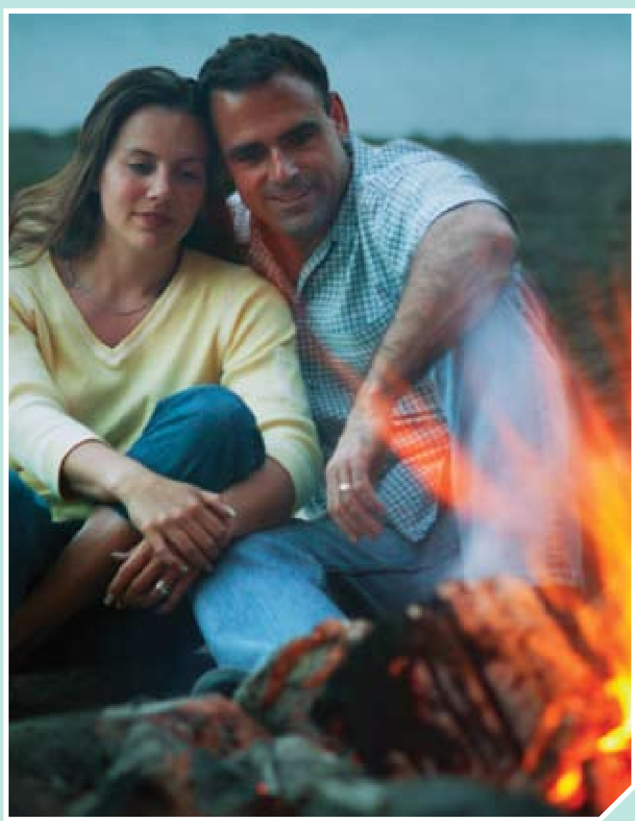

Research Addresses Potential Risks of Atrazine and Related Pesticides

ISSUE:

Atrazine is an agricultural herbicide used worldwide since 1958. In the United States, approximately 75 million pounds of atrazine are applied each year, making it the most widely used agricultural herbicide. In states where atrazine is heavily used, the chemical has been found in both surface and groundwater. Consequently, scientists with the U.S. Environmental Protection Agency's Office of Research and Development are studying atrazine to understand if the herbicide has human health implications.

SCIENCE OBJECTIVE:

Atrazine and other chlorotriazines are being reviewed by EPA because they are widely used and have been reported to cause adverse health effects in the aging female rat. Ongoing research to identify the range of biological effects and the mode and mechanism of action through which atrazine has its primary effect on endocrine function is important in understanding how the herbicide impacts laboratory animals and potentially human health.

APPLICATION AND IMPACT:

Research on atrazine demonstrated that effects in animals of initial concern (mammary cancer) were not likely to be relevant to humans. The mode of action for atrazine suggests that humans would be at risk for different toxic effects such as premature aging, developmental effects, reproductive function, and delayed puberty.

Investigators found that atrazine alters the way the brain controls pituitary function, an observation that would be consistent with atrazine-induced premature aging. They found that atrazine suppressed two hormones – the luteinizing hormone (LH) and prolactin hormone (PRL) – by altering the hypothalamic control of pituitary hormone secretion. Although scientists are still studying the precise mechanism through which atrazine causes these changes, they have demonstrated the adverse outcomes of the changes in LH and PRL.

Research showed that a brief atrazine exposure to a lactating mother can influence development in the offspring by modifying endocrine constituents of the mother's milk. Second, this work has identified a sensitive period of time for this type of early lactation exposure and raises the issue of whether other environmental compounds may similarly affect reproductive function in the offspring of mothers exposed to atrazine and potentially other similar chemicals.

Other HHRP research showed that juvenile exposures to atrazine and the primary metabolites of atrazine result in delayed puberty in the male and female rats. Three of the primary metabolites of atrazine appear to be just as potent as the parent compound in inducing these effects on pubertal development. The research has had a valuable impact on the risk assessment for this chemical. Data has been used to set the no effect level for the developing animal and to understand cumulative effects of atrazine and its metabolites.

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Research Shows the Potential Impact of Chemical Mixtures on Thyroid Function

ISSUE:

Chemicals pervade our world – in the air we breathe, the water we drink, and the products we use. The HHRP constantly studies the many ways our bodies are affected by different types of chemicals. In one area, scientists are learning more about the risk of simultaneous exposure to multiple chemicals that disrupt thyroid hormones. A goal of this research is to protect the most sensitive populations, especially children and older adults, from adverse effects on the development of their nervous systems.

Proper thyroid operation is essential for the developing child before and after birth, and for a number of physiological processes in adults. It's widely known in the scientific community that a number of individual chemicals on their own and at high concentrations can lead to disruption of thyroid activity. Relatively little is known, however, about how combinations of chemicals at natural exposure levels affect the thyroid. For example, are mixtures of such chemicals additive, synergistic or antagonistic? In other words, do their effects simply combine, multiply upon combination, or tend to cancel each other out?

