PUTTING CHILDREN FIRST

Making Pesticide Levels in Food Safer for Infants & Children

NATURAL RESOURCES DEFENSE COUNCIL

April 1998

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Pesticides are designed to be poisonous. Yet pesticides are found almost everywhere-in households and schools, in drinking water, even in baby food Pesticide **metabolites** are also found consistently in children's urine, when such testing is performed.

Mounting evidence shows that children have daily exposure to pesticides. The Scientific Advisory Panel to EPA's Office of Pesticide Programs recently reviewed a study concluding that every ***day***, nine out of ten American children age six months through **5** years ingest organophosphate insecticides in their food. Organophosphates kill pests by poisoning the brain and nervous system. Yet the study further estimated that more than a million children each day eat an amount of these chemicals that 'exceeds the safe adult daily dose set by EPA.

Children are not simply little adults. A child's potential susceptibility to the toxic effects of pesticides, including effects on the developing brain, nervous, immune and reproductive systems, is often greater than an adult's. This vulnerability may not extend to all pesticides. But specific data are often lacking to distinguish individual pesticides that are particularly toxic to children.

Children are not ***simply little*** adults. A child's potential susceptibility to the toxic ***effects*** of pesticides, including effects on the developing brain, nervous, immune and reproductive systems, is often greater than an adult's.

FOOD QUALITY PROTECTION ACT & THE PROTECTION OF CHILDREN

The Food Quality Protection Act (FQPA) of 1996 aims to assure for all pesticides used on food that EPA's tolerances-the pesticide levels legally allowed to remain in or on raw or processed foods-would protect infants and children, taking into account their potentially greater susceptibility, as well as their unique patterns of exposure. In particular, the FQPA directs EPA to use an additional, tenfold (10X) safety factor in its tolerance risk assessments, unless there are "reliable data" on children's toxicity and exposure that support the use of some other safety factor. This means that under the FQPA, the amount of pesticide residue legally allowed to remain in or on foods will be set ten times lower then it would have been previously, until reliable data is generated describing both children's exposure to that pesticide and its toxicity to infants and children.

This report reviews the information on children's exposure to pesticides typically available to EPA in determining whether there are reliable data to justify alteration of the children's tenfold safety factor. This includes data on dietary exposures through contaminated food and drinking water, exposure through contaminated air, soil, and surface water, and exposure through other non-dietary sources. We also scrutinize EPA's testing requirements, and the most **up–to–date** testing guidelines used to guide the generation of toxicity data on which the Agency bases its tolerance-setting decisions for infants and children under the new law.

Do these tests and data typically provide EPA with **sufficiently** "reliable data" to depart from use of the child-protective FQPA safety factor? We find, in most cases, they do not.

DATA ON CHILDREN'S EXPOSURES TO PESTICIDES

For some pesticides, such as the organophosphate insecticides, existing data on children's exposure through contaminated food alone should cause concern.

Evidence suggests that these nervous system poisons are present in food at levels that can drive many children eating a normal diet to exceed EPA's safe daily dose (set for adults) -- even without using additional safety factors.

For other pesticides, however, EPA's Office of Pesticide Programs (OPP) usually lacks the comprehensive and reliable data on children's exposure needed to alter the tenfold FQPA safety factor. For example:

- Water may well be the single item most consumed by children. EPA admits that it does not have sufficient monitoring data on pesticide contamination of drinking water to include in its tolerance-setting decisions. For pesticides like organophosphates, where known exposures through contaminated food are already worrisome, a child's additional exposure through pesticide-laced tap water will only drive the level of concern higher, making the need for stringent tolerances even greater. Yet contamination of drinking water is common, often with multiple pesticides.

- For individual pesticides, EPA typically lacks much (if any) data on children's non-dietary exposures. Pesticides used on foods may have other non-food uses, on gardens or in homes, for example. Pesticides used for agricultural or other purposes may also contaminate the surrounding environment, including the air, soil and water. Under the FQPA, children's exposure via these other sources must be taken into account in setting a tolerance. Studies confirm that children are exposed to multiple pesticides in the household carpets, on countertops, even in their toys. Pesticides are used frequently in schools, often without notifying parents or teachers. Pesticide contaminants have also been found frequently in soil, rainwater, fog and air-all of which a child can inhale or ingest.

DATA ON PESTICIDE TOXICITY TO CHILDREN

The toxicity testing that EPA requires of pesticide manufacturers, which is largely performed in laboratory animals and then used in setting tolerances, is often inadequate to protect children as well. Our analysis of EPA guidelines used by manufacturers to complete these tests reveals data gaps falling into three categories.

- Failure to expose animals during all critical periods of development corresponding to ages when children are known to have the greatest potential susceptibility to the toxic effects of chemicals. Most toxicity testing for food-use pesticides uses only adult animals. Of the two tests required for food-use pesticides which actually do expose developing animals, one fails to continue dosing the animal after birth, when many organ systems are still developing. How can pesticide tolerances based upon these tests be said to carry a reasonable certainty of no harm to infants and children?

- Failure to assess all endpoints, or toxic effects, of critical concern to the fetus, infant or child. None of the tests EPA typically requires of food-use pesticides will assess their toxicity to the developing brain – including effects on learning and memory, toxicity to the immune system, or their potential

for disrupting the endocrine (hormonal) system. In fact, specific testing for toxicity to the immune system has been requested for only two chemical pesticides; developmental neurotoxicity testing has only been completed for six pesticides. How can pesticide tolerances be said to have a reasonable certainty of no harm to infants and children without these tests? Children depend on healthy brains, nervous and immune systems to become learning, productive, healthy adults.

