

US EPA ARCHIVE DOCUMENT

CONSIDER OTHER SOURCES OF PESTICIDE EXPOSURE WHEN PERFORMING RISK ASSESSMENTS AND SETTING TOLERANCES

Pesticides in children's food are the rule, not the exception. The U.S. Department of Agriculture's Pesticide Data Program (PDP) was established specifically to monitor pesticide levels in the fruits and vegetables most often eaten by children.¹ Of the 4,856 fruit and vegetable samples tested by PDP in 1996, 71.3 percent contained at least one pesticide residue. In addition, 91 percent of the wheat **samples** tested by PDP had at least one pesticide residue.

Milk comprises one-quarter of the diet for a non-nursing infant? In Iowa, which routinely monitors milk for pesticides, concentrations of dieldrin are consistently found between 8 ppb (parts per billion) and 16 **ppb**.⁴ One recent study of organophosphate pesticide residues in food found that each **day** nine out of ten children between 6 months and 6 years of age ingest these pesticides, which are known to be toxic to the brain and nervous system?

The Food Quality Protection Act requires that tolerances for individual pesticides take into account not only potential dietary exposures, but also exposures from any non-dietary sources. This aggregate approach is particularly important for the protection of children, who are known to ingest higher quantities of the foods that contain pesticide residues most often, and whose patterns of behavior often lead to additional pesticide exposure. For a child who crawls and puts a hand in his or her mouth, for example, exposure to pesticide residues in the household may be much more significant than it is for adults.

A description of various pathways (other than food) by which children may be exposed to pesticides, and which must be taken into account under the FQPA provisions, includes the following:

Pesticides in Water

Water has been called the most consumed food of children! Drinking water, however, increasingly comes from water bodies polluted with the pesticides used upstream or in surrounding areas.⁵ From 1991 to 1995, the U.S. Geological Survey tested about 5000 samples of ground and surface water for pesticides, **from** twenty of the country's chief watersheds.⁶ At least one pesticide was found in every stream

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sample, and in around half of the ground water samples. In Illinois, at least **one-third** of all the finished drinking water samples collected in 1993 and 1994 had multiple pesticides.¹ In other words, many pesticides sprayed on crops do not degrade, but persist in water supplies, even in home tap water.

Pesticide contamination of drinking water occurs at significant levels, and can carry significant health consequences. In 1995, the Environmental Working Group (EWG) tested drinking water from 29 Midwestern cities for certain pesticides. Its study found that in 35 percent of all drinking water samples, levels of cyanazine exceeded federal health guidelines, or **MCLs** (Maximum Contaminant Levels), while levels for atrazine exceeded standards in 17 percent of the cases.² Over the **six-week** testing period, it was also estimated that 10,000 infants in the 29 cities drank formula constituted with drinking water containing atrazine above the federal health standards. It must be noted, however, that federal standards for pesticides in tap water have been set without taking into account their possible effects in children.

The exceedances above were often repeated and sustained, sometimes lasting more than a month. Water utilities, however, are mandated to test drinking water for pesticide contaminants only four times a year, often missing specific periods when pesticides are being applied.

Pesticide contamination of water, even at relatively low levels, has been linked to changes in hormone levels in wildlife.³ In addition, a 1997 epidemiologic study compared communities in 12 southern Iowa counties that shared a pesticide contaminated drinking water supply with nearby communities using different drinking water sources. It found that levels of several pesticides, including atrazine, cyanazine and metolachlor, were associated with significantly higher rates of intrauterine growth retardation (IUGR) in the affected communities.* IUGR describes low fetal weight for a given gestational age—its presence predicts higher rates of infant illness and death. Atrazine has also been found, by both industry and independent investigators, to cause an increased number of mammary tumors or masses of the breast tissue—in exposed **rats**.^{13,14}

In its testing, the Environmental Working Group found that water supplies in two-thirds of the 29 tested cities contained at least four, and as many as nine, different pesticides.⁵ Yet pesticide mixtures are not currently tested for their combined toxicity under federal guidelines.

Pesticides in Breast Milk

Another source of children's exposure to pesticides may be through breast milk. Although the overall benefits of breast feeding outweigh concerns about possible pesticide contaminants, breast milk must still be considered when aggregating various sources of exposure to pesticides among infants and children.

Metabolites of DDT, a potent organochlorine pesticide with estrogenic properties, have been detected in women's breast **milk**.^{16,17} These traces can be detected even when exposure to DDT may have occurred many years prior to pregnancy, presumably because DDT can remain in the fat cells of breast tissues for long periods of time. While DDT is now banned for use in the United States, USDA's Pesticide Data Program detected it in more than 3 percent of the fruit and vegetable samples for which it was tested.* Other organochlorine pesticides with estrogen-like effects remain in use including dicofol, endosulfan, and lindane, the latter of which is used for body lice.¹⁸

Pesticides in the Home

Approximately 90 percent of U.S. households use **pesticides**.²⁰ Homeowners accounted for an estimated 74 million pounds of the conventional pesticides used in 1995, representing a nearly \$2 billion industry.²¹ Household use of pesticides, apart from lawn and garden chemicals, includes fumigation products, pet care products and insect **repellents**—the latter containing high amounts of pesticides as well as other ingredients.

Pesticide residues persisting in household soil and dust are considered significant sources of exposure for small children? One study estimates that the pesticide 2,4-D, used on lawns and gardens, can persist in carpet dust up to a year after its **application**.²³ A study of household exposure to 32 pesticides in Jacksonville, Florida found an average of 12 pesticides in samples of carpet dust from nine **homes**.²⁴

In another household study, Gurnathan et al. discovered that semi-volatile pesticides, such as chlorpyrifos, can volatilize, absorbing onto surfaces and objects during and long after pesticide application.²⁵ Chlorpyrifos was found to volatilize and accumulate on plush toys, which acted as pesticide reservoirs, with increasing levels of pesticide found even two weeks after application; pillows, cushions, bedding and other foam items could act as similar reservoirs. The study indicates that in homes treated with semi-volatile pesticides, chlorpyrifos in this case, children may receive exposures up to 20 times greater than EPA's reference dose, which is 3 **ug/Kg/day** for chlorpyrifos. In addition, the persistence of elevated residues on household items, like toys, contrasts starkly with the suggested period for **re-entering** the home—typically, one to three hours after pesticide **application**.²⁶

Agricultural pesticides may also find their way into the home, in dust or on the clothes of farm workers. A study of pesticide residues in house dust showed that high levels were detected not only in the homes of farming families, but also in homes of non-farming families living more than a quarter of a mile away from a **farm**.²⁷

Home pesticide use results in many acute poisonings involving children, and has been linked with chronic effects including cancer. In 1995, more than 123,000 cases of pesticide exposure were reported to poison control centers, roughly 53 percent involved children under age six.²⁸ Of the 628,000 unintentional pesticide exposures reported to poison control centers between 1985 and **1993**, **92** percent took place in a home, around 24 percent involved treatment at a health care facility, and 8 percent required hospitalization? The Poison Control Center of San Francisco reported that from 1991 to 1992, about 20 percent, or 200, of adverse health outcomes from reported pesticide exposure occurred in children under age six?

Studies have linked home pesticide use and a higher incidence of various childhood cancers. One study found a 3.8 times higher likelihood that children would develop leukemia in homes where pesticides were regularly used? In the same study, home use of lawn pesticides was associated with a 6.5 times greater risk of leukemia. This and other studies raise serious concerns about the safety of such products.

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Pesticide Use In Schools

In a recent survey of 46 California school districts, 93 percent reported using a total of 73 different pesticides? Seventy percent of the surveyed school districts use pesticides classified by state or federal agencies as "known," "probable" or "possible" human carcinogens; 52 percent use pesticides labeled by EPA as developmental or reproductive toxins; and 54 percent employ pesticides that EPA ranks as acutely toxic to the nervous system?

Another study found that 87 percent of New York City schools apply pesticides? Many states, including California and New York, have no law requiring that parents and teachers be notified before schools apply pesticides. In less than 3 percent of the New York schools were staff, students or parents notified before an indoor pesticide application.?

Using data collected from Poison Control Centers nationwide, EPA found at least 2,766 incidents of pesticide poisoning in schools from 1985 to 1992.³⁷ Kaplan et al note that both local and federal reporting systems are likely to under-report actual poisonings. They note as well that there is no attempt to monitor long-term illness which may result from pesticide exposure in schools, including such illnesses as learning disorders, cancer and developmental and reproductive effects?

Pesticides in Air

Pesticides suspended in indoor and outdoor air can be a major source of exposure for adults and children. Children can inhale aerosolized pesticide residues directly, eat food that has been contaminated, or ingest residues in household dust. Studies have found that inhalation of pesticides may sometimes exceed exposure through the diet, particularly for pesticides used in the home? Infants, toddlers and full-time mothers spend up to 2 1.5 hours per day at home, plus more time in other buildings.⁴⁰ Older children spend a substantial portion of their days in school buildings which may be treated with pesticides.

