

Facing Scientific Realities, Debunking the “Dose Makes the Poison” Myth

The Big Picture: Linking pesticide science and health effects

by **Warren Porter, Ph.D.**

Warren Porter, Ph.D., professor of Zoology at the University of Wisconsin-Madison, WI delivered the following talk at the 25th National Pesticide Forum, Changing Course in a Changing Climate: Solutions for health and the environment, June 1-3, 2007 in Chicago, Illinois. Dr. Porter is a board member of Beyond Pesticides.

Introduction

I am very honored to have the opportunity to be here with many old friends, and to be making many new friends. Tonight what I want to talk about is linking pesticide science and health effects, particularly related to what is happening to our children and wildlife —because our children are getting cancer, but there are also a whole lot of very subtle and maybe not so subtle things that are happening. In terms of the science, it is amazing how much information is out there. My biggest challenge is how to get this talk down to a reasonable amount of time so I do not take up your whole evening.

An explosion of childhood learning disabilities

I am going to start by asking you, when you see this picture of a boy and a girl looking at each other, what does it say to you? What do you see in this picture? When I asked my Zoology 101 class that I teach every fall, “What do you see in this picture?” somebody in the back of the room the first time called out, “Raging hormones!” I laughed just like you did, and I said, “Yes, that’s true. But clearly, it is also our future that we are looking at here.” And we can spend great amounts of energy and time and money on our children; we love them, we nourish them, and we give up sports cars for

college education funds for them.

There are things, though, that are happening to our children. On the tenth of February, 1997, in Madison Wisconsin, where I live, the *Wisconsin State Journal* was running a series of articles on our schools. We have many schools of national excellence in Madison, and we are very proud of them. But this particular issue was entitled, “Cost of Accommodating: As special education grows, so does the cost of staffing.” There was a chart with statistics that are very chilling.

From 1990 to 1995, in the Madison school district, by disability we had an increase of 87 percent in the emotionally disturbed category over a five year period. The learning disabilities category jumped 70 percent and birth defects increased 83 percent in a five year period. This was astonishing, so I began to dig further. We were having big increases in the state of Wisconsin. California was having big increases. Pennsylvania was having big increases. Iran, where my wife is from, was having big increases. Australia, which I had visited a couple of years earlier, was having big increases. Something was happening to our children. And so I am going to start this talk by talking a bit about learning disabilities and behavioral disorders. What is the science on this? What are some of the things we know?

In 2006, a paper appeared by Chensheng Lu, Ph.D. et al.,¹ where the researchers looked at the urine of children in the Seattle area, and monitored a couple of pesticide metabolites — in one

case the insecticide malathion, which is neurotoxic by design. The children in the study were on standard ordinary diets, and then they put them on organic diets, and then they put them back on their regular diets. The researchers measured the daily concentration in parts per billion (ppb) of a malathion metabolite. Then, they also looked at another pesticide, chlorpyrifos. They used the same study design: regular diet, organic diet, and then regular diet again. An organic food diet dramatically reduced chlorpyrifos metabolite levels in the urine. This metabolite measurement is important because, as Robert Foxenberg, Ph.D. et al.² showed, the chlorpyrifos metabolite is close to the same concentration as a highly reactive oxon also produced by the breakdown of chlorpyrifos. Thus, the metabolite urine concentration is an indirect measure of the formation of a highly reactive form of chlorpyrifos in the body. Chlorpyrifos is particularly cogent here, in the sense that the U.S. Environmental Protection Agency (EPA) has failed to remove it from agricultural usage, which means that it winds up on the food of our children.



Pesticide exposure impacts brain development and affects children's ability to learn.

Inverse dose response

Could this kind of compound possibly be impacting children's ability to learn? In 2002, Edward Levin, Ph.D. and his colleagues in North Carolina³ ran tests on chlorpyrifos with rats—both male and female rats. They put them in a maze and then the rats had to learn a bunch of problems to solve. They made errors at first and, as they gained more experience, they learned and their error rate dropped. However, the females, especially the females on the intermediate concentration of exposure, took much longer to figure things out. When they summarized the results, the control animals that had no exposure had a low level of error (4 errors/trial), the males were in the same range as the controls, but the females were very much higher (7 errors/trial), or showing greater effects. Then at the high concentration, 5 ppm, the effect dropped off again.