In compliance with the FQPA, EPA is still developing guidelines for testing a chemical's potential for disrupting normal function of the endocrine (hormonal) system. Normal development of the fetus, infant and child depends upon the timely release of low levels of various hormones from endocrine organs and their action on different organs. Until guidelines and testing are implemented, a pesticide's untested potential for endocrine disruption should be reflected in the tolerance for that chemical.

- Failure to monitor test animals for a lifetime to allow all adverse or toxic effects which might occur to become evident. The only two toxicity tests required for food-use pesticides which employ developing animals, tests for developmental and reproductive toxicity, fail to follow the dosed animals to their natural death. These tests therefore cannot reflect what will happen to exposed children as they mature, accumulate exposure to other toxic chemicals, and as their organs lose their full capacity to function.

RECOMMENDATIONS FOR PROTECTING CHILDREN UNDER THE FQPA

Despite the data gaps described above, many in the agribusiness and pesticide industries have recently suggested that EPA back away from routine use of the additional FQPA safety factor to protect infants and children. For its part, the Office of Pesticide Programs recently issued a draft policy on use of this child-protective tenfold factor that falls short of articulating a strong and presumptive use.

In addition, some industry members have suggested that EPA should wait to make decisions until more complete data are collected. It is important to emphasize that despite certain data gaps for children's exposure and toxicity, the Agency generally has more than enough data for many pesticides (such as organophosphates and carbamates) to necessitate immediate serious reductions in, or revocations of their tolerances. More data on children's toxicity and exposure to these pesticides could only add to the reasons for reducing or revoking these tolerances. Thus, there is absolutely no reason for EPA to wait to make these decisions. The agency should use the best data available, and where there are data gaps for fetuses', infants', or children's toxicity or exposure, EPA should retain the presumptive tenfold safety factor.

Even without generating new data on infants and children, OPP has ample data on pesticide toxicity and exposures, generally, to justify concern about their long-term effects on infants and children. In 1993, a National Academy of Sciences panel presented a compelling summary of this data in its report, Pesticides in the Diet of *Infants* and Children. Building on the NAS panel's recommendations, Congress made strong presumptive use of an additional tenfold safety factor central to the FQPA.

Nevertheless, the most recently available information from EPA indicates that it has retained the tenfold children's safety factor in less than 10 percent of the initial tolerances issued under the FQPA. We believe our children deserve better. NRDC therefore makes the following recommendations:

1. Strong Presumptive use of the 10X Safety Factor. In its tolerance decisions, EPA must make strong, presumptive use of the additional tenfold children's safety factor, as is required by law in the Food Quality Protection Act, pursuant to the National Academy of Sciences report in 1993.

2. Convene a Panel of Children's Experts. The FQPA allows departure from use of this child-protective 10X safety factor ***only if*** **there** are reliable, **chemical-**specific data to use some other factor. EPA should immediately convene a blue ribbon panel, comprised of independent pediatricians, pediatric neurologists, pediatric immunologists, pediatric endocrinologists, and developmental or other biologists with expertise in effects of in ***utero*** or early childhood exposure to toxic chemicals. This panel should be augmented with EPA developmental toxicologists and pediatric exposure assessors. It should be charged with reviewing the state of the science on what complete and reliable set of toxicity and exposure data would be sufficient to warrant departure from use of the tenfold FQPA children's safety factor. EPA should:
   - Convene these experts under the Children's Health Protection Advisory Committee, whose charter is to assist EPA in the development of regulations, guidance and policies to address children's health. This group, currently formed and functioning, already includes many of the pediatric experts needed to answer the charge above.
   - Make the panel's deliberations transparent and public, and its members free of conflicts of interest.

3. Finalize Revised Data Requirements and Testing Guidelines. EPA should immediately finalize its revised pesticide data requirements and its most **up-to-**date toxicity testing guidelines. Though imperfect, and typically drafted prior to passage of the FQPA, these revisions are more stringent and better reflective of the state of the science than are existing requirements and guidelines.

4. Review Guidelines. On receiving the determination of the blue ribbon panel, the EPA should again review its toxicity testing guidelines to ensure that they reliably assess-individually and collectively-the full range of toxic effects most relevant to the health of fetuses, infants, and other children, including effects on the developing brain and nervous, immune, endocrine and reproductive systems, and revise the guidelines accordingly. Special attention should be paid to the number and adequacy of existing criteria, or triggers, by which EPA scientists determine when to request testing of a pesticide's effect on the developing brain and nervous system, and other critical organs.

5. Review Exposure Databases. On receiving the blue ribbon panel's determination, EPA should also review existing EPA, FDA, and USDA exposure data in terms of their reliability in describing the exposure of fetuses, infants and other children to potentially toxic pesticides.

6. Use of the 10X Safety Factor Pending Reliable Data. EPA must not depart from use of the additional, child-protective **10X** factor in setting tolerances until the Agency has collected a body of toxicity and exposure data for that pesticide that meets the standard of reliability determined by the blue ribbon panel.

Awareness of the lack of child-specific data for individual pesticides dates back to before the National Academy of Sciences first convened its expert panel in 1988. In the ensuing decade, **OPP's** pesticide data requirements and testing guidelines have remained largely unchanged; gaps in the data provided by pesticide manufacturers have also remained largely the same. The biggest change has come with the increasing recognition that large numbers of children are exposed to these pesticides each day.

Given this history, suggestions by agribusiness, the pesticide industry and others that EPA should wait for additional data before implementing the **FQPA's child–** protective uncertainty factor are self-serving. Strong and immediate presumptive use of this tenfold safety factor is necessary not only to protect infants and children, but also ensures that ten years from now we are not still waiting for data to show, with reasonable certainty, that pesticides pose no harm to our children. In other words, strong presumptive use of the FQPA safety factor is needed to finally generate the data to overcome the uncertainty that made the FQPA necessary in the **first** place.