SCIENCE OBJECTIVE:

A team of researchers with HHRP designed a study to test the additivity theory for a large mixture of polyhalogenated aromatic hydrocarbons (PHAH's), a family of chemicals that are known to disrupt thyroid activity. At low dosing, researchers concluded that the thyroid disrupting chemicals interacted in an additive manner in an animal model. This suggests that while each individual chemical alone may not be enough to cause any noticeable effect, the cumulative affect of several chemicals could. At higher exposures, above those to which humans are normally exposed, researchers found a small synergistic effect on thyroid hormone disruption, meaning that the affects of the chemicals don't simply accumulate; essentially, they multiply by some new factor.

APPLICATION AND IMPACT:

Research analyzing the additive effect of thyroid disruptors is illustrating the importance of studying chemical mixtures and the potential impact on human health. This research is filling knowledge gaps and providing critical science needed to improve the ability to assess the risk of multiple chemicals that impact thyroid function. Research in this area falls under the Food Quality Protection Act (FQPA) of 1996 which mandates the assessment of risks that result from exposure to multiple, similar-acting chemicals.

Ongoing research will provide a broader understanding of the ways in which chemicals interact to disrupt the functioning of thyroid hormones, providing important information to environmental risk assessors and managers.

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Research Contributes to Cumulative Risk Assessments for Organophosphates

ISSUE:

Organophosphates are pesticides used in agriculture and non-agriculture settings that affect functioning of the human nervous system through inhibition of a specific enzyme. They are among the HHRP's first priority group of pesticides to be reviewed under the Food Quality Protection Act (FQPA) of 1996. The act mandated a re-evaluation of tolerances for pesticides by 2006, in consideration of the human health effects that result from exposure to two or more chemicals that act in a similar fashion. The Agency was able to meet the requirements of that mandate by developing and conducting a complex assessment of cumulative exposure and risk to human health from these pesticides.

SCIENCE OBJECTIVE:

HHRP scientists in the Office of Research and Development developed a more thorough examination of risk associated with commonly used pesticides. Since the routinely used organophosphates all have a similar mode of action, which is to say they all inhibit the enzyme acetylcholine esterase [AChE], they were selected for the first cumulative risk assessment conducted by EPA. This assessment evaluates the potential for people to be exposed to more than one organophosphate at a time and considers exposures from food, drinking water, and residential sources. In addition, this evaluation considers a full set of reliable assessments of toxicity to characterize the potential risk of cumulative exposure to organophosphates.

Several aspects of this assessment represent an advance on previous practice, leading to a far more comprehensive and accurate method of assessing exposure to similar-acting pesticides. The prevailing practice has been to select a single experiment with which to characterize potency; in this study all reliable experiments were used. This gives a more robust estimate of potency and allows a more refined look at the relationship between dose and effect.

APPLICATION AND IMPACT:

This research program has reduced uncertainty in risk assessment in several significant ways. First, it has demonstrated the usefulness of HHRP methods, tools, and data, as well as an innovative approach for conducting cumulative risk assessments under the FQPA mandates. The research program also has improved understanding of exposure scenarios, key risk factors, and biological mechanisms that point to the usefulness of additional safety factors when analyzing whether pesticide usage poses health risks to susceptible populations. From that knowledge, several organophosphates that previously had been in use have since had their availability canceled or curtailed.

The program also has served to provide a basis for assessing risks from other classes of pesticides that come under the FQPA mandate. This broad new framework can be considered by Agency risk assessors when addressing cumulative risks to other classes of compounds and mixtures.

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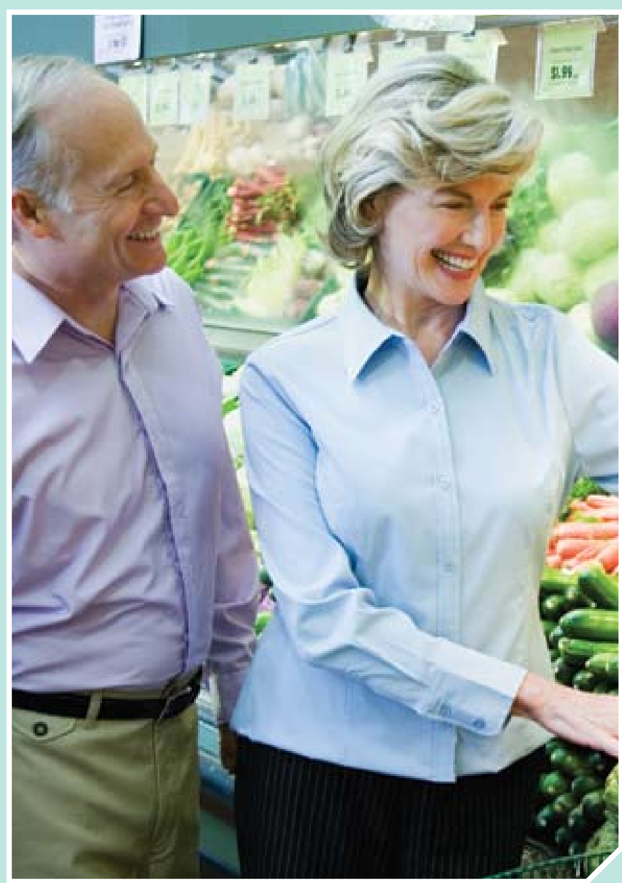

Researchers Develop Model to Estimate Cumulative Exposures to Chemicals

ISSUE:

On a daily basis people encounter a variety of chemicals that enter the body through food, water, air, and skin. Scientists are developing the tools necessary to estimate how we are exposed to different chemicals and to understand better the human health risks from daily exposure to mixtures of chemicals. New and sophisticated computer models are needed to simulate the concentrations of pollutants that people come in contact with during their daily activities. The need for reliable probabilistic models of human exposure is critical as EPA considers cumulative exposures in its risk assessments.