A study of household pesticide exposure conducted in Jacksonville, Florida suggests that 88 to 100 percent of the homes in that city have detectable indoor air levels of chlorpyrifos, depending on the time of year." In the winter months, the authors anticipated that four of the 32 pesticides monitored by the study would be found in at least 92 percent of the Jacksonville homes. Twelve of the 32 pesticides were thought to be detectable in the air of more than 20 percent of the homes. An average of 7.5 different pesticides were found in each air sample collected from nine Jacksonville residences."

Chlorpyrifos and other semi-volatile pesticides are often applied in schools? Earlier, it was noted that such chemicals can alternate between their gas and solid phases, accumulating on indoor surfaces for weeks after application. At one San Francisco elementary school, 396 children and 67 staff members were sickened after the pesticide **Microban** was sprayed into the ventilation system." The particular formulation of **Microban** that was used had not even been registered in California, since animal testing had already raised concerns about its inhalation toxicity.

Outdoors, pesticides are often applied as sprays, either from airplanes or hand-held applicators. Particles of diluted pesticide can thus be carried through the air into other areas." Anyone breathing the contaminated air can absorb suspended particles; people who live closer to the fumigated areas will receive higher doses. Acute pesticide poisonings have been documented in persons simply living near

fields treated with chloropicrin and methyl bromide? Schools may be situated immediately adjacent to fields or orchards treated with highly toxic pesticides.

Illegal Use of Pesticides

Even if pesticides were to be thoroughly tested, there is no guarantee they will be used properly and responsibly. Illegal use of pesticides often puts people at risk, particularly children. Methylparathion, for example, is an organophosphate insecticide approved only for killing boll weevils and other biting and sucking insects in agricultural crops, particularly cotton. Seven young siblings were sickened and two died from illegal home use of methylparathion in Tunica, Mississippi in 1984." After identifying illegal indoor use of methylparathion in Ohio in 1994, EPA had to decontaminate 232 homes at a cost of over \$20 million. Another episode occurred in Detroit in 1995. And in 1996, the Agency for Toxic Substances and Disease Registry (ATSDR) and the EPA discovered still more examples of indoor malathion use in Mississippi, Tennessee, Arkansas, Alabama and Louisiana and Illinois. Renovation of just the 1,100 contaminated homes in Jackson County, Mississippi will cost more than \$50 million, according to government estimates? While these represent cases of extreme exposure from illegal acts, they illustrate the degree to which illicit exposures can sometimes occur.

INADEQUATE DATA FOR AGGREGATING PESTICIDE EXPOSURES

The Food Quality Protection Act requires that children's pesticide exposures be aggregated across all potential sources. This includes contaminated food, breast milk, drinking water, indoor and outdoor air, as well as non-air sources at school and at home. EPA is hampered in doing adequate aggregate exposure assessments both by the lack of data on individual avenues of pesticide exposure, but also by the lack of biological monitoring data, especially in infants and children.

The human body naturally aggregates pesticide exposures in exactly the way envisioned by the Food Quality Protection Act. Exposure occurs through inhalation, ingestion or absorption of the pesticide across the skin. The chemical is distributed in the bloodstream, eventually is metabolized, and is excreted in urine unchanged or as a metabolite. Biological monitoring refers to the measurement of pesticides or pesticide metabolites in human blood or urine to gain a better idea of the aggregate dose faced by the exposed person.

The technology for measuring pesticides in blood and urine exists, chiefly at the Centers for Disease Control and Prevention (CDC). But the tests can be expensive. As a result, only very limited testing has been done to date. In the third National Health and Nutrition Examination Survey (NHANES III), over 900 adult volunteers had their urine sampled between 1988 and 1994 for a panel of pesticides or their metabolites. Chlorthalidone metabolites were detected in 82 percent of the samples." Similarly, preliminary results from a recent study involving children from 60 agricultural families in eastern Washington found that they had metabolites in their urine from several organophosphorus pesticides (OPs) at median levels of 24 ppb (parts per billion).⁵⁰ In the same study, it was found that younger children tended to have higher levels of OP urinary metabolites than their older siblings.'

Dr. Richard Fenske, the University of Washington researcher who presented the above data at a March 1998 conference on children's pesticide exposures sponsored

by EPA, estimates that around one-third of the children whose urine was collected in this study have exposures to OP insecticides more than three times higher than EPA's safe daily dose, or chronic reference **dose**.⁵² This estimate raises a question. Given the uncertainty surrounding effects from long-term exposure to pesticides, especially in children, is there any amount of pesticide or pesticide metabolite in a child's urine that can be considered safe?

Chlorpyrifos and certain other OP pesticides are exceptional in that some limited biological monitoring data on children are available. The same cannot be said for the vast majority of the nearly 300 pesticides used on food. For all food-use pesticides, however, there are additional hurdles to gathering adequate exposure data, including the following:

- 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 adequate analysis on infants' and children's aggregate exposure as is required under the FQPA. In other words, there is no exposure equivalent to the Agency's IRIS (Integrated Risk Information System) database where toxicity data on individual chemicals is collected, summarized, and made available to risk assessors and the public.
- Despite numerous studies suggesting that children face exposure to pesticides in contaminated soil, dust, water and air in their parks, yards, homes and schools, EPA has little comprehensive data quantifying such exposures for food-use pesticides." The lack of reliable data on children's household exposures and exposure through drinking water, in particular, were also highlighted by panelists at the March 1998 meeting of **OPP's** Scientific Advisory Panel. In 1993, the NAS noted that water, both as drinking water and as a component of food, was not adequately considered in most food consumption surveys.⁵⁵ EPA has also admitted in recent tolerance notices that it lacks drinking water monitoring data on which to base its exposure estimates?
- Even for areas where OPP has relatively more exposure data, such as dietary exposure, data have often been outdated or inadequate. Human dietary exposure to pesticides, for example, is estimated using both food consumption data and data on pesticide residues in the food supply. OPP, however, has based its tolerances under FQPA largely on **food** consumption data from the USDA's 1977-78 surveys, even though dietary habits have changed significantly over the last 20 years? The NAS also noted in 1993 that existing food consumption surveys generally involve small numbers of infants and children, and even then collect only a few days worth of consumption data for each individual? Thus, it would accurate to say that we have often not really known what children eat.

- Pesticide residue data has also been problematic. The Food and Drug Administration (FDA), and the U.S. Department of Agriculture (USDA), collect food residue data via three major testing programs and each has its weaknesses. FDA's programs in particular have long been criticized (See Box).⁵⁹

FDA PESTICIDE TESTING UNDER SCRUTINY

Among federal agencies, FDA has the largest volume of data on pesticides in the food supply. The failings of FDA's pesticide monitoring program have been detailed in at least 22 reports by the U.S. General Accounting Office (GAO) since 1980. As summarized in a 1995 study by the Environmental Working Group, these criticisms include the following points: First, the equipment in an average FDA test lab is inadequate; it can detect only around half of the pesticides used on food crops grown throughout the world. Second, FDA lacks the legal authority to compel the reporting of which pesticides are used on which crops—this leaves FDA's chemists with little idea of which pesticides to look for in a particular food sample. Since FDA has no means of knowing what pesticides are applied to a particular crop, it has to randomly sample every crop and this is an impossible task. EWG's analysis suggests that FDA may sample less than 1/10,000th of one percent of the total fruit and vegetables shipped each year in the United States. Finally, even if FDA inspectors find pesticide residues on food, they have no computerized database to check and ensure that these measurements comply with U.S. regulatory standards. Moreover, the 1993 NAS study found that FDA's food surveys tend to under-represent foods eaten by infants and children.

Given the general lack of data about children's exposure to pesticides, the risk assessments currently being done to set pesticide tolerances rely heavily on the use of models and assumptions. What EPA has failed to establish, however, is what constitutes the minimum data needed to assure the appropriate use of models and assumptions in the first place. In other words, when is actual exposure data on infants and children so lacking as to make the use of any model to predict true patterns of exposure unreliable? The frequently heard claim is that current assumptions about children's exposure are so conservative as to greatly exaggerate risk. But in the absence of data, how does one judge conservatism? In September 1997, the FIFRA SAP reviewed a draft handbook of exposure assumptions listing, as one of its assumptions, that an average child puts a hand in his or her mouth an average of 1.56 times per hour? One does not have to be a parent to question the degree of conservatism in this assumption.

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DETERMINE THAT TOLERANCES PROVIDE A REASONABLE CERTAINTY OF NO HARM

Tolerances are the levels of pesticide residue allowed by EPA to legally remain in or on food. They carry at least an implicit assurance of safety. Under the FQPA, EPA must set tolerances that offer a "reasonable certainty" of no harm to infants and children.