Any delay in implementing the new child-protective provisions of the FQPA should be viewed, at best, as bare-knuckle politics. At worst, it amounts to a massive experiment on large numbers of fetuses, infants and children, an experiment where we knowingly expose them on a daily basis to pesticides–chemicals designed to be poisonous in small amounts.

INTRODUCTION AND FINDINGS

Pesticides are found nearly everywhere. They are used to kill a variety of pests, including insects and weeds, mice and rats, fungi and microbes, cockroaches and termites. Agricultural pesticides are used on food and non-food crops, on corn and soybeans, cotton and trees. Sometimes the same pesticides are sprayed inside households, schools and businesses, or used on pets, lawns and gardens.

About 875 different pesticide "active ingredients" are registered with the U.S. Environmental Protection Agency (EPA), and these are mixed with other chemicals to produce around 21,000 pesticide products.[1] Among registered active ingredients, nearly 60 percent (489 pesticides) are allowed to be used on food or feed crops.*

Pesticides are found in nearly three-quarters of the fruits and vegetables most commonly eaten by children? Pesticides and their metabolites contaminate baby food,[3] and drinking water.[5] They have been found to persist on countertops and on toys,[6] in households and schools;[7] even in children's urine.[8]

Pesticides are big business. Each year, more than 4.5 billion pounds of pesticides are used in the United States. In 1995, this included around 1.2 billion pounds of conventional pesticides—i.e. chemicals used in homes, on farms and gardens and for industrial applications-and other pesticide chemicals (sulfur, petroleum etc.). Chlorine and hypochlorites make up the bulk of the remaining pesticides used. More than $11.3 billion was spent on pesticides in 1995, with 70 percent of this spent on agricultural uses.[9]

Pesticides concern the public because they are specifically designed to kill—often being engineered to disrupt the nervous, reproductive and other organ systems in insects, rodents and other crop pests. Since humans share with these pests many of the same biological building blocks, pesticides can also poison the people who are exposed to them. EPA has acknowledged, "All pesticides are toxic to some degree. This means they can pose some risk to you, to your children and pets...."[10]

A child's susceptibility to pesticides, and their potentially toxic effects on the developing brain, nervous, immune and reproductive systems, is often greater than an adult's. Children's vulnerability can stem from an inherent sensitivity, due to their rapidly developing organs and immature protective systems, as well as from greater pesticide exposures. Pound for pound, children breathe, eat and drink more than adults; they put more into their mouths, and their activities are closer to the ground, where pesticide residues in air, in dirt and on floors are often greatest." When it comes to pesticides, children are not just little adults.[12]

Children are not necessarily more vulnerable than adults to *all* pesticides, Much needed and often lacking, however, are specific data to fully describe children's

Pesticides are found in nearly *three–quarters* of the *fruits* and vegetables most commonly eaten by children. Pesticides and their metabolites are also often *found* in baby food, in drinking water, in *households* and schools

exposures to individual pesticides, and to distinguish those pesticides particularly toxic to children from those which are less toxic.

Not all pesticides lack such data. Organophosphorus insecticides, or **OPs,** are a class of widely used pesticides known to be poisonous to the brain and nervous system. The Scientific Advisory Panel (SAP) to EPA's Office of Pesticide Programs (OPP) recently reviewed a study prepared by the Environmental Working Group (EWG) finding that each day, 1.1 million children between six months and 6 years of age ingest OPs at levels which exceed EPA's safe daily dose, or "chronic reference dose."[13] EPA reference doses are based largely on tests performed on adult animals.

The excessive levels found in this study did **not** even include the potential organophosphate exposures children face from contaminated drinking water and **from** non-dietary sources of exposure. The study's findings, based on the most recent food consumption data and pesticide residue data from FDA and USDA, suggest that strong and immediate action is needed to adequately protect infants and children from this group of pesticides. Not to act on this information is itself a decision to continue exposing potentially huge numbers of children to chemicals known to be toxic to children's brains.

Given the ubiquity of pesticides, their inherent toxicity, children's potential vulnerability, and gaps in the scientific data with respect to children, why not just limit children's exposure to pesticides-at least until reliable toxicity and exposure data can assure that these exposures pose no harm? Common sense would seem to demand it. But historically, health concerns have not always been paramount in the regulation of pesticides (See opposite page for a Brief History of Pesticide Laws and Regulations).

PROVISIONS FOR PROTECTING CHILDREN UNDER THE FQPA

In 1993, the National Academy of Sciences-National Research Council **(NAS)** released a landmark report finding that existing pesticide regulations did not adequately protect children **from** pesticide exposure in foods." The report, Pesticides in the Diets of ***Infants*** and Children, highlighted research showing that children are more than just "little adults" in their susceptibility to pesticides? The study also recognized numerous shortcomings in the ability of EPA's testing protocols to **fully** address children's exposure to a pesticide and its toxicity to infants and children?.

The NAS report gave impetus to passage and signing of the Food Quality Protection Act (FQPA) of **1996.**[17] In contrast to earlier pesticide laws, the FQPA set a clear health-based standard for pesticide safety, one based on "a reasonable certainty that no harm will result **from** aggregate exposure to the pesticide chemical residue, including all anticipated dfetary exposures and all other exposures for which there is reliable information.'"