SCIENCE OBJECTIVE:

The Stochastic Human Exposure and Dose Simulation (SHEDS) Multimedia Model developed by HHRP is the primary tool used for simulating exposures to a variety of chemicals that enter the body in multiple ways. This model predicts, for specified populations, human exposures to chemicals from eating, drinking, and breathing, as well as from contacting surface residues and from hand-to-mouth and object-to-mouth ingestion. To perform these calculations, the model combines information on chemical use, human activities, environmental residues and concentrations, and other important exposure factors, using probabilistic sampling methods. The model enables decision makers to address questions like:

- How do chemicals distribute into the air and on to surfaces under real-world use or application scenarios?
- What are populations' real-world exposures for different chemicals/chemical classes?
- Which exposure pathways are the most important?

APPLICATION AND IMPACT:

The dietary (food and drinking water) component of the SHEDS-Multimedia model has been applied to support EPA's cumulative risk assessment for n-methyl carbamate pesticides. The SHEDS-Multimedia dietary module can be used to answer regulatory-related questions regarding the contribution of different foods and number of eating occasions. The SHEDS-Multimedia algorithm for simulating children's exposures via hand-to-mouth contact was used in EPA's final n-methyl carbamate assessment.

Ongoing modeling research is focused on developing a publicly available, state-of-the-science modeling tool for improving estimates of human exposure to multimedia, multipathway chemicals. This research is identifying critical exposure routes, pathways and factors to help guide future field study measurements and is expected to provide probabilistic exposure assessments that can help reduce uncertainty in risk assessments and enhance risk management decisions.

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Research Models Estimate Exposure to Chromated Copper Arsenate (CCA) from Playsets and Decks

ISSUE:

Little is known about the potential health risks to young children who play on or around wooden structures treated with a chemical preservative known as Chromated Copper Arsenate (CCA). CCA-treated wood is most commonly used in outdoor settings for decks, walkways, fences, gazebos, boat docks, and playground equipment to protect wood from dry rot, fungi, molds, termites, and other pests. The compound contains chromium, copper, and arsenic. Arsenic is a known carcinogen that has been shown to increase the risk of certain types of cancer. However, information is needed on real-world exposures to estimate potential health risks.

SCIENCE OBJECTIVE:

To understand the extent to which children are exposed to arsenic and chromium while playing on or around CCA-treated playground equipment and residential decks, scientists from HHRP's Office of Research and Development used a simulation model to predict human exposure. The Stochastic Human Exposure and Dose Simulation model for wood preservatives (SHEDSWood) is a probabilistic computer model which allows researchers to estimate exposure from skin contact with treated wood and nearby soil, and from ingesting wood residues and soil around playsets and decks.

The results have shown that children are exposed to CCA chemicals the most when they put their hands in their mouths after playing on CCA-treated wood. The research also showed that there are several variables that impact exposure the most including: 1) the ease with which residue on the wood surface can be transferred to children's skin, 2) the amount of residue on the wood, 3) the surface area of the child's hands that are mouthed, 4) the amount of time a child plays on or around treated playsets, and 5) how often the child's hands are washed.

APPLICATION AND IMPACT:

The SHEDS-Wood model exposure estimates are being used in EPA's risk assessment for CCA. As a result of this research, EPA has the data needed to advise the public on how to limit children's exposure. In addition, the findings are informing overall risk management strategies and providing the science needed to make decisions regarding re-registration eligibility for CCA.

HHRP is conducting additional studies to evaluate the effectiveness of different wood sealants on reducing arsenic residues in treated wood and surrounding soil.

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Research Shows How Biomarkers Can be Used to Understand Environmental Exposures

ISSUE:

Every day, people come into contact with a variety of environmental chemicals through the food they eat, the water they drink, the air they breathe, and objects they touch. This contact with chemicals – known as exposure – affects everyone. To understand exposures and their potential health risks, HHRP scientists are working to identify tools, called biomarkers, that can be used to assess a person's exposure to chemicals and, in some cases, identify an early health effect from the exposure. Biomarkers are substances, structures or processes that can be measured in biological samples (such as urine, blood, or saliva) that indicate an exposure or susceptibility, or predict the incidence or outcome of disease. They help us to understand how chemicals move through the body and cause biological changes that can lead to illness and disease.