Tolerances are based upon risk assessment, a methodology that combines information on a pesticide's toxicity with what is known about human exposure to that chemical to derive an estimate of its overall risk. The very first step in risk assessment, identifying a chemical hazard, relies upon data from tests of a chemical's toxicity.

Available data about the toxicity of a particular pesticide will in most cases reflect EPA's pesticide data requirements and toxicity testing guidelines. The former are described in the Code of Federal Regulations (40 CFR § 158). These requirements guide pesticide manufacturers in determining which kinds of tests they must perform to register and legally sell their product. From the public's perspective, the data requirements give a rough indication of how extensively a pesticide has been tested on animals and cells to uncover the toxic effects that might occur among people exposed to it. The requirements have not changed since 1984.

Scientists in **academe** or in government laboratories may also perform tests on an individual pesticide, independently of those required by EPA and carried out by the manufacturer. But toxicity testing in animals, particularly long-term testing, is quite expensive—a single 2-year test for carcinogenicity costs **\$2-4 million**.¹ For individual pesticides, the manufacturer is likely to **perform** or pay for the vast majority of toxicity testing. Pesticide manufacturers have the greatest motivation, as well as the financial resources, to complete such testing. Conversely, they have little motivation to perform toxicity testing in excess of EPA's data requirements. For these reasons, the codified data requirements in 40 CFR § 158 are critical in determining the likely body of data upon which EPA will draw in setting the tolerance for a particular pesticide.

EPA's data requirements vary for any single pesticide according to certain criteria, including whether or not it is to be used on food crops. Because the FQPA specifically directs EPA in how to set tolerances for pesticides used on food crops, this chapter examines data requirements for that category.¹ The chapter looks even more closely at the Office of Pesticide Programs' most **up-to-date** (though not

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finalized) toxicity testing guidelines to judge how effective they might be in generating **data that can provide a reasonable certainty of no harm to infants and children.**

EPA'S TOXICITY TESTING GUIDELINES

EPA's data requirements for food-use pesticides include: a set of acute screening tests, tests of genetic toxicity (or mutagenicity), subchronic tests, chronic tests (including cancer studies) and tests of metabolism, developmental and reproductive toxicity. EPA has conditional requirements for some tests of neurotoxicity, but only for organophosphates or structurally related pesticides—in other words, pesticides already known or suspected of being neurotoxic. These requirements are summarized in the box below.

PESTICIDE TESTING REQUIREMENTS

Required for non food-use pesticides:

- Acute Toxicity Tests (Set of 6): Oral, dermal, and inhalation toxicity; plus primary eye irritation, skin irritation, and skin sensitization
- Mutagenicity Battery: Tests of gene mutation, structural chromosomal aberrations, and other genotoxic effects

Required for food-use pesticides:

Acute Toxicity and Mutagenicity Tests, as above; plus,

- Subchronic (90-day) Feeding Study, typically rat & dog
- Chronic (**2-year**) Combined Feeding Study /**Carcinogenicity** Study in 2 species
- General metabolism study, in rats
- Developmental Toxicity Study, typically rabbits & rats
- Reproductive, or **Two-Generation**, Study, typically rats

Additional Tests:

- Acute Delayed Neurotoxicity-test (only required for organophosphates or related chemicals)
- Developmental Neurotoxicity Study in Rats (as needed)

Source: 40 CFR **§158.34**

EPA's toxicity testing guidelines, which are not codified, tell manufacturers how to conduct tests that are acceptable in meeting the data requirements. They also provide further guidance on when certain data are required, guidance on the evaluation and reporting of data, and examples of acceptable test protocols?

The Office of Pesticide Programs' toxicity testing guidelines form a special focus of this report. In *Pesticides in the Diets of Infants and Children*, the National Academy of Sciences found that EPA's testing guidelines or protocols were, for the

most part, adequate only for assessing pesticide toxicity in sexually mature animals. **Specifically, the report** concluded that EPA's testing guidelines and protocols did not "adequately address the toxicity and metabolism of pesticides in neonates and adolescent animals or the effects of exposure during early developmental stages and their sequelae later in later life."⁴ Other investigators have also noted that current testing methods are not adequate for predicting effects on children.⁵

Since at least 1993, OPP has been updating its toxicity testing guidelines for pesticides, including major revisions to those for testing developmental toxicity, reproductive toxicity, immunotoxicity and dermal absorption. Public drafts of the revisions have been available since 1996.⁶ The individual revised guidelines are described at length in Appendix A.

Compared to previously issued guidelines, the revisions more clearly describe guideline requirements and help ensure that tests done using the same duration of exposure (i.e. acute or chronic) are uniform. Revised guidelines for developmental and reproductive toxicity better describe what investigators should look for during examination of the gross tissues from fetal, infant and maternal animals, as well as during the microscopic (histopathology) examination. Many pesticide registrants may already be performing toxicity tests according to the draft guidelines, because they are generally more stringent, and in anticipation of their eventual adoption. But registrants are under no obligation from EPA to do so.⁸

Though in development for over five years, OPP has not finalized any of its revised toxicity testing guidelines as this report goes to press. More importantly, the updated guidelines still fall short of addressing the concerns first raised by the NAS in 1993. This chapter looks carefully at why toxicity data generated according to these newer guidelines will still fail to provide a reasonable certainty of no harm to infants and children. The shortcomings of the revised guidelines are described here, and are summarized in Table 1 at the end of this report. In reading this chapter, however, one must bear in mind that a tolerance decision today will likely draw upon data largely generated according to the previously issued guidelines, and not according to the revised toxicity testing guidelines reviewed here.

Acute and **Subchronic Toxicity** Tests

OPP's revised guidelines for both acute and subchronic toxicity testing fail to expose test animals in a way that reflects actual exposure among infants and children. (See Appendix A for a description of the revised guidelines.) They then fail to monitor the tested animals for development of all the adverse effects of greatest concern to infants and children. More specifically:

- Both acute and subchronic toxicity tests use young, healthy adult animals, rather than fetal, newborn or developing animals. At the earliest, animals in these tests are exposed to the test pesticide beginning at 6 weeks of age, the age of sexual maturity—roughly equivalent to mid-adolescence in humans. Under OPP's tiered toxicity testing regime, however, it is largely a positive result on these acute and subchronic tests performed in adult animals that is intended to trigger, for a particular pesticide, the request for additional toxicity testing to look at more specific health effects. For non-food pesticides, for example, the six screening tests for acute toxicity (known as the "six-pack") are the only tests

done to uncover poisonous effects other than cancer. Food-use pesticides undergo routine testing for developmental and reproductive toxicity, but these tests are specifically designed to look at developmental and reproductive effects, or **endpoints**—not acute effects on the skin, eyes, or respiratory tract of the immature animal. These acute toxicity tests in adult animals are also the basis for most EPA determinations as to whether the tested pesticide requires additional labeling, packaging or restrictions on how it is applied.

- Manufacturers of food-use pesticides retain considerable flexibility as to whether they must perform the full array of acute toxicity tests. According to **OPP's** revised guidelines, for example, certain tests of acute toxicity may be foregone if the pesticide's physical properties make it an obvious irritant—an example might be a chemical with obvious corrosiveness or high acidity. On its face, this seems reasonable, except for the fact that the guidelines are unclear as to which tests may be skipped. Similarly, the guidelines suggest that a pesticide may not need to be thoroughly tested if "judged to be relatively non-toxic." Again, the guidelines fail to include criteria for how to judge this relative lack of toxicity.

Finally, manufacturers may argue under the guidelines that so-called structure-activity **data—data** that a test chemical is structurally related to another chemical of known toxicity is sufficient to avoid doing **otherwise** required acute tests. Structure-activity relationships have been shown to have useful, though limited, value in predicting chemical toxicity. DDT, a pesticide now banned in the United States, is known to be toxic via interaction of its metabolites with certain cell receptors for hormones. DDT's chemical structure, however, is not at all similar to that of estrogen or estradiol, the natural hormones that bind to these same receptors. In short, DDT's structure-activity relationship would not have predicted its toxic, estrogenic **effect**.⁹ DDT's estrogenic properties were predicted using evidence from studies on laboratory animals, along with evidence **from** human populations. These resulted in the chemical being taken off the market in this country."

Certain neurological diseases of the elderly, such as Alzheimer's or Parkinson's disease, have been postulated to occur after an accumulation of toxic insults and other damage over a lifetime.

- Acute and subchronic tests cannot, by their design, detect effects that occur after a long period of latency. Latency, or delayed **manifestation** of toxic effects, is characteristic of many substances that cause cancer and other effects; DDT exposure early in life, for example, with accumulation in the fatty tissues, is thought to be related to the onset of cancer many years later." Latency may be particularly important in children whose developing brains are vulnerable to injury and who, after being exposed to toxic chemicals, have a much longer period of time in which to manifest health **effects**.¹² Normal aging and senescence of brain cells may unmask acute damage inflicted by neurotoxins during childhood. Certain neurological diseases of the elderly, such as Alzheimer's or Parkinson's disease, have been postulated to occur after an accumulation of toxic insults and other damage over a lifetime?