Passed unanimously by Congress, the new statute makes protection of infants and children the top priority in setting pesticide residue limits on food. The FQPA directs the EPA to assure that the tolerance-or amount of pesticide allowed to remain on or in raw or processed foods-for any particular pesticide used on food crops, fully accounts for a child's potential susceptibility, especially when children's toxicity and exposure data for that pesticide are lacking. When signing the FQPA

A BRIEF HISTORY OF PESTICIDE LAWS AND REGULATIONS

Historically, pesticide regulation has balanced the risks of pesticide use against any economic benefits. The Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), the first attempt to regulate pesticide usage in 1947 (it has subsequently been amended several times), did so on the basis that a pesticide would not cause "unreasonable adverse effects"—defined as "any unreasonable risk to man or the environment taking into account the economic, social and environmental costs and benefits of its use." Under FIFRA, some adverse effects from exposure to a pesticide could be judged reasonable when weighed against the economic benefits from its use.

While FIFRA regulated pesticide use, the Federal Food, Drug and Cosmetic Act (FFDCA) established a standard for setting tolerances, or the amount of pesticide residue legally permitted to exist in foods. Prior to the FQPA, tolerances were based primarily on the manufacturer's determination as to the highest level of pesticide normally found on food following standard agricultural practice, rather than on human health considerations?

As it became more evident that pesticide residues could produce harmful health effects in humans, Congress passed the Delaney Clause under the FFDCA in 1958. The Delaney Clause stipulated that no pesticide could be present in food if it were known to cause cancer in laboratory animals, and to concentrate in processed foods. While this provision had the beneficial effect of embodying a prevention-based approach to regulating toxic chemicals (ie. if a chemical causes cancer, it should not be added intentionally to the food supply), its application presented several thorny issues. First, it meant that cancer-causing pesticides alone would be banned from processed foods on the basis of their ability to concentrate. Restrictions on non-carcinogenic pesticides were much weaker. Many hazardous pesticides therefore were allowed to remain in processed foods despite well-known, non-cancer effects on the nervous, immune, reproductive and endocrine systems.

A second problem was that while the Delaney Clause banned certain cancer-causing pesticides in food crops destined for processing, EPA continued to grant tolerances for certain cancer-causing pesticides on some raw foods. Two contradictory sets of standards resulted: one set for processed foods restricting the use of certain carcinogenic pesticides, but allowing use of pesticides with other toxic effects; and another set for raw foods allowing residues of any approved pesticide, often without meaningful consideration of its toxicity or carcinogenicity. As a general matter, neither set of standards, however, took into account the impact of pesticide exposure on infants and children, who are known to have a unique potential vulnerability to their toxic effects.

These were the statutes and policies that set the stage for the National Academy of Sciences landmark 1993 study, Pesticides in the Diets of Infants and Children, and for subsequent passage of the Food Quality Protection Act of 1996.

into law, President Clinton stated: "I like to think of it as the 'peace of mind' act, because it'll give parents the peace of mind that comes from knowing that the fruits, vegetables, the grains that they put down in front of their children are safe. It's long overdue. The old safeguards that protected our food from pesticides were written with the best of intentions, but they weren't up to the job."[19]

Several FQPA provisions are aimed at better protecting infants and children. Four in particular stipulate that EPA must:

- Consider children's special susceptibility and often unique exposure patterns to pesticides (FFDCA Sect. 408 (b)(2)(C)(i)(II));

- Consider both dietary and non–dietary sources of exposure when setting tolerances (FFDCA Sect. 408 (b)(2)(D)(vi));
- Establish that pesticide tolerances carry a reasonable certainty of no harm to infants and children (FFDCA Sect. 408 (b)(2)(C)(ii)(I)); and
- Adopt an additional safety factor of tenfold (10X) to account for incomplete toxicity or exposure data relative to infants and children, unless there is reliable data that a different factor should be used (FFDCA Sect. 408 (b)(2)(C)).

RELIABLE DATA UNDER THE FQPA

The regulation of pesticides in food is only as accurate as the testing on which it is based. Uncertainty factors are traditionally used in risk assessments, including those done to determine tolerances for pesticides used on food crops, to account for uncertainty in the underlying science. They account, for example, for the uncertainty faced by regulators as the try to set tolerances that are safe for people based upon toxicity testing using animals. These uncertainty factors also account for the fact that people are much more diverse than the population of healthy, genetically similar rats of a certain age in which toxicity testing is usually performed.

A National Academy of Sciences panel in 1993 suggested that an additional child-specific uncertainty factor should be used routinely in setting pesticide tolerances whenever toxicity data was incomplete, to explicitly account for prenatal and postnatal periods of potential vulnerability in children.*' The Food Quality Protection Act of 1996 improved upon this recommendation by making this third uncertainty factor tenfold in size, and by making its use mandatory unless there is "reliable data" on children's toxicity and exposure that supports the use of a different safety factor? This means that under the. FQPA, the amount of pesticide allowed to remain in or on raw or processed foods will be set ten times lower than it would have been previous to the law, at least until there is reliable data describing both children's exposure to that pesticide and its toxicity to infants and children.

This report reviews the information on children's exposure to pesticides typically available to EPA in determining whether reliable data exist to justify alteration of the children's tenfold safety factor. We also scrutinize EPA's testing requirements and its most up–to–date testing guidelines, both used to guide the generation of toxicity data on which the Agency will typically base its tolerance setting decisions for infants and children under the new law.

Do these tests and data typically provide EPA with sufficiently "reliable data" to depart from use of this child-protective FQPA safety factor? We find, in most cases, they do not. Instead, this report highlights certain kinds of exposure and toxicity data so basic to children's health that no reasonable person would exclude them from a definition of reliable data under the FQPA. Yet many of these basic data are not collected under EPA's existing testing requirements and toxicity testing guidelines, and typically will not be available for setting tolerances. They are summarized below, and described in later chapters in greater detail.

CHILDREN'S EXPOSURE TO PESTICIDES

A child's unique diet and behavior will result in greater potential exposure to pesticides. For example, children eat foods more commonly contaminated with pesticides.[23] Children drink more water than adults, on average (on a weight–adjusted basis), and infant formula is constituted with drinking water.[24] Yet pesticide contamination of drinking water is common.*' Pesticide residues also have been found in breast milk?