SCIENCE OBJECTIVE:

Scientists in biomarkers research are developing and validating biomarkers that can be used in clinical screening, epidemiological studies, and risk assessments. The EPA's Science to Achieve Results (STAR) grants program supports biomarkers research including:

- **MECONIUM VALIDATION STUDIES**. Researchers have studied meconium, an infant's first set of stools, as a potential biomonitoring matrix for analyzing fetal exposure to pesticides.
- **SALIVA RESEARCH**. Saliva offers an easy, noninvasive way to collect samples for assessing exposure to chemicals. Several projects have demonstrated that saliva is a useful biomarker for measuring children's exposure to pesticides.
- **APPLICATION OF BIOMARKERS IN EPIDEMIOLOGY**. Research has incorporated biomarkers of exposure (for example, organophosphate metabolites) into epidemiology studies in the U.S. and internationally.

APPLICATION AND IMPACT:

Biomarkers help scientists understand what makes some individuals or groups of people more susceptible to the harmful effects of toxins. Biomarkers also can be used to improve risk assessment and evaluate the impact of regulatory actions. Biomarker research has provided data showing that EPA regulatory action was successful at reducing prenatal exposures to certain insecticides among African-American and Dominican mothers and newborns in New York City. Researchers also have shown that saliva can be used as a simple and noninvasive biomarker to measure exposure to certain pesticides in both children and adults. In another study, researchers used validated biomarkers to demonstrate that pest management techniques provided an effective strategy for reducing internal doses of pesticides during pregnancy.

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Human Health Research Supports National Buy Clean Program

ISSUE:

Cleaning products are widely used in schools, offices, and homes to keep hard surfaces such as furniture, floors, and toilets sanitary. Some of these consumer products may pose potential health risks. Cleaning products are known to generate emissions that potentially have adverse health effects.

EPA's national buy clean program promotes the purchase of products and services that contribute to healthy indoor environments in schools and identifies effective ways to develop, market, and buy lower-risk products. HHRP scientists are evaluating these cleaners so that schools and building managers can select the least hazardous products and reduce human exposure to these chemicals.

SCIENCE OBJECTIVE:

The objectives of research on hard-surface cleaners are twofold: to identify the major volatile chemicals – that is, those that are easily released into the air – in commercially available products, and to develop screening methods to estimate potential exposures. Scientists identified potential hazardous chemicals in cleaners by reviewing individual material safety data sheets developed by the product manufacturers, and developing and evaluating models to screen emissions.

The review identified more than 150 chemical ingredients in the 267 cleaning products analyzed. They include hazardous air pollutants (HAPs) such as glycol ethers, hydrochloric acid, and methanol. In addition, other chemical ingredients found in the cleaning products include 28 that are regulated by occupational standards; some of these are potential irritants while others can affect the central nervous system. Through these findings, researchers have concluded that products containing high concentrations can produce adverse health effects.

Two models have been developed to screen emissions. The first, called the film model, estimates the potential exposure from the liquid cleaning products applied to hard surfaces such as furniture and floors. The other, the bucket model, estimates exposure to a worker or others due to emissions generated from the product in a bucket or other container used during cleaning. The film model has potential as a screening tool to compare the cleaner products and to select less hazardous ones.

APPLICATION AND IMPACT:

The results of this research are being used by EPA to develop control techniques guidelines for industrial cleaning solvents.

REFERENCES:

Potential Inhalation Exposure to Volatile Chemicals in Water-based Hard-surface Cleaners, U.S. EPA, Washington, DC, EPA/600/R-05/005, 2005

For more information on environmentally preferable products, visit, http://cfpub.epa.gov/schools/top_sub. cfm?t_id=45&s_id=28.

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Research Shows the Role of Mold in Causing or Exacerbating Asthma

ISSUE:
The number of Americans diagnosed with asthma, particularly children, has reached epidemic proportions. To improve understanding of the human health implications of asthma, HHRP has developed a targeted asthma research program.

One area of asthma research involves the potential role that mold plays in the development or exacerbation of asthma. Recently, there has been much media attention devoted to *Stachybotrys chartarum*, a type of black mold or fungus that has been associated with a range of health problems including asthma.

SCIENCE OBJECTIVE:
Few hypotheses about mold exposure, its influence on asthma, or methods for prevention have been tested scientifically. As a result, HHRP has made mold, or fungal bioaerosols, a major focus of its asthma research program.

Researchers are currently working to identify and describe the many different molds commonly present in household environments. They hope to determine which molds pose the greatest risks and whether any has the capacity to cause asthma.

Scientists also intend to determine how much mold a person must inhale to cause an effect. Inhaling just a few particles may sensitize people's lungs, making them more likely to react to future exposure. In addition, genetic variations in humans may cause cells to respond differently which may explain why mold and other allergens cause or exacerbate asthma in some people but not in others. Researchers are working to determine the specific ways in which cells and organs respond to molds and other environmental pollutants.

APPLICATION AND IMPACT:
In one study, scientists exposed mice to samples of *Stachybotrys* taken from homes and looked for immune system responses typical of allergies as well as inflammation and functional changes in the animals' lungs. The results showed that the mold can indeed cause a disease similar to asthma in mice. Meanwhile, other HHRP scientists have developed sophisticated procedures for identifying *Stachybotrys* and other molds in indoor environments, making it possible to determine which molds are present in a given household. These procedures include methods for rapidly measuring the amounts of different fungi present in dust and measuring a biomarker that, when found in a person's blood, indicates exposure to *Stachybotrys*. These studies set the stage for further research that will help determine if humans are responding to the same allergens as mice and whether these responses can be associated with asthma.