The possibility of latency makes acute and subchronic testing particularly lacking as first-tier tests. In a tiered system of testing, a negative result on a fairly insensitive acute test may be presumed to act as an adequate surrogate for

longer-term tests which have more sensitive measures of toxicity and a longer period of time over which effects may become evident.

Neither tests on adult animals, nor structure-activity relationships, nor tests of an abbreviated length will be sufficient to paint an accurate picture of the short- and long-term risks facing children who have been exposed to pesticides during the periods of life when they have the greatest potential vulnerability. Relatively nonspecific and insensitive short-term testing may also be ineffective as a trigger for signaling the need for second tier, longer-term toxicity testing which include more sensitive endpoints, especially in developing animals. Based upon tests performed according to the revised guidelines for acute and subchronic toxicity, EPA cannot presume to have "reliable evidence" for using an uncertainty factor of less than 10X to ensure the safety of infants and children.

CHRONIC TOXICITY AND CARCINOGENICITY TESTS

As with acute and subchronic tests, revised guidelines for chronic toxicity and carcinogenicity fail to require dosing of immature or developing animals. (See Appendix A for a description of the revised guidelines.) Exposure of laboratory rodents to the test agent in the chronic test usually begins at 8 weeks, equivalent to young adulthood in humans. The chronic toxicity test guideline does stipulate that "studies using prenatal or neonatal animals may be recommended under special conditions." However, it does not state what those special conditions may be, or how these additional tests would be conducted.

On the other hand, the National Academy of Sciences recommended in 1993 : "[T]hat the testing guideline for a rat chronic toxicity/carcinogenicity study be modified to include in utero exposure during the last trimester, exposure through the mother's milk, and after weaning, oral exposure through the diet." The FQPA also directs EPA to assess pesticide residue risks based upon information about the "special susceptibility of infants and children to the pesticide chemical residues, including... effects of in utero exposure to pesticide chemicals." Other studies suggest that cancer testing, in particular, should include developing animals, since it has been shown that for a variety of chemicals, early exposures can cause cancer later in life.¹⁶ These effects may be missed or minimized if chemicals, particularly pesticides, are only tested in mature animals.

OPP's Health Effects Division reviewed the scientific literature and recommended to the Scientific Advisory Panel in September 1997 that EPA not routinely require carcinogenicity testing involving perinatal exposure of the test animals. Its review concludes that "currently available data do not support routinely incorporating a perinatal exposure component in the standard **carcinogenicity** assay." OPP also proposed to the SAP several criteria for potentially triggering perinatal **carcinogenicity** testing. The SAP concurred with both the recommendation against routine in utero testing and the triggering criteria.

However, two items in the scientific review should be noted. First, OPP's analysis admits that the data on which it bases its recommendation are not very robust? Second, OPP's recommendation came despite evidence that perinatal exposure of test animals to carcinogens in the perinatal period may serve both to increase the incidence of tumors found, as well as shorten the latency period between

exposure and onset of the tumor.¹⁹ Given these two points, it is less clear how **carcinogenicity** testing without perinatal dosing can provide a reasonable certainty of no harm to infants and children sufficient to allow departure from the use of the tenfold FQPA safety factor.

In addition, neither **OPP's** revised chronic feeding guideline nor the carcinogenicity testing guideline calls for test animals to be followed throughout their natural lives. If done separately, the chronic feeding test may last just 12 months, or less than half a rat's typical life span. Tests of **carcinogenicity** generally run for two years. Both long-term test protocols therefore ensure that test animals will be sacrificed at or before the human equivalent of age 65. Two-thirds of cancer cases, as well as much chronic illness, including Alzheimer's and Parkinson's disease, onset after age 65. A study by Peto and colleagues suggests the possible impact of shortening the duration of testing: rats exposed to two known carcinogens for only two years were found to have an incidence of tumors seven times less than when exposure was extended to two and one-half years?

Both EPA and its Scientific Advisory Panel have endorsed a policy of not requiring routine perinatal dosing in **carcinogenicity** testing. This policy was derived from the standpoint of whether the latter provided any added value to the standard adult animal assay.²¹ On the other hand, it does not reflect the FQPA requirement that toxicity testing provide a reasonable certainty of no harm to infants and children.

In order for EPA to depart from use of the child-protective tenfold uncertainty factor in setting tolerances, it should immediately require prenatal and neonatal exposure of animals in carcinogenicity tests, especially for any pesticide already identified as a known, probable or possible carcinogen. These assays should also be carried to the end of the tested animal's natural life. Another prudent step, given the ready availability and established use of human cells in in vitro studies, would be for EPA to require use of human cells for as many of the in vitro tests in the mutagenicity guidelines as possible."

METABOLIC TESTS

As with earlier tests, the major shortcoming of revised guidelines for tests of metabolism and pharmacokinetics is that they are not done in developing animals. (See Appendix A for a description of the revised guidelines.) Animals exposed to toxic chemicals while in the womb or early in life may have very different metabolic reactions than adults. The fetus may not yet have functional liver enzymes to detoxify pesticides, or may not possess them in adult quantities. Also, chemical toxicants that enter the bloodstream may be distributed to different tissues or organs in the fetus as compared to adults, primarily due to the effects of the placenta.²³ Without specific testing to discover how pesticides are, in fact, metabolized by the fetus, infant or child, we simply do not know what effect that substance will have on a child. In addition:

Revised metabolism testing guidelines fail to assure that the most appropriate species and strain of animal is tested. Guidelines for all studies of absorption, metabolism or pharmacokinetics recommend that rats be used as the test animal, probably because more of these studies have been done in rats than in other species making it easier to compare results to the existing literature. Rats, however,

have been shown to differ from humans in various aspects of **metabolism**.²⁴ For particular chemicals, there may be other species in which testing would better approximate human metabolism.

Choosing an appropriate animal species in which to test chemical toxicity gets more complicated when one considers that susceptibility also varies among strains within a species. Scientists already recognize that people vary in whether or not they possess certain enzymes that confer different degrees of susceptibility to toxins. Children who possess a form of the gene that codes for **ALAD**, an enzyme present in blood, accumulate higher blood lead levels than children without this **gene**.²⁵ Similarly, different animal strains of the same species may have diverse susceptibility. Genetic susceptibility to lead, for example, has been found to vary across two different strains of **mice**.²⁶

EPA cannot assume to know the metabolism or **pharmacokinetics** of pesticides in fetal and developing animals until it actually begins to request such tests. Further, EPA might consider requiring that tests of chemical metabolism be run in more than one strain of animal, to better characterize the range of genetic susceptibility in that species and by implication, the range of genetic susceptibility known to exist in humans. Until these steps are taken, metabolic testing in adult animals makes it more difficult to assure a reasonable certainty of no harm to infants and children.

TESTS OF NERVOUS SYSTEM TOXICITY

Depending on the food-use pesticide, neurotoxicity testing may or may not be requested of the manufacturer. (See Appendix A for a description of the revised guidelines.) It is therefore worth discussing not only the shortcomings of individual guidelines, but also the situations in which EPA requests testing according to these guidelines in the first place.

- When done, the Neurotoxicity Screening **Battery—OPP's** basic neurotoxicity screening test, is performed not on newborn or developing animals, but on young adult animals. In 1993, the National Academy of Sciences (**NAS**) cautioned that the extrapolation of toxicity data from adult and adolescent animals to young humans may be **inaccurate**.²⁷ At the same time, the NAS reported that "data strongly suggest that exposure to neurotoxic compounds at levels believed to be safe for adults could result in permanent loss of brain function..." if those exposures occur **pre-natally** and during early **childhood**.²⁸ Since it does not use immature animals, the Neurotoxicity Screening Battery's usefulness in predicting possible toxic effects on the developing brain in an exposed fetus, infant or child may be limited. (See Developmental Neurotoxicity Study on page 34 for more detail)
- There is no uniform requirement that pesticides used on food be specifically tested for toxicity to the brain and nervous system. **OPP's** pesticide testing requirements require neurotoxicity screening largely as a response to positive findings from the required acute toxicity testing, or if the pesticide has already exhibited delayed neurotoxicity? General acute toxicity testing may detect most chemicals with neurotoxicity, but as a screen it lacks the design specificity of the Neurotoxicity Battery and therefore may not assess all critical indicators of toxicity to the brain and nervous system. In 1987, EPA proposed to include

neurotoxicity screening as part of its required acute, **90-day** and chronic toxicity studies.³⁰ OPP's Scientific Advisory Panel endorsed the requirement of routine neurotoxicity screening in both acute and subchronic studies, and EPA followed that recommendation in its revised (though still not finalized) pesticide data requirements? Though reviewed and largely endorsed by the SAP in 1994, these new requirements remain unfinalized.