Children spend more time at home than adults, often crawling or playing at ground level where pesticide residues in household air, dust, carpets, and even on toys,*' may be higher. In schools, children are often exposed to pesticides applied without their knowledge, and without notice to parents, teachers or health professionals.[28] Finally, children's hand-to-mouth behavior can lead to the ingestion of contaminated dust indoors, and contaminated dirt outside where pesticides are often applied to lawns, gardens, and playgrounds.

For some pesticides, existing data on children's dietary exposures alone are sufficient to raise a red flag of concern. The recent study reviewed by the OPP Scientific Advisory Panel analyzed dietary data alone and still found plenty of cause for concern about children's daily exposure to organophosphate pesticides. Any new data on additional, non-dietary exposures can only worsen fears about a child's overall exposure to organophosphates, and strengthen the need to act to reduce these exposures.

But organophosphates represent only 39 of the 489 pesticide "active ingredients" used on food crops, and often used in homes and schools and on pets, lawns and gardens as well? For the rest of the active ingredients, existing studies often fall short of providing the complete, up–to–date exposure data on infants and children which EPA legally needs to set pesticide tolerances that protect children without the use of an additional tenfold safety factor. For example:

- EPA often lacks comprehensive, up-to-date data on children's exposure to pesticides through contaminated food and drinking water that are sufficient to justify altering the tenfold children's safety factor. EPA has admitted in recent tolerance notices that it lacks drinking water monitoring data on which to base its exposure estimates? EPA's tolerances under the FQPA have also largely relied on food consumption data derived from surveys done by the U.S. Department of Agriculture over twenty years ago?

- EPA data on non-dietary routes of exposure to pesticides are even more sparse, especially data specific to infants and children. The missing data includes that on exposure through pesticide use in homes and schools, as well as pesticide levels in air, rainwater and fog, which have been found to be potentially significant for many classes of pesticides? If these more detailed exposure data were available, known exposures could only increase, meaning more stringent tolerances might well be needed.

- No integrated database exists within EPA for collecting and collating data on pesticide exposure through the diet, as well as through various contaminated media-including indoor and outdoor air, surface water, soil and household dust. This presents a serious hurdle to performing an aggregate exposure analysis as required under the FQPA.

PESTICIDE TOXICITY TO CHILDREN

EPA bases its tolerance determinations, in large part, on toxicity data obtained from tests performed by pesticide manufacturers according to OPP's toxicity testing guidelines, and in response to the Agency's codified data requirements? We find that for most pesticides, OPP's testing guidelines and requirements will generate data that, by themselves, fail to provide a "reasonable certainty" that no harm will come to infants and children. In other words, even if a pesticide manufacturer has supplied the full set of toxicity data requested by EPA, this data set typically contains gaps that make it exceedingly difficult to adequately assess health effects from early childhood exposure to that chemical.

Even *if* a pesticide manufacturer has supplied the fill set of toxicity data requested by EPA, this data set typically contains gaps that make it exceedingly ***difficult*** to adequately assess health effects ***from*** early childhood exposure to that chemical.

Shortcomings can be found not only in OPP's existing testing guidelines, but also in the revised guidelines on which OPP has been laboring for several years. This means that even if a pesticide manufacturer were to meet existing data requirements using these revised guidelines, the resultant set of data would probably still contain significant gaps, hampering EPA's ability to assure a reasonable certainty of no harm to infants and children under the FQPA. For example:

- EPA fails to routinely require that pesticides used on food crops be tested specifically for toxicity to the brain and **nervous** system, in either adult or developing animals. In fact, EPA has received data on toxicity to the developing brain and nervous system for only six pesticides-even including the 39 organophosphorous pesticides known and designed to be neurotoxic. Yet of all the tests which EPA requests of pesticide manufacturers, this developmental neurotoxicity test is the only one that assesses for toxic effects on learning or memory. A child's developing brain can be particularly vulnerable to the neurotoxic effects of pesticides and other chemicals. Children rely upon learning and memory to become productive adults.

- EPA also fails to routinely require that food-use pesticides be tested specifically for toxicity to the immune system. According to EPA scientists, this testing has been requested for only two chemical pesticides. A child's immune system, and his/her ability to fight infection and disease, continues to develop from birth through adolescence.

- Most tests required for food-use pesticides are performed only in adult animals. They fail to expose fetal and immature animals. How can pesticide tolerances based upon these tests be safe for infants and children, when children have unique windows of vulnerability absent in adults?

The **exception**—two required tests for developmental and reproductive toxicity-fail to follow the exposed animals to their natural death. In other words, they do not evaluate the exposed animal long enough to allow all delayed effects which might occur to become evident. These tests, therefore, cannot reflect what will happen to exposed children as they grow, age, accumulate exposure to other toxic chemicals, and as organs naturally lose some of their full capacity to function.

The required test for developmental toxicity, which does expose developing animals to the chemical prenatally, does not continue to expose the animal after birth, when many organ systems are still developing. It therefore will fail to adequately reflect potential effects on the developing brain, nervous, immune and reproductive systems in a child who receives post-natal exposure to pesticides--through contaminated breast milk, dust, carpets, toys or other sources.

- Neither existing tests, nor tolerances based upon their results, fully reflect a pesticide's potential to disrupt the endocrine (hormonal) system. EPA is developing guidelines for such testing, but tolerances issued in the interim cannot reflect possible disruption of the endocrine system. Normal development of the fetus, infant and child depends upon the timely release of hormones at low levels, and the subsequent action of these hormones on various organs.

- EPA requires no testing, nor do specific test guidelines exist, to assess the interactive effects of multiple pesticides. Yet children are exposed to pesticide mixtures on a daily basis.