Investigators have also been evaluating strategies for preventing mold growth. Strategies include applying antifungal sealants for fiberglass and galvanized steel used in heating and air conditioning systems. Studies show that sealants can reduce mold growth on fiberglass and can completely prevent growth on galvanized steel.

REFERENCES:
Environmental Protection Agency, Asthma Research Results Highlights, EPA 600/R-04/161, Washington, D.C., 2005.

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Research Shows Effectiveness of Integrated Pest Management

ISSUE:

Pesticides often are used in large quantities in urban dwellings to control cockroaches and other pests. However, these chemicals pose potential health problems to humans, especially children and expectant mothers. HHRP research has shown Integrated Pest Management (IPM) to be a safe, effective way to reduce pest infestation as well as to minimize pesticide exposure, compared to standard pest control methods. IPM relies on non-chemical methods, including the cleaning of food residues, the removal of potential nutrient sources, the sealing of building cracks and crevices, and the sparing use of minimally toxic pesticides such as baits and gels.

SCIENCE OBJECTIVE:

HHRP-sponsored researchers investigated whether IPM techniques and education practices could reduce cockroach infestation and indoor exposure to pesticides among urban residents. Following intervention, cockroach levels declined significantly from baseline levels among households in which IPM was used. Infestations remained constant in control households. Additionally, levels of pesticides were found to be significantly lower in IPM households, but not in control households. These results show that in this study, not only did IPM lead to a reduction in infestations, but also in lowered exposure to potentially harmful chemicals.

Researchers of other HHRP-sponsored studies examined the effectiveness of IPM practices in urban residences in which pregnant women lived. Previous studies had shown detectable levels of chemical pesticides in the urine of pregnant women, as well as in the blood of their newborns. Further, those newborns were found to have lowered weight and length at birth, and slower mental and motor development at age three. Cockroach infestation levels and pesticide levels in indoor air samples were both sharply reduced following intervention. Additionally, chemical levels were detectable in women from a control group, but not from the intervention group.

APPLICATION AND IMPACT:

Based on the science of these studies and other research into IPM practices, there has been a movement toward more widespread use of IPM. New York City, for example, has enacted legislation that Integrated Pest Management be used as the preferred method of pest control in all buildings in which children spend much of the day. The Agency's research on IPM was used in support of this legislation.

This research effort also is being shared with regional risk assessors and EPA's Office of Pesticides. The research has provided the quantitative science needed to gain acceptance in communities and enabled establishment of regional and national goals in pest management.

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Researching Trends in Human Health and the Environment

ISSUE:

Protecting the health of Americans from environmental pollution is a top priority of EPA. To accomplish this mission, it is clear that we need to understand the current state of the environment and how it may be changing over time. HHRP launched an Environmental Indicators Initiative in 2001 to develop better indicators that the Agency can use to measure and track the state of our environment and support improved environmental decision making. In 2003, the Agency generated the Report on the Environment (ROE) to describe what is known and what is not known about the nation's environment. The ROE found that:

- Many studies had demonstrated an association between environmental exposure and certain diseases and other health problems, including radon and lung cancer, arsenic and cancer, and lead and developmental nervous systems disorders.
- Several measures such as life expectancy, the number of infant deaths, and the major causes of deaths are useful in assessing health trends over time.
- Measurements of outside pollutant concentrations in air, water, or land – combined with estimates or measures of frequency and duration of human exposures to contaminated media – have provided a valuable foundation for many regulatory and non-regulatory actions taken by the Agency to limit exposure to environmental pollutants.

SCIENCE OBJECTIVE:

HHRP is developing the scientific basis for the use of health outcome measures to evaluate environmental policy decisions or interventions. It is also developing health indicators that could provide a clearer understanding of how environmental factors contribute to public health. Many other factors may also be linked to the manifestation of disease in addition to exposure to environmental pollutants, providing a scientific challenge.

APPLICATION AND IMPACT:

HHRP has provided scientific support for the use of outcome measures such as mortality data to document the success of major public health programs. For example, research supported the promulgation of anti-smoking campaigns aimed at males, which related to a decrease in deaths from lung cancer. Other research supported the development of biomonitoring data through the National Health and Nutrition Examination Survey and other databases, which documented decreases in the presence of specific environmental agents following regulatory decisions.

HHRP is conducting research to address the need for more disease-specific indicators (i.e., cardiovascular, pulmonary, and reproductive) that can be linked to actual exposure information at different geographic scales (i.e., local, regional, national) and to improve understanding of the linkages between source, exposure, and health effects.