- Absent specific requirements, OPP's tiered testing scheme rarely leads it to request that more specialized tests of neurotoxicity be done, especially those involving complex performance, learning and memory. According to its guideline, the Neurotoxicity Screening Battery "is not intended to provide a complete evaluation of neurotoxicity..."³² The functional observational battery (FOB) portion of the Neurotoxicity Screening Battery, for example, excludes any assessment of learning and memory? OPP has one discretionary guideline, the Schedule-Controlled Operant Behavior (SCOB) guideline, which does measure an exposed adult animal's ability to perform a complex task. While primarily a test of cognition and complex behavior, it may indirectly test learning and memory as well? While scientists disagree on the validity and usefulness of the SCOB test,³⁵ it is the only guideline which describes the direct assessment of an exposed animal's performance of a complex task.

Yet OPP has never requested that a pesticide be tested according to the SCOB guideline? The Developmental Neurotoxicity guideline is the only other revised OPP guideline requiring assessment of learning and memory. Unlike the SCOB, it was fully validated more than a decade ago.³⁷ However, OPP has received data from tests according to this testing guideline for only six pesticides? OPP's failure to require these tests of cognition, learning and memory more often-so important for the assurance of safety to the fetus, infant and child-suggests that the criteria or "triggers" for doing so are either inadequate, or are not being strictly followed.

- OPP's Neurotoxicity Screening Battery is inadequate to uncover long-term delayed (or latent) effects on the brain, especially those stemming from *in utero* or childhood exposure to pesticides. Most obviously, this is because the Neurotoxicity Screening Battery is not carried out on immature animals. But it is also due to the fact that the **90-day** Battery, for example, follows the test animal for less than one-eighth of its natural life span (the acute battery even less). Humans are born with the greatest number of neurons they ever possess, then gradually lose them until death. The longer one lives, the more one's reserve of functional neurons decreases, and the greater the risk that toxic insults suffered earlier in life will manifest as decreased neurological function or disease. For example, some have postulated that Alzheimer's and Parkinson's disease are at least partly related to toxic insults suffered earlier in life.³⁹

Given the vulnerability of the brain to toxic effects, EPA must move to finalize pesticide testing requirements that would routinely require neurotoxicity testing for pesticides used on food. This step, however, cannot address the fact that OPP's Neurotoxicity Screening Battery, a short-term test performed on adult animals, cannot give assurance that exposed infants and children will not suffer short-term or

latent toxic effect on their developing brains and nervous systems. Nor will it address the failure of OPP's current tiering scheme to trigger more frequent requests for testing of cognition, learning and memory, such as are found on the SCOB and **Developmental Neurotoxicity** guidelines. Where EPA has established criteria for triggering additional testing, it needs to use them. Where guidelines exist for unvalidated tests, EPA should move to validate them.

TESTS OF DEVELOPMENTAL TOXICITY

As one of only two tests required for food-use pesticides which are performed in immature animals, the Prenatal Developmental Toxicity Study is expected to not only reveal potential teratogens, but also to serve as a surrogate for uncovering other risks—both cancer and non-cancer—to a child's developing endocrine, immune and nervous systems. (See Appendix A for a description of the revised guidelines.) For example, the FIFRA Scientific Advisory Panel has affirmed that one of the criteria to be used in deciding whether to perform in utero **carcinogenicity** testing is a chemical's demonstrated ability to exert effects on tests of developmental toxicity? Shortcomings in the developmental toxicity guideline, which raise doubt as to its ability to meet these expectations, include the following:

- The Prenatal Developmental Toxicity Study only exposes animals before birth. It does not expose test animals during crucial vulnerable periods after birth, such as the immediate **post-partum** period and during breastfeeding, when various organs are growing and rapidly developing. The NAS found in 1993 that nervous, immunologic, reproductive and endocrine systems "continue to mature and demonstrate particular sensitivity (to toxicants) during the postnatal period." The Prenatal Developmental Toxicity Study test, therefore, cannot reflect the full risk of developmental toxicity as it actually occurs in human infants and adolescents—risk due to pesticide exposure both before and after birth. This is particularly concerning given that young children have been shown to have direct exposure to significant levels of pesticides, including those in breastmilk and baby **food**.⁴²
- The Prenatal Developmental Toxicity Study also cannot fully demonstrate toxic effects which might arise selectively after birth, since it sacrifices and then examines fetal animals for toxic effects. Yet a newborn animal—even an adult-exposed in utero to a toxic chemical can differ significantly from a fetus harvested even one day before its anticipated birth. Experience with DES demonstrates that in utero exposure may result in reproductive and development effects which are not readily appreciated until well after childhood? Full characterization of toxicity to the developing animal therefore requires that tests of developmental toxicity include assessments during **all** stages of the animal's development—both pre- and post-natally.

In 1993, a National Academy of Sciences committee reported: "The committee believes it is essential to develop toxicity testing procedures that specifically evaluate the vulnerability of infants and children. Testing must be performed during the developmental period....and the adverse effects that may become evident must be

monitored over a lifetime. Five years later, OPP's newly-revised developmental toxicity guidelines still do not comply with this NAS recommendation.

DEVELOPMENTAL NEUROTOXICITY TESTS

EPA scientists have noted that a child's developing brain and nervous system are "sufficiently unique to warrant testing independent from adult neurotoxicity testing and general developmental toxicity testing."⁴⁵ This uniqueness stems largely from the long period of nervous system development and its many critical windows of vulnerability, ensuring a child's unique susceptibility to chemical exposures.⁴⁶

- The Developmental Neurotoxicity Study, OPP's only guideline specifically for testing toxicity to the developing brain and **nervous** system, is not required for food-use pesticides. It is not routinely requested for pesticides known to be toxic to the brain and nervous system. In fact, OPP has received completed developmental neurotoxicity studies for only six pesticides total, even including the 39 pesticides in the organophosphate **class**.⁴⁷

OPP scientists use any one of five criteria for deciding when to request, or "trigger", developmental neurotoxicity testing. (See Appendix A for a description of the revised guideline itself.) Three of the five criteria require some toxic effect to have shown up on other testing in developing animals. Yet EPA only requires two tests using developing animals for every food-use pesticide, tests of developmental and reproductive toxicity. Moreover, Dr. Lynn Goldman, EPA Assistant Administrator for Prevention, Pesticides and Toxic Substances (and a pediatrician) has written, "We agree that the standard protocols for developmental toxicity studies and reproductive toxicity studies do not provide much information on the effect of neurotoxic pesticides on the performance of the nervous or immune system in developing animals."^{*}

A fourth criteria for requesting developmental neurotoxicity testing depends on there being evidence for chemical changes to the endocrine or hormonal system. Yet EPA has not yet instituted any screening tests for endocrine disruption as is eventually required under the FQPA. **The** fifth and final criteria depends on evidence **from** tests showing changes in neuropathology. Neuropathology is included on the Neurotoxicity Screening Battery, but the latter is not routinely required for all food-use pesticides.

On the other hand, these triggers for developmental neurotoxicity testing do exist, and it has been suggested that if EPA were to actually use them it would have to request developmental neurotoxicity testing for most pesticides." Yet developmental neurotoxicity testing is rarely requested.

If it were requested more frequently, the Developmental Neurotoxicity Study guideline would still have shortcomings. Before EPA considers whether or not to depart from use of the tenfold, child-protective FQPA safety factor, these must be addressed:

- **As** with the Prenatal Developmental Toxicity Study, the Developmental Neurotoxicity Study fails to expose the developing animal to the test pesticide throughout all critical periods of development. The period of exposure covers only from day 6 of gestation through day 10 postnatally. It includes no exposure during the early gestation period nor during the full period of weaning.
- The Developmental Neurotoxicity Study fails to assess the test animals for a long enough period to capture delayed, or latent, effects from toxicity to the developing brain. Certain chemical effects on brain function may not be apparent until long after the exposure has occurred. In rats exposed to triethyl tin during development, for example, investigators found that no evidence of learning disabilities at 3 months of age; at 12 and 24 months, however, the animals showed increasingly severe indices of learning impairment? Similarly, Needleman and others have found that low-dose exposure to lead during childhood can lead to increased risks for a variety of profound neurobehavioral effects in high school, including reading **difficulties**, diminished vocabulary and antisocial behavior?

The Developmental Neurotoxicity Study provides for continued observation of developing animals at specified intervals into sexual maturity, roughly 60 days after birth for rats. However, it has been observed that extending the observation period through sexual maturity and into late adulthood would enhance the possibility of observing neurological changes that may not be apparent until that time (OTA 1990).

EPA rarely requests tests of developmental neurotoxicity. It also admits that every other required test which uses immature animals tells the Agency little about the effects of pesticide exposure on the developing brain. EPA has triggers for when to request developmental neurotoxicity testing, but apparently does not heed them. The agency should use its existing triggers, or else **re-examine** their number and adequacy. Until this is done, there will be no testing routinely done on immature animals to ensure with "reasonable certainty" that no harm will come to the developing brains of fetuses, infants and children. In particular, developmental neurotoxicity testing must be done to protect children from the potential long-term effects of pesticide exposure on learning and memory. In addition, the developmental neurotoxicity protocol must be **re-evaluated** to ensure that it exposes animals to the test agent throughout the critical periods of development, and then monitors them for potential neurotoxic effects which may manifest over the course of their lives.