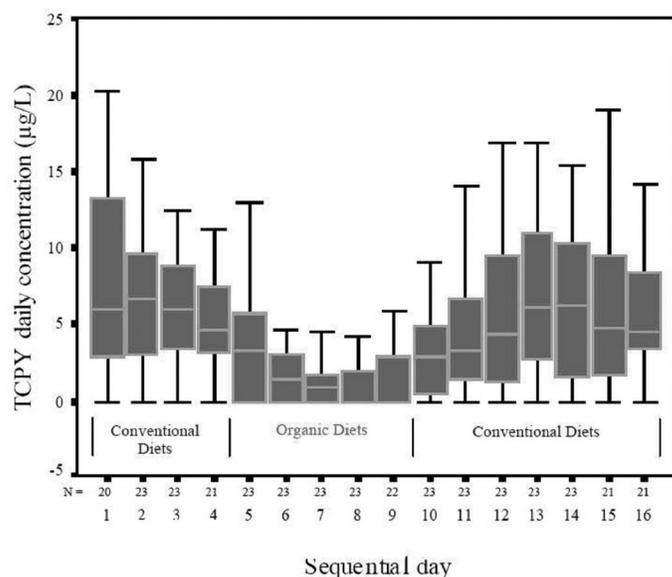
Basically, this research suggests an inverse dose response. The lower doses had a greater effect, and it was the females that were being affected the most. What may be typically going on in these circumstances is that we are just beginning to drop into the realm of concentrations where physiological responses occur. If we were to continue to decrease the dose, the response would reach a maximum, then decline as we continue to decrease the dose. Male rats also suffer in terms of the impact on learning at higher doses, but the big deal is their reproductive impairment. There is a major reduction in their capacity to reproduce when exposed to chlorpyrifos at these concentrations.

Replicating previous effects on learning

Just this spring we finished repeat experiments, but with mice instead of rats. We looked at this same question of induced learning deficiencies and got slightly different results, but showed again how chlorpyrifos can affect learning abilities. We used the

same chemical, chlorpyrifos, at the same doses, using the same protocols as Dr. Levin. This time we measured how long it took the hungry control and treated mice to find food. There were four pieces of food in the eight arm maze that they run. The control animals run the maze the quickest. Those exposed to one part per million (ppm) did not do quite so well, and the 5 ppm group, which is the highest dose, did much more poorly. There is a significant difference in learning abilities between control female animals and treated animals. The study showed no effect on male mice.

Figure 1. Organophosphates are neurotoxic by design (TCPY = chlorpyrifos metabolite)



Lu et al. Organic diets significantly lower children's exposure to organophosphorus pesticides. *Env. Health Persp.* 114 (2) Feb. 2006.

Why is this significant? It is significant because rats and mice, the two species that were used in these experiments, are very different physiologically. Rats are capable of a lot of detoxification because they live in dumps and places where they are ingesting all kinds of noxious food. Mice are not so much that way. Yet, we see the impacts in learning abilities in physiologically widely different kinds of mammals, and we see our children ingesting these kinds of compounds and excreting levels of these pesticide metabolites that are beginning to approach the same levels that cause learning disabilities in two different species of other mammals. This is of great concern.

Adverse brain effects

It is not just chlorpyrifos that is capable of altering neurological function. The herbicide atrazine can increase estrogen levels because it affects the enzyme involved in the production of estrogen, aromatase. It also changes the concentration of neurotransmitters in the prefrontal cortex of the brain, responsible for decision-making capabilities. It shows up in a paper by Veronica Rodriguez, Ph.D. et al.,⁴ in *Environmental Health Perspectives*, with findings that in the prefrontal cortex there are three treatment levels. There is a control, there is a 5 ppm, which is what we just saw in chlorpyrifos and there is a 10 ppm exposure group. But what is interesting is, again, the low dose effect is the greatest effect, for the prefrontal cortex. The striatum, which plays a pivotal role in modulating motor activity and higher cognitive function, is affected by the highest dose. Chlorpyrifos is impacting two very critical parts of the brain, changing the ability of neurons to function appropriately.