REFERENCES:

2003 Report on the Environment, www.epa.gov/indicators/roe/html

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Summary of Progress

As illustrated in the previous section in this report, EPA's Human Health Research Program (HHRP) has made major contributions to a number of problem-driven research areas. HHRP science has contributed to a more systematic understanding of the physical and biological processes that underlie how humans can be affected by environmental stressors. We have developed broadly applicable research tools for analyzing and using information in science-based decision making, and generated methods, models, and data used by risk assessors and managers to improve the risk assessment process. Other highlights of key accomplishments for the research program over the last five years include the following:

Biological Research:

- Provided mechanistic information that decreased reliance on default assumptions used in Agency-related risk assessments for several chemicals, including atrazine; arsenic; 1,3 butadiene; bromate; chloroform; chlorpyrifos; dichloroacetic acid; dioxin and related chemicals; dimethoate; and methamidophos. These assessments were published in databases accessible to the general public, e.g., Integrated Risk Information System. They are used by Agency program and regional risk assessors, as well as international human health advisory bodies (e.g., Organization for Economic Cooperation and Development, International Program on Chemical Safety of the World Health Organization) and governmental groups.

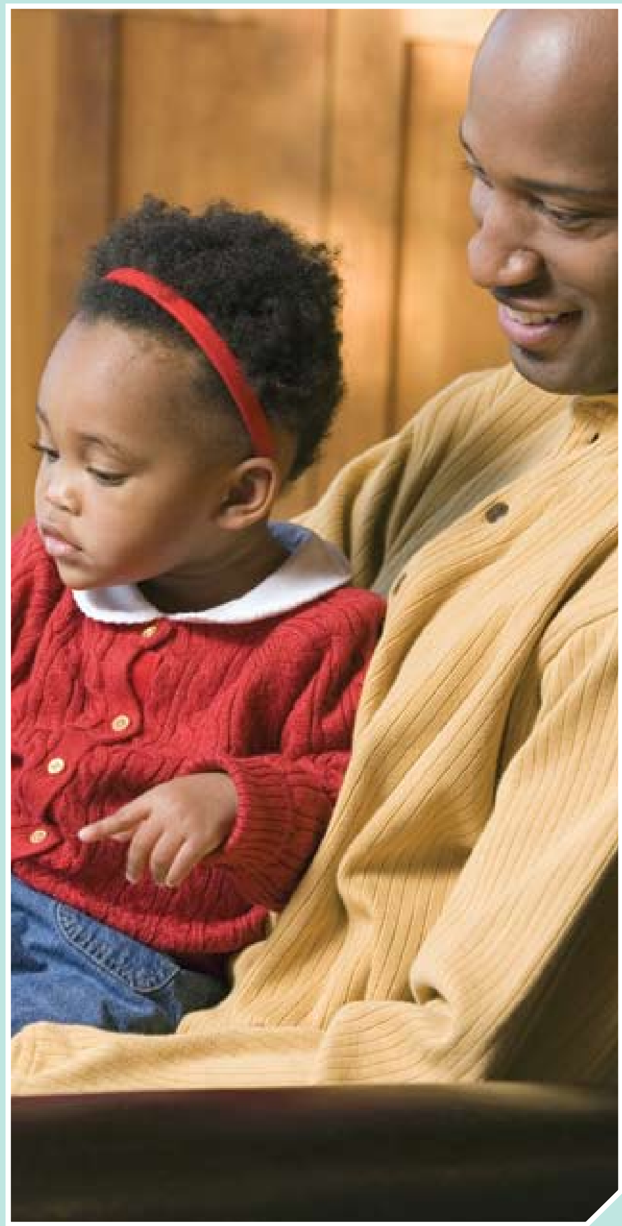
- Developed the Benchmark Dose Software online training program to evaluate dose-response relationships for chemicals. This software was made available to the public at, www.epa.gov/ncea/bmds_training/software/overp.htm.

- Research contributed to the de-listing of ethylene glycol monobutyl ether and retention of methanol as hazardous pollutants (OMB PART Review, 2005).

- Research contributed to the revised guidelines for carcinogen risk assessment, http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=116283

- Research contributed to the document evaluating the Reference Dose/Reference Concentration process in risk assessment, http://cfpub.epa.gov/ncea/raf/RAFRPRTS.CFM?detype=document&excCol=archive.

- Research contributed to the draft framework for computational research at ORD, www.epa.gov/comptox/comptox_framework.html



Cumulative Risk Research

- Developed models and data to support the cumulative risk assessment of organophosphate and carbamate pesticides, www.epa.gov/pesticides/cumulative/common_mech_groups.htm.
- Developed probabilistic exposure model for risk assessment of chromated copper arsenate (CCA), www.epa.gov/oppad001/reregistration/cca/.
- Developed a physiologically based pharmacokinetic model to simulate absorption, storage, metabolism, and elimination of chemicals in humans, www.epa.gov/heasdweb/erdem/erdem.htm.
- Developed stochastic human exposure and dose simulation model to predict multimedia, multi-pathway aggregate exposures for user-specified populations, www.epa.gov/nerl/research/2003/g1-5.html.
- Provided databases for full and open public access for risk assessors, including the Technology Transfer Network (www.epa.gov/ttn/atw/), the Air Pollutants Exposure Model (www.epa.gov/ttn/fera/human_apex.html), the Consolidated Human Activity Database (CHAD) (www.epa.gov/chadnet1/), and the Human Exposure Database System (HEDS), www.epa.gov/heds/aboutheds.htm
- Research contributed to the development of the National Health Exposure Assessment Survey (NHEXAS), www.epa.gov/nerl/research/nhexas/nhexas.htm.
- Provided analytical methods to support environmental assessments such as the American Healthy Homes Survey, www.epa.gov/nerl/news/isea2006/abstract/healthyhomes_abstract.html
- Research contributed to the updates of the Exposure Factors Handbook, http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=12464
- Research contributed to drafting the framework for conducting cumulative risk assessments, http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=36941
- Research contributed to characterizing exposures to toxic agents related to the World Trade Center disaster, www.epa.gov/wtc/.
- Research contributed to developing the Integrated Pest Management Program for intervention by local health departments and housing authorities, www.epa.gov/pesticides/ipm/.