EPA rarely requests tests of developmental neurotoxicity. **It** also admits that every other required test which uses immature animals tells the Agency little about the effects of pesticide exposure on the developing brain.

TESTS OF EFFECTS ON REPRODUCTION AND INHERITANCE

Revised toxicity testing guidelines include both a two-generation test of reproductive toxicity and tests for inherited mutations. (See Appendix A for a description of the revised guidelines) Current pesticide testing requirements call for a Two-Generation Reproductive Study to be performed for food-use pesticides. As one of only two required tests performed in immature animals, this study is also expected to serve as a surrogate for uncovering other risks to a child's **developing**

endocrine, immune and nervous systems, including cancer. Problems with this expectation include the following:

- The **Two-Generation** Reproductive Study never directly exposes post-natal, developing animals to the test substance. Exposure occurs only through the dam's breast milk. If, for any reason, a chemical is not readily transmitted from mother to child through breast milk, the **two-generation** study will lend a false sense of security. In contrast, actual pesticide exposure among toddlers would be expected through various avenues (diet, dirt, carpeting etc.), rather than just via breast milk.
- The **Two-Generation** Reproductive Study calls for both generations of exposed animals to be sacrificed at around three months of age—roughly equivalent to a person in their late teens. This animal study therefore cannot anticipate any delayed (or latent) toxic effects in humans which might arise after adolescence, including latent effects on the reproductive tract, brain or nervous system.

With respect to tests of heritable mutations—tests designed to see if mutations are passed from parent to **offspring**—EPA has indicated, "For technical reasons, males rather than females are generally treated with the test agent."⁵² We believe this to be an important but scientifically unjustified rationale. Exposure of females to environmental agents that cause inheritable mutations may be just as important in producing still births and birth defects. Early animal experiments on the effects of irradiation on the ovaries showed this treatment can induce mutations and result in cytogenic changes in the ova that may manifest in defects of the conceived offspring. There is much uncertainty about the effects of this kind of exposure in women?

Given these shortcomings, testing done according to existing or revised guidelines for reproductive toxicity cannot assure a reasonable certainty of no harm to infants and children.

TESTS OF EFFECTS ON THE IMMUNE SYSTEM

Studies in laboratory animals suggest that numerous pesticides, including dieldrin, aminocarb, **captan**, lindane, malathion, dichlorophos, **O,O,S-trimethylphosphorothioate** (an impurity of malathion), and the herbicide TCDD (**2,3,7,8-tetrachlorodibenzo-p-dioxin**), can induce changes in the immune system.^{54,55} More recently, the FIFRA Scientific Advisory Panel "reiterated its belief that the immune system is a legitimate target organ for toxicity."⁵⁶ The National Academy of Sciences also found in 1993 that the immune system was one of several in children which have demonstrated an increased sensitivity to toxic insult.⁵⁷ Because pesticides have myriad potential effects on the developing immune system, it has been proposed that immunotoxicity testing be routinely **required**.⁵⁸ (See Appendix A for a description of the revised guideline)

- Immunotoxicity testing is not routinely required for food-use pesticides. EPA's latest, though never finalized, revisions to the pesticide data requirements would have required immunotoxicity testing for all pesticides? Moreover, the

Scientific Advisory Panel to OPP recently deemed the immunotoxicity testing methodology "sufficiently validated" to be included in routine toxicology studies.⁶⁰ Yet EPA scientific staff indicate that testing according to OPP's sole revised immunotoxicity guideline has been requested for just two chemical pesticides—less than the number of pesticides cited above that have been already observed to have an effect on the immune system in animals? This disparity between the number of suspected immunotoxic pesticides, and the number actually being tested for neurotoxicity suggests that EPA's tiering scheme may be inadequate for triggering immunotoxicity testing when appropriate.

- OPP's sole, revised guideline for immunotoxicity employs only adult animals. In *Pesticides in the Diets of Infants and Children*, the NAS stressed that extrapolation of toxicity data **from** adult and adolescent animals to young humans may be inaccurate. To specifically evaluate the vulnerability of children, the NAS highlighted the importance of "tests for neurotoxicity and toxicity to the developing immune and reproductive systems." Yet neither a requirement nor a guideline exists for testing a pesticide's toxicity to the immune system of developing animals, despite the fact that a human child's immune system continues to mature through adolescence, and is potentially more vulnerable than that of adults. Moreover, as mentioned, Lynn Goldman, EPA's Assistant Administrator for Prevention, Pesticides and Toxic Substances, has admitted that OPP's standard protocols for developmental toxicity studies and reproductive toxicity studies do not provide much information on the effect of neurotoxic pesticides on the performance of the nervous **or** immune system in developing **animals**.⁶³

Given that developmental and reproductive toxicity studies are the only studies required of food-use pesticides that are carried out in developing animals, how can EPA provide a "reasonable certainty" that no harm will come to the developing immune systems in fetuses, infants and children?

- Immunotoxicity testing according to OPP's revised guideline, even if requested, will only direct testing for a limited range of the immunologic endpoints of concern to infants and children. Most critically, this guideline only serves to indicate whether the immune system of an exposed person might be suppressed. Disorders where the immune system has been sensitized or made hyper-reactive, as may be the case with asthma, are of critical importance to children. OPP's immunotoxicity guideline has no provision for testing sensitization.

Further, this guideline largely directs for immunologic testing around 30 days after exposure to the test chemical. When reviewing this guideline, the FIFRA Scientific Advisory Panel cited its belief that most immunotoxic changes, if they occur, would be noted by 30 days. However, the SAP gave no indication there could not be some delayed immunotoxic effects manifesting arising after the **30-day** assessment period. Further, the NAS has noted that, to specifically evaluate for the vulnerability of children, "adverse effects that may become important must be monitored over a lifetime."⁶⁴

EPA must **re-examine** the delay in finalizing its revised pesticide testing requirements that would make immunotoxicity testing mandatory for food-use pesticide. In the interim, EPA should also reevaluate the adequacy of a tiering scheme that has resulted in only two chemical pesticides being tested specifically for immunotoxicity according to that OPP guideline. Finally, since this guideline was developed prior to the FQPA, EPA must reassess its adequacy in generating test results that assess a chemical's ability both to suppress and sensitize the immune system, as well as the ability of this test in young adult animals to provide results relevant to a child's developing immune system.

GENERAL **SHORTCOMINGS OF THE** GUIDELINES

This chapter has outlined shortcomings of the Office of Pesticide Programs' individual toxicity testing guidelines in their revised form. The section below looks more closely at OPP's pesticide testing requirements and toxicity testing guidelines as a whole. This serves to summarize earlier points, and to highlight some of the gaps in the entire set of toxicity data as EPA typically would find it for a particular pesticide.

Inadequate Dosing of Developing Animals

Most of OPP's toxicity testing guidelines, used to meet the codified data requirements for food-use pesticides, fail to expose developing animals to the pesticide. This includes all required testing for acute, subchronic and chronic toxicity, and for tests of carcinogenic effects, as well as tests only conditionally required to evaluate effects on the brain and nervous system. Yet the NAS emphasized in 1993 that, "Extrapolation of toxicity data from adult and adolescent laboratory animals to young humans may be inaccurate.*"

Of the two tests required for food-use pesticides which do expose immature animals, one (developmental toxicity) exposes them only prenatally. The other test (for reproductive toxicity) includes some post-natal exposure but this is only indirect, through breast milk, and abbreviated-ends at weaning.

Inadequate Length of Assessment

Timing of both exposure and assessment greatly impact the kinds of toxic effects that will be observed in an exposed individual? OPP's revised toxicity testing guidelines, however, fail to assess the test animals throughout all portions of their lives where toxic effects might reasonably be expected, and where assessment is necessary to assure that such testing is protective of infants and children. In particular, these guidelines fail to prescribe monitoring of animals for toxic effects with long periods of latency, especially long-term effects on the nervous, immune and endocrine systems.

Inadequate Tiering of Tests

OPP toxicity testing is based upon the principle of tiering. That is, a series of screening tests that give animals relatively higher doses of pesticide are expected to trigger the need for additional testing using more elaborate protocols with more sensitive indicators of toxicity. Tiering itself, however, presumes that animals exposed to the test pesticide in **the** first tier of tests will reflect, or act as surrogates

for, the susceptibility of the animals in the second, more sensitive tier of tests in every respect but the dose of chemical used.