Childhood brain and hormonal effects in Sonora, Mexico

Of course we must not forget the classic work of Elizabeth Guillette, Ph.D. at the University of Florida, who with her colleagues studied the children in the Yaqui Valley of Sonora, Mexico, which is where we get a lot of our winter fruits and vegetables. This is a story of the purchase of the valley by chemical agriculture interests to “advance” agriculture with

intensive pesticide spraying. Half of the population left and went up into the mountains, and after a while the women in the valley began to get breast cancer and the children were very different. So they called in Dr. Guillette and her Mexican colleagues, and they began to study these preschool children to control for possible economic differences between the kids in the highlands and the valley, where the families were working in these fields.

One of the things Dr. Guillette and her colleagues did was to ask the children to draw a human figure. The kids up in the mountains who were not exposed were drawing standard stick figures that you would expect from a four or five year old —facial features, digits on the hands and feet. The children in the valley were drawing abstract and incomplete figures. The valley children began their drawing at the bottom and worked up. Any occupational therapist who sees this happening will immediately attribute this behavior to major neurological problems in terms of integration of motor skills. These children are also very aggressive. They have very short memories and they are very weak physically. They cannot jump rope long or do a whole lot of other physical tasks. Now these children are reaching puberty. The boys are developing breasts, which are very painful and they have mammary tissue in those breasts. The girls have breasts which have nothing but fat,

resulting in an inability to ever nurse any of their children. So it is the boys who might get a chance to nurse if they are given the right hormone, not the women.

I have a sister who is an occupational therapist, and she told me that they are trying to deal with these problems now because they know that the vestibular, or the balance centers, and the auditory impulses travel in the same nerve bundles. So what they are doing in private practice in Madison, WI and other places is treating children with attention deficit hyperactivity disorder (ADHD), autism and bipolar conditions, using sound or music of certain rhythms to help them improve their communication and interpret their environment and their behavior. These children have had their developmental profiles changed permanently by the exposures that they have experienced in utero and postnatally.

Figure 2.

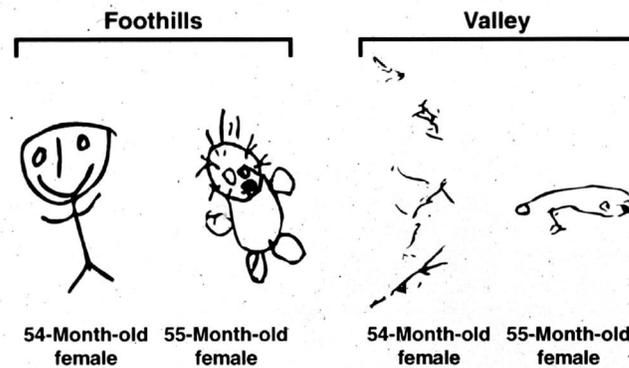


Figure 1. Representative drawings of a person by 4-year-old Yaqui children from the valley and foothills of Sonora, Mexico.

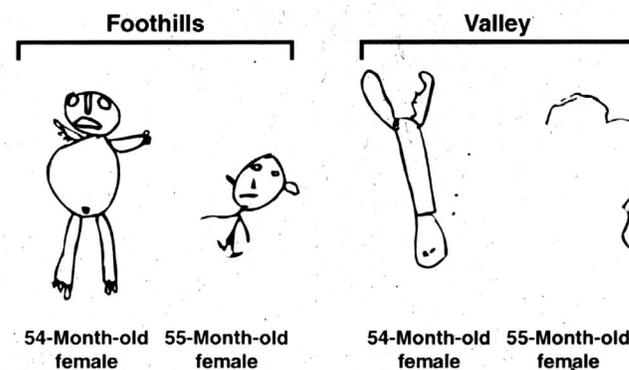


Figure 2. Representative drawings of a person by 5-year-old Yaqui children from the valley and foothills of Sonora, Mexico.

Designed to Kill: The mechanism of poisoning

I want to talk a little bit about how one designs a pesticide to kill. Because once we understand this, we understand why all pesticides are biologically active. This is a very, very important concept.