- Research contributed to the development of the National Agenda for the Environment and the Aging, www.epa.gov/aging/agenda/index.htm.

- Research contributed to the development of protocols for the National Children's Study (NCS), www.nationalchildrensstudy.gov.

- Research contributed to the drafting of the child-specific exposure factors handbook, http://fn.cfs.purdue.edu/fsq/WhatsNew/KidEPA.pdf

- Research contributed to the supplemental guidance for assessing cancer susceptibility from early-life exposure to carcinogens, http://yosemite.epa.gov/opa/admpress.nsf/0/33d8dfc4dfe30aa085256fd3005bdbeb?OpenDocument

- Research contributed to the writing of the framework for assessing risks of environmental exposures to children, http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=116283.

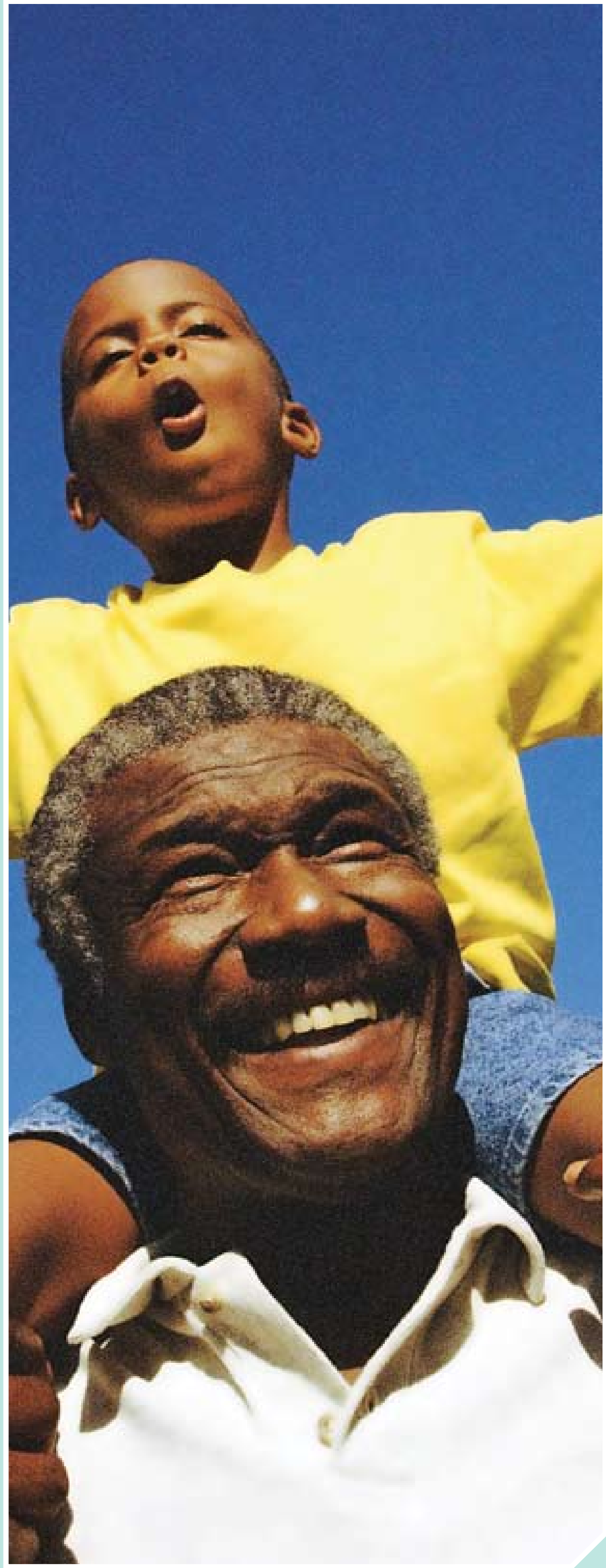
- Research contributed to the development of guidance for selecting appropriate age groups for assessing childhood exposures.

- Research contributed to the characterization of aggregate exposures of young children to common contaminants in their everyday surroundings in the Children's Total Exposure to Persistent Pesticides Study, www.epa.gov/nerl/research/1999/html/g8-10.html.

Tools for Evaluating Risk Management Decisions

- Conducted exposure research to determine pesticide levels in children in border regions between the U.S. and Mexico, www.nmsu.edu/~frontera/old_1996/nov96/1196heal.htm.