Many of these problems are noted in Table **1.**

ABOUT THIS REPORT

This report is structured to examine whether, for any particular pesticide, EPA's Office of Pesticide Programs is likely to have "reliable" data on children's toxicity and exposure to **justify** alteration of the tenfold FQPA children's safety factor in setting tolerances. The report's next four chapters mirror the four FQPA provisions mentioned earlier, provisions specifically designed to protect children.

The first provision requires that in setting a tolerance OPP will consider all available evidence that children may be more vulnerable to the toxic effects of that particular pesticide. Chapter Two reviews many of the 1993 NAS findings which showed compellingly that children, generally, are more susceptible than adults to pesticides' toxic effects. The chapter also looks at dietary and behavioral factors giving children unique exposure to pesticides.

The second and third FQPA requirements mandate an assessment of OPP's access to reliable, pesticide-specific, toxicity and exposure data on children. Chapter Three looks at non-dietary sources of children's exposure in light of the FQPA provision that all such sources, along with dietary sources, be aggregated as part of the risk assessment for an individual pesticide tolerance. Chapter Four focuses on OPP's pesticide testing requirements and its most up-to-date guidelines

for assessing pesticide toxicity. It lays out the gaps in the toxicity data generated by these guidelines and requirements, and used by EPA to determine whether reliable data exists to fully characterize the pesticide risks to fetuses, infants and children.

Chapter Five re–examines the completeness of toxicity data likely to result from OPP's current pesticide data requirements and testing guidelines, as well as its database on pesticide exposures relative to infants and children. This is done as a prelude to answering the question of whether, typically, OPP is likely to have sufficiently "reliable" data on children's toxicity and exposure to depart from use of the child-protective FQPA safety factor. This conforms to the decision process outlined in the key fourth provision of the FQPA.

Given the findings outlined above, as well as the requirements found in the new law, the report concludes with a set of recommendations for OPP as it seeks to comply with the child–protective provisions of the new law.

TABLE 1: Adequacy of EPA's Guidelines for Testing Toxicity to Children

Tests		Test includes *in utero* exposure	Test includes post–natal exposures	Tests for latent effects[1]	Tests for effects on offspring
Tests Required for Food–Use Pesticides:					
Acute Tests:	Oral toxicity (rat)	No	No	No	No
	Dermal toxicity	No	No	No	No
	Inhalation toxicity (rat)	No	No	No	No
	Primary eye irritation (rabbit)	No	No	No	No
	Primary dermal irritation	No	No	No[2]	No
	Dermal sensitization	N/A	N/A	N/A	N/A
Mutagenicity:	Gene mutation[3]	No	No	No	Yes[4]
	Structural chromosomal aberration	No	No	No	No
Subchronic:	90–day feeding (rodent & non–rodent)	No	No[6]	No	No
Chronic:	Feeding study (rodent & non–rodent)[5]	No[5]	No[7]	No[8]	No
Cancer:	Carcinogenicity[5]	No	No	No	No
Metabolic:	General metabolism tests	Yes	No	No	No
Developmental:	Developmental toxicity (rat and rabbit)	Yes	Yes	No	Yes
Reproductive:	Two–generation study (rat)				
Significant Tests, Occasionally or Rarely Required					
Acute delayed neurotoxicity (hen)[9]		No	No	No[10]	No
Developmental neurotoxicity study (rat)		Yes	Yes	No	Yes

Tests required for non food–use pesticides are indicated by shading.

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1 Latent effects are defined as those observed a significant period of time after exposure has ceased— a rodent's natural life span could be considered significant.

2 This test is designed to assess skin sensitization just 14 days after exposure to the test substance; testing is typically completed another 48 to 72 hours beyond that.

3 Most gene mutation tests are done on cell culture systems. Per 40 CFR §158, there may be other tests of genotoxicity done, but this determination is only made on an *ad hoc*, or chemical–by–chemical, basis.

4 Second–generation offspring are tested only indirectly, by examining effects on the sperm of exposed animals.

5 The chronic feeding study and the carcinogenicity study may be combined into one single test using the same animals.

6 Exposure is recommended to start immediately after weaning.

7 Pre– and perinatal exposure of test animals may be required under certain conditions, according to guideline language, but is atypical.

8 Tests of carcinogencity are not considered to test for delayed effects because they continue to dose the animal throughout the entire test.

9 Only required for organophosphate or structurally related pesticides.

10 After initial dosing, hens are observed for 21 days for acute effects. Only if the latter occur is there another round of testing, 28 days after exposure, for delayed effects.

CONSIDER CHILDREN'S SENSITIVITIES AND OFTEN UNIQUE EXPOSURE PATTERNS TO PESTICIDES

Children are not little adults. This maxim, one of the guiding principles of pediatric medicine, is only now being extended to the protection of children from environmental hazards, including pesticides in food.

Children need special protection to guarantee their safety from pesticides and other potential environmental hazards for a variety of reasons. These include the fact that children have unique periods of vulnerability during the process of development; they may lack the mature protective mechanisms normally present in adults; they may absorb toxic chemicals more quickly, due to a variety of factors; and children's unique behavior patterns and diet often may give them greater exposure and risk to toxic chemicals.

These factors are explored below. Additional comments indicate where EPA might need to better incorporate these factors into its toxicity testing or research agenda.

The organs most susceptible to toxic effects ***will typically*** be those undergoing critical developmental processes at 'the time of exposure.

PERIODS OF **VULNERABILITY**

During normal development of the fetus and in early childhood, there is rapid growth of cells. Actively growing and dividing cells are generally more susceptible than mature cells to chemical injury. Dividing cells need more nutrients and energy, and their genetic material replicates often, allowing greater opportunity for mutations to occur.

Whether exposure to a toxic chemical causes injury or abnormality, and the nature of that effect, can depend on the precise timing of development. For example, a standard embryology text points out that a human fetus exposed to a particular chemical during the 22nd day of gestation may develop **spina** bifida, a deformation of the spinal column. When exposed to the same chemical on the 42nd day of gestation, the same fetus might instead develop a cleft palate, while still later exposure may cause no developmental effect at all.'

The organs most susceptible to toxic effects will typically be those undergoing critical developmental processes at the time of exposure. Organ development begins **in the** womb, but major growth and development continues long after birth; periods of especially rapid growth occur in infancy and **puberty.**[2] The brain and nervous system, immune and reproductive systems, in particular, undergo important changes

all the way through adolescence.[3] Exposure to chemical toxins after birth may therefore have a lasting impact on these organ systems. For example, researchers have found that mice exposed to urethane shortly after birth developed leukemia at a rate six times higher than those exposed at around 45 days of age, the age of sexual maturity.[4]

The nervous system is particularly sensitive during its development (See box below). The human fetus generates new nerve cells which migrate to permanent locations within the fetal brain. As the infant grows to early childhood, these nerve cells lay the connections that are vital for normal brain function throughout life.

PESTICIDES AND THE DEVELOPING BRAIN AND NERVOUS SYSTEM

When a small child falls, a parent often first checks for injury to the head. Yet how many parents are aware of the potential effects of chemicals-including pesticides—on the normal development and function of their child's brain and nervous system? Children are born with almost twice as many nerve cells as they will eventually need in adulthood. Nevertheless, the developing brain is exquisitely sensitive to certain poisons, termed neurotoxins. This is because the brain's precise wiring is not entirely in place at birth. Normal brain function depends on the migration during development of nerve cells to specific areas of the brain, and on the fine-tuning of the connections that form between these cells. Until this critical period of nervous system maturation is completed, the connections between cells are malleable and subject to change. Thus, a newborn's interaction with her surroundings will determine both the quantity and quality of the connections between her nerve cells.

Because these processes are so delicately balanced, maturation of the nervous system is susceptible to any change in the uterine environment, including those induced by maternal exposure to toxic chemicals.' The fetal effects of a mother's abuse of alcohol or illicit drugs provide well-documented examples. Pesticides and other environmental toxins can also impair the process of maturation, causing more severe nervous system impairment than might be seen in adults.[6] Lead, in particular, has been associated with profound and lasting neurobehavioral effects in adolescents who were first exposed to fairly low doses as children – effects including a higher risk of failing to complete high school, of impaired reading skills, of deficits in vocabulary, of worse fine motor skills, reaction time and hand-eye coordination, and of antisocial and delinquent behavior.[7,8]

Testing Need Because of their unique potential vulnerability to toxic chemicals, the protection of children requires that laboratory testing of pesticides include the dosing of fetal, newborn and immature animals through all critical windows of development, and also the monitoring of such animals through to old age, allowing sufficient time for delayed effects to manifest. Only then will regulators be able to predict the possible long-term impact of exposure to pesticides on human fetuses, infants, and young children.

IMMATURE PROTECTIVE SYSTEMS

Compared to adults, children may have immature or absent mechanisms to protect them from toxic chemicals and other environmental insults.' The *blood–brain* barrier, which in adults protects the brain from many toxins circulating in the bloodstream, does not develop fully in children until one-and-a-half to two years of age." Children too young to have a fully developed blood-brain barrier may be more susceptible to brain damage from chemicals or pesticides in circulation. Differences in blood-brain barrier development may thus affect the degree of protection that an animal or child has against poisons that affect the brain."

In other respects, too, the fetus may be susceptible to the toxic effects of various chemicals. The placenta, for example, presents little barrier to many toxic substances in the maternal bloodstream, including alcohol and other solvents. Fetuses may also lack fully functional livers until after the middle of gestation.[12,13] Since the liver serves as a critical detoxifying organ, an immature liver can leave the fetus vulnerable to whatever toxic chemicals its mother ingests or is exposed to.

The immune system is another protective mechanism not fully developed in infants and children. The delicate balance between various components of the immune system is normally established through maturation of immune cells during childhood. Pesticides interfering with this maturation may produce abnormal development of the immune system, depending on the timing of a child's exposure, the mode of action of a particular chemical, and the site or organ it typically affects." For example, the developing immune system in rats has been shown to be more susceptible to the immunotoxic effects of 2,3,7,8–tetrachlorodibenzo–p–dioxin (TCDD).[15] And two different impurities in the organophosphorus pesticide, malathion, have been shown to suppress and to stimulate the immune system.[16,17] Suppression or overstimulation of the immune system can contribute to a variety of diseases in both children and adults. Abnormalities of the immune system may, in turn, potentially lead to allergies, asthma and autoimmune disease, or increased susceptibility to infections.[18,19]

Testing Need Both the blood-brain barrier and immune system continue developing after birth and during childhood. It is therefore imperative that pesticides be tested for their possible impact on the developing nervous and immune systems. Testing of the immune system must reflect potential effects on both suppression and overstimulation.

ABSORPTION AND METABOLISM

Metabolism refers to the action of various enzymes to biochemically alter the structure of a chemical. For example, chemicals are often metabolized by enzymes in the liver and then excreted in urine via the kidneys. Metabolism may either activate a non-toxic chemical to a toxic metabolite, or change a toxic chemical to a non-toxic metabolite.

Children are known to vary from adults in their ability both to absorb and to metabolize chemicals. For example, adults absorb into the bloodstream only about one-tenth of the lead they ingest, while children will absorb about one–half.[20] On the other hand, newborns metabolize caffeine more than 16 times slower than adults,

although this is probably a greater age-related difference than would be typical for other chemicals.[21]

The developmental age of a child helps determine whether or not he or she will be more or less susceptible than an adult to a chemical's toxic effects. Liver metabolism, for example, changes dramatically in the first year of life. Thus, ethylnitrosourea, which does not require metabolic activation, is more likely to cause cancer in neonatal rodents than in adults, while the converse is true for diethylnitrosamine, which requires metabolic activation to be toxic.[22]

Similarly, the rate at which toxic or non-toxic metabolites are filtered through the kidneys and excreted varies with age. A premature newborn's kidneys may filter at only 1/20th the adult rate, a full-term newborn at 30–40 percent of adult values.[23] However, infants typically reach an adult rate of filtration by 3-to-5 months of age.[24] At the cellular level, too, the NAS has noted that certain metabolic reactions in children may vary with increasing age from one-third to six times greater than the adult rate, while other reactions may not reach mature or adult levels for up to five years.[25]

Children's metabolism, including the development of particular enzyme systems, needs to be better explored? But metabolism of chemicals is compound–specific, or at least specific to a particular class of chemical. Ignorance about children's general metabolism is only compounded by a lack of data on how infants and young children metabolize specific chemicals, or classes of chemicals including pesticides.

Testing ***Need.*** Children may generally absorb and metabolize toxic substances differently than adults. In 1993, the NAS pointed out that EPA tests of pesticide metabolism are designed to provide information only about the adult rat.[27] But children's metabolism of specific pesticides cannot be accurately modeled or predicted based upon tests of adult animals. The only way to develop definitive data for particular pesticides is to conduct metabolic studies on developing animals.

CHILDHOOD BEHAVIORS

When young children explore their environment, they touch things and put fingers and hands in their mouths much more than would adults. The extent to which individual children engage in this behavior varies as well. Among toddlers and young children, hand-to-mouth behavior is an important mechanism of potential exposure to certain toxic chemicals, including the lead in peeling paint. Recent studies have also found that infants and children – particularly those who live on or near farms – will ingest significant amounts of pesticides by crawling and playing at ground level, and by touching surfaces inside the home which contain pesticides, either from windblown dust, from nearby lawns, or from indoor applications.[28,29]

Testing Need The FQPA calls explicitly for dietary and non-dietary exposures to be aggregated as part of risk assessments done to establish a pesticide tolerance. In the absence of much actual data, EPA typically models children's exposures using assumptions about their behavior. It is often claimed that EPA's exposure assumptions are overly conservative.

But OPP recently submitted a draft document, Standard Operating Procedures (SOP) for Residential Exposure ***Assessments***, to its Scientific Advisory Panel for review which suggested as a reasonable assumption that **3–to–5–year–old** toddlers exhibit hand-t-mouth behavior at a mean frequency of 1.56 times per ***hour***.[30] Fortunately, both the SAP and Assistant Administrator Goldman asked that this handbook of standard assumptions for risk assessment be further revised. This example serves to illustrate, however, that exposure assumptions may not be as uniformly conservative as is often claimed.

GREATER AND MULTIPLE EXPOSURES

One of the greatest differences in pesticide exposures among adults and children is in their respective diets. Pound per pound, children under five eat about three times more food and drink more water than do adults?' The USDA has found that American one-year+lds drink about 2 1 times more apple juice and 11 times more grape juice than the average adult. Children also eat more fresh fruits such as bananas, cherries and **apples.**[32] If these foods contain pesticide residues, as they often do, then the average child may be exposed to considerably higher levels of these potentially dangerous chemicals than the average-adult, and these exposures may be occurring at an age when the child can be most susceptible to their hazardous effects.

Pound per pound, children under ***five*** eat about three times more food and drink more water than do adults.

Organophosphorus insecticides, or **OPs,** are a class of widely used pesticides known to be poisonous to the brain and nervous system. The Scientific Advisory Panel to OPP recently reviewed a study prepared by the Environmental Working Group finding that each day, 1.1 million children between six months and 6 years of age ingest **OPs** at levels which exceed EPA's safe daily dose, or chronic reference dose? These excessive levels did not even include the potential organophosphate exposures children face from contaminated drinking water, and **from** non-dietary sources of exposure. Organophosphate insecticides have had many home uses as well.

Baby food presents an additional concern in that it typically contains produce from several sources, and may therefore contain several different pesticide residues. A 1995 study sampled a group of the baby foods most commonly sold in the United States and found 16 different pesticides present?' These included eight pesticides known to be toxic to the nervous system, five known to affect the endocrine system, as well as eight potential carcinogens. Iprodione, designated by the EPA as a probable human carcinogen, was the pesticide found at highest levels in the baby food samples. Many of the baby foods tested were laced with multiple pesticide residues.

Moreover, children drink more water on a weight-adjusted basis, both from the tap and as it is used to constitute infant formula and juices. In 1996, tests showed that tap water from 104 Midwestern communities with 3.3 million people was contaminated with five or more herbicides?

Testing Needs. Analyses presented at the March 1998 meeting of OPP's Scientific Advisory Panel suggest that more up-to-date dietary exposure data are available than those which have typically been used by EPA in setting tolerances? EPA should also take steps to ensure that all data used in setting tolerances are robust with respect to children of different ages.

In addition, EPA's pesticide data requirements fail to call for tests of pesticide mixtures on a routine basis. EPA does not even have finalized protocols for testing chemical mixtures. As a result, EPA's pesticide reference doses and tolerances have been set only on a chemical-by-chemical basis, as though we are exposed to them one at a time. They therefore fail to reflect the possible health effects of children ingesting pesticide mixtures, despite studies showing that children are routinely exposed to these mixtures, through food or otherwise, on a daily basis.