First, you want to get a pesticide into the body of the organism that you want to kill, whether it be a plant or an insect or anything else. So you take the active ingredients and the so-called “inert ingredients.” The inert ingredients consist of two categories: **(i) Non-ionic solvents**, with no electrostatic charges on it. Loosely I am calling these “organic soaps,” which have nothing to do with the kind of organic we think about. You add these solvents to pesticides and that allows them to get through the waxy surfaces because these solvents are fat-soluble. So you get right through anything that has a waxy surface on it. **(ii) Surfactants**, a kind of soap, if you will, that is designed to penetrate the water film bubble that lines the respiratory surface of a leaf, for example. The hole through which they breathe, the stomate, as it is technically called, has a little hemisphere of a film of water and it acts as a physical barrier to block dust and other material from entering. But if you have a surfactant, you weaken that surface tension barrier and you get more rapid penetration. Unfortunately, our skin, is a waxy surface, and in our lungs, every single little tiny respiratory surface in our lungs, little hollow air sacs called alveoli, has a thin film of water with surface tension on it.

So the addition of these solvents and surfactants is anything but benign or inert because it promotes rapid penetration through the skin and in the lungs, which means you get it right into the blood. Then these same properties allow it to cross the blood-brain barrier and get to the brain, the command and control center of the body. This process largely bypasses the liver and the kidneys, which means it is getting around the defenses of our body by being able to get in by these routes of entry instead of through the gut.

Once it gets inside the body, how does it kill? That is the next question. A pesticide design, whether an insecticide or herbicide, is typically a ring-shaped structure of some kind. These ring-shaped structures confer lipid solubility, fat-solubility. Fat solubility is the master-key, the cell-entry key to any cell in the body. What you do is hang off of these rings charged particles, like a nitrogen



Because pesticides are biologically active, their toxic properties usually have impacts far beyond the intended target.

and two hydrogens to provide an electrostatic charge. This allows the chemical to be water-soluble. So we have, collectively, a molecule that can dissolve both in fat and in water. The way it works, and the way you get into every cell of the body is that the fat part dissolves in the cell membrane, which is a lipid surface. Once you dissolve in that, you get inside and now the electrostatic charge can take over, and this positive group will go to anything negatively charged, because opposite charges attract. You might be targeting the mitochondria, which have a net negative charge. This is the powerhouse of the cell and by getting in there you could disrupt the flow of electrons and “turn off” the energy supply of the cell, thereby killing it. It turns out, of course, that other molecules like DNA also have a negative charge.

If the pesticide has a positive charge, opposite charges attract and the flat, round, dinner plate-shape ring can slide right in between the rungs of the DNA ladder. When the DNA unwinds to copy itself and comes to this point it breaks. We call that a mutation. If you start this at the right chromosome at the right position, you can start cancer on the first break. But typically, there are anywhere from six to a dozen breaks needed in chromosomes to start cancer in a cell. It is not just the DNA that has a net electrostatic charge. Many other organelles, molecules and ions in the cell like sodium, potassium, and chloride ions, have electrostatic charges. These ions are communication ions, both within the cell and between the cells. They are critical in neurotransmission (the transmission of nerve impulses), for example. They are electrostatic and so anything that enters the cell with an electrostatic charge can interact with the fundamental communication mechanisms of the cell, including the way the cell sends out its instructions in some cases. And so we have, essentially, a generic pesticide that is a molecular bull in a china shop here, and it is why we can get such a wide diversity of responses to a single molecule that might enter the cell.

Real world findings

If we look at the work of Paul Winchester, M.D. in Indiana, who has been looking at month of conception in humans compared to the presence of the amount of atrazine in one river in the state, and the rate of malformed baby male genitalia problems, we see that the peaks of atrazine and the male malformations coincide. It is not just in Indiana that he finds these kinds of results. When he looked at all the data in the U.S. from 1996 to 2002 and looked

Lawn Chemicals that Kill

Here is an example of what is put on lawns all across the country: 2,4-D, mecoprop, and dicamba, a very common mix in lawn chemicals. 2,4-D has a ring-shaped structure, strong negative charges on the chlorides and the acid group; a ring-shaped structure for mecoprop, negative chloride acid group; ring-shaped structure in dicamba, negative charges on the chloride and acid groups. These molecules are fat-soluble and water-soluble. And, by the way, I just found out today in our board meeting from one of our members that Monsanto and Nebraska have just come up with a dicamba-resistant soybean to replace the Roundup-resistant soybeans. These will be dissolving in the soy that children may eat.

When we saw this 2,4-D, mecoprop and dicamba mix (we just bought it off the shelf), we wondered whether it might be capable of changing or altering the capacity to keep fetuses in utero. So we decided we would take what EPA said was a relatively safe dose, about 77 ppm 2,4-D, and we would allow mecoprop and dicamba in this mixture to go along for the ride, and we would dilute it because we had a very concentrated solution. We brought it down to 400 ppm as a super high dose, 77 ppm, then a low dose at 0.32 ppm and 39 ppb here as the very lose dose.

We would dose in two different ways: we would dose either from the day of fertilization to day 15, the end of organ formation, or from day five, which is implantation, to day 15.

So how do you find out whether or not you are getting fetal losses? The way we get at embryo losses is to determine how many are born, and then after the ones that are born are weaned, we remove the uteri from the moms. And we can stain them with an ammonium sulfide stain and every black spot shows us where a placenta was attached. The uterus of a mouse is a bifurcated uterus, and so you can just count them like peas on a pod. That is how we can determine how many were implanted, and the difference between the implants and the number born is how many were lost.

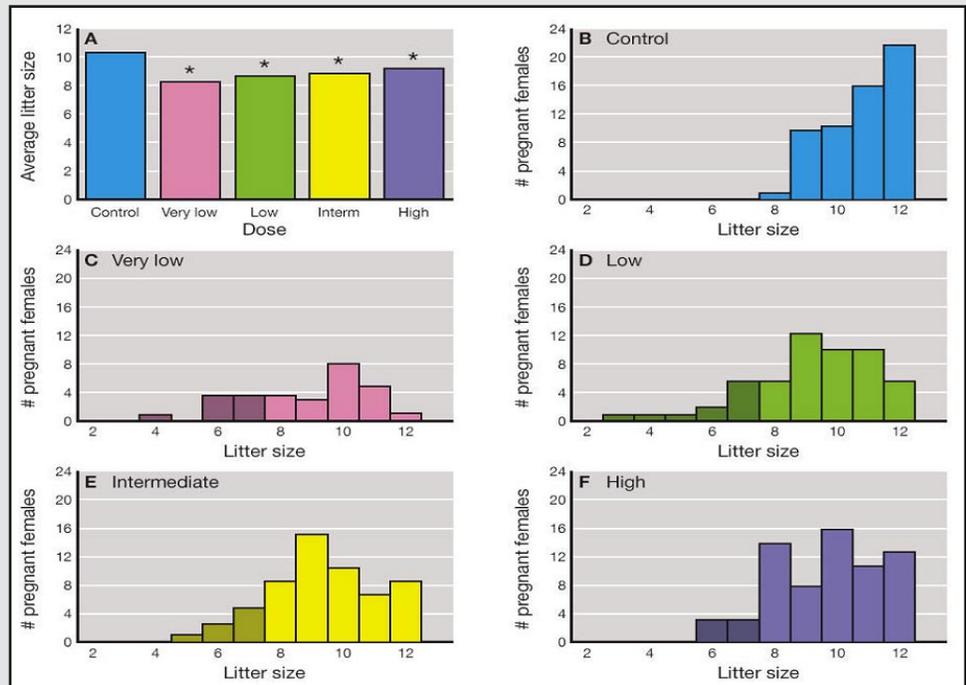
We put this together several times, multiple research efforts by one of my students, Fernanda Cavieres, myself, and another student in the lab, and we found that when we looked at the dosage, very low doses have the greatest effect—a very common endocrine response.

at the presence of nitrate and atrazine, he found a very similar pattern. He has recently announced the results of additional work where instead of looking at birth defects, he looked at the month of conception and related that to the scores on IQ tests, on learning tests for language and mathematical skills in children and found a similar correlation. I cannot show you those data because he has not published them yet, but he has announced them in a talk about two weeks ago.

We see birth defects in fawns in Montana. We see lower jaws that are thrust forward. When we look in Yellowstone National Park, we see fawns with a lower jaw protruding forward, teeth sticking

out, and eyes that are very much pressed in the head. These things are happening to animals that are living in supposedly pristine environments. However, they use herbicides to control weeds in the forests.

As long ago as 1945, we were spraying DDT, and there were marketing ads on trucks (see picture) that pointed out what we were told about DDT: "Powerful insecticide, harmless to humans." And yet we discovered afterwards that alligators in Lake Apopka, Florida that Louis Guillette, Ph.D. studies, were having a hard time finding their penises, as were Dr. Guillette and his coworkers. Lake Apopka is a lake near Disney World that had a spill of a chemical



very much like DDT and breakdown products that looked like estrogen, and when you feminize males, especially when they are developing in the eggs, they do not have much of a penis and certainly do not have much in the way of sperm.

Immune Suppression

It is not just the endocrine (hormonal) or the neurological changes that are inversely sensitive to these doses, but a 1987 paper that caused us to lose EPA funding showed that aldicarb, the number one product for then-Union Carbide, (of Bhopal fame), was immunosuppressive relative to the controls, and the greatest effect was at the lowest dose. EPA said 100 ppb was totally safe. We did this four times, had the best statisticians in the world helping us analyze these data, and well, anyway, that is a long story.

Recently, Rodney Dietert, Ph.D. and Janice Dietert, Ph.D.⁵ at Cornell published a very interesting paper talking about developmental immunotoxicity: what are the variables that affect the immune system during fetal development? We see that they indicate that certain herbicides, insecticides and biocides cause effects very early in conception. This is what the data of Paul Winchester, M.D.,⁶ Indiana University School of Medicine professor of clinical pediatrics, also suggests.

Then there are a whole lot of other exposures all the way through the developmental process: heavy metals, xenoestrogen, certain fungi, toxins, PCHs, TCDD, polyaromatic hydrocarbons, and on and on. It is remarkable. The range of factors that can affect developmental immunotoxicity illustrates that various kinds of immune suppressions are consequently showing up as asthma and allergic diseases, autoimmunity, infectious diseases and ineffective vaccine responses, cancer, neurodegenerative diseases and neurocognitive loss, cerebral palsy, atherosclerosis, hypertension, and male sterility. All of them are consequences of early fetal exposures that resulted in immunotoxic responses that were to show up later in life.

Lately, another box could be added, and that's something that maybe many of you have not even heard about, and that is polycystic ovary syndrome (PCOS). At least ten percent of women in the United States today who are reproductively active suffer from this, and recently a colleague of mine, David Abbott, Ph.D. of University of Wisconsin-Madison, the Primate Center, showed



The sign on the truck reads, "DDT: Powerful Insecticide, Harmless to Humans."

that you could induce this very difficult disease, which has a long list of properties associated with it, but especially a tendency toward obesity, type-2 diabetes, health problems related to heart problems and atherosclerosis. The only way to deal with it is to keep your weight down. There is no cure for it, and it is extremely difficult to diagnose. You diagnose it only by exclusion. You exclude everything else and if nothing else fits, it is PCOS. What is really interesting is that PCOS is now starting to appear to be a disease that is a consequence of chronic, low-level immune suppression that generates

a host of responses in people that have it. Dr. Abbott is able to induce this in Rhesus monkeys, monkeys that have placentas like humans. The way he induces this PCOS in his animals is to androgenize (masculinize with a chemical) the moms when they are pregnant.

How might this happen under natural conditions? Well, one way could be to change the concentration of the enzyme aromatase. Aromatase converts testosterone to estrogen, and it does it irreversibly. It goes only one way. The herbicide Roundup (glyphosate) can down regulate aromatase.⁷ What happens when you reduce the amount of aromatase? Well, you are going to keep on making testosterone and you are going to build it up, so you conceivably could androgenize anything that has aromatase reduction happening. That means if you have a female fetus exposed to male hormones in utero, that female may become androgenized and may not be able to reproduce appropriately. Right now we do not know the answer to this question. We need research to explore this question.

Looking at the whole

Here is how it may all fit together, how the neurological, endocrine, and immune and developmental processes may be fit together. When we had supper tonight, we were consuming mass and energy and nutrients, and fueling our cellular and molecular systems that keep us alive. We have organ systems like the central nervous system, the endocrine system, and the immune system, and these talk to each other all the time. There are almost 60 known right now that naturally communicate between these three systems. So if you hit one system, you are likely going to hit the other two just because of the communication going on.

Two systems, cellular-molecular and organ systems, support individual functions of reproduction, growth and behavior, and at the population level they support birth and death rates and social

structure, and at the community level they support immigration and emigration and relative species abundance.

What is becoming apparent from all the scientific literature is that pesticides, which include herbicides, insecticides and fungicides, can act as nerve poisons, as well as altering hormone levels in various ways. Because of the interconnections and direct effects on immune function, they are impacting organ systems too. Because our ability to take in nutrients is a function of our ability to find food and have appetites and coordinate that, we may be

subverting the very foundation on which this entire superstructure rests (see Figure 4).

These concerns are not quite so obvious to the general public, but it certainly illustrates how very important it is to understand the interconnectedness of the whole body. If we fail to remember this, then we are going to focus very narrowly and not get at fundamental issues of concern. We have to get at the causes, not just deal with the symptoms. Thank you very much!

Sperm Count Declining, Organic Farmers' Higher

You remember, of course, that animals are often canaries in the mine for what could happen to humans, and when you look at the human sperm counts that are known from the literature now, about 168 of these studies, we have very strong data now that the sperm count in human males is now declining at a rate of 2.5 percent per year on a global average. This was all started by Elisabeth Carlsen, Ph.D. and Niels E. Skakkebaek, Ph.D.⁸ in Denmark because most Danish males have very low sperm counts. And then Jacques Auger, M.D.⁹ in France and his colleagues published a paper showing that in 1972 the average Parisian male had about 90 million sperm per milliliter (ml), but by 1992 that had dropped to about 60 million sperm per ml, and it is dropping faster than the global average here.

Then Annette Abell, Ph.D.¹⁰ and her colleagues in 1994 looked at the Danish population in general and then looked at the sperm counts of organic farmers, and it was pretty clear that something in the environment was causing changes in sperm count. Then finally, Jarkko Pajarinen, M.D.¹¹ says, okay, maybe the sperm count is dropping but how are we doing for normal sperm? So they looked at males in Helsinki, Finland. In 1981 about 50 percent of those sperm were normal. By 1991, 10 years later, about 25 percent of those sperm counts were normal. So the quality and the quantity of sperm are dropping very rapidly, and it is very clear that if this trend continues, within one generation we will have a negative population growth of this entire planet, on average.

Figure 3. Human sperm counts declining in quantity and quality

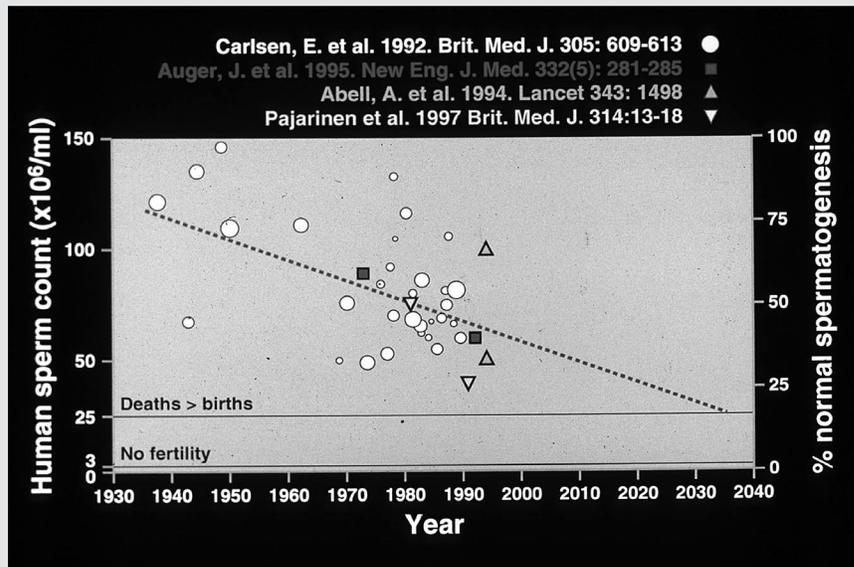
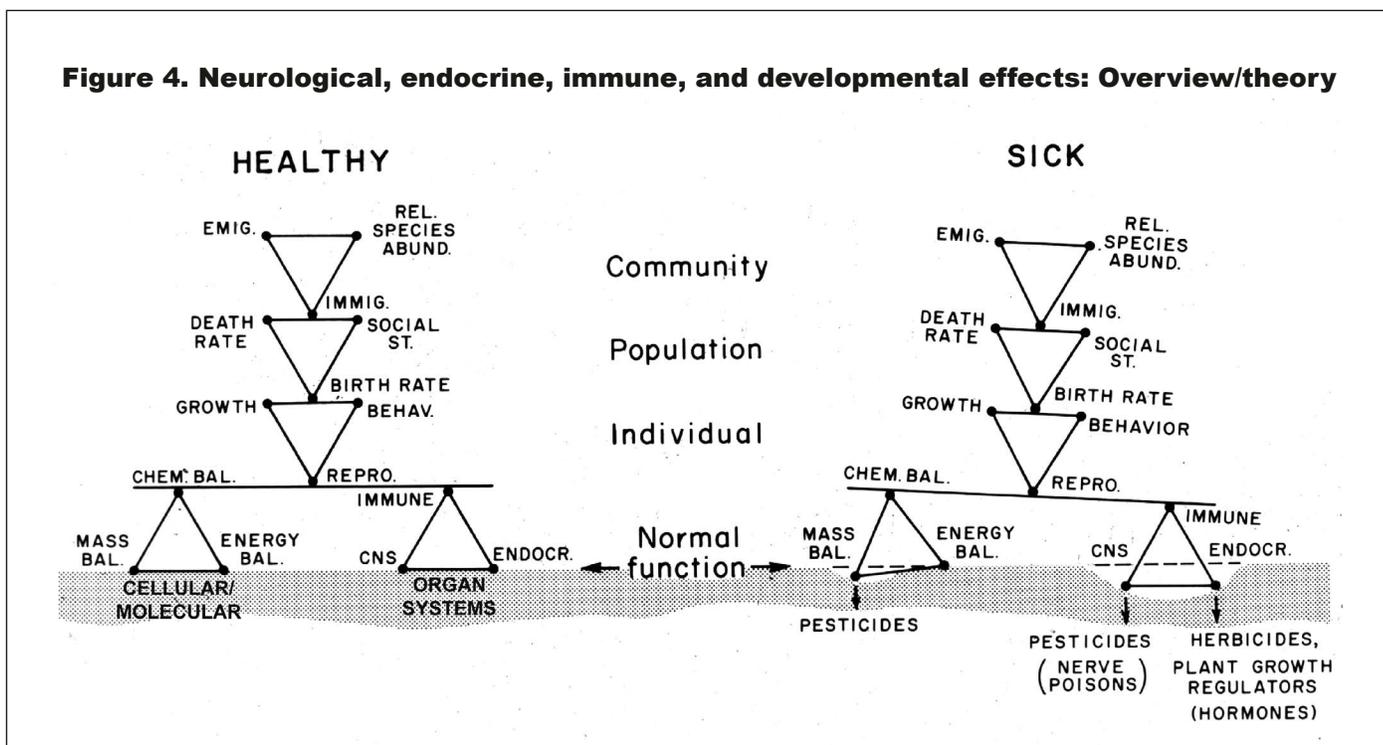


Figure 4. Neurological, endocrine, immune, and developmental effects: Overview/theory



This graphic depicts the impact of pesticides on the delicate balance of life. Porter, et al. 1999. Toxicol. & Indust. Health. 15 (1-2): 133-150.

Endnotes

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