- Scientists contributed significantly to the Health Chapter in the Agency's Report on the Environment (RoE), www.epa.gov/indicators/.



Future Directions

Major knowledge gaps related to evaluating risk to human health have been outlined by many groups (NRC, 1994; Presidential/Congressional Commission on Risk Assessment and Risk Management, 1997; U.S. EPA, 2005). As described previously, EPA's Human Health Research Program (HHRP) has addressed many of these gaps and has laid the groundwork for addressing others. Looking ahead, HHRP will sustain its commitment to this area to ensure that future evaluations of human health risk can be done in a cost-effective manner based on sound science. Highlights of future efforts include the following:

Biological Research:

PHYSIOLOGICAL MODELS: Risk assessors are often faced with the uncertainty of relating external exposure to a chemical and subsequent adverse health effects. HHRP research will develop integrated physiological models to predict the relationship between exposure and effect based on available biological data and extrapolation of knowledge within chemical classes.

METHODS FOR PRIORITIZATION OF CHEMICALS: There are many chemicals that have not been tested for potential human health risk. HHRP research will contribute to the development of a framework for using emerging genomic and proteomic approaches to prioritize chemicals or chemical classes for subsequent screening and testing.

BIOLOGICAL MECHANISMS UNDERLYING ADVERSE HUMAN HEALTH EFFECTS: Recently published guidelines for cancer risk assessment promote the use of mechanistic or mode-of-action information in assessing human health risk. Application of mode of action for non-carcinogenic chemicals also has been proposed. In addition, HHRP is conducting mode-of-action research on high priority environmental agents (e.g., fungicides, insecticides, endocrine disruptors, air pollutants) to promote harmonization of cancer and non-cancer risk assessments.

Cumulative Risk Research:

BIOMARKERS FOR HUMAN HEALTH EXPOSURE AND EFFECTS: Knowledge of all of the events between exposure to an environmental agent and subsequent health effect is often difficult to understand, especially in the context of evaluating human health risk. HHRP is conducting research to identify surrogate indicators that are known to change in the same direction as exposure to environmental agents. EPA will use valid biomarkers to facilitate assessment of exposure to multiple chemicals via multiple pathways and to evaluate the effectiveness of risk management decisions.

Looking ahead, HHRP will sustain its commitment to this area to ensure that future evaluations of human health risk can be done in a cost-effective manner based on sound science.

CUMULATIVE RISK ASSESSMENTS: HHRP conducts cumulative risk assessments for certain chemical classes, e.g., carbamate and pyrethroid insecticides as required by Congress. HHRP conducts research to provide Agency risk assessors with methods and models for conducting cumulative risk assessments based on mode-of-action information.

SOURCE-TO-EFFECT MODELS: Knowledge of actual conditions for all possible exposure scenarios is frequently difficult to obtain, especially for understanding all possible routes and pathways for cumulative risk. HHRP will develop source-to-effect models using stochastic statistical approaches to address ongoing cumulative risk assessments for environmental agents such as the carbamate and pyrethroid pesticides.

COMMUNITY RISK: Humans are rarely exposed to a single environmental stressor. How to evaluate the interaction between chemical and non-chemical stressors such as nutrition and other lifestyle factors has not been widely studied, especially as it relates to risk to populations. HHRP research will identify and develop exposure assessment methods and models that can be used for community-based risk assessments.

Subsceptible Subpopulation Research:

LONG-TERM EFFECTS OF EARLY EXPOSURES: Environmental factors related to the increased incidence of diseases such as obesity and diabetes in the U.S. have been proposed, but not identified. HHRP research will determine the role of developmental exposure to environmental chemicals and emerging health risks in adulthood.

SUSCEPTIBLE POPULATIONS: EPA is required to account for the differential sensitivity of subpopulations in risk assessment. The scientific basis for identifying and protecting subpopulations such as children and older individuals, however, is not fully understood. HHRP research will identify exposure and biological factors that will help identify who is at greater risk and why and will promote increased protection of these subpopulations.

ASTHMA IN CHILDREN: The incidence of asthma in children is increasing rapidly in the U.S. (DHHS, 2001). How changes in the environment are associated with this observation is not known. HHRP research will focus on the potential long-term effects of developmental exposure to air pollutants such as diesel exhaust and molds and the formation and expression of asthma.

Tools for Evaluating Risk Management Decisions:

EVALUATION OF RISK MANAGEMENT DECISIONS: EPA currently uses process-oriented measures of the effectiveness of its regulatory decisions, e.g., how many smoke-stacks meet compliance specifications. There is a need to develop more outcome-oriented means of evaluating effectiveness of its decisions. For example, do indicators of human health actually change following a risk management decision? HHRP research will develop and validate environmental health indicators that reflect actual impact of risk management decisions on human health. Such information will help risk managers clarify health benefits and costs associated with incremental environmental improvements.

In addition to the research directions highlighted above, HHRP will rely on directions from cyclical, external peer review by its Board of Scientific Counselors, input from the Agency's Program and Regional Offices, and collaborations with EPA's National Center for Environmental Assessment.

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http://www4.law.cornell.edu/uscode/7/ch6.html

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www.epa.gov/safewater/sdwa/

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