But is this the **case?** OPP's screening tests, including its acute and chronic tests, tests for **carcinogenicity** and for neurotoxicity, are all performed on adult animals. Immature and **fetal** animals, however, as with immature humans, may have susceptibility to a chemical which is completely unique to their age. As was mentioned earlier, alcohol, illicit drugs such as cocaine, and lead may all have lasting effects on a fetal or child's still-developing brain at levels which may cause little permanent effect in adults. OPP tiering may rely on tests performed in a sometimes insensitive age group to act as triggers for when to perform more specific and more sensitive tests on a frequently more sensitive age group.

A second problem is with the criteria used by OPP to determine when to request second tier testing. The fact that specific tests to assess effects on the immune system, the developing brain and nervous system, and the ability to perform complex tasks (SCOB) have each been triggered for fewer than six chemical pesticides suggests either that the criteria themselves are inadequate, or that OPP staff are simply not following them. With respect to developmental neurotoxicity, the latter has been **suggested**.⁶⁷

Inadequate Indicators of Toxicity: Learning, Memory, and Endocrine Disruption

The Neurotoxicity Screening Battery, itself not even required for food-use pesticides, is an incomplete measure of toxicity to the brain, and is performed on adult animals. It includes a "functional observational battery" or FOB, which includes limited observations of animal behavior, but lacks any quantitative assessment of behavior or measures of Learning **and** memory? Those OPP neurotoxicity tests which do assess learning and memory—namely, the SCOB and Developmental Neurotoxicity Studies—have seldom been requested of pesticide manufacturers.

EPA's pesticide requirements also include no testing for disruption of the endocrine **disruption**.⁶⁸ The endocrine system consists of glands and the hormones produced by them, such as the male testes and female ovaries and their estrogens and androgens. Endocrine-disrupting chemicals have been shown, in some cases, to be biologically active enough to interfere with the function of hormones even at very small **doses**.⁷⁰ Because of their rapidly developing immune, reproductive and nervous systems, children are particularly vulnerable to toxic effects **from** synthetic, hormone-like substances. Dieldrin, toxaphene, chlordane, and DDT are all pesticides found to have been **estrogenic**, as is **endosulfan**, a commonly used pesticide in the United States."

Both the Food Quality Protection Act and amendments to the Safe Drinking Water Act (SDWA) mandate EPA to develop and implement a strategy, under FIFRA and TSCA respectively, for screening and testing chemicals for endocrine disruption by August, 1999. EPA's Endocrine Disrupter Screen and Testing Advisory Committee (EDSTAC) is helping the Agency determine how to begin meeting the FQPA and SDWA requirements.

In the months or years before testing for endocrine disruption begins, **OPP** will continue issuing tolerances for pesticides without the benefit of such testing—some, perhaps, for pesticides with potential **endocrine-disrupting effects**. Since EPA has

Those OPP neurotoxicity tests which do assess learning and memory have seldom been requested of pesticide manufacturers.

acknowledged the potential of pesticides, generally, to act as endocrine disrupters, tolerances issued in the interim must reflect this potential.

Failure to Test Using the Most Sensitive Animals

Different species of animal may exhibit very different genetic susceptibility to a particular chemical. Moreover, different strains within the same species may also vary in their genetic susceptibility. For example, a study by Ciba Corporation found that the pesticide, atrazine, produced endocrine changes and increases in mammary tumors in Sprague-Dawley female rats, but did not cause noticeable changes in rats of the Fischer 344 strain.⁷² In setting tolerances, this **intra-** and **inter-species** variability must be accounted for, to ensure that testing reflects the full potential for toxic effects in an equally diverse human population, made up of individuals with often different genetic susceptibilities. This has traditionally been accomplished using two tenfold uncertainty factors. However, **OPP's** toxicity testing guidelines might easily incorporate an assurance that the animal species tested is at least as sensitive as humans, and that the species strain used is that known to be most sensitive to that chemical or class of chemicals. This assurance is currently missing from nearly every OPP toxicity testing guideline.

Yet it is more than conceivable that two pesticides which are relatively harmless separately might chemically interact in a way that increases their combined toxicity.

Failure to Test For Interactive Effects of Multiple Pesticides

The Food Quality Protection Act recognizes that pesticide exposures typically do not occur as single discrete exposures to a particular pesticide, but as mixtures of different pesticides acting together to produce a certain level of toxicity. For example, USDA data from 1990 to 1992 showed that 80 percent of apples, celery and peaches surveyed contained more than one pesticide residue, and 10 percent of these residues remained even after thorough washing and preparation of food." Using the same data, assessment of residues in carrots revealed the presence of three different carcinogens, while a single servings of apples had three different pesticides on them categorized as neurotoxicants.

But while the FQPA directs EPA to consider pesticides with a common mechanism of toxicity in setting tolerances, it does not consider potential interactions or synergy between chemicals with different mechanisms of action. Nor do EPA's pesticide data requirements include any requirement that common pesticide mixtures be tested for their joint toxicity. Finally, EPA most **up-to-date** set of toxicity testing guidelines lack any that would direct assessment of potential interactivity of chemicals. It is more than conceivable, however, that two pesticides which are relatively harmless separately might chemically interact in a way that increases their combined toxicity. This type of synergy has been demonstrated between at least two pesticides: malathion and **O-ethyl O-p-nitrophenylphenyl phosphonothioate (EPN)**, which until recently were used on the same crops, and were found as residues on the same **foods**.⁷⁴

• EPN is no longer on the market, however.

ADOPT AN ADDITIONAL SAFETY FACTOR OF TENFOLD (10X) TO ACCOUNT FOR INCOMPLETE DATA RELATIVE TO INFANTS AND CHILDREN

THE USE OF UNCERTAINTY FACTORS IN SETTING TOLERANCES

The regulation of pesticides in food is only as accurate as the testing on which it is based. Because human testing is unacceptable, regulatory agencies rely on laboratory tests conducted in animals, and occasionally in cultured cells, to provide data on the toxicity of pesticides. The previous chapter summarized some of the problems with current methods for performing such tests, particularly their inadequacy for with assuring, with a reasonable certainty, that infants and children who are exposed to a particular **pesticide** will come to no harm.

Although humans and laboratory animals **often** respond similarly to chemicals, they have important differences that cannot always be quantified. Human populations are incredibly diverse in age, diet, behavior, genetics, and other factors, making some groups of people more susceptible to pesticide exposures than others. Laboratory tests, on the other hand, are carried out on healthy animals bred to be virtually identical in age and genetics. In addition, some toxic effects of critical concern to children—such as effects on intelligence, reading comprehension and attention—are particularly difficult to measure in animals.

Pesticide regulators add "uncertainty factors" to their tolerance-setting, or risk assessment, process to account for some of the factors mentioned above. These serve to build an explicit margin of safety into the process, while acknowledging the underlying scientific uncertainty of the data. Before the FQPA, EPA traditionally used two uncertainty factors in setting pesticide tolerances. One tenfold factor, the "interspecies" uncertainty factor, accounted for potential differences in susceptibility between **the** animal species tested and humans. A second, the "intraspecies" tenfold uncertainty factor, accounted for the variability between individuals in a species in terms of their susceptibility to the test chemical.

In 1993, a study by the National Academy of Sciences, *Pesticides in the Diets of Infants and Children*, concluded that a third uncertainty factor should be used routinely in setting pesticide tolerances whenever toxicity data was incomplete, to explicitly account for periods of potential vulnerability among children, both before and after birth.¹ The Food Quality Protection Act of 1996 improved upon this recommendation by making the use of this additional uncertainty factor mandatory,

to ensure the protection of infants and children when data on children's exposure to a particular pesticide, and its toxicity to children were not complete. Moreover, the FQPA mandates that the child safety factor be tenfold (10X) in size, unless there are "reliable data" that support the use of a different margin of safety.² This additional FQPA children's safety factor means that the amount of pesticide residue legally allowed to remain in or on food will be set ten times lower than it would have been previously, until reliable data are generated describing children's exposure to that particular pesticide and its toxicity to infants and children.

EPA USE OF AN ADDITIONAL 10X SAFETY FACTOR UNDER FQPA

Despite the FQPA's straightforward mandate that use of the additional tenfold safety factor be strong and presumptive to protect infants and children, EPA's Office of Pesticide Programs (OPP) has not typically incorporated this additional safety factor into the pesticide tolerances issued since passage of the law. According to the latest information provided, OPP has retained the child-protective safety factor in only 9 of the first 91 tolerances issued under the new law—or less than 10 percent.³

Given EPA's failure to routinely use the tenfold FQPA safety factor, one must question what the Agency considers to be "reliable data" on children's exposure to pesticides and the toxicity of these substances to infants and children? A recent draft policy on OPP's use of the 10X safety factor did not directly answer this question. But on February 25th, EPA Administrator Carol Browner issued a memorandum calling upon OPP to convene, along with the Office of Research and Development and the Office of Children's Health Protection, an internal panel of EPA scientists to answer this question for the agency.⁵ As this report goes to press, the 45 day deadline for this panel's first report to Administrator Browner has just passed. We would hope its final recommendations reflect the issues raised in this report.

Meanwhile, EPA and USDA issued a joint memorandum on April 10, 1998 announcing the formation of another advisory panel to "begin consulting with a broad range of interested parties" on FQPA issues. The panel will be established under the Federal Advisory Committee Act, to be conducted through EPA's National Advisory Council on Environmental Policy and Technology. According to the memorandum, the panel will address specific scientific questions related to FQPA including "what documentation is necessary" to make pesticide tolerance decisions. It also charges the committee with "deciding if there is adequate scientific information for making decisions" under the law. The memo's list of "qualified participants," however, includes "farmers, other pesticide users, public health officials, pesticide companies, environmental groups, public interest groups, and state, tribal and local governments." Some of these participants have direct financial conflicts of interest. Conspicuous by their absence from the list are pediatricians and other experts in children's health and development.

We believe that only pediatricians, children's health professionals and other scientists—not groups with direct financial conflicts of interest—should decide the critical scientific question of how best to protect infants and children under the FQPA. In other words, children's experts must determine what are "reliable data" on children's toxicity and exposure to justify altering the child-protective 10X safety

factor mandated by the new law? Moreover, EPA has already established the Children's Health Protection Advisory Committee which is explicitly charged to "assist the agency in the development of regulations, guidance and policies to address children's health."⁷ This committee has broad stakeholder involvement, including **representatives** from the food and agriculture industries. In stark contrast to the above panel, however, its participants include pediatricians and children's health professionals who have the scientific expertise to grapple with the questions raised by the April 10th memorandum.

In addition, EPA already has a functioning Pesticide Program Dialogue Committee and the FIFRA Scientific Advisory Panel, both also advising on one or another aspect of FQPA implementation. EPA does not need to appoint an endless stream of advisory bodies with overlapping jurisdictions before acting to protect infants and children under the new law.

In this report, we offer no definition of our own as to what constitutes reliable data under the FQPA. We do, however, identify significant gaps that often render existing data sets unreliable. Specifically, in Chapters Three and Four we find numerous gaps in the data typically available to EPA on children's exposure to pesticides, and on pesticide toxicity to infants and children, respectively. Many of these gaps or shortcomings are summarized below.

SHORTCOMINGS IN EXPOSURE DATA AVAILABLE TO EPA

For some pesticides, such as the organophosphates, existing data on children's exposures through diet alone are sufficient to require lower tolerance levels, even disregarding the additional safety factor required under the Food Quality Protection Act. For the majority of pesticides used on food however, EPA often lacks the exposure data needed to do an adequate analysis of children's aggregate exposure to a pesticide, across dietary and **non-dietary** avenues, as required under the new law. More specifically, for many pesticides used on foods, there is:

- Inadequate data on pesticide exposure through food.
Water has been called the most consumed food. EPA admits in recent tolerance notices that it lacks drinking water monitoring data on which to base its estimates of pesticide exposure.* OPP has also been issuing tolerances largely based upon 20 **year-old** food consumption data which may well fail to reflect consumption patterns of today's population. EPA lacks the comprehensive, updated data on children's exposure through food **that** might be sufficient to justify altering the tenfold children's safety factor.
- Little or no current, specific information on non-food exposures.
The lack of reliable data on children's household exposures was highlighted by panelists at the March 1998 meeting of the **FIFRA** Scientific Advisory Panel.⁸ In addition, EPA lacks reliable data on children's non-dietary exposures to **food-use** pesticides that are also registered for use on lawns, gardens, pets, and especially for use in homes and schools.

- No ability to combine information on various exposures. EPA has no integrated database for collecting and collating data on pesticide exposure through the diet and 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.

Given preliminary findings from a recent study of organophosphate metabolites in children's urine¹¹, EPA should also consider the need to fund or perform biological monitoring for a much broader array of pesticide and pesticide metabolites in children's urine, especially among highly susceptible groups such as children living in agricultural areas. Though expensive, biological monitoring provides actual data on the pesticides that children ingest and are exposed to internally.

SHORTCOMINGS IN PESTICIDE TOXICITY DATA

Chapter Four identifies shortcomings in both EPA's existing pesticide data requirements, as well as its most **up-to-date** toxicity testing guidelines.

Inadequacy of EPA's Pesticide Data Requirements

EPA's data requirements fail to require that manufacturers test food-use pesticides for their toxicity to various organs of critical importance to the health and well-being of fetuses, infants and children, including:

- A child's developing brain and nervous system .
A child's developing brain is particularly vulnerable to the neurotoxic effects of pesticides and other chemicals. **EPA's** pesticide data requirements fail to routinely require either specific testing to assess a pesticide's potential toxicity to the adult brain and nervous system , or toxicity to the developing brain and nervous system .
- A child's developing immune system .
A child's immune system , and their ability to fight infection and disease, continues to develop from birth through adolescence. EPA's pesticide data requirements fail to routinely require specific tests of immunotoxicity, including tests for both immunosuppression and sensitization.
- In addition, EPA requires no testing to assess the interactive effects of multiple chemicals. There is demonstrable evidence that pesticides may sometimes act synergistically, and mounting evidence that infants and children are routinely exposed to multiple pesticides in their water, food and home environment. On the other hand, EPA lacks even a validated guideline for assessing these interactive effects.

Since the early 1990s, EPA has been revising the existing pesticide data requirements. Yet even after being submitted and generally endorsed by OPP's Scientific Advisory Panel in November 1994, these revised requirements remain **unfinalized**.¹¹ The proposed revisions substantiate many of the shortcomings identified in this report. They would, for example, require manufacturers of **food-use** pesticides to perform a neurotoxicity screening battery on animals using both acute and **90-day** exposure periods. Testing of toxicity to the immune system would also be required, although only in adult animals.

While an improvement over existing requirements, EPA's revised data requirements would still lead to significant gaps in the toxicity data available to EPA in determining whether there are reliable data to justify alteration of the children's tenfold safety factor in setting tolerances. Even under the revised requirements, pesticides with known toxicity to the brain and nervous system would not be routinely tested for effects on the developing brain and nervous system. Moreover, OPP's current triggers for requesting developmental neurotoxicity testing have been exercised so infrequently that it seems unlikely these vital tests will be performed without an explicit new requirement.

Immunotoxicity testing under the revised requirements would still be carried out on adult animals. It would still ignore the need to assess a pesticide's capacity for making the immune system hyper- or overly-sensitive. Finally, these revised data requirements would fail to reflect evolving concerns about the potential for pesticides and other chemicals to disrupt the endocrine system.

Inadequacy of EPA's Toxicity Testing Guidelines

While EPA's data requirements describe which toxicity tests will be done for a particular pesticide, the Agency's guidelines describe how these tests will be done. Yet even EPA's most updated toxicity testing guidelines, which will determine the quality and breadth of toxicity data collected in the future, fail to adequately protect the fetus, infants and children. Specifically, for most pesticides, toxicity testing according to these guidelines:

- Will not assess the effects of exposure at **all** critical stages of development. Animals must be exposed to the chemical being tested during all the periods of development which correspond to the ages when children are known to have the greatest potential susceptibility to toxic effects. Yet most toxicity testing for food-use pesticides only expose adult animals. This includes all required tests for acute and chronic toxicity, **carcinogenicity**, and metabolism, as well as the sometimes-required screen for toxicity to the brain and nervous system. Of the two tests required for food-use pesticides which actually do expose developing animals, the test for developmental toxicity fails to continue exposing the test animal after its birth, when many organ systems are still developing.

How can pesticide tolerances based upon these tests be said to be safe for infants and children? The test of developmental toxicity in particular will fail to reflect toxic effects on the developing brain and nervous, immune or reproductive systems which might arise in a child who receives post-natal exposure to **pesticides**—through contaminated breast milk, dust, carpets, toys or other sources.

- Will not look at all toxic effects of importance to children. None of the toxicity tests which 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. EPA does have guidelines to specifically assess toxic effects on the immune system and on a child's brain and nervous system, but these tests or guidelines are seldom requested of pesticide manufacturers. In fact, the former has been requested for only two chemical pesticides, while developmental neurotoxicity testing has been completed for only six pesticides. EPA has criteria for deciding when to request such testing, but, at least for developmental neurotoxicity, the agency apparently fails to heed its own criteria. Yet children rely upon a healthy immune system to become healthy adults, and depend upon their ability to learn and remember to become productive adults.

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

- Will not uncover toxic effects that show up later in life. The only two toxicity tests required for food-use pesticides which employ developing animals-tests for developmental and reproductive toxicity-fail to follow the exposed animals to their natural death. This means they do not allow all toxic **effects** which might occur to become evident. 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.

Given the array of data gaps outlined above, it is clear that EPA will typically not have complete and reliable data to justify alteration of the children's tenfold safety factor for most food-use pesticides. In these cases, the FQPA is straightforward in prescribing use of this additional child-protective factor until complete and reliable data have been generated.