Generations at Risk:

How Environmental Toxicants May Affect Reproductive Health in California

A Report by

Physicians for Social Responsibility (Greater SF Bay Area & Los Angeles Chapters) and
The California Public Interest Research Group Charitable Trust

Principal Authors

Organizations, Authors and Acknowledgments

Physicians for Social Responsibility (Greater San Francisco Bay Area and Los Angeles Chapters)

We also thank Joel Tickner, Andy Bray, Carolyn Ruddy, Maribeth Connolly, and Hillel Gray, as well as Rich Hannigan and Tony Dutzik of Public Interest GRFX, for their assistance in data analysis, research, editing, and graphic production of the original Massachusetts version. We extend deep appreciation to Richard Puchalsky of Grassroots Connection and to the resourceful staff at the Right-to-Know Network.

Funders

We are most grateful to the W. Alton Jones Foundation, the Clarence E. Heller Charitable Foundation and the Jenifer Altman Foundation for making this project possible.

Supporters

Thanks to the organizations and central staff of Californians for Pesticide Reform (CPR), a growing coali-

Contents

California based Physicians for Social Responsibility (PSR) and the California Public Interest Research Group (CALPIRG) Charitable Trust have joined together to prepare the report *Generations at Risk: How Environmental Exposures May Affect Reproductive Health in California.* This report brings together for the first time information about the reproductive health effects of selected chemical exposures with California chemical use and emissions data.

Major findings of the report include:

1. Of the more than 75,000 synthetic chemicals in commercial use today, only a small fraction have been adequately examined for toxic effects in humans and other life forms.
2. Despite limited scientific information, there is solid evidence of the reproductive toxicity of many substances that are widely used in commerce, including solvents, metals, and pesticides. Emerging evidence suggests that hormone (endocrine) disruption, which has long been identified but largely ignored, is a frequently occurring mechanism of toxicity.
3. Federal and state regulations are frequently not written or implemented in ways protective of human health and the environment.
4. Of industries required to report chemical use or release, including pesticide applicators, California businesses used or released more than 306.8 million pounds of chemicals associated with reproductive or developmental disorders from 1991 to 1995.
5. While California facility emissions of reproductive and developmental toxicants have declined over this period, use of these chemicals in agriculture is rising steadily. Total releases of these chemicals is increasing.
6. Right-to-know legislation like the federal Toxics Release Inventory (TRI) and California pesticide use reporting system provide the public with essential information which is rightfully theirs about toxicants to which they may be exposed. However, information gaps and accessibility problems show that these laws do not go far enough. While the TRI has been widely used to encourage facilities to reduce emissions, the California Pesticide Use Reporting Program data remains under-utilized and bears untapped potential for reducing pesticide use.
7. In order to protect the public from known and suspected reproductive toxicants, policymakers, industry managers, members of the medical and scientific communities and individual citizens must all adopt a precautionary approach when making personal and public decisions that may result in exposure to these chemicals.

The Scope of the Problem—Extensive Exposure, Limited Information

More than 75,000 synthetic chemicals and metals are currently in commercial use in the US. The toxicity of most of these is unknown or incompletely studied. In humans, exposure to some may cause cancer, reproductive and developmental disorders, adverse neurological and immunological effects, or other injury. Reproductive

workers, are exposed to mixtures of pesticides and are at increased risk of spontaneous abortion and birth defects in offspring. Some pesticides, like the fumigant, ethylene oxide, used to sterilize medical equipment, or the fumigant, methyl bromide, and herbicide, cyanazine, used in California agriculture, are identifiable as particularly associated with adverse reproductive outcomes. While the scientific evidence is weaker and still emerging, many other chemicals are also likely to adversely impact human reproduction. Suspects include manganese, several solvents including xylene, styrene, and perchlorethylene, and numerous pesticides and plasticizers.

Animal testing reveals that a single dose of a tiny amount of dioxin administered during a critical “window of vulnerability” in pregnancy can lead to life-long health effects in offspring. Men exposed to Agent Orange, an herbicide containing dioxin, are more likely to father children with birth defects. In addition, maternal exposure to PCBs seems to result in developmental delays in children. Dioxin and PCBs are examples of chemicals which appear to derail human reproduction and development by interfering with hormones. Other chemicals which may also be endocrine disruptors in humans are commonly found in consumer products such as plastics, paints,

What Right-to-Know Data Reveal:

Trends in Selected Chemical Use and Environmental Releases — Leading Industries, Facilities, Municipalities

Policy Recommendations

We base our policy recommendations on three fundamental principles. They are:

1. Minimization of Chemical Use and Exposure

Though it has been known for decades and, in some

Government oversight of prescription drugs, pesticides, and other industrial chemicals varies widely. But what are the fundamental reasons why the interactive effects of pharmaceuticals are so widely studied while similar effects of pesticides and tens of thousands of industrial chemicals to which entire populations are exposed are largely unknown? Why do we know so little about the extent of those exposures? The burden often falls on a regulatory agency to prove an exposure unsafe rather than the opposite, allowing human and environmental exposures to untested materials for economic and political reasons.

For example, the Toxic Substances Control Act (TSCA) requires that the Administrator of the EPA must find that there is a reasonable basis to conclude that a chemical presents an unreasonable risk of injury to health or the environment - and must also consider the benefits of the chemical and the economic consequences of regulation—before proposing action to control exposures. And when considering the registration of newly-proposed pesticides, EPA must consider cost-benefit analyses as well as animal toxicity testing. Figures used in cost-benefit analyses are usually supplied by the affected industry and often emphasize the cost of regulatory controls to their operations while minimizing or ignoring potential health-related or environmental costs resulting from exposures during production, use, disposal, or complete life-cycle analysis. Human health costs are, of course, impossible to estimate if related health effects are unstudied, unknown, or unrecognized.

We intend this document to have varied uses for groups and individuals from diverse backgrounds and interests. Broad-brush summaries of normal reproductive and

reproductive and developmental toxicants. The consequences of these exposures are largely unknown to the general public, occupationally-exposed workers, and health-care providers. One of our goals is to shed additional light on this important topic for those who wish to make more informed decisions. But beyond that, we hope that readers will consider this material an example of the need for a broader public health perspective in their own work and when analyzing health care, research, social, political, and economic activity.

Chapter 1 The Reproductive System

Overview

The following section describes normal female and male reproductive function in preparation for discussing the effects of toxic exposures.

The reproductive process is characterized by cycles and feedback loops. There is no obvious beginning or end. This description begins with the messages that link the system together. From the moment of conception, physical, electrical, and chemical messages between cells, then among cells and organs, lay down the foundation on which everything which follows is built. Hormones are the chemical messengers that link remote organs together, coordinating form and function.

The Brain Connection: The Hypothalamic-Pituitary-Gonadal System

Hormones produced by the *pituitary gland,* just beneath the brain, circulate through the blood stimulating the ovaries to produce *estrogen* and *eggs* — and the testes to produce *testosterone* and *sperm.* The *hypothalamus,* a portion of the base of the brain lying just above the pituitary gland, produces its own hormones which heavily influence pituitary output.

In order to keep the system balanced and in check, estrogen and testosterone circulate back to the pituitary and hypothalamus, fine tuning the amount of pituitary hormone produced, in a *feedback loop.*

In men, the loop maintains testosterone and pituitary hormone at fairly constant levels. But in women, at a critical level of estrogen, a surge of pituitary hormone pushes the ovary to release an egg which may then be fertilized. Normal functioning of a feedback loop may be disrupted at any point by chemicals, drugs, malnutrition, or other factors causing a change in hormone production.

The ovarian *follicle,* from which the egg is released, now known as a *corpus luteum,* continues to produce both estrogen and another hormone, *progesterone.* The two once again suppress the pituitary. If the egg is not fertilized, the corpus luteum dies, and the pituitary once again begins to stimulate the ovary to produce estrogen in the next menstrual cycle.

Detail

In men, a fairly constant level of *gonadotropin-releasing hormone (GnRH)* from the hypothalmus stimulates *follicle stimulating hormone (FSH)* and *luteinizing hormone (LH)* which, in turn, act on the testes to produce sperm and

Mechanisms of Hormone Action

Hormones exert their effects by binding to *hormone receptors* located on the surface or inside of cells. Their ability to influence the biochemical inner-workings of a cell depends on attachment to these receptors.

When the hormone attaches to its specific receptor on the surface or inside of a cell, much like a key fits into a lock, the linkage causes changes in the shape of the receptor, triggering a series of biochemical events. This amplifies the effect of each linkage. An entire cascade of biochemical events with significant effects may be triggered by tiny amounts of hormone attaching to few receptors.

Peptide hormones, including LH and FSH, attach to receptors on the cell surface. *Steroid hormones,* like the sex hormones testosterone, estrogen, or progesterone, pass through the cell membrane and attach directly to their specific receptors on the cell nucleus. They then interact directly with DNA in the nucleus, triggering genes to produce their programmed chemicals (gene products).

Function of the Reproductive Organs

The Ovary

Unlike males, in whom sperm production normally continues steadily throughout adult life, an infant girl is born with all of the immature eggs in her ovaries that she will ever have. She will never form more.

Ovaries consist of follicles, each containing an immature egg (the germ cell or *oocyte*) surrounded by an envelope of cells capable of producing hormones. With the onset of each menstrual cycle, and in response to hormonal stimulation from the pituitary, a group of follicles begins to mature in the ovaries. Eventually one of them releases its egg at the time of ovulation; the others deteriorate.

The follicle is then transformed into a corpus luteum which produces progesterone, a hormone necessary to prepare the uterus for implantation of the fertilized egg. If fertilization fails to occur, the corpus luteum dies. The uterine lining is shed during menstruation.

If the egg is fertilized, dividing cells of the new embryo produce *human chorionic gonadotropin (HCG),* a hormone which maintains the corpus luteum, enabling continued preparation of the uterus for implantation.

Critical hormone balances from the pituitary, follicle, and corpus luteum are necessary for maintenance of this complex system.

The Testes

Like the ovaries, the testes also serve two important reproductive functions — *production of sperm* (spermatogenesis) and *hormones.* There are several different kinds of cells in the testes: 1) the *germ cells* or immature sperm, 2) those that produce the hormone testosterone (

Sexual Differentiation of the Brain

■ *Many functions that more fully develop later in life as an individual matures sexually are largely determined during fetal life and early childhood—at a time when the brain is developing its lifelong tendency for receptor and hormone levels and when it is less fully protected from toxic exposures by the blood brain barrier.*

The male, whose sex is determined by a Y chromosome, undergoes a complex series of events which masculinize many different organs and tissues including the genitals and brain, controlling endocrine function and sexual behavior.

Fetal testicles produce testosterone. In the brain, testosterone is chemically converted by an enzyme (aromatase) to *estrogen* which is largely but not exclusively responsible for *masculinizing* the nerve connections in the brain. We are accustomed to thinking of estrogen as a female hormone — this is true in the adult; but in the fetal and childhood brain, estrogen produced from testosterone is necessary for male-type brain development. Diethylstilbesterol (DES), an estrogen-like compound, given to female rats soon after birth will masculinize the hypothalamus.[2]

Estrogen receptors are present not only in the hypothalamus but also in other portions of the brain. For example, the cerebral cortex, responsible for many more advanced neurological functions in humans and protected by the blood-brain barrier later in life, has estrogen receptors in the fetus and early infancy. Their role is unknown.

Though converted to estrogen in the brain, fetal testosterone is altered to another form of testosterone — dihydrotestosterone (DHT) — in the testicles, continuing to masculinize the genitals.

This sequence of events suggests that many functions and processes that more fully develop later in life as an individual matures sexually are largely determined during fetal life and early childhood — at a time when the brain is developing its lifelong tendency for receptor and hormone levels and when it is less fully protected from toxic exposures by the blood brain barrier.

Summary

This brief summary of normal human reproduction is intended to provide the foundation for the discussion of reproductive and developmental toxicology which follows. This outline of anatomy, functional interactions, chemical feedback loops, and development leads to a discussion of where, how, and why toxicants exert their effects. However, a word of warning — this outline has glossed over a large amount of subject matter — including that about which there is minimal or no understanding. For example, little is known about the cellular mechanisms of regulation or repair after toxic insult to the embryo. The time at which specific cells are committed to a certain fate is largely unknown but is obviously important. Details of the timing of functional development of the brain are sketchy. These uncertainties should be kept in mind.

References

1. Developmental Toxicology, 2nd ed. Kimmel CA, Buekle-Sam, J., Eds, Raven Press, NY , 1994., pg 69.
2. Swaab, DF and Hofman MA. Sexual Differentiation of the human hypothalmus: ontogeny of the sexually dimorphic nucleus of the preoptic area. Developmental Brain Res 44: 314-18, 1988.

Chapter 2

How Toxic Chemicals Can Affect the Reproductive System

Overview

A variety of organs and processes whose smooth and coordinated function ensures normal reproduction and development are potential targets of toxic exposures. Normal function requires timing, balance, properly set feedback loops, and communication among cells and organs from the time of conception through the reproductive years. There are numerous opportunities for disruption. This section discusses the mechanisms and sites of action of toxicants, the variety of reproductive and developmental health effects, and some of the problems associated with trying to determine safe exposure levels.

Reproductive Toxicology

Mechanisms of Action

Toxicants may

- *Directly damage the structure of cells,*
- *Interfere with biochemical processes necessary for normal cell function,*
- *Require biochemical alteration before they become toxic.*

Toxic chemicals may directly damage cell structure or biochemical function. Some trigger the production of enzymes which, in turn, transform other chemicals into more toxic substances. This mechanism often explains how mixtures of chemicals may be more harmful than individual exposures.

They may also exert their effects through similarity to normally present compounds. By mimicking hormones, for example, they stimulate or block hormone receptors. This either triggers a cascade of inappropriate events or blocks events required for normal function. Very small amounts of hormone mimics or antagonists may influence a system that functions by amplifying the effects of individual hormone-receptor linkages.

Indirect-acting agents require metabolism or breakdown into a direct-acting toxicant before causing harm. Test-tube studies of these chemicals will fail to reveal their toxicity since their transformation into harmful substances depends on metabolism in the intact animal.

Species Differences

- *Since not all animal species have identical metabolism or timing of growth patterns, toxicity may vary considerably among them.*

Most studies of reproductive toxicants have been conducted in animals — commonly rats and mice though sometimes in primates, rabbits, guinea pigs, or hamsters. There is often considerable uncertainty about how well animal tests predict human toxicity. Biochemical and developmental pathways may differ from one species to

Thalidomide — The Failure to Predict Human Toxicity

In the 1960's, thalidomide was responsible for limb defects in many children born to mothers who had taken the drug during pregnancy. Studies performed in rodents before the medication was released for human use failed to show evidence of maternal toxicity or obvious birth defects in the young. It was only later that the discovery of differences in rat and human metabolism of the drug explained its lack of toxicity in rats. Rabbits, tested later, did show evidence of damage from exposure. Since then, protocols for testing pharmaceutical products for reproductive toxicity have changed, requiring that testing be conducted in at least two mammalian species.

another, sometimes in ways not fully understood.
The timing of brain “growth spurts” during fetal and

There is no consensus among reproductive toxicologists about the relative importance of various outcomes or "endpoints," particularly in developmental toxicity studies. Some scientists believe that one of these outcomes in one species may be predictive of a different outcome in another species. Others are more concerned about one outcome than another — for example, malformations rather than functional deficits.

Functional abnormalities resulting from events during pregnancy may not be obvious to visual inspection or initial physical examination of infants — in fact, they may not become apparent for years. A registry of birth defects which depends on reports of abnormalities within a short time after birth is useful for collecting data on visible or easily detectable structural abnormalities. But it is an inadequate tool for documenting functional disturbances which may result from fetal exposures but may not be immediately obvious.

Caution! The Interpretation of

References

1. Dobbing J, Sands J. Comparative aspects of the brain growth spurt. Early Human Development. 3(1): 79-83, 1979.
2. Sharpe RM, Fisher JS, Millar MM, et. al. Gestational and lactational exposure of rats to xenoestrogens results in reduced testicular size and sperm production. Environ Health Perspect. 103(12):1136-1143, 1995.
3. Reproductive Toxicology, 2nd ed. Witorsch RJ, Ed., Raven Press, NY, 1995, pg 112-113.
4. Reproductive Toxicology, pg. 102.
5. Causes of developmental defects NEJM 320:19-23, 1989.
6. Mably TA, Moore RW, Peterson RE. In utero and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-p-dioxin: 1. Effects on androgenic status. Toxicol Appl Pharmacol 114:97-107, 1992.
7. Wilson JG. Experimental studies on congenital malformations. J Chronic Dis 10:111-130, 1959.
8. Developmental Toxicology, 2nd ed., Kimmel CA, Buekl, Sam J., Eds., Raven Press, NY, 1994, pg 54
9. Shenefelt RE. Morphogenesis of malformations in hamsters caused by retinoic acid: relation to dose and stage of treatment. Teratology. 5:103-118, 1972.
10. Developmental Toxicology, pg. 254.
11. Wilcox AJ, Weinberg CR, O'Connor JF, et. al. Incidence of early loss of pregnancy. NEJM. 319(4): 189-194, 1988.
12. Lemasters GK. Occupational exposures and effects on male and female reproduction. In: Rom WN, Environmental and Occupational Medicine, 2nd ed., Little, Brown and Co. Boston, 1992.
13. Committee on pesticides in the diets of infants and children, Board on Agriculture and Board on Environmental Studies and Toxicology, Commission on Life Sciences, National Research Council, Pesticides in the Diets of Infants and Children, National Academy Press, Washington DC, 1993.
14. Marcus M, Silbergeld E, Mattison D, et al. A reproductive hazards research agenda for the 1990s. Environ Health Perspect 101 (Suppl2):175-180, 1993.

Additional Reading

Occupational and Environmental Reproductive Hazards: A Guide for Clinicians. Ed.: Maureen Paul, Williams and Wilkins; Baltimore, MD; 1993.

Chapter 3

How Toxic Chemicals Are Tested and Studied

Risk Assessment

Introduction

The reproductive toxicity of chemicals can be evaluated scientifically by studies in animals or in humans. Animal studies are widely used and often are the first indicators of the possible reproductive or developmental effects of a chemical. Studies in animals can be useful because the animal can be exposed to a very specific dose of the chemical under controlled conditions in the laboratory. Some outcomes can be measured quite accurately; others are difficult to diagnose or measure. Unfortunately, because of differences in metabolism, size, and lifespan, it can be difficult to extrapolate from effects found in rodents to effects that might be expected in people.

Because they cannot ethically be done in laboratories if there is any risk of long-term consequences, human studies are subject to the uncertainty of the real world: the duration, size, or timing of a dose is often uncertain, people sustain multiple exposures, and the outcomes can be hard to measure. The following sections summarize the current methods for animal testing and for epidemiologic studies in human populations. They are useful as a foundation for understanding the difficulty of studying reproduction and development and for understanding the sections that follow.

Animal Testing

Reproductive toxicity testing has evolved considerably over the past several decades, stimulated by an obvious need, public demand for information, and increasingly sensitive laboratory techniques. As early as the 1930s, some food additives and pesticides were studied with early forms of multigeneration animal tests, but those tests were not sufficient to demonstrate the full spectrum of reproductive and developmental toxicity. Despite improvements, deficiencies in both design and application persist and are under review.

In general, reproductive toxicity animal tests fall into two categories — *segment* and *multigenerational* studies. *Segment* studies examine specific portions of the reproductive process and give detailed information about male or female toxicity. They examine fertility and reproductive function in males and females separately and also evaluate development of offspring.

Multigenerational studies expose both males and females to a substance and measure various parameters in succeeding generations including fertility, ability to carry offspring through full pregnancy, the delivery and rearing of offspring, size and sex of litters, microscopic examination of offspring organs, and organ weights. Multigenerational studies conducted through two or three generations of test animals include the period of nursing, weaning, and sexual maturation after which reproductive function is similarly evaluated.

Continuous breeding animal studies involve dosing male and female rats or mice for one week with the agent being studied, continuing to treat during mating and production of successive litters, treating the last litter from the time of weaning, and then mating them to examine their ability to reproduce.

More recent protocols examine developmental neurotoxicity by evaluating functional and structural effects on the developing nervous system that may arise after maternal exposure during pregnancy or nursing. Motor activity, noise startle responses, learning and memory, microscopic examination of the brain, and brain weight may be studied. When considering a pesticide for registration, the EPA only requires this protocol on a case-by-case basis, depending on what other information is available on the specific chemical or class of chemicals.
Animal studies are designed to examine for a range of

health effects in different species. For non-cancer effects, including reproductive and developmental toxicity, investigators generally assume that there is an exposure level (dose) that will not cause a health effect seen at higher doses. This is a threshold below which exposures are considered "safe" for the animal. Regulators must then decide the exposure level at which they believe humans are safe from the same effect. In practice they generally apply uncertainty factors — a factor of 10 for the uncertainty about species differences and another factor of 10 for particularly sensitive individuals — giving a total adjustment of 10×10 or 100. They conclude that humans will avoid the effect if exposures are 100 times less than the no-effect level in animal studies.

On the surface, this appears to be a conservative approach — one likely to be health protective. However, there is debate about whether thresholds really exist.[1,2] For example, if a particular developmental defect is rare, large numbers of animals will need to be tested in order to detect the unusual event. Testing with inadequate numbers will fail to reveal the toxicity. Moreover, important health effects, such as delayed neurotoxicity or functional developmental abnormalities, may not be adequately tested in animal studies. This concern prompted the National Research Council in its report on *Pesticides in the Diets of Infants and Children* to recommend revised dosing during late pregnancy and infancy and additional examination for delayed neurological effects.

One of the most pressing needs in reproductive toxicology is more comprehensive evaluation of developmental abnormalities. Neurotoxicity and reproductive functional abnormalities in offspring are studied on a case-by-case basis, but functional alterations of the immune system and other organs are examined even more sporadically and without standardized protocols in the regulatory agencies. Meanwhile, the inventory of commercial chemicals to which workers and communities are exposed continues to grow rapidly. Given the backlog of chemicals for which there has been no developmental testing, persistent exposures of varying levels and duration, and industrial resistance to full disclosure, the prospects for full analysis and public protection are limited.

Finally, animal testing for registration and regulatory

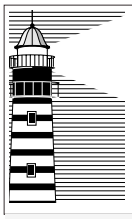
importance of timing, carbendazim, a fungicide, causes birth defects in some rat embryos when given in mid- to late- pregnancy. But, it does not have the same effect when given to pregnant animals early in pregnancy, even when given in the same amount.[3] The younger embryo is apparently able to repair or compensate for the damage more easily.

Since each toxicant and health effect has its own dose-response relationship, which may change as the fetus develops, truly comprehensive toxicity testing requires examination for the full range of possible effects using a variety of dosing schedules and amounts. Interpreting animal studies is therefore a challenge since the absence of a particular health effect in an animal study may not indicate that exposure is safe but may rather reflect failure to test a critical amount at a vulnerable time for sufficient duration.

Regulatory agencies responsible for controlling human or wildlife exposures to potential toxicants in the workplace, home, community, food and water supply, or pharmaceuticals attempt to identify a threshold level of exposure, below which reproductive or developmental effects are unlikely. As we will see, this is often difficult, time-consuming, and at times, highly politicized, resulting in large data gaps for many chemicals currently in use.

Epidemiologic (Human) Studies

In addition to animal studies, studies on exposed human populations are a major source of information about



Spotlight on

Toxic Ignorance: Most Chemicals in U.S. Commerce are Inadequately Studied[1]

Because of inadequate chemical safety testing, the public has no way of knowing whether or not a large majority of the highest-use chemicals in the United States pose health hazards. In 1980, the National Academy of Sciences began an extensive study to determine what need there was for additional toxicity testing of chemicals in commerce. In 1984, it concluded that 78% of the chemicals in U.S. commerce with a production volume greater than one million pounds lacked "even minimal toxicity information."[2] In 1997, researchers at the Environmental Defense Fund updated this study and concluded that there has been no significant improvement in the intervening 13 years.

Using a random-sample approach (as did the National Academy), the EDF study estimates that 71% of the most

Types of Epidemiologic Studies

- ***Correlation studies*** use aggregate information to generate theories. For example, the decline in sperm counts worldwide can be graphed against the boom in chemical manufacture since World War II to demonstrate a striking correlation. Such studies are unable to make any claim about causation.

- ***Cross sectional surveys*** are frequently used because they are fairly quick and inexpensive, yet they provide more information than correlation studies. Their weakness is that they only look at one point in time. Studies on sperm counts in exposed men are often of this type, where sperm samples and exposure measurements are taken at the same time. It is often hard to prove causation from cross sectional surveys because there is no evidence that the exposure came before the outcome (that is, that the men's sperm counts dropped after, and

because of, the exposure).

• ***Case reports*** and ***case series*** (a group of case reports) are not true epidemiologic studies. They are important, however, because many serious medical problems first appear as case reports. For example, the effects of diethylstilbesterol (DES) exposure were first reported in a case series in the *New England Journal of Medicine* describing a group of young women with a very rare vaginal cancer who were exposed to this drug before birth.

• ***Case-control studies*** are extremely important because they look at populations over time. Such studies identify people with a health outcome of particular interest (cases), choose a comparison (control) group without the outcome of concern and look back to see whether the "cases" were more likely to have been exposed to any particular risk factor than the "controls." An example would be comparing a group of women who recently suffered a spontaneous abortion (cases) with an otherwise similar group of women who recently delivered a healthy baby (controls). Both groups of women would then be asked about a history of exposures during the pregnancy.

• ***Cohort studies*** start with an exposed group and an unexposed comparison group and follow them over time watching for the outcome of interest. Thus, it is possible to identify a group of children with fairly high lead exposures in infancy and a similar group who had very little lead exposure. Both groups of children are then followed for years to observe whether there are differences in behavior and learning between the two groups. Some cohort studies are *retrospective cohorts*, in that they go into old records and identify a group of exposed people and a comparison group from many years ago (this is often done by looking through company records in an industry where workers were exposed to a chemical of interest.) These people are then tracked down (where possible) and their current health status is discovered.

Weaknesses of Epidemiologic Studies

It is important to remember that epidemiologic studies trying to link exposure to a particular chemical and outcomes, such as infertility, spontaneous abortion, birthdefects, and later behavioral problems or cancers in children, suffer from a number of major difficulties.

Case-control studies and retrospective cohort studies, because they are interested in exposures that occurred in the past, usually can only estimate the degree or the pattern of chemical exposure at the time. The result can be *exposure misclassification,* in which individuals may be incorrectly assigned to the exposed or unexposed group. It is easy to see how this might happen, particularly if job titles or place of residence are used to decide who was exposed and who was not. Clearly not all people who work in plant nurseries have the same level of exposure to pesticides. If the investigators do not (or cannot) actually measure individual exposures, there is risk of misclassification. In most studies, this misclassification of exposure is random (that is, exposed and unexposed individuals are equally likely to be misclassified). This will tend to bias the study toward finding no association between the exposure and the outcome and will result in a falsely negative study or in an underestimate of the magnitude of the risk.

Relying on memory may result in a different kind of bias: *recall bias.* This means, for example, that those parents who had an unfavorable outcome will search their memories for any possible exposure, while those who had healthy pregnancies will tend to forget chemical exposures they may have had months before. Such a problem is usually only an issue in case-control studies that rely on memory to determine exposure and can bias these studies toward finding associations between exposures and the outcome under study, when in fact no such association exists.

Often various interacting associations can muddy the ability to pinpoint particular risk factors. Such interactions can create the appearance of an association that does not really exist. *Confounding factors* are independently associated with both the exposure and the outcome. For example, if women who work in a particular industry are more likely to smoke than women who do not, and if women who smoke are more likely to have low birth weight babies (which they are), then it would be incorrect to assume that the industry work is responsible for the small babies, unless the difference in smoking is first taken into account.

A particular problem in reproductive and developmental epidemiology is that some of the outcomes are hard to measure. Many spontaneous abortions are unrecognized

or unreported because they occur so early in pregnancy, and a large number of spontaneous abortions are thought to occur in healthy, unexposed women. Fertility is even harder to accurately measure, because it depends on so many other personal, social, and religious factors.

at home. It is very hard to pin the blame on any one exposure. Of this combination of exposures, some may be benign, some hazardous, and others may interact with one another in ways that may be difficult to predict. It is important to look closely at the epidemiologic studies, remain aware of the limitations discussed, and evaluate the weight of evidence as to whether or not particular chemicals are of concern.

Risk Assessment and Risk Management

Regulators may use several methods to estimate the public health risks of chemical exposures. The accuracy of quantitative risk assessment is limited by being based on:

- Assumptions about the extent of exposure, often failing to account for specific groups who may be disproportionately exposed like infants, children, or workers in high exposure occupations;
- Single-chemical exposures, failing to account for multiple exposures and interactive effects;
- Assumptions about the shape of dose-response curves for each of the possible health outcomes;
- Assumptions about species differences when extrapolating from animals to humans;
- Identified and easily recognized health outcomes, failing to include those difficult to diagnose or delayed (for example, delayed neurological, reproductive, or developmental abnormalities).

Mathematical models used for quantitative risk assessment often create an illusion of scientific knowledge and certainty that is unjustified.
Among a series of recommendations in an analysis of chemical risk assessment in occupational health, the authors include:[4]

- Aggregate risks, untested chemicals, and sensitive populations are issues that need critical attention and are not treated conservatively in current approaches to risk assessment.
- Risk managers should keep in mind that complex analyses and models are not necessarily better; they often just obfuscate the process, making it more difficult for diverse participation in the regulatory process itself. Computationally and structurally complicated models that have not been demonstrated to do a better job of predicting risk should be viewed with skepticism.
- Qualitative representations of risk should receive additional attention since numerical estimates often imply more precision than our current scientific understanding warrants.
- Precautionary principles should receive more attention in regulating occupational risks, especially when dealing with poorly characterized chemical or complex exposure scenarios.
- Risk assessment and risk management decisions should be clearly elaborated and explained via open process with opportunity for scientific, labor, community, and management participation.

A critique of risk assessment methods is far beyond the scope of this document, but we caution the reader to beware of quantitative risk assessments that fail to acknowledge their limitations, assumptions, and imbedded values.

References

1. Daston GP. Do thresholds exist for developmental toxicants? In: Issues and Reviews in Teratology, Vol. 6, Ed: Kalter, H. Plenum Press, NY, 1993.
2. McMaster SB. Developmental toxicity, reproductive toxicity, and neurotoxicity as regulatory endpoints. Toxicol Lett. 68:225-230, 1993.
3. Cummings A, Harris S. Carbendazim and maternally mediated early pregnancy loss in the rat. Biol Repro 42:66, 1990.
4. Chemical Risk Assessment and Occupational Health: Current Applications, Limitation, and Future Prospects. Ed: Smith, CM, Christiani, DC, Kelsey, KT. Auburn House, Westport, CT 1994.

Overview

Lead and mercury are the most extensively studied reproductive and developmental toxicants known. Widely dispersed throughout the environment, everyone is exposed to them. Three other common metals, cadmium, arsenic and manganese, are also likely reproductive toxicants,

in this country. However, leaded gasoline is still used throughout the world and will continue to expose untold millions for years to come.

Table 1: Some Sources of Lead Exposure:
Painting/Removing old paint
Construction
Battery manufacturing or recycling
Automobile repair
Electronics
Ceramics and pottery
Printing
Welding and soldering
Firearm shooting and cleaning
Jewelry making and repair
Stained glass window making

Distribution in the Body

When lead enters the body it distributes throughout the organs, including the brain, and crosses the placenta with ease.[2] Blood lead levels in the fetus are up to 90% of the maternal blood lead levels.[3] While some lead is excreted, the rest accumulates in bone, and can be released months or years later. Pregnancy is a time of increased bone turnover in the mother, and any lead stored in her bones may be released and result in significant exposures to the fetus.[4]

Lead exposure can be measured through blood testing, urine testing, and X-ray fluorescence of bone. Blood testing is the most common, though it only reflects exposure over the past three months. Lifetime exposure to lead can be measured with either bone x-ray fluorescence or urine testing done after administration of a chelating medication which increases excretion of lead. These tests are generally done at academic medical centers for research purposes.

Lead Dose and Health Effects

Over the past ten years there has been increasing evidence that lead may have serious health effects at exposure levels much lower than previously thought to be harmful. Most of the other substances discussed in this report are either disputed reproductive or developmental toxicants, or known reproductive or developmental toxicants with unclear dose-response ranges. Lead is a known toxicant with a well-studied dose-response relationship, which allows us to discuss specific effects (see table 2).

Table 2: Health Effects of Lead at a Range of Doses

The average blood lead level in the U.S. population is now about 2.0 µg/dl (micrograms per deciliter) in women of childbearing age, and about 4.2 µg/dl for men in the same age range.[5] Levels were much higher in the 1970's: around 13.7 µg/dl in children aged one to five and around 11 µg/dl in women of childbearing age.[6] A

Reproductive and Developmental Effects at High Doses

Men

At blood lead levels over about 50 µg/dl, lead impairs fertility in males and females.[9 10 11 12 13] In men, lead may act directly on the testes to lower the sperm count and in the past was used as a spermicide contraceptive. A recent study in male workers found effects on sperm function and quantity at blood lead levels near 40 µg/dl.[14] Blood lead levels of 40-50 µg/dl occur regularly in the workplace, and employers are not required to remove workers from exposure until their blood level rises over 50 µg/dl. Evidence that lead may interfere with the endocrine system comes from studies which have shown an effect on testosterone levels and on the hypothalamic-pituitary axis in men with severe lead poisoning.[15 16] Unfortunately, insufficient study size and few studies involving male exposure make it difficult to conclude at what dose lead may affect male reproduction.[17]

Women

With exposure at or above levels encountered in the workplace, lead causes spontaneous abortions and stillbirths.[18] In the past, it was used to induce abortion. At lower blood levels, up to around 15 µg/dl, several studies have not found any increased risk of spontaneous abortion.[19 20] One study tracked down women who had been lead poisoned as children 40 years before and asked them about their reproductive history, and found a 60% increase in risk of spontaneous abortion.

Mercury

There are three forms of mercury with different effects on reproduction and development.

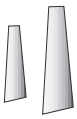
- *Organic mercury has caused epidemics of birth defects and neurological effects.*
- *Organic mercury is toxic to the developing brain.*
- *Inorganic mercury may lead to spontaneous abortions and birth defects.*

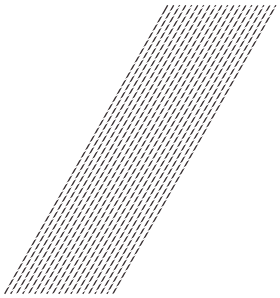
Exposure and Absorption of Mercury

Mercury is found in the environment in three forms: elemental mercury vapor, inorganic mercury compounds, and organic (usually methyl) mercury. There are significant differences among the three forms, as they are produced and used for different purposes, they are absorbed by the body differently, and they have different effects on reproduction and development (see table 3).

Organic mercury is the most dangerous form of mercury because it is the most easily absorbed orally, and because it crosses into the brain and into the fetus so easily. Levels in the fetal circulation are usually higher than levels in maternal blood, and methyl mercury appears in significant levels in breast milk.[32] Bacteria in the environment transform other forms of mercury into organic mercury. This is taken up in algae and eaten by fish, and makes its way into the human diet (see table 4). Contaminated fish, particularly carnivorous fish such as swordfish, tuna, shark, and pike are the major source of organic mercury exposure for many people.[33]

2 m





abortion.[50] [51] One large cohort study demonstrated spontaneous abortion and other pregnancy complications in exposed women.[52] Several additional studies suggest that women occupationally exposed to elemental mercury may have an increased risk of menstrual disorders, particularly heavy bleeding and severe menstrual cramps.[53]

Inorganic mercury exposure in young children can lead to acrodynia, or "pink disease." Symptoms include a rash and peeling of the skin of the hands and feet, irritability, photophobia (being bothered by bright light), excessive hair growth, and profuse perspiration. This syndrome is seen when mercury is used as a disinfectant in diaper laundries, or when mercuric salts are applied to the baby's skin as a disinfectant. This syndrome seems to be an allergic-type reaction to mercury.

Summary

hobbies, including metal plating, semiconductor manufacture, wire, plastic, or battery manufacture, welding, soldering, ceramics, or painting. One other important source of cadmium is cigarette smoke; smokers typically have blood levels of cadmium approximately twice those of nonsmokers.[54] Cadmium can also be a contaminant of drinking water, air, and food, particularly shellfish. In the 1940's and 50's there was an epidemic of poisoning in Japan due to contamination of water and rice crops with cadmium run-off from a zinc mine. Poisoned villagers experienced severe bone pain, a waddling walk, poor kidney function, and thinning of the bones.[55]

Everyone has cadmium in their bodies, where it concentrates in the kidneys, liver, pancreas, and adrenal glands and tends to slowly accumulate over time. Individuals with iron, calcium, or zinc deficiency, or with protein malnutrition, absorb cadmium more readily. A protein, metallothionein, binds to cadmium, and is thought to help protect against the toxic effects of the metal. Normally very little cadmium is captured by metallothionein, but repeated low level exposure to cadmium causes increased production of this protective protein. Thus short-term higher-level exposures may be more dangerous than low-level chronic exposures.[56]

Testicular Toxicity in Males

In male animals, cadmium severely damages the testes and kills the cells which produce sperm, even at low dose levels that do not cause general toxicity to the animal.[57] [58] [59] In the few human studies done to date, the results are less clear-cut. Four men occupationally exposed to cadmium had 100-fold higher levels of cadmium in their testes on autopsy compared to three unexposed men. Although the testes of the exposed men appeared essentially normal, almost no sperm were seen microscopically.[60] Another study showed no effects on the reproductive hormones testosterone, LH, or FSH in a group of exposed workers, but no semen analysis was done.[61] Finally, recent research demonstrates an association between elevated cadmium levels in seminal plasma and varicocele-related infertility in men.[62]

Placental Toxicity

In both humans and animals there is strong evidence for placental toxicity. Studies in female animals show that cadmium accumulates in the placenta.[63] Initially this accumulation was thought to be protective of the developing fetus, but there is now evidence that cadmium damages the placenta's ability to provide oxygen and nutrition to the fetus and can result in fetal damage or death.[64] Cadmium concentrates in the human placenta, and levels of exposure that cause placental toxicity are at least 10-fold lower than those which result in other toxic effects in the adult, such as kidney damage. Cadmium leads to decreased production of a hormone, human chorionic gonadotropin (ß-HCG), which is essential for maintaining the pregnancy; it also interferes with the transfer of zinc across the placenta and causes structural damage, initially to the blood supply, and eventually to the rest of the placenta.[65] Cadmium does cross the placenta to some degree in humans. The level of cadmium ilt in TJT*[(t6.71 650 TmT*aol9Eb7e dev)7(el-)]TJ0 -1.2sentl3Tmyg

c*[(ilt in555ulates in 0 5.2)6(oduction ofl9Eb7e t aehv)6(el.6(elsu77d

A series of other important animal studies exposed pregnant rats to cadmium and examined the lungs of the offspring. All found that exposed rats have smaller lungs than expected. In addition, the important lung surfactants, which keep the air sacs in the lung from sticking together, were markedly decreased in the exposed rats. Not surprisingly, these exposed rats were found to have a high risk of respiratory distress syndrome and sudden infant death.[72] Again, no human studies have looked for an association between respiratory distress or sudden infant death syndrome (SIDS or "crib death") in infancy and cadmium exposure.

Summary

Extensive evidence from experimental studies on rodents and on human placentas shows that cadmium can be toxic to the placenta at doses below those which cause other adverse effects of cadmium exposure. It is unclear whether this placental toxicity leads to adverse effects on the human fetus, though such effects were found in animals and would be expected in humans. The dramatic testicular toxicity found in animals has not been shown in humans exposed to low doses. There is worrisome evidence in animals that cadmium may affect neurological and behavioral development and may affect development of the lungs. These issues remain to be studied in humans, and urgently require further attention. While awaiting further research, this metal should be treated with extreme caution as a probable human reproductive and developmental toxicant.

Arsenic

- *Known to cause malformations in animals at high doses.*
- *Human studies suggest a connection with spontaneous abortion and stillbirth.*
- *May have effects on neurologic development, particularly on hearing.*

Uses and Routes of Exposure:

Arsenic, like mercury, is found in organic and inorganic forms. In general, organic forms of arsenic appear to be of low toxicity and different organic forms are found naturally in animals and plants.

Manganese

- *Evidence of toxicity to male reproductive function in animals.*
- *Evidence of growth retardation in animal fetuses.*
- *Probably toxic to the brain in infants and adults.*

Sources of Exposure

Manganese is naturally quite abundant in the environment. Necessary to human growth and development at low levels, it is found in many foods, such as grains, cloves, and tea. Inhalation of manganese appears to be much more hazardous than eating manganese in foods, and at high levels manganese is toxic to the brain and the lungs.

A major environmental source of manganese is emission from coal-fired power plants. Occupational exposure occurs in mining and metal products manufacturing (particularly iron and steel), dry-cell battery manufacture, and manufacture and use of certain paints, fertilizers, fungicides, and fireworks. Manganese is also used, in the form of permanganate, in glass and ceramic manufacture. The neurologic and reproductive hazard of manganese is an extremely important issue at this time because manganese

study in which workers were exposed at slightly lower levels, however, found no effect on birth rates.

References:

1. Clarkson TW, Nordberg GF, Sagar PR. Reproductive and developmental toxicity of metals. Scand J Work Env Health 11:145-154, 1985.
2. Goyer RA. Transplacental transport of lead. Env Health Persp 89:101-105, 1990.
3. Ibid.
4. Silbergeld EK. Implications of new data on lead toxicity for managing and preventing exposure. Env Health Persp 89:49-54, 1990.
5. Brody DJ, Pirkle JL, et al. Blood lead levels in the US population. JAMA 272:277-283, 1994.
6. Pirkle JL, Brody DJ, et al. The decline in blood lead levels in the United States. JAMA 272:284-291, 1994.
7. Crocette AF, Mushak P, and Schwartz J. Determination of numbers of lead-exposed women of childbearing age and pregnant women: an integrated summary of a report to the U.S. Congress on childhood lead poisoning. Environ Health Persp 89:121-124, 1990.
8. Ibid
9. Winder C. Reproductive and chromosomal effects of occupational exposure to lead in the male. Reprod Toxicol 3:221-233, 1989.
10. Thomas JA, Brogan WC. Some actions of lead on the sperm and on the male reproductive system. Am J Ind Med 4: 127-134, 1983.
11. Rom W. Effects of lead on the female and reproduction: a review. Mt Sinai J Med 43:542-552, 1976.

34. West CR, and Smith CM (eds.) Mercury in Massachusetts: An Evaluation of Sources, Emissions, Impacts, and Controls (Draft). Massachusetts Department of Environmental Protection, November 1995.
35. Bakir F, Damluji SF et al. Methylmercury poisoning in Iraq. Science 181:230-241, 1973.
36. Marsh DO, Myers GJ, et al. Fetal methylmercury poisoning: clinical and toxicological data on 29 cases. Ann Neurol 7:348-355, 1980.
37. Harada H. Congenital Minamata disease: intrauterine methylmercury poisoning. Teratology 18:285-288, 1978.
38. Cox C, Clarkson TW, et al. Dose-response analysis of infants prenatally exposed to methyl mercury: an application of a single compartment model to single-strand hair analysis. Env Research 49:318-332, 1989.
39. Burbacher T, Rodier R, and Weiss B. Methylmercury developmental neurotoxicity: a comparison of effects in humans and animals. Neurotox Teratol 12:191-202, 1990.
40. Rodier PM, Aschner M, Sager PR. Mitotic arrest in the developing CNS after prenatal exposure to methylmercury. Neurobehav Tox Teratol 6:379-385, 1984.
41. Goyer RA. Toxic effects of metals. in Amdur MO, Doull J, and Klaassen CD (eds). Casarett and Doull's Toxicology: the Basic Science of Poisons, 4th Edition. New York: McGraw-Hill Inc., 1993.
42. Myers GJ, Davidson PW, et al. Summary of the Seychelles child development study on the relationship of fetal methylmercury exposure to neurodevelopment. Neurotox 16:711-716, 1995.
43. Myers GJ, Marsh DO, et al. Main neurodevelopmental study of Seychellois children following in utero exposure to methylmercury from a maternal fish diet: outcome at six months. Neurotox 16:653-664, 1995.
44. Grandjean P, Weihe P, White RF, et al. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. Neurotox and Teratol 19(6):417-428, 1997.
45. Miller RK and Bellinger D. Metals. In Paul M. (ed.) Occupational and Environmental Reproductive Hazards: A Guide for Clinicians. Philadelphia,PA: Williams and Wilkins, 1993.
46. Lauwerys R, Roels H et al. Fertility of male workers exposed to mercury vapor or to manganese dust: a questionnaire study. Am J Ind Med 7:171-176, 1985.
47. Alcser KH, Birx KA, Fine LJ. Occupational mercury exposure and male reproductive health. Am J Ind Med 15:517-529, 1989.
48. Cordier S, Deplan F, et al. Paternal exposure to mercury and spontaneous abortions. Br J Ind Med 48:375-381, 1991.
49. Ibid.

102. summarized in: Tabacova S. Maternal exposure to environmental chemicals. Neurotoxicology 7:421-440, 1986.
103. Rom WN (ed.) Environmental and Occupational Medicine. 2nd Edition. Boston, MA: Little Brown and Company, 1992, pp.817-818.
104. Gray LE, Laskey JW. Multivariate analysis of the effects of manganese on the reproductive physiology and behavior of the male house mouse. J Tox Env Health 6:861-867, 1980.
105. Laskey JW, Rehnberg GL, Hein JF, and Carter SD. Effects of chronic manganese (Mn3O4) exposure on selected reproductive parameters in rats. J Tox Environ Health 8:677-687, 1982.
106. Lauwerys R, Roels H, et al. Fertility of male workers exposed to mercury vapor or to manganese dust: a questionnaire study. Am J Ind Med 7:171-176, 1985.
107. Gennart J-P, Buchet J-P, et al. Fertility of male workers exposed to cadmium, lead, or manganese. Am J Epi 135:1208-1219, 1992.
108. Allessio L, Apostoli P, Ferioli A, Lombardi S. Interference of manganese on neuroendocrinal system in exposed workers.

Overview

Organic solvents are widely used in our society, both in industry and in the home. There have been many human studies on the reproductive and developmental effects of solvents. Although these studies are often unable to pinpoint specific solvents or specific doses of exposure, they have found a number of worrisome health effects.

Animal studies show variable effects on reproduction and development from one specific solvent to another, but many, if not most solvents tested, have been shown to be toxic to the fetus in animals. A few solvents cause birth defects in animals and some have effects on male reproductive function. Unfortunately, animal studies almost always use a high dose of only one solvent, while humans are exposed to low or moderate levels of numerous solvents every day. Thus most reports of effects in humans involve mixed solvents and may not allow us to specifically identify one culprit, while animal studies may not accurately reflect human risks.

In humans, there is consistent evidence that solvents may raise the risk of spontaneous abortion among exposed women by two to four fold. There are two studies which

quantities of solvents. Toxic waste sites frequently contain solvents, and exposure may occur on or near the site through air, water and soil contamination.

Organic solvents have physical properties which allow them to easily enter the human body: they evaporate in air at room temperature and are therefore easily inhaled; they penetrate the skin easily; and they penetrate the placenta, sometimes accumulating at higher doses in the fetus.[2] In addition, many solvents enter breast fat and are found in breast milk, sometimes at higher concentrations than in maternal blood.[3] Solvents contaminating drinking water enter the body through skin absorption and inhalation in the shower, as well as through drinking. In fact, the total exposure from taking a 10 minute shower in contaminated water is greater than the exposure from drinking two quarts of the same water.[4] Solvents are generally short-lived in the environment and in the human body, lingering for no more than several days. On the other hand, exposures may occur daily.

Reproductive and Developmental Effects in Humans

A large number of human epidemiological studies have examined the reproductive effects of solvents. In most, people were exposed to complex mixtures of these chemicals at work or in their environment, so the studies rarely allow us to pinpoint specific solvents as responsible for the observed reproductive effects. Animal testing has looked almost exclusively at one solvent at a time, and provides information about the variability of effects within this class of chemicals. The rich scientific literature on the reproductive effects in humans from exposure to solvent mixtures is the subject of the first part of this section. The majority of the animal studies will be discussed in the Solvent Profiles at the end of this section.

Organic Solvents and Spontaneous Abortions

■ *There is consistent evidence that maternal exposure to solvents during pregnancy increases the risk of spontaneous abortion by two to four fold.*

The increased risk of spontaneous abortion in women occupationally exposed to solvents was initially identified in Finland, where there is a nationwide database on births and spontaneous abortions. Finnish workers potentially exposed to organic solvents may undergo blood and urine testing for solvents at the Finnish

Table 2
Studies on Spontaneous Abortion and Solvent Exposure in Women

Location	Study Type	Solvent	Result
Finland[16]	Case-Control	Various unspecified	2.2 times more likely*
Finland[17]	Case-Control	Various unspecified Methylene chloride (dichloromethane)	2.2 times more likely 2.3 times more likely
Finland[18]	Case-Control	Toluene Xylene Formaldehyde	4.7 times more likely 3.1 times more likely 3.5 times more likely
Finland[19]	Case-Control	PCE	3.6 times more likely
California, Utah[20]	Retro-Cohort	Glycol Ethers	1.4 times more likely NS**
Massachusetts[21]	Case-Control	Glycol Ethers	2.2 times more likely
Eastern US[22]	Retro-Cohort	Glycol Ethers	2.8 times more likely
California[23]	Case-Control	Various unspecified PCE TCE	1.1 times more likely NS 4.7 times more likely 3.1 times more likely NS
California[24]	Cross-Sectional	Various unspecified	4.4 times more likely
Singapore[25]	Retro-Cohort	Toluene	2.8 to 5.7 times more likely
Santa Clara, CA[26]	Retro-Cohort	1,1,1-TCA	2.3 times more likely
Santa Clara, CA[27]	Retro-Cohort	1,1,1-TCA	1.4 times more likely
Italy[28]	Retro-Cohort	PCE	4.0 times more likely NS

*In a case-control study this means that women who had a spontaneous abortion were 2.2 times more likely to have been exposed to organic solvents during pregnancy.
**In a cohort study this means that women who were exposed to organic solvents were 1.4 times more likely to have a spontaneous abortion.
NS = not statistically significant; all other results statistically significant at the 0.05 level
PCE=Perchlorethylene (tetrachlorotheylene), TCE= Trichloroethylene, 1,1,1-TCA= 1,1,1-Trichloroethane

Table 3:
Maternal Exposure to Solvents and Birth Defects

Location	Study Type	Solvent	Defect	Result
New Jersey[36]	Case-Control	Trihalomethanes	CNS, Cleft lip/Palate	3 times more likely*
		Trichloroethylene	CNS	2.5 3:

significant increase in heart defects in the contaminated zone.[33] Unfortunately the comparison groups were poorly chosen, weakening this study. Other studies have also shown associations between solvent exposure and cardiac malformations.[34, 35] There is no information yet about the degree of risk, the vulnerable time period, or the amount of exposure necessary to increase the risk, yet there is fairly consistent evidence implicating solvents as a potential cause of birth defects.

Other Effects - Infertility, Low Birth Weight and Preeclampsia

- *There is insufficient evidence regarding whether solvents may affect female fertility.*
- *Solvents may affect birth size and weight.*
- *Solvents may increase the risk of pre-eclampsia.*

In addition to the increase in spontaneous abortions, one

Benzene

■ **Uses**	Paint, rubber, degreaser, septic tank cleaner, ingredient in gasoline, range of chemical processes.
■ **Routes of Exposure**	Occupational: Some manufacturing jobs, gas stations, refineries, rubber manufacture, and some other industries. Environmental: Contaminated drinking water, tobacco smoke, and gasoline stations.
■ **Reproductive Effects**	Animals: Damages fetal blood producing cells, leads to bone deformities, and reduced fetal weight. Humans: Maternal and paternal exposures linked with neural tube defects, cardiac defects and low birth weight, damaged testicular function and menstrual effects.

Summary of Studies

Benzene has long been recognized as a known cause of cancer in humans. Though its effects on reproduction and development have been less well studied there is evidence in both animals and humans that benzene also interferes with these processes.

The State of California conducted an extensive review of the scientific literature before concluding that benzene is a reproductive toxicant.[102] The California review summarized studies in rabbits, rats and mice which consistently found fetal growth retardation and delayed bone information in animals exposed before birth. In some cases these effects were seen at levels which did not produce maternal toxicity. Benzene does not appear to cause malformations in prenatally exposed animals. In mice, benzene exposure resulted in fetal chromosomal abnormalities, as well as changes in the blood forming cells in the liver and spleen. Finally, benzene has adverse effects on testicular and sperm form and function in animals.

Data on human effects have been fairly limited, but suggest a hazard. An early study from Eastern Europe reported menstrual disturbances in women who work with benzene, while another reported prolonged or heavy menstrual bleeding in women exposed to a mixture of benzene, toluene and xylene.[103 104] More recently, researchers have found fetal effects after exposure through contaminated drinking water. In a study conducted in 75 New Jersey towns, mothers whose drinking water was contaminated with benzene were more likely to have a child with neural tube defects or major heart defects.[105] In Michigan, the presence of benzene and chlorinated solvents in drinking water was associated with an increased likelihood of low birth weight.[106] This association was as strong as the association between low birth weight and poor prenatal care, but did not reach statistical significance, possibly due to the small sample size. Finally, men exposed to benzene were more likely to father a child with anencephaly or spina bifida, malformations of the brain and spinal cord.[107]

Perhaps most worrisome is evidence that parental exposures may lead to childhood cancer.[108] One study found that the mother's exposure to benzene in the year prior to the child's birth significantly increased the risk of childhood cancer. Parental employment in industries where benzene is heavily used is associated with the development of a variety of childhood cancers, including leukemia, lymphoma, brain, urinary tract, and nervous system cancers.[109 110 111 112 113] Fathers' employment in gasoline exposed jobs has also been linked with increased rates of childhood cancer.[114 115 116] It is impossible to say whether benzene exposure alone is responsible for these results, as people in these occupations may be exposed to a variety of chemicals. Still, given what we know about chromosomal damage from benzene, and the fact that it is a known carcinogen in adults, this evidence is indicative of a real risk of childhood cancer from parental benzene exposure.

In summary, benzene is an important hazard to reproduction and development. Its ability to damage chromosomes is unquestioned, and the probability that this damage can lead to adverse effects in the children of exposed individuals is supported by several studies. Less dramatic, but still troublesome, are the connections between environmental benzene exposure and low birth weight. Animal studies indicating testicular toxicity and limited human studies indicating menstrual dysfunction require further investigation.

Drinking water may be contaminated with pesticides and nitrates from agricultural run-off, metals from natural or manmade sources, and solvents from leaking storage tanks or toxic waste sites. Water can also be contaminated with microbes, and to prevent infectious disease, many water supplies are chlorinated. Chlorine kills most infectious organisms and is inexpensive. Unfortunately it reacts with organic compounds in the

Summary of Studies

Many materials used in daily life emit formaldehyde for some time after manufacture, so many people are exposed to this chemical in their homes. While formaldehyde is a known irritant and a suspected carcinogen, evidence regarding its effects on reproduction and development is less clear, although human studies indicate reason for concern.

Glycol Ethers

■ **Uses**	Jet fuel de-icing, brake fluid, ink, dye, varnish, paint, printing, photography, circuit board production, cleaning solutions, some pesticides,[142] perfumes and cosmetics.[143]
■ **Routes of Exposure**	Occupational: Where used as de-icers, in cleaning solutions, or as additives in inks, dyes, or photographic chemicals. Environmental: Home use of cosmetics, perfumes, paints, inks, varnishes, or stains.
■ **Reproductive Effects**	Animals: Testicular toxicity, infertility in males, birth defects and toxicity to the fetus. Humans: Damage to male reproduction, possible risk of spontaneous abortion, and possible birth defects.

Summary of Studies

The glycol ethers are a class of related compounds, some of which, the short chain glycol ethers, are reproductive toxicants. These include ethylene glycol monomethyl ether (EGME), ethylene glycol monoethyl ether (EGEE), ethylene glycol monoethyl ether acetate (EGMEA), and ethylene glycol monoethyl ether acetate (EGEEA). Other glycol ethers may also be hazardous to reproduction based on limited animal studies.[144] Animal studies demonstrate reproductive toxicity at low doses, close to those encountered in occupational settings.[145]

In male animals glycol ethers cause microscopic testicular damage, testicular atrophy, spermatotoxicity and infertility.[146, 147, 148, 149] In female animals, these compounds cause infertility, prolonged pregnancy, and increased reabsorptions.[150] These solvents lead to decreased fetal weight, abnormalities in the bony skeleton, and birth defects in the offspring, including defects of the heart, kidneys and urinary system.[151, 152, 153] In addition, there is some evidence that exposure to some glycol ethers during development affects later neurologic function in offspring.[154] Similar effects have been found in five animal species, increasing the likelihood that humans will also be affected.

In humans, two studies show lowered sperm counts in exposed workers.[155, 156] Another smaller study found no effect on sperm count, but did find decreased testicular size in occupationally exposed men.[157] There is one case report of a woman who used a cleaning product containing EGMEA throughout two pregnancies and had two sons with hypospadias, an abnormality of the penis.[158] Women in the semiconductor industry have a significantly increased risk of spontaneous abortion and reduced fertility; these effects have been attributed to exposure to glycol ethers.[159, 160, 161, 162, 163, 164] A large multicenter study in Europe using six regional birth defects registries identified women who had a child, a stillbirth, or an aborted fetus with a birth defect and matched these women with controls who had healthy babies. All women were contacted and questioned about their occupation and experts ranked the probability of occupational exposure to glycol ethers. Women who had a child with a birth defect were 44% more likely to be rated occupationally exposed to glycol ethers. The risks increased to 94% for central nervous system defects, and over two-fold for cleft lip and for multiple anomalies. Most of the sources of bias in this study would tend toward underestimating actual risk. In this case, exposures were not confined to the four short-chain glycol ethers, but encompassed the entire class of these compounds.[165]

The short chain glycol ethers may lead to reduced fertility, spontaneous abortion, a variety of birth defects, and behavioral changes in the offspring. The National Institute of Occupational Safety and Health and the State of California have designated the four short-chain glycol ethers as known reproductive and developmental toxicants.

Methylene Chloride (Dichloromethane)

■ **Uses**	Paint and varnish remover, degreaser, aerosol propellant, decaffeination of coffee, food processing, fumigant for grains and fruits, urethane foam production, pharmaceutical manufacture, and acetate film production.
■ **Routes of Exposure**	Occupational: Various manufacturing jobs, some food processing jobs, furniture refinishing. Environmental: Home use of paint and varnish removers, and some aerosol products.
■ **Reproductive Effects**	Due to metabolism to carbon monoxide. Humans: Malformations of the limbs and face, psychomotor disturbances, subnormal mental development, and central nervous system damage.

Summary of Studies

In the human body, methylene chloride (also called dichloromethane) is quickly metabolized into carbon monoxide. The amount of carbon monoxide found in the body is directly related to the amount of methylene chloride absorbed. Exposure to methylene chloride thus may result in health problems due to the toxic effects of carbon monoxide.[168] Health effects are due to an inability to provide sufficient oxygen to body tissues, a condition known as hypoxia.[169]

Fetal animals are less able to increase blood flow to compensate for low blood oxygen levels, and are more likely to suffer damage from hypoxia than is the mother.[170, 171] Relatively low maternal exposures to carbon monoxide result in decreased fetal weight gain and neurobehavioral problems in rodents.[172, 173, 174] Higher exposures result in lower fetal survival.[175] Mice chronically exposed to moderate levels of carbon monoxide had increased incidence and severity of cleft lip and palate in their offspring.[176] Monkeys exposed to carbon monoxide at levels well tolerated by the mothers, had moderate to severe fetal hypoxia. While the least hypoxic fetuses survived without significant injury, the severely hypoxic fetuses suffered brain damage and early death.[177, 178] One important study looked at the combined effect of protein deficiency and carbon monoxide exposure in mice. While protein deficiency did not influence the effect of carbon monoxide on the mother, it did worsen the hypoxic effect on the fetus suggesting greater susceptability.[179]

Few animal studies have looked at the effects methylene chloride itself. These studies did not find any evidence of birth defects or fetal toxicity, though one did find reduced fetal body weight in rats exposed to methylene chloride at levels which affected the mother's liver.[180, 181, 182] Little is known about the effects of methylene chloride itself in humans. Among 34 men exposed to methylene chloride, eight were infertile.[183] Four of these men submitted semen samples, and all had abnormal sperm movement, shape, and density. Female pharmaceutical workers exposed to methylene chloride had a slight increase in spontaneous abortions, though other job factors may have contributed.[184]

More is known about the impact of hypoxia on the human fetus. A review of case reports of pregnant women exposed to carbon monoxide found that fetuses either died or developed significant problems when their mothers experienced unconsciousness or coma as a result of the exposure.[185, 186] Outcomes included malformations of the limbs and face, psychomotor disturbances, subnormal mental development, and central nervous system damage.

Methylene chloride exposure should be considered a potential threat to the health of the fetus. While the chemical itself is not known to have any direct effects on the fetus, its metabolism to carbon monoxide can result in low oxygen levels, potentially leading to deformities, functional problems, and death. Since the fetus is even more susceptible to hypoxia than the mother, any exposure to methylene chloride which causes symptoms in the mother may threaten the fetus.

Summary of Studies

NMP is a popular new solvent marketed as a safer alternative to chlorinated solvents. Little is known about the reproductive and developmental effects of NMP in humans. Animal studies, however, have shown toxic and even deadly effects on fetuses at doses at or below those causing maternal toxicity.

Mice fed or injected with NMP at a range of doses suffered increased rates of fetal resorption.[188, 189] Surviving offspring had lower birthweights, decreased size, an increase in cleft palate, and delayed bone formation, yet the mothers did not exhibit any toxic effects. Other researchers exposed rats to NMP orally, dermally, and through inhalation. Each route of application led to significantly increased fetal resorption, increased stillbirths, and in some cases delayed bone formation in surviving offspring.[190, 191, 192, 193] These studies generally showed no, or mild, evidence of maternal toxicity at these doses, as shown by reduced weight gain during gestation in one study, and dry skin at the application site in the dermal study.[194] A multi-generational rat reproduction study found fetal death and reduced body weight at a dose which did not affect the mother.[195] Fetal death and some malformations were also found in rabbits, although some maternal toxicity occured.[196, 197]

Researchers have also looked at postnatal physical and behavioral development in rats exposed to NMP in utero. The mothers inhaled NMP at a dose which did not cause significant fetal loss. The exposed pups had lower body weight throughout the preweaning period, and had delayed physical development. Neurobehavioral studies revealed abnormalities in dealing with difficult tasks.[198]

Information on human reproductive and developmental impacts of NMP is extremely limited. One case report suggests a connection between NMP exposure and stillbirth. A young laboratory technician was regularly exposed to NMP at work through her 20th week of pregnancy. She subsequently developed intrauterine growth retardation, and ultimately delivered a stillborn fetus with no evidence of malformations.[199]

In summary, NMP has consistent fetotoxic effects on animals at, or slightly below, levels which cause mild toxicity in adult animals. The results are stillbirth, low birthweight, some skeletal malformations, and perhaps neurologic impairment. The mechanism for these effects is unclear, but the finding across species, with different routes of exposure, and in a dose-dependent

Summary of Studies

Perchlorethylene (also called tetrachloroethylene) is widely used and relatively well studied in humans. According to one study, men who work in dry cleaning shops had more sperm abnormalities than men working in laundries.[204] The findings are hard to interpret because both the exposed and unexposed group had high percentages of men with low sperm counts and it is not clear if the abnormalities have any significance for reproductive function.

A partner study looked at fertility in male dry cleaners and their wives, compared with laundry workers. The dry

Summary of Studies

Summary of Studies

Styrene has been studied extensively in animals and humans. Two animal studies suggest an effect on hor-

Toluene

■ **Uses**	Glues, coatings, inks, paint, cleaning agent, gasoline additive; used in manufacturing, cleaning, chemical production, coke ovens, and dye making.
■ **Routes of Exposure**	Occupational: Widespread in painting, assembly work, cleaning, general industry, chemical plants. Environmental: Consumer products such as stain removers, nail polish, paint thinners, dyes, inks, adhesives, and some cosmetics. Lower level exposure from automobile exhaust, cigarette smoke, gasoline, and sometimes in drinking water.
■ **Reproductive Effects**	Increases risk of spontaneous abortion by two to five fold; causes birth defects of the head, face, urinary tract, and limbs; may disrupt hormones, particularly in men.

Summary of Studies

Animal studies show that toluene has a fetotoxic effect in rats and mice, including a reduction in fetal weight, delayed development of the skeleton, spontaneous abortion and fetal resorption.[250, 251] In addition, some, but not all, studies have found evidence of learning impairment and behavioral changes in rodents exposed during the period of brain development.[252, 253, 254, 255] Effects on the fetus occur at doses below those causing toxicity to the mother. Extrapolation from the animal studies show that human occupational exposure levels are near levels shown to have adverse effects on fetal development in rats and mice.[256]

Several studies of spontaneous abortion in solvent-exposed women have particularly implicated toluene, with risks up to nine-fold higher than among unexposed women.[257] Women exposed to toluene alone experienced five times more spontaneous abortions than unexposed women.[258] Wives of men exposed to high/frequent quantities of toluene had a two-fold increased risk of miscarriage.[259]

A large questionnaire-based case-control study found that exposure to aromatic solvents (toluene, xylene, benzene) was significantly associated with birth defects.[260] Odds of toluene exposure, in particular, were almost four-fold higher among cases than controls. The defects included urinary and cardiac abnormalities and congenital cataract in the group reporting toluene exposure. Numerous case reports describe serious congenital defects among children of women who sniffed toluene-containing glue or paint during pregnancy. These infants suffered from intrauterine growth retardation, neurologic abnormalities, abnormalities of the head, face, and urinary tract, and malformations of the arms and legs. The resemblance to babies with Fetal Alcohol Syndrome led some investigators to propose the existence of a Fetal Solvent Syndrome.[261, 262] Solvent sniffing leads to higher exposures than occupational or home use of toluene.

Men exposed to toluene had dose-related decreases in luteinizing hormone (LH), follicle stimulating hormone (FSH), and testosterone, hormones which regulate the reproductive system.[263] A young man who died from sniffing a toluene-based paint thinner had testicular atrophy and suppression of sperm production.[264] At least one animal study found a reduction in sperm counts and reduced epididymal weight in rats exposed to high levels of toluene.[265] These reports indicate a probable effect on male.9664 -lJT* babictiveed to hand

Trichloroethylene

■ **Uses**	Vapor degreasing, textile processing, refrigerant; production of polyvinyl chloride, pharmaceuticals, insecticides; in stains, finishes, lubricants, adhesives, and rug cleaners.
■ **Routes of Exposure**	Occupational: Vapor degreasing and various production processes. Environmental: Contaminated drinking water, inhalation indoors from building materials, and consumer products.
■ **Reproductive Effects**	Animals: Cardiac abnormalities and impaired brain development. Humans: Possible association with miscarriage and cardiac abnormalities.

Summary of Studies

Trichloroethylene (TCE) is a common indoor air pollutant, widely used in building materials and consumer products.[267, 268] The most common organic contaminant in ground water, it appears in one tenth to one third of all samples tested.[269, 270]

In animals, TCE appears to target the reproductive organs, concentrating in the ovaries and spermatocytes.[271, 272] Mice exposed by inhalation had an increase in abnormally shaped sperm , suggesting genetic damage.[273] However, rats exposed orally had no changes in sperm count, shape or movement.[274] Two studies in rats showed an association between TCE inhalation and reduced fetal weight; one used extremely low levels of TCE.[275, 276] However, numerous other studies in rats found no significant increases in birth defects after maternal exposure to TCE.[277, 278, 279, 280] Similarly, research in rabbits and mice found no significant changes in measures of fetal and maternal health.[281, 182, 283]

When rats were exposed to TCE in drinking water during pregnancy at doses which did not cause maternal toxicity, the offspring had more heart deformities than expected at the higher dose. Interestingly, when maternal rats were also exposed before conception, the offspring had heart deformities even at the lower dose.[284] Investigators also found increases in heart deformities in chicks from eggs injected with TCE.[285] Finally, some evidence suggests that maternal exposure to TCE in drinking water may affect brain development and behavior in offspring. In rodents, maternal exposure leads to structural and functional changes in the brain, as well as behavioral change.[286, 287, 288, 289]

In humans, an early study found an increase in miscarriages among nurses exposed to TCE in the operating room, but concurrent exposure to other chemicals makes it impossible to specify TCE's role.[290] A comparison of women who had spontaneous abortions with those who did not found that affected women were more likely to report exposure to TCE during pregnancy.[291] This study design was prone to recall bias. A study focusing on parents exposed to TCE and other chemicals at work found no increases in malformations in their children.[292] A study of male workers exposed to TCE found levels of testosterone and sex-hormone binding globulin that were lower with increasing years of exposure, while levels of an adrenal hormone were greatly increased.[293] Male workers exposed to TCE also had sperm abnormalities.[294]

Researchers have tried to assess effects from TCE in drinking water , but results are far from clear. One Massachusetts population exposed to TCE and other solvents in drinking water had an apparent increase in eye, ear, central nervous system, chromosomal and oral cleft abnormalities.[295] However, this research has been criticized for lumping the anomalies together in ways that may not be scientifically valid. Researchers studying the occurence of certain congenital heart defects in Arizona found an association with parental exposure to TCE contaminated drinking water.[296] Maternal exposure before pregnancy and during the first trimester was associated with a threefold increase in the risk of congenital heart defects. While this study too had its limitations, the result is particularly interesting in connection with animal studies showing that TCE exposure can lead to heart abnormalities. The Massachusetts population with TCE-contaminated water also had an unusually high incidence of childhood leukemia, leading some investigators to implicate TCE.[297]

similar to those encountered in the workplace, as well as suppression of maternal sex hormones in rats. This is of considerable concern since human exposures to xylene are common. The evidence that xylene causes birth defects is based on animal studies with large doses of xylene, and on a few human reports. The fact that caudal regression was reported both in humans and in chickens is important and implies that xylene might be involved in the causation of this unusual birth defect.

References:

1. MacFarland HN. Toxicology of Solvents. Am Ind Hyg Assoc J 47:704-707, 1986.
2. Dowty BJ, Laseter JL, Storer J. The transplacental migration and accumulation in blood of volatile organic constituents. Pediat Res 10:696-701, 1976.
3. Fisher J, Mahle D, Bankston L, Greene R, Gearhart J. Lactational transfer of volatile chemicals in breast milk. Am Indust Hyg Assoc J 58:425-431, 1997.
4. Weisel CP, Jo, W-K. Ingestion, inhalation, and dermal exposures to chloroform and trichloroethene from tap water. 104:48-51, 1996.
5. Lindbohm ML, Taskinen H, et al. Spontaneous abortions among women exposed to organic solvents. Am J Ind Med 17:449-463, 1990.
6. Lindbohm ML, Taskinen H, et al. Effects of parental occupational exposure to solvents and lead on spontaneous abortion. Scand J Work Environ Health 18 Suppl 2:37-9, 1992.
7. Lindbohm ML, Taskinen H, et al. Spontaneous abortions among women exposed to organic solvents. Am J Ind Med 17:449-463, 1990.
8. Taskinen H, Kyyronen P, et al. Laboratory work and pregnancy outcome. JOM 36:311-319, 1994.
9. Agnesi R, Valentini F, Mastrangelo G. Risk of spontaneous abortion and maternal exposure to organic solvents in the shoe industry. Int Arch Occup Environ Health 69:311-316, 1997.
10. Lipscomb JA, Fenster L, et al. Pregnancy outcomes in women potentially exposed to occupational solvents and women working in the electronics industry. JOM 33:597-604: 1991.
11. Pastides H, Calabrese EJ, et al. Spontaneous abortion and general illness symptoms among semiconductor manufacturers. JOM 30:543-551, 1988.
12. Taskinen H, Kyyronen P, et al. Laboratory work and pregnancy outcome. JOM 36:311-319, 1994.
13. Schenker MB, Gold EB, Beaumont JJ, Eskenazi B, Hammond SK, Lasley BL, McCurdy SA, et al. Association of spontaneous abortion and other reproductive effects with work in the semiconductor industry. Am J Ind Med 28(6):639-659, 1995.
14. Correa A, Gray RH, Cohen R, Rothman N, Shah F, Seacat H, Corn M. Ethylene glycol ethers and risks of spontaneous abortion and subfertility. Am J Epidemiol 143(7):707-717, 1996.
15. Windham GC, Shusterman D, et al. Exposure to organic solvents and adverse pregnancy outcome. Am J Ind Med 20:241-259, 1991.
16. Lindbohm ML, Taskinen H, et al. Spontaneous abortions among women exposed to organic solvents. Am J Ind Med 17:449-463, 1990.
17. Lindbohm ML, Taskinen H, et al. Effects of parental occupational exposure to solvents and lead on spontaneous abortion. Scand J Work Environ Health 18 Suppl 2:37-9, 1992.
18. Taskinen H, Kyyronen P, et al. Laboratory work and pregnancy outcome. JOM 36:311-319, 1994.
19. Kyyronen P, Taskinen H, et al. Spontaneous abortions and congenital malformations
20. Schenker MB, Gold EB, Beaumont JJ, Eskenazi B, Hammond SK, Lasley BL, McCurdy SA, et al. Association of spontaneous abortion and other reproductive effects with work in the semiconductor industry. Am J Ind Med 28(6):639-659, 1995.
21. Pastides H, Calabrese EJ, et al. Spontaneous abortion and general illness symptoms among semiconductor manufacturers. JOM 30:543-551, 1988.
22. Correa A, Gray RH, Cohen R, Rothman N, Shah F, Seacat H, Corn M. Ethylene glycol ethers and risks of spontaneous abortion and subfertility. Am J Epidemiol 143(7):707-717, 1996.
23. Windham GC, Shusterman D, et al. Exposure to organic solvents and adverse pregnancy outcome. Am J Ind Med 20:241-259, 1991.
24. Lipscomb JA, Fenster L, et al. Pregnancy outcomes in women potentially exposed to occupational solvents and women working in the electronics industry. JOM 33:597-604, 1991.
25. Ng TP, Foo SC, Yoong T. Risk of spontaneous abortion in workers exposed to toluene. Br J Indust Med 49:804-808, 1992.
26. Deane M, Swan SH, et al. Adverse pregnancy outcomes in relation to water contamination, Santa Clara County, California, 1980-1981. Am J Epi 129:894-904, 1989.
27. Wrench M, Swan S , et al. Pregnancy outcomes in women potentially exposed to solvent-contaminated drinking water in San Jose, California. Am J Epi 131:283-300, 1990.

28. Bosco MG, Figa-Talamanca I, Salerno S. Health and reproductive status of female workers in dry cleaning shops. Int Arch Occup Env Health 59:295-301, 1986.
29. Holmberg PC, Hernberg S, et al. Oral clefts and organic solvent exposure during pregnancy. Int Arch Occup Environ Health 50:371-376, 1982.
30. Tikkanen J, Heinonen OP. Cardiovascular malformations and organic solvent exposure during pregnancy in Finland. Am J Ind Med 14:1-8, 1988.
31. Torfs CP, Katz EA, Bateson TF, Lam PK, Curry CJ. Maternal medications and environmental exposures as risk factors for gastroschisis. Teratology 54:84-92, 1996.
32. Holmberg PC. Central nervous system defects in children born to mothers exposed to organic solvents during pregnancy. The Lancet 2:177-179, 1979.
33. Goldberg SJ, Lebowitz MD, et al. An association of human congenital cardiac malformations and drinking water contaminants. Journ Am Coll Cardiol 16:155-164, 1990.
34. Sever LE. Congenital malformations related to occupational reproductive hazards. Occ Med State of the Art Reviews 9:471-494, 1994.
35. Swan SH, Shaw G, Harris JA, Nefvp86, 1986.

20:17-35, 1991.

94. Cutler JJ, Parker GS, et al. Childhood leukemia in Woburn, Massachusetts. Pub Health Reports 101:201-205, 1986.
95. Durant JL, Chen J, et al. Elevated incidence of childhood leukemia in Woburn, Massachusetts: NIEHS Superfund Basic Research Program Searches for Causes. Env Health Persp 103(Suppl 6):93-98, 1995.
96. Lagakos S, Wessen BJ, Zelen M. An analysis of contaminated well water and health effects in Woburn, Massachusetts. J Am Statistical Assn 81:583-596, 1984.
97. Beavers JD, Himmelstein JS, et al. Exposure in a household using gasoline-contaminated water. JOEM 38:35-38, 1996.
98. Ahlborg G, Hogstedt C, et al. Pregnancy outcome among working women. Scand J Work Environ Health 115:227-233, 1989.
99. Lindbohm ML, Hemminki K et al. Parental occupational exposure and spontaneous abortions in Finland. Am J Epidem 120:370-378, 1984.
100. Taskinen H. Effects of parental occupational exposure on spontaneous abortion and congenital malformations (Review). Scand J Work Environ Health 16:297-314, 1990.

B18(3):333-349, 1983.

126. Land PC, Owen EL, Linde HW. Mouse sperm morphology following exposure to anesthetics during early spermatogenesis. Anesthesiology 51:259, 1979.
127. Land PC, Owen EL, Linde HW. Morphologic changes in mouse spermatozoa after exposure to inhalation anesthetics during early spermatogenesis. Anesthesiology 54:53-56, 1981.
128. Landrigan PJ. Formaldehyde. pp. 867-871 in RomWN, ed. Environmental and Occupational Medicine. Boston, MA: Little, Brown and Co., 1992.
129. Majumder PK, Kumar VL. Inhibitory effects of formaldehyde on the reproductive system of male rats. Indian J Physiol Pharmacol 39(1):80-82, 1995.
130. Shah BM, Vachharajani KD, Chinoy MJ, Roy Chowdhury A. Formaldehyde-induced changes in testicular tissue of rats. J Reprod Biol Comp Endocrinol 7:42-52, 1987.

JOM 30:543-551, 1988.

160. Schenker MB, Gold EB, Beaumont JJ, Eskenazi B, Hammond SK, Lasley BL, McCurdy SA, et al. Association of spontaneous abortion and other reproductive effects with work in the semiconductor industry. Am J Ind Med 28(6):639-659, 1995.

192. Jakobsen BM, Hass U. Prenatal toxicity of N-methylpyrrolidone inhalation in rats: a teratogenicity study. Presentation at the 18th conference of the European Teratology Society. Teratology 42:18A-19A, 1990.
193. Lee KP, Chromey NC, Culik R, Barnes JR, Schneider PW. Toxicity of N-methyl-2-pyrrolidone (NMP): teratogenic, subchronic, and two-year inhalation studies. Fund Appl Tox 9:222-235, 1987.
194. Becci PJ, Knickerbocker MJ, Reagan EL, Parent RA, Burnette LW. Teratogenicity study of N-methylpyrrolidone after dermal application to Sprague-Dawley rats. Fund Appl Toxicol 2:73-76, 1982.
195. Exxon Biomedical Sciences Inc. Multi-generational rat reproduction study on N-methyl-2-pyrrolidone. EPA/OTS, Doc #89-900000099, 1991.
196. Letter from GAF Chem Corp to US EPA submitting preliminary results of N-methyl-2-pyrrolidone developmental toxicity study with attachments. EPA/OTS, Doc #89-910000217, 1991.
197. Letter from BASF Corp submitting results of studies of the prenatal toxicity of N-methylpyrrolidone. EPA/OTS, Doc #89-920000111,1992.
198. Hass U, Lund S, Elsner J. Effects of prenatal exposure to N-methylpyrrolidone on postnatal development and behavior in rats. Neurotox Teratol 16:241-249, 1994.
199. Solomon GM, Morse EP, Garbo MJ, Milton DK. Stillbirth after occupational exposure to N-methyl-2-pyrrolidone. J Occup Environ Med 38(7), 1996.
200. Wallace D, Groth E, et al. Upstairs, downstairs: perchlorethylene in the air in apartments above New York City dry cleaners. Consumers Union, October 1995.
201. Popp W, Muller G, et al. Concentrations of tetrachloroethene in blood and trichloroacetic acid in urine in workers and neighbors of dry-cleaning shops. Int Arch Occup Env Health 63:393-395,1992.
202. Aggazzotti G, Fantuzzi G, Predieri G, Righi E, Moscardelli S. Indoor exposure to perchlorethylene (PCE) in individuals living with dry cleaning workers. Sci Total Environ 156:133-137, 1994.
203. Aschengrau A, Ozonoff K, et al. Cancer risk and tetrachloroethylene-contaminated drinking water in Massachusetts. Arch Environ Health 48:284-292, 1993.
204. Eskenazi B, Wyrobek AJ. A study of the effect of perchlorethylene exposure on semen quality in dry cleaning workers. Am J Ind Med 20:575-591, 1991.
205. Eskenazi B, Fenster L, et al. A study of the effect of perchlorethylene exposure on the reproductive outcomes of wives of dry-cleaning workers. Am J Ind Med 20:593-600, 1991.
206. Sallmen M, Lindbohm ML, et al. Reduced fertility among women exposed to organic solvents. Am J Ind Med 27:699-713, 1995.
207. Rachootin P, Olsen J. The risk of infertility and delayed conception associated with exposures in the danish workplace. JOM 253:394-402, 1983.
208. Kyyronen P, Taskinen H, et al. Spontaneous abortions and congenital malformations among women exposed to tetrachlorethylene in dry cleaning. J Epi Commun Health 43:346-351, 1989.
209. Windham GC, Shusterman D, et al. Exposure to organic solvents and adverse pregnancy outcome. Am J Ind Med 20:241-259, 1991.
210. Bosco MG, Figa-Talamanca I, Salerno S. Health and reproductive status of female workers in dry cleaning shops. int arch occup env Health 59:295-301, 1986.
211. Olsen J, Hemminki K, Ahlborg G, et al. Low birthweight, congenital malformations, and spontaneous abortions among dry-cleaning workers in Scandinavia. Scand J Work Environ Health 16:163-168, 1990.
212. Ahlborg G. Pregnancy outcome among women working in laundries and dry-cleaning shops using tetrachlorethylene. Am J Ind Med 17:567-575, 1990.
213. Taskinen H, Anttila A, et al. Spontaneous abortions and congenital malformations among the wives of men occupationally exposed to organic solvents. Scand J Work Environ Health 15:345-352, 1989.
214. Bove FJ, Fulcomer MC, Klotz JB, Esmart J, Dufficy EM, Savrin JE. Public drinking water contamination and birth outcomes. Am J Epid 141: 850-862, 1995.
215. McDonald JC, LaVoie J, et al. Chemical exposures at work in early pregnancy and congenital defect: a case-referent study. Br J Ind Med 44:527-533, 1987.
216. Bagnell PC, Ellenberger HA. Obstructive jaundice due to a chlorinated hydrocarbon in breast milk. CMA Journal 5:1047-1048, 1977.
217. Schreiber JS. Predicted infant exposure to tetrachlorethylene in human breastmilk. Risk Analysis 13:515-524, 1993.
218. van der Gulden JW, Zielhuis GA. Reproductive hazards related to perchlorethylene: a review. Int Arch Occ Env Health 61:235-242, 1989.
219. Ibid.
220. Schreiber JS. Predicted infant exposure to tetrachlorethylene in human breastmilk. Risk Analysis 13:515-524, 1993.
221. Korshunov SF. Early and late embryotoxic effects of phenol (Experimental data). Gig Tr Sostoyanie Spetsificheskikh funkts RAB Neftekhm Khim. Promsti. 149-153, 1974. (as cited in Chemical Abstracts 87-16735).
222. Minor JL, Becker BA. A comparison of the teratogenic properties of sodium salicylate, sodium benzoate, and phenol. Toxicol Appl Pharmacol 19:373, 1971.
223. Jones-Price C, Ledoux TA, Reel FR, Fisher PW, Langhoff-Paschke L. Teratologic evaluation of phenol (CAS No. 108-95-2) in CD rats. NTIS PB83-247726. 1983.
224. Jones-Price C, Ledoux TA, Reel FR, Langhoff-Paschke L, Maur MC, Kimmel CA. Teratologic evaluation of phenol (CAS No. 108-95-2) in CD-1 mice. NTIS PB85-104451. 1983.

225. Bulsiewicz H. The influence of phenol on chromosomes of mice Mus musculus in the process of spermatogenesis. Folia Morphol (Warsz.) 36(1):13-22, 1977.
226. Kolesnikova TN. Effect of phenol on sexual cycle of animals in chronic inhalation poisoning. Gig Sanit 37(1):105-106, 1972.
227. Scow K, Goyer M, Payne E, Perwak J, Thomas R, Wallace D, Wood M. An exposure and risk assessment for phenol. Office of Water Regulations and Standards, US EPA, 1981.
228. Wysowski DK, Flynt JW, Goldfield M, Altman R, Davis AT. Epidemic neonatal hyperbilirubinemia and use of a phenolic disinfectant detergent. Pediatrics 61:165-170, 1978.
229. Doan MH, Keith L, Shennan AT. Phenol and neonatal jaundice. Pediatrics 64:324-325, 1979.
230. Science News, Sept 17, 1994: 191.
231. Izumova AS. The action of small concentrations of styrol on the sexual function of rats. Gig Sanit 37:29-30, 1972 as discussed in Brown NA. Reproductive and Developmental Toxicity of Styrene. Repro Tox 5:3-29, 1991.
232. Brown NA. Reproductive and developmental toxicity of styrene. Repro Tox 5:3-29, 1991.
233. Ragule N. The problem of the embryotropic action of styrol. Gig Sanit 85-6, 1974 as discussed in Brown NA. Reproductive and developmental toxicity of styrene. Repro Tox 5:3-29, 1991.
234. Vergieva T, Zaikov KH, Palatov S. Study of the embryotoxic action of styrene. Khig Zdraveopaz 22:39-43, 1979 as dis-

Br J Ind Med 44:527-533, 1987.
261. Hersh JH, Podruch PE, et al. Toluene embryopathy. J Pediatr 106:922-927, 1985.
262. Goodwin TM. Toluene abuse and renal tubular acidosis. Obstet Gynecol 71:715-718, 1988.
263. Svensson B-G, Nise G, Erfurth E-M, Nilsson A, Skerfving S. Hormone status in occupational toluene exposure. Am J Ind Med 22:99-107, 1992.
264. Suzuki T, Kashimura S, and Umetsu K. Thinner abuse and aspermia. Med Sci Law 23:199-202, 1983.
265. Ono A, Sekita K, Ogawa Y, Hirose A, Suzuki S, Saito K, Naito K et al. Reproductive and developmental toxicity studies of toluene. II. Effects of inhalation exposure on fertility in rats. J Environ Pathol Toxicol Oncol 15:9-20, 1996.
266. Office of Environmental Health Hazard Assessment. Safe Drinking Water and Toxic Enforcement Act of 1986 (Prop. 65): Status Report. California Environmental Protection Agency. January 1994.
267. Wallace LA, Pellizzari ED, Leaderer B et al. Emissions of volatile organic compounds from building materials and consumer products. Atmos Environ 21:385-395, 1987.
268. Wallace LA, Pellizzari ED, Hartwell TD et al. The influence of personal activities on exposure to volatile organic compounds. Environ Res 50:37-55, 1989.
269. Andelman JB. Human exposures to volatile halogenated organic chemicals in indoor and outdoor air. Environ Health Perspect 62:313-318, 1985.
270. Andelman JB. Inhalation exposure in the home to volatile organic contaminants of drinking water. Sci Total Environ 47:443-460, 1985.
271. Manson JM, Murphy M, Richdale N, Smith MK. Effect of oral exposure to trichloroethlylene on female reproductive function. Toxicology 32:229-242, 1984.
272. Land PC, Owen EL, Linde HW. Morphologic changes in mouse spermatozoa after exposure to inhalation anesthetics during early spermatogenesis. Anesthesiology 54:53-56, 1981.
273. ibid
274. Zenick H, Blacburn K, Hope E et al. Effects of trichloroethylene exposure on male reproductive function in rats. Toxicology 31:237-250, 1984.
275. Healy TEJ, PooleTR, Hopper A. Rat fetal development and maternal exposure toTrichloroethylene 100 p.p.m. Br J Anaesth 54:337-341, 1982.
276. Dorfmueller MA, Henne SP, York RG, Bornschein RL, Molina G, Manson JM. Evaluation of teratogenicity and behavioral toxicity with inhalation exposure of maternal rats to trichloroethylene. Toxicology 14:153-166, 1979.
277. Beliles RP, Brucik DJ, Mecler FJ. Teratogenic-mutagenic risk of workplace contaminants: trichloroethlyene, perchlorethylene, and carbon disulfide. U.S. Department of Health, Education and Welfare. Contract no. 210-77-0047, 1980.
278. Dorfmueller MA, Henne SP, York RG, Bornschein RL, Molina G, Manson JM. Evaluation of teratogenicity and behavioral toxicity with inhalation exposure of maternal rats to trichloroethylene. Toxicology 14:153-166, 1979.
279. Hardin BD, Bond GP, Sikov MR et al. Testing of selected workplace chemicals for teratogenic potential. Scand J Work Environ Health 7(Suppl 4):66-75, 1981.
280. Schwetz BA, Leong KJ, Gehring PJ. The effect of maternally inhaled trichloroethylene, perchloroethlylene, methly chloroform, and methylene chloride on embryonal and fetal development in mice and rats. Toxicol Appl Pharmacol 32:84-96, 1975.
281. Beliles RP, Brucik DJ, Mecler FJ. Teratogenic-mutagenic risk of workplace contaminants: trichloroethlyene, perchlorethylene, and carbon disulfide. U.S. Department of Health, Education and Welfare. Contract no. 210-77-0047, 1980.
282. Hardin BD, Bond GP, Sikov MR et al. Testing of selected workplace chemicals for teratogenic potential. Scand J Work Environ Health 7(Suppl 7):66-75, 1981.
283. Cosby NC, Dukelow WR. Toxicology of maternally ingested trichloroethylene (TCE) on embryonal and fetal development in mice and of TCE metabolites on in vitro fertilization. Fundam Appl Toxicol 19:268-274, 1992.
284. Dawson BV, Johnson PD, Goldberg SJ et al. Cardiac teratogenesis of halogenated hydrocarbon-contaminated drinking water. J Am Coll Cardiol 21:1466-1472, 1993.
285. Loeber CP, Hendrix MJC, Diez de Pinos S, Goldberg SJ. Trichloroethylene: a cardiac teratogen in developing chick embryos. Pediatr Res 24:740-744, 1988.
286. Isaacson LG, Taylor DH. Maternal exposures to 1,1,2-trichloroethylene affects myelin in the hippocampal formation of the developing rat. Brain Res 488:403-407, 1989.
287. Noland-Gerbec EA, Pfohl RJ, Taylor DH, et al. 2-Deoxyglucose uptake in the developing rat brain upon pre- and postnatal exposure to trichloroethylene. Neurotoxicology 7:157-164, 1986.
288. Taylor Dh, Lagory KE, Zaccaro DJ, et al. Effect of trichloroethylene on the exploratory and locomotor activity of rats exposed during development. Sci Total Environ 47:415-420, 1985.
289. Fredriksson A, Danielsson BRG, Eriksson P. Altered behavior in adult mice orally exposed to tri- and tetrachloroethylene as neonates. Toxicol Lett 66:13-19, 1993.
290. Corbett TH, Cornell RG, Enders JL, Leiding K. Birth defects among children of nurse anesthetists. Anesthesiology 41:341-344, 1974.
291. Windham GC, Shusterman D, Swan SH, et al. Exposure to organic solvents and adverse pregnancy outcome. Am J Ind Med 20:241-259, 1991.
292. Tola S, Vilhunen R, Jarvinen E, et al. A cohort study on workers exposed to trichloroethylene. J Occup Med 22:737-740, 1980.

293. Chia SE, Goh VHH, Ong CN. Endocrine profiles of male workers with exposure to trichloroethylene. Am J Indust Med 32:217-222, 1997.
294. Chia SE, Ong CN, Tsakok MF, Ho A. Semen parameters in workers exposed to trichloroethylene. Reprod Toxicol 10(4):295-299, 1996.
295. Lagakos SW, Wessen BJ, Zelen M. An analysis of contaminated well water and health effects in Woburn, Massachusetts. J Am Stat Assoc 81:583-596, 1986.
296. Goldberg SJ, Lebowitz MD, Graver EJ, Hicks S. An association of human congenital cardiac malformations and drinking water contaminants. J Am Coll Cardiol 16:155-164, 1990.
297. Durant JL, Chen J, et al. Elevated incidence of childhood leukemia in Woburn, Massachusetts: NIEHS Superfund Basic Research Program Searches for Causes. Env Health Persp 103(Suppl 6):93-98, 1995.
298. Mirkova E, Zaikov C, et al. Prenatal toxicity of xylene. J Hyg Epi Micro and Immun 27:337-343, 1983.
299. NIOSH. Pocket Guide to Chemical Hazards. U.S. Department of Health and Human Services. June 1990.
300. Ibid
301. Marks TA, Ledoux TA, Moore JA. Teratogenicity of a commercial xylene mixture in the mouse. J Toxicol Environ Health 9: 97-105, 1982.
302. Hudak A, Ungvary G. Embryotoxic effects of benzene and its methyl derivatives: toluene, xylene. Toxicology 11:55-63, 1978.
303. Ungvary G, Tatrai E. Studies on the embryotoxic effects of ortho- meta- and para- xylene. Toxicology 18: 61-74, 1980.
304. Ungvary G. The possible contribution of industrial chemicals (organic solvents) to the incidence of congenital defects caused by teratogenic drugs and consumer goods - an experimental study. Prog Clin Biol Res 163B:295-300, 1985.
305. Hass U, Lund SP, Simonsen L, Fries AS. Effects of prenatal exposure to xylene on postnatal development and behavior in rats. Neurotoxicol Teratol 17(3):341-349, 1995.
306. Ungvary G, Bertalan V , et al. Study on the role of maternal sex steroid production and metabolism in the embryotoxicity of para-xylene. Toxicology 19:263-268, 1981.
307. Ungvary G. Solvent effects on reproduction: experimental toxicity. Prog Clin Biol Res 220:169-177, 1986.
308. Kucera J. Exposure to fat solvents: a possible cause of sacral agenesis in man. J Pediatr 72:857-859, 1968.
309. Taskinen H, Kyyronen P, et al. Laboratory work and pregnancy outcome. JOM 36:311-319, 1994.
310. Holmberg PC. Central nervous system defects in children born to mothers exposed to organic solvents during pregnancy. The Lancet 2:177-179, 1979.

Throughout California enormous quantities of pesticides are used on food, forests, nurseries, golf courses, lawns, gardens, pets, in public spaces, and homes. Approximately 600 active ingredients are used in over 20,000 pesticide products as insecticides, herbicides, rodenticides, and fungicides; over 10,000 products are actively registered for use in California. Most formulations contain "inert" ingredients with their own toxicity and health risks. In 1995, the U.S. used approximately 1.2 billion pounds of pesticide active ingredients or about 5 pounds for each person in the country, accounting for 20% of world use. California uses 25% of all pesticides used in the U.S.[1] Repeated year after year, the environmental and health effects of this volume and mixture of chemicals are extraordinarily important.

Chemical pesticides are designed to kill insects, fungi, plants, or other unwanted organisms, usually by interfering with some essential biochemical process in the target. However, their acute and chronic toxic properties also pose risks to the health of exposed humans, pets, wildlife, and entire ecosystems. Pesticides may cause cancer, adverse reproductive, developmental, neurological, or immune system effects, or other organ damage at varying exposure levels. Each of these outcomes must be considered for each chemical.

Institutional protection from toxic effects depends largely on pesticide registration and regulation. But there are significant gaps in the registration and regulatory processes which agencies have only partially addressed. Toxicity testing for many pesticides in use for years is inadequate. One source estimates that complete toxicologic data are available for only about 100 of the approximately 600 active pesticide ingredients.[2] Reproductive and developmental toxicity data are often particularly deficient.

Active ingredients and "inerts"

A final pesticide product includes a mixture of "active" and "inert" ingredients. Active ingredients "kill, repel, attract, mitigate or control a pest, or acts as a plant growth regulator.[3]" So-called "inert" ingredients are

Northwest Coalition for Alternatives to Pesticides

Groundwater used for drinking in large areas of the U.S. is contaminated with pesticides. In California, pesticides and their breakdown products have been discovered in over 3,845 wells.[9] Spray drift or pesticide runoff from treated land enters surface water and large aquatic ecosystems. Concentrations in surface water rise dramatically with heavy pesticide use in the spring.

Exposure to Pesticides

■ *Human pesticide exposure comes from many*

pounds which result from the metabolic breakdown of about 30 different pesticides with a detection limit of 1 microgm/liter urine.[23] More than 50% of the individuals tested had at least six of the pesticide residues in their urine. Chlorpyrifos residues were detected in 82% of the study group, pentachlorophenol in 64%, lindane in 20%, and 2,4-D in 12%. A survey of the U.S. population between 1976-80 led to an estimate of 2,300,000 residents with dicamba residues in urine.[24] Such widespread exposure in the general public further justifies concern about health effects and supports arguments for more comprehensive toxicity testing.

Health Effects of Pesticide Exposure and Use

- *A wide range of health effects may result from pesticide exposure.*
- *Health effects depend on the nature of the chemical(s), the amount, timing, and duration of exposure, and the susceptibility of the individual.*
- *There are often short time-windows of vulnerability during which developing organisms are particularly sensitive to toxic exposures.*
- *Comprehensive testing requires a search for and ability to detect all types of health effects, whether immediate or delayed.*

Pesticides are intended to be toxic to living organisms. But, in addition to their effect on target pests, they may also harm non-target organisms like beneficial insects, earthworms, soil fungi and bacteria, fish, wildlife, domestic animals, and humans. Features of ecosystems such as predator-prey relationships, wildlife distribution, biodiversity, and the organic quality of soil are also altered by pesticide use.

Reproductive and Developmental Toxicity of Pesticides

Epidemiological evidence

Epidemiological studies are not used in the registration process but are useful for examining health effects of real-world exposures. Agricultural workers exposed to multiple pesticides are studied most often, but this makes it difficult to attribute adverse health effects to a specific agent. Moreover, there is no group of people that serves as a perfect comparison group since the entire world's population has some exposure to multiple pesticides.

Epidemiological studies are often limited by inaccurate or inadequate exposure assessment or inadequate data on health outcomes, potentially masking any true relationship between exposure and health effect. A large agricultural health study underway in N. Carolina and Iowa may partially address these concerns.[25] Investigators estimate that 90,000 people will be questioned about or

nancy and occupational exposure to pesticides in male fruit growers.[27] Increased time-to-pregnancy depends on a number of biological factors including frequency of intercourse, egg and sperm production, fertilization, embryo transport and implantation, and early fetal survival. Pregnancy was delayed among farm-owner couples trying to conceive when the farm owner was the only pesticide applier. This was most noticeable in the period from March to November when pesticides are applied. During that time, in the high exposure group, time-to-pregnancy more than doubled, and 28% of the pregnancies were preceded by a visit to a physician because of fertility problems compared with 8% in the low exposure group. These results indicate an adverse effect of pesticide exposure on fertility and may be related to very early spontaneous abortions.

Developmental Abnormalities— Birth Defects and Low Birth Weight

Table 3 summarizes a series of studies of the association between parental pesticide exposure and birth defects or growth retardation in their offspring. Birth defects are relatively rare events, and large numbers of people must be included in analyses if results are to achieve statistical significance. Moreover, the type of birth defect associated with an exposure before or during pregnancy may vary to some degree with each chemical, and investigators must decide whether or how to subdivide defects into categories. Their choices may influence the significance of study results. In addition, maternal interviews may provide less reliable information than birth defects registries, but registry-based data may fail to include all defects, including those discovered after the first year of life. For these reasons, one must interpret these data with care.

In one well-conducted Finnish study of women in agricultural occupations, trained industrial hygienists estimated the amount and duration of pesticide exposure. Investigators found that exposure to pesticides during the first trimester of pregnancy nearly doubled the risk of cleft lips and palates in offspring. (95% CI 1.1-3.5)[38] There was also a slightly increased risk for nervous system defects. These results are of particular significance because the Finnish birth defects registry is generally considered to be of high quality.

A study in Minnesota concluded that pesticide use may be associated with birth defects in the general population as well as agricultural workers.[39] Using statewide data from birth certificates, investigators determined that the birth defect rate was significantly increased for pesticide appliers and included circulatory, respiratory, skin, musculoskeletal, and urogenital abnormalities. Further analysis showed that the birth defect rate was highest in the western part of the state where chlorophenoxy herbicides (e.g. 2,4-D) and fungicides are most heavily used. Moreover, families from the general population living in western regions were 85% more likely to have a child with a birth defect than those from other parts of the state. And, both the general population and pesticide appliers were more likely to have a child with birth defects when the child was conceived in the spring, the time of heaviest pesticide use. This seasonal effect was not seen in other areas of the state. The use of birth certificates to identify birth defects is a weakness of this study inasmuch as abnormalities identified after birth were not included in the analysis. It is also unfortunate that the investigators did not consider neural tube defects (spina bifida) separate from other central nervous system defects since that subclass may have a unique relationship to pesticide exposure as appears to be the case for dioxin.

In Iowa, a study of municipal drinking water contaminated with commonly used herbicides suggests that the general population may be at increased risk of having children with retarded intrauterine growth. However,

Table 3 Studies of birth defects and low birth weight in offspring of women and/or men* exposed to pesticides

Exposure	Outcome	Observed effect
male pesticide applier Minnesota[40]	birth defects in offspring from state birth registry	
	all defects combined	1.4 times more likely
	circulatory/respiratory defects	1.7 times more likely
	urogenital defects	1.7 times more likely
agric. occ. as farmer's wife or gardener[41]	nervous system defects, oral clefts, musculoskeletal defects	musculoskeletal defects 5 times more likely for gardeners
agric. occ. at least 15 hr./wk beginning of preg.[42]	chromosomal, developmental, musculoskeletal defects	developmental defects 4.5 times more likely
agric. occ. - either or both parents[43]	malformations, premature birth, low birth weight	no effect
agric. occ - either or both parents[44]	limb defects	no effect
agric., fishing, forestry occupation[45]	congenital malformation	no effect
floriculture**[46]	birth defects (parent report)	1.3 times
	prematurity	1.7 times more likely
floriculture[47]	birth defects - confirmed from medical data	birth marks only 6.6 times more likely
paternal occupational pesticide exposure-estimated[48]	birth defect-anencephaly (child born with no brain)	no effect
agric. work >30 hr/wk until 13th week preg and pesticide exposure estim. by interview later[49]	congenital defects from med record	no effect
exposure to pesticides 1st trimester as estimated by occupational hygienist on basis of interview[50]	oral clefts, nervous system defects, skeletal defects	oral clefts 1.9 times more likely
	any defect -	no effect
	nervous system defect	no effect
agric. exposure to pesticides estimated from occup and industry - reported on birth certificates of child[51]	limb defects	no effect
exposure to pesticides based on interview of mother (China)[52]	birth defects - hospital diagnosis	no effect
	intrauterine growth retardation	2.9 times more likely
municipal water contaminated with herbicides - Iowa[53]	intrauterine growth retardation	1.8 times more likely
agric. occ. at beginning of preg.[54]	low birth weight	no effect
agric. occ. at any time in preg[55]	low birth weight	no effect

* maternal unless otherwise noted

** In this study information about congenital defects was collected through maternal interview and proved to be unreliable when checked against hospital records. When repeated with confirmed defects from medical record, the association with floriculture work was positive only for birth marks.

The mechanisms by which parental pesticide exposure may increase the risk of certain childhood cancers are not well understood. Possible explanations include mutations in the chromosomes of the eggs or sperm, alterations in the immune system, hormone function, or DNA repair mechanisms of offspring, or mutations in the chromosomes of the developing fetus resulting from pesticides crossing the placenta.

Spermatotoxicity

Dibromochloropropane (DBCP), a nematocide, and ethylene dibromide (EDB), a fumigant, are toxic to sperm and have been banned from agricultural use in the US, though EDB is used for other industrial purposes.[62] [63] DBCP and EDB still contaminate groundwater in some areas where they were previously used; DBCP is found in 70% of California's 3,845 pesticide contaminated wells.[64]

2, 4-D is a heavily used chlorophenoxy herbicide which is toxic to sperm. Sperm counts declined and abnormal sperm increased with exposure to 2,4-D in a study of farm sprayers.[65] Many weed killers for large scale, commercial use as well as over-the-counter preparations for home and garden use contain 2,4-D. The urine of an estimated 12% of the US population contains 2,4-D residues though the health significance of this finding is uncertain.[66]

Chromosome abnormalities

many currently registered pesticides is necessary. Re-registration of chemicals “grandfathered” when current regulations became effective is underway but will not be complete for at least another ten years.

The EPA uses animal test data, usually from at least two mammalian species, to determine what they believe to be safe exposure levels for humans and the need for use restrictions and warning labels. An oral reference dose (RfD), intended to be without adverse health effects in exposed individuals, is calculated from the data. When animal tests are conducted, different health effects occur at different levels or timing of exposure. For example, for one pesticide, birth defects in test animals might occur only with a higher exposure at a different time of pregnancy than spontaneous abortions or kidney toxicity. For another chemical, it might be the opposite. Regulators typically attempt to discover the highest oral dose that fails to elicit any adverse health effect in the test animals. This is called the “no observable adverse effect level” (NOAEL). They then usually divide that dose by an uncertainty factor of 100, to account for species differences and particularly susceptible individuals, calling that the RfD - the oral reference dose for humans which, they believe, is “safe” - i.e. protective of health. Therefore, the lower the RfD, the more toxic the chemical in animal studies - for some adverse health effect. Occasionally the uncertainty factor used is only 10 when there is considerable information about species differences in metabolism of the chemical and therefore, less uncertainty. Inhalation or skin absorption is not considered in establishing an RfD. Regulators sometimes attempt to acknowledge important gaps in the data used to calculate the RfD by indicating a level of confidence in the final figure. For some pesticides in current use the level of confidence is low.

Profiles

The following profiles summarize the reproductive and developmental toxicity of some members of various pesticideacw46(They then[(Pri04heate)]TJT* membe9v)83c6u8epso1tittast two

death. Chronic exposure to lower doses of some organophosphates may also lead to delayed damage to nerves supplying the arms and legs resulting in weakness and clumsiness. This delayed neurological syndrome is less likely to occur after exposure to carbamates than organophosphates.

Since many different organophosphates and carbamates are used for various purposes, total human exposure to these pesticides is likely to be higher than predicted from consideration of individual agents and single routes of exposure. Indeed, it has been known for some time that some farmworker exposures, many of which are in violation of state and federal regulations, are sufficient to depress cholinesterase enzyme levels.[70] Low enzyme levels may be associated with acute symptoms such as diarrhea, nausea, vomiting, and increased sweating, many of which go unreported or are unrecognized by health professionals as associated with pesticide exposure. Indoor use of organophosphates according to label directions may also lead to excessive exposures.[71 72]

Recent research provides insight into mechanisms by which fetal exposures to organophosphates and carbamates may have long-term effects on brain function in offspring. Acetylcholine is but one of a number of different neurotransmitters which transmit nerve impulses across the connections (synapses) in established networks of nerve cells (neurons). However, during fetal and early infant brain development, these same neurotransmitters serve the very important additional function of signaling information for further development of the brain.[73] Abnormal fluctuations in neurotransmitter levels during fetal and early infant life interfere with differentiation of maturing brain cells and the development of normal nerve connections in the brain. The number and distribution of neuroreceptors, to which the transmitters attach, may also be altered. These are distinctly unlike effects in adults, whose brain connections are already established, where neurotransmitters temporarily alter nerve impulse traffic rather than the connections themselves.

One study found that a single low dose of an organophosphate given to mice on day 3 or 10 after birth caused increased activity in the animals when measured at 4 months of age and permanent alterations in neurotransmitter receptor levels in the adult brains.[74] In another study, when chlorpyrifos was administered to neonatal rats at doses which showed no other evidence of toxicity, both protein and DNA synthesis were inhibited in the brain.[75] It is important to note that the first 10 days of postnatal life in the rodent represent stages of brain development corresponding to the last trimester of gestation in humans.[76] The large majority of animal tests have not examined subtle long-term effects of these chemicals on the developing fetal brain after exposure during pregnancy.

Conclusion

Organophosphates and carbamates are used for many purposes and are found in a number of home-use and commercial pesticide formulations. In animals, they have a variety of effects on reproduction and development, many of which occur only at levels of exposure which are higher than humans are likely to experience with ordinary use. However, effects on neurological development and behavior at low doses in animals are of more concern at current human exposure levels. Animal studies demonstrate the need to re-design required toxicological testing of these pesticides to include better examination of neurodevelopmental effects as called for in the Food Quality Protection Act (see Table 4).

Table 4
Reproductive/developmental toxicity of selected organophosphates and carbamates

acephate	Reduces luteinizing hormone in mice.[77]	RfD 0.0003 mg/kg/day, high confidence
chlorpyrifos	In a study of pregnant rats exposed to chlorpyrifos at 6.25, 12.5, or 25 mg/kg/day by injection on days 12-19 of a 21-day pregnancy, the investigators concluded that marked neurochemical and behavioral alterations occur in the developing organism following repeat exposures in the absence of overt maternal toxicity; Cholinesterase levels were reduced in maternal and fetal brains in all exposure groups.Young chlorpyrifos-exposed rats had markedly reduced performance in these two tests, yet the animals had no visible evidence of birth defects and would have been judged "normal" by more traditional developmental measures.[78] Rats injected with 0.03-0.3 mg chlorpyrifos/kg/day during days 7-21 of pregnancy; found a dose-related increase in fetal deaths, birth defects and neurobehavioral toxicity in the highest dose group.[79] Exposed mouse/rat associated with increased birth defects at 25 mg/kg/day[80 81.] Associated with behavioral neurotoxicity in exposed rats. [82]	RfD 0.003 mg/kg/day - medium confidence
diazinon	Pregnant mice exposed daily (0.18, 9.0 mg/kg/day) gave birth to normal appearing offspring.[83] However, even mice in the low exposure group showed impaired endurance and coordination on neuromuscular testing as they developed into adults. Increased abnormal/dead sperm, decrease testosterone level, increase fetal deaths (resorptions), and increases of some birth defects (rat/mouse). [84 85] Associated with neurotoxicity in mouse offspring[86]	No RfD. Currently under review by U.S. EPA.
dimethoate	Decreased testes weight,sperm motility, abnormal sperm, decreased testosterone at 6-12 mg/kg/day for 65 days (rat)[87]	RfD 0.0002 mg/kg/day -medium confidence
malathion	Decreased progesterone at 1mg/kg (cows). [88] Smaller litters, reduced pup wgt (rats).[89]	RfD 0.02 mg/kg/day -medium confidence, under review by EPA
naled	Decreased survival, litter size, and pup body wgt at 18 mg/kg/day (rat). [90]	RfD 0.002 mg/kg/day – medium confidence
parathion	Rats exposed on days 6-20 of pregnancy at doses that showed no evidence of maternal toxicity gave birth to offspring with altered postnatal development of neurons and subtle alterations in behavior.[91] Birth defects (chick) [92]	Under review by U.S. EPA
tetrachlorvinphos	Ovarian follicles show poor growth, premature ovulation, and egg development (mouse) [93]	RfD 0.03 mg/kg/day – medium to high confidence
Carbamates carbaryl (Sevin)	Birth defects at 5-6 mg/kg/day (dog) (not in monkeys at 20 mg/kg/day) Decreased reproductive capacity, trend to sterility with inc. dose (rat/gerbil)[94]	RfD 0.1 mg/kg/day - medium to low confidence

Insecticide	Uses
dicofol	mite control on fruit, vegetable, ornamental, field crops
endosulfan	

Organochlorine insecticides are used in agriculture, forestry, and building and human protection from insects. DDT was among the first of this class of chemicals to be developed in the 1930's. Organochlorines were of particular concern to Rachel Carson who, in *Silent Spring*, protested the growing use of pesticides with harmful effects that cascaded through the food-chain, decimating populations of birds and threatening other species. Years later, heightened scientific, governmental, and public awareness of the environmental persistence of these chemicals with harmful effects on non-target organisms finally prevailed over entrenched industry resistance and led to withdrawal or bans on DDT, heptachlor, kepone, aldrin, dieldrin, and chlordane in the U.S. Many organochlorines, including DDT, continue to be widely used in other parts of the world, particularly in developing countries, for controlling insects responsible for crop loss and human disease (e.g., malaria). Short-term benefits and established manufacturing and trade practices perpetuate their use. In the U.S. endosulfan, methoxychlor, and dicofol are still used on the food supply.

Organochlorines exert their toxic effects by altering the normal transport of sodium and calcium across nerve cell membranes. The net result is an increase in the sensitivity of the neurons to small stimuli that would not otherwise elicit a response in an unexposed nerve. Symptoms of acute toxicity from organochlorine poisoning include numbness and tingling, increased susceptibility to stimuli, dizziness, tremors, and convulsions. Studies in wildlife and laboratory animals at lower exposure levels have demonstrated hormonal and other biochemical (enzyme-inducing) properties of organochlorines. Developing animals are more sensitive than adults, and there is considerable concern about their long-term effects on human and wildlife fertility, reproduction, and development (see Chapter 7).

Organochlorines in use in the U.S. are not as persistent in the environment as older members of the class. Half-lives are generally measured in weeks (Table 1), but lindane may be detected in pine needles and forest soil years after spraying, with a typical half-life of 400 days.[95] All have some tendency to bioaccumulate so that small exposures result in much larger tissue levels over time. Bioaccumulation sometimes occurs in the middle of the food chain where, for example, methoxychlor bioconcentrates in mussels and snails, about 10,000 fold higher than concentrations in the surrounding water or soil, but not in fish which tend to metabolize the chemical rapidly.[96] Lindane, however, does tend to bioaccumulate in mammals at the top of the food chain.

Conclusion

Organochlorine pesticides may adversely affect reproduction and development through hormone-disrupting mechanisms. A number of organochlorines have been banned from use in the U.S. because of marked environmental persistence and bioaccumulation, but several remain in use. One (lindane) is registered for direct application to humans for treating lice. Laboratory and field studies show that exposures higher than those humans are likely to encounter may severely disrupt normal reproduction and development. Less clear are the health and environmental effects at current levels of exposure. These effects are more difficult to study because they are often subtle and may be delayed, perhaps even for years or decades, in humans. This complex set of issues is discussed more fully in Chapter 7.

lindane	Acts as an anti-estrogen, weakly interfering with the effect of naturally-occuring estrogen on target tissues. Chronic treatment of newborn rats delays vaginal opening, disrupts normal ovarian cycles, and reduces pituitary and uterine weight.[97 98] In adult male rats, lindane retards testicular growth when given at 4 and 8 mg/kg over 45 days.[99] Pregnant mice exposed to 10 mg lindane/kg/day throughout gestation produced offspring with overactive immune responsiveness.[100] Exposures in mice of 40mg/kg/day produced absence of implantation of fertilized eggs in uterus (exposure in early pregnancy); loss of fetuses (exposure mid-pregnancy); and newborn deaths (late pregnancy).[101] Persists for years after spraying.[102 103]	• RfD 0.0003 mg/kg/day
endosulfan	Estrogenic as shown in a large number of animal and other laboratory studies (see Chapter 7). Causes shrinkage of testicles in rats; inhibits hormone synthesis (FSH, LH) at 7.5 mg/kg/day.[104] Associated with reduced sperm count in mice. [105]	RfD 0.006 mg/kg/day
methoxychlor	Investigators injected fertile gull eggs with either DDT or methoxychlor at levels found in eggs from Southern California in the early 1970's and demonstrated feminization of developing male embryos.[106 107] Mice treated with methoxychlor or estrogen on days 6-15 of their 21-day pregnancy have female offspring whose vaginal opening (evidence of sexual maturation) occurs earlier than normal. When these same mice are mated again, female offspring from their second pregancies show a similar result, indicating a89 -1.02ychlorw Ifsct ogmpregvios egtment	RfD 0.005 mg/kg/day (low confidence due to lack of definitive chronic toxicity studies)

Insecticide	Uses
cypermethrin	cotton, fruit, vegetables, cockroaches, household insects, termites
fenvalerate	broad spectrum for wide range of crops, Christmas trees, pine seed orchards, tree nurseries,
resmethrin	household, greenhouse, indoor landscaping, mushroom houses, stored prod-

Pyrethrins are naturally occurring pesticide compounds derived from chrysanthemums. Pyrethroids, which are chemically similar to pyrethrins, are synthesized for commercial use. These chemicals are widely used throughout the world and are found in many home-use pesticide products. Pyrethrins and pyrethroids have a rapid knock-down or paralytic action on insects. The nervous system is their primary target of action. They cause repetitive nerve discharge and interfere with enzyme levels in the brain. The offspring of rats treated with fenvalerate or cypermethrin during days 5-21 of pregnancy have abnormal brain levels of chemical neurotransmitters.[116] Similarly, neonatal mice given 0.21-0.42 mg bioallethrin/kg for 7 days soon after birth have permanent changes in brain neuroreceptor levels and increases in their level of activity.[117] But, when bioallethrin was administered at 100 times the doses that caused these effects, the animals showed decreased activity and no change in receptor levels. This observation raises important questions about the appropriateness of using high-dose testing when studying the toxicity of pesticides for registration purposes.

Some pyrethroids also compete with testosterone for attachment to the androgen receptor and displace testosterone from its carrier protein in the circulation (see Chapter 7). [118]

Conclusions

Pyrethrins and synthetic pyrethroids are used as insecticides on food crops, in the home, and to treat human lice. Their toxicity is primarily to the nervous system. Some have adverse effects on reproduction at levels of exposure which are higher than likely for humans. However, there has been no systematic study of their effect on brain devel-

opment in the fetal or neonatal period. The neurological response of fetal and newborn animals to low doses of at least one pyrethroid differs from that in adult animals, causing changes in brain function and neuroreceptor levels which are permanent. The adverse effects are not apparent with high-dose testing. This observation alerts us to the possibility of a false sense of safety if low-dose studies are not conducted at critical times of brain development with these and other chemical compounds. These findings require further investigation to determine if other members of the class have similar action and if they are of concern at likely levels of human or wildlife exposure.

Fungicides

Fungicide	Uses
dithiocarbamates	fruits, vines, hops, vegetables, potatoes,ornamentals, tobacco
benomyl, thiabendazole	fruits, nuts, vegetables, grains, nuts, turf,bulbs, flowers, ornamentals
vinclozolin, iprodione	grapes, strawberries, soft fruit, vegetables, ornamentals, hops, rape oilseed

Reproductive Health Effects
Birth defects, testicular toxicity, and endocrine disruption in animal tests

Fungicides are used to prevent fungal growth on agricultural and various consumer products. Foliar fungicides, applied to the leaves of plants, and soil fungicides, applied as liquids, powders, or granules, may be taken up into the plant. Dressing fungicides are applied after harvest to protect crops like cereals and grains. There is a long history of controversy surrounding the use of fungicides since most cause gene mutations in bacterial test systems, raising concerns about carcinogenicity.[124] Some, like hexachlorobenzene, are no longer used in the U.S. because of their toxicity and long life in the environment (though over 11,000 pounds of this chemical were transferred from California facilities in 1995 – see Part IV). Others are being re-investigated because of new findings of toxicity in animal studies. Chemicals used as fungicides fall into several classes.

Dithiocarbamate fungicides

The dithiocarbamates include maneb, mancozeb, thiram, ziram, and zineb which are used on a variety of fruit and vegetable crops. These fungicides are broken down into ethylene thiourea (ETU) in the environment and in mammals. ETU causes mutations, birth defects, and cancer and may be formed by cooking food contaminated with the fungicides.[125 126]

Since 1977 the various uses and tolerances for dithiocarbamates have been the subject of ongoing negotiation between the EPA and manufacturers, based largely on concerns about carcinogenicity and thyroid effects. These effects, rather than reproductive effects, drive current tolerances of dithiocarbamates on food. Dithiocarbamates are currently registered for use on cucumbers, melons, pumpkins, squash, lettuce, greens, onions, potatoes, corn, tomatoes, grains, and apples. However, tolerances and crop-uses have frequently changed and may be further influenced by provisions of the 1996 Food Quality Protection Act which requires the EPA to issue health-based tolerances after considering total exposure to agents with similar mechanisms of action.

Benzimidazole fungicides

The benzimidazole fungicides, benomyl and thiabendazole, are used before and after harvest on different foods, bulbs, flowers, ornamentals, and shade trees. Thiabendazole is used not only as a fungicide but also to treat certain parasitic diseases in humans. Benomyl is metabolized into carbendazim which is thought to be the chemical responsible for most of the toxicity of the parent compound.[127] Benomyl causes birth defects and testicular toxicity in rats and rabbits and is on the California Proposition 65 list of reproductive hazards.

Dicarboximide fungicides

Vinclozolin and iprodione are fungicides used to control a variety of crop diseases. Vinclozolin is an androgen antagonist and causes demasculinization of male offspring when given to pregnant rats. Abnormalities include reduced anogenital distance (more female-like), nipple development, and abnormal penises with hypospadias (see Chapter 7).[128]

Herbicides	Uses
triazines - (atrazine, cyanazine, simazine, prometryn)	grasses and weeds in field crops, orchards, vineyards, turf
phenoxy-herbicides - (2,4-D, diclofop,dicamba)	wild oats and annual grassy weeds
Substituted urea herbicides - (linuron, diuron)	annual and perennial broadleaf and grassy weeds, field and vegetable crops, sugar
bromoxynil	post-emergent control of annual broadleaved weeds in corn, cereal, sorghum, onions, flax, mint, and turf.
metribuzin	control of grasses and broadleaved weeds in field and vegetable crops, turf.

Herbicides are used to control unwanted vegetation and often replace mechanical cultivation. They are used on large tracts of forest, farm land, tree farms, along roadsides, beneath power lines, and on lawns and gardens. Their chemical structures and toxicities vary considerably. Herbicides are often referred to as pre- or post-emergent herbicides, depending on whether they are applied to soil to prevent weed growth or directly to weeds after sprouting. Monoculture favors the emergence of particular weeds which are often treated with herbicides. These chemicals may contaminate the soil for long periods, migrate to groundwater, or run off in surface water to lakes, streams, and rivers. Aquifers beneath much of the nation's farmland contain a mixture of agricultural chemicals, including herbicides.

Triazines

Atrazine, simazine, cyanazine, and prometryn are triazine herbicides. These chemicals may act independently or synergistically. One study examining a pesticide/fertilizer mixture of alachlor, atrazine, cyanazine, metolachlor, metribuzin, and ammonium nitrate at 1, 10, and 100 times the concentrations found in groundwater in Iowa was evaluated for reproductive toxicity in mice. There was no significant reproductive toxicity at any of the concentrations tested. [147] However, in a study of chromosome damage, N-nitrosoatrazine, readily formed from atrazine and nitrate in an acid environment such as that found in the stomach, was thousands of times more damaging to chromosomes than atrazine and nitrates separately or combined.[148]

Atrazine is associated with estrogen disrupting effects and may increase risk of breast cancer, though this is subject to debate (see Chapter 7).
Cyanazine causes fetal toxicity in rabbits at 2 mg/kg/day and birth defects in rats at 25 mg/kg/day. It is on the California Proposition 65 list of reproductive hazards and manufacturers say that they intend to eliminate its production by 2002.

The toxicity database for prometryn is old, and very few reproductive and developmental data are available. One study reports fetal toxicity in rabbits at 72 mg/kg/day. The EPA has low confidence in the established tolerance and lists prometryn as a developmental toxicant subject to TRI reporting.[149]

Chlorinated phenoxy herbicides

Chloro-phenoxy herbicides have been in extensive and uninterrupted use since 1947.[159] 2,4-dichlorophenoxy-

mental toxicant subject to TRI reporting.[173]
Molinate is a selective herbicide that causes fetal losses, decreased fetal and pup weight, and skeletal abnormalities when given to pregnant rats at 35 mg/kg/day. When given to male rats at 4 mg/kg/day, molinate causes abnormal sperm, decreases fertility, and causes fetal death. The EPA lists molinate as a reproductive and developmental toxicant subject to TRI reporting.[174]

EPTC (S-ethyl dipropylthiocarbamate) is a cholinesterase inhibitor used as a selective herbicide. When given to pregnant rats at 40 mg/kg/day it causes reduced pup weight.[175] However, at even lower doses, pregnant females develop degenerative heart disease. Exposure during days 6-15 of pregnancy at 300 mg/kg/day caused fetotoxicity in rats.[176]

Acaricides (mite and tick poisons)

Acaricide	Uses
propargite	Used to kill mites on a variety of crops, particularly cotton, grapes and almonds.

Reproductive Health Effects
Fetal losses, decreased fetal weight, delayed/impaired bone development.

According to the California Department of Pesticide Regulation, propargite ranks highest among pesticides as a candidate for evaluation as a toxic air contaminant in that state.[177] In a developmental toxicity study in which rabbits were given propargite (6 mg/kg/day) during days 6-18 of pregnancy, there was an increase in fetal losses, decreased fetal weight, and delayed bone development in offspring.[178] Bone developmental abnormalities also occur in rats at similar doses. The US EPA lists propargite as a reproductive toxicant subject to TRI reporting.

Fumigants

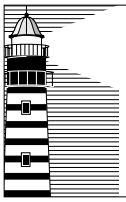
Fumigant	Uses
ethylene dibromide	No current pesticidal uses in U.S. Was used as a soil and spot fumigant of grain milling machinery, to control infestations of fruits, vegetables, and grain. Is used as a lead scavenger in gasoline and as a solvent
ethylene oxide	Manufacture of antifreeze, polyester fiber and film, many organic chemicals; fumigant and fungicidal sterilizing agent for medical supplies, drugs, books, leather, clothing, and furniture.[179]
methyl bromide	Pesticidal gas that is injected into soil before planting strawberries, grapes, almonds, tomatoes, tobacco, and other crops; as a grain fumigant; to treat imported produce and timber at ports of entry; in industrial chemical manufacturing; as a solvent for extraction of oils from nuts, seeds, and wool.
metam sodium	Used to sterilize soil before planting, by killing seeds, weeds, bacteria, nematodes, fungi, and insects.

Reproductive Health Effects
Spermatotoxicity, chromosome damage, mutations.

Ethylene dibromide

Ethylene dibromide (EDB) was widely used for many purposes until it was discovered to cause chromosome damage, cancer, and toxicity to sperm. An EPA review of its use as a pesticide began in 1977. Most agricultural uses were cancelled in 1983 when it was discovered in stored grain and wells. Traces of EDB have been found in some Connecticut soils up to 20 years after their last known fumigation.[180] Improper disposal of EDB and fuels led to contamination of groundwater as well. As of 1995, EDB remained a contaminant of over 10 drinking water wells in California.[181]

Both human and animal studies demonstrate EDB's toxicity to sperm. Bulls exposed to dietary EDB develop



Spotlight on

Methyl Bromide: A Case Study in Pesticide Politics

submitted by Pesticide Action Network

Spotlight on Methyl Bromide).

The toxicity of methyl bromide is well known. Large short-term exposures may rapidly cause death. Smaller non-lethal exposures over a period of weeks damage the brain, kidneys, nasal cavity, heart, adrenal glands, liver, testes, esophagus, and stomach.

The reproductive and developmental toxicity of methyl bromide has been studied in mice and rats. Some animals exposed to 160-400 parts per million (ppm) methyl bromide, by inhalation, 6 hr/day, 5 days/wk, for up to 6 weeks show degeneration of the seminiferous tubules in the testes.[191] [192] Mice are more susceptible than rats to this effect. Another study in rats exposed to 200 ppm methyl bromide 6 hrs/day for just 5 days failed to show any toxicity to testes or sperm but did show a marked decrease in testosterone levels.[193] However, plasma testosterone levels returned to normal with cessation of exposure. In a two-generation reproduction study of rats whose diets contained up to 500 ppm methyl bromide, no adverse

References:

1. US EPA. Pesticides industry sales and usage: 1994 and 1995. Market estimates. 1997.
2. Weisenburger DD. Human health effects of agrichemical use. Human Pathology 24(6): 571-6, 1993.
3. US EPA. Prevention, Pesticides, and Toxic Substances, Selected Terms and Acronyms, Office of Pesticide Programs, June, 1994.
4. Northwest Coalition for Alternatives to Pesticides, Worst Kept Secrets: Toxic Inert Ingredients in Pesticides, January, 1998.
5. Whitmore RW, Immerman FW, Camann DE, et al. Non-occupational exposures to pesticides for residents of two U.S. cities. Arch Environ Contam Toxicol 26:1-13, 1993.
6. Government and Regulatory Affairs Committee, SETAC: The Society of Environ Toxicol and Chem News 11(4):9, 1991.
7. Bright DA. et al. Effects of local and distant contaminant sources: polychlorinated biphenyls and other organochlorines in bottom-dwelling animals from an Arctic estuary. Sci Total Environ 15:265-283, 1995.
8. Dewailly E, et al. Inuit Exposure to organochlorines through the aquatic food chain in Arctic Quebec. EHP 101(7): 618-20, 1993.
9. Pease WS et al, Pesticide Contamination of Groundwater in California, Center for Occupational and Environmental Health, School of Public Health, University of Bety of Bety SETn

35. Goulet L, Theriault G. Stillbirth and chemical exposure of pregnant workers. Scand J Work Environ Health 17:25-31, 1991.
36. Ibid
37. Rupa DS, Reddy PP, Reddi OS. Reproductive performance in population exposed to pesticides in cotton fields in India. Environ Research 55:123-128, 1991.
38. Nurminen T, Rantala K, Kurppa K, Holmberg PC. Agricultural work during pregnancy and selected structural malformations in Finland. Epidemiology. 6:23-30, 1995.
39. Garry VF, Schreinemachers D, Harkins ME, et al. Pesticide appliers, biocides, and birth defects in rural Minnesota. Environ Health Perspect 104:394-399, 1996.
40. Ibid.
41. Hemminki K, Mutanen P, Luoma K, Saloniemi I. Congenital malformations by the parental occupation in Finland. Int Arch Occup Environ Health 46:93-98, 1980.
42. McDonald AD, McDonald JC, Armstrong B, et al. Congenital defects and work in pregnancy. Br J Ind Med. 45:581-588, 1988.
43. Schwartz DA, Newsum LA, Markowitz, et al. Parental occupation and birth outcome in an agricultural community. Scand J Work Environ Health 12:51-54, 1986.
44. Schwartz DA, LoGerfo JP. Congenital limb reduction defects in the agricultural setting. Am J Public Health. 78:654-658, 1988.
45. Bjerkedal T. Use of medical registration of birth in the study of occupational hazards to human reproduction. In: Hemminki K, Sorsa M, Vainio H., eds. Occupational Hazards and Reproduction. Hemisphere Pub Co. Washington DC, 1985.
46. Restrepo M, Munoz N, Day NE, et al. Prevalence of adverse reproductive outcomes in a population occupationally exposed to pesticides in Columbia. Scand J Work Environ Health. 16:232-238, 1990.
47. Restrepo M, Munoz N, Day N, et al. Birth defects among children born to a population occupationally exposed to pesticides in Columbia. Scand J Work Environ Health. 16:239-246, 1990.
48. Brender JD, Suarez L. Paternal occupation and anencephaly. Am J Epidem 131:517-521, 1990.
49. McDonald JC, Lavoie J, Cote R, et al. Chemical exposures at work in early pregnancy and congenital defect: a case-referent study. Br J Ind Med. 44:527-533, 1987.
50. Nurminen T, Rantala K, Kurppa K, Holmberg PC. Agricultural work during pregnancy and selected structural malformations in Finland. Epidmiology 6:23-30, 1995
51. Lin S, Marshall EG, Davidson GK. Potential parental exposure to pesticides and limb reduction defects. Scand J Work Environ Health 20:166-179, 1994.
52. Zhang J, Cai W, Lee DJ. Occupational hazards and pregnancy outcomes. Am J Ind Med 21:397-408, 1992.
53. Munger R, Isacson P, Hu S, et al. Intrauterine growth retardation in Iowa communities with herbicide-contaminated drinking water supplies. Environ Health Perspect 105:308-314, 1997.
54. Heidam LZ. Spontaneous abortions among dental assistants, factory workers, painters, and gardening workers: a follow-up study. J Epidemiol Community Health 38:149-155, 1984.
55. Fenster L, Coye MJ. Birthweight of infants born to Hispanic women employed in agriculture. Arch Environ Health 45:46-52, 1990.
56. Robison LL, Buckley JD, Bunin G. Assessment of environmental and genetic factors in the etiology of childhood cancers: the childrens cancer group epidemiology program. Environ Health Perspect 103(Suppl 6):111-116, 1995.
57. Daniels JL, Olshan AF, Savitz DA. Pesticides and childhood cancers. Environ Health Perspect 105:1068-1077, 1997.
58. Davis JR, Brownson RC, Garcia RB, et al. Family pesticide use and childhood brain cancer. Arch Environ Contam Toxicol 24:87-92, 1993.
59. Daniels JL, Olshan AF, Savitz DA. Pesticides and childhood cancers. Environ Health Perspect 105:1068-1077, 1997.
60. Laval G, Tuyns AJ. Environmental factors in childhood leukaemia. Br J Ind Med 45:843-844, 1988.
61. Robison LL, Buckley JD, Bunin G. Assessment of environmental and genetic factors in the etiology of childhood cancers: The childrens cancer group epidemiology program. Environ Health Perspect 103(Suppl 6):111-116, 1995.
62. Potashnik G, Porath A. Dibromochloropropane (DBB20:1edsiTJT*NnvirondmtJTd1

67. Dulout FN, Pastori MC, Olivero OA, et al. Sister-chromatid exchanges and chromosomal aberrations in a population exposed to pesticides. Mutat Res 143:237-244, 1985.
68. Nehez M, Berencsi G, Paldy A, et al. Data on the chromosome examinations of workers exposed to pesticides. Reg Toxicol Pharmacol 1:116-122, 1981.
69. Mohammad O, Walid AA, Ghada K. Chromosomal aberrations in human lymphocytes from two groups of workers occupationally exposed to pesticides in Syria. Environ Res 70:24-29, 1995.

Biomedica Biochimica Acta 49(10):1059-1065, 1990.
100. Das SN, Paul BN, Saxena AK, Ray PK. Effect of in utero exposure to hexachlorohexane on the developing immune system of mice. Immunopharmacol Immunotoxicol 12(2):293-310, 1990.
101. Sircar S, Lahiri P. Lindane causes reproductive failure and fetotoxicity in mice. Toxicology. 59(2):171-7, 1989.

131. Beck SL. Prenatal and postnatal assessment of maneb-exposed CD-1 mice. Reprod Toxicol 4(4):283-290, 1990.
132. Maci R, Arias E. Teratogenic effects of the fungicide maneb on chick embryos. Ecotoxicol Environ Saf 13(2):169-173, 1987.
133. Munk R, Schulz V. Study of possible teratogenic effects of the fungicide maneb on chick embryos. Ecotoxicol Environ Saf 17(2):112-118, 1989.
134. Kaloyanova F, Ivanova, Chemishanska L. Dose effect relationship for some specific effects of dithiocarbamates. J Hyg Epidem Microbiol Immunol 33(1):11-17, 1989.
135. Kackar R, Srivastava MK, Raizada RB. Induction of gonadal toxicity to male rats after chronic exposure to mancozeb. Ind Health 35(1):104-111, 1997.
136. Petrova-Vergieva T, Ivanova-Tchemishanska L. Assessment of the teratogenic activity of dithiocarbamate fungicides. Food Cosmet Toxicol 11:239-244, 1973.
137. Stoker, et al. The dithiocarbamate fungicide thiram disrupts the hormonal control of ovulation in the female rat. Repro Toxicol 7 (3):211-218, 1993.
138. Mishra VK, Srivastava MK. Testicular toxicity s. F

167. 59 FR 1788-1844
168. US EPA. IRIS database, 1988.
169. US EPA. IRIS database, 1984.
170. 59 FR 1788-1844.
171. 59 FR 1788-1844.
172. US EPA. IRIS database, 1987.
173. 59 FR 1788-1844.
174. 59 FR 1788-1844.
175. US EPA. IRIS database. 1987.
176. 59 FR 1788-1844.
177. Pesticides for evaluation as candidate toxic air contaminants. Calif. EPA, Dept. Pest. Reg. EH 96-01.
178. US EPA. IRIS database. 1986.
179. Landrigan PJ. Ethylene oxide In: Environmental and Occupational Medicine 2nd ed. Ed: Rom WN, Little, Brown, and Co. Boston, 1992.
180. Frink CR, Bugbee GJ. Ethylene dibromide: Persistence in soil and uptake by plants. Soil Sci 148(4):303-307, 1989.

Introduction

Hormones are chemical messengers which circulate in the blood and regulate many critical biological functions through intricate signalling mechanisms. Endocrine disruptors (EDs) are chemicals which mimic or block hormones or otherwise interfere with normal hormone activity, often at extremely small doses. Evidence for endocrine disruption comes from studies of animals, humans, and laboratory cell cultures. Chemicals released into the environment have dramatically affected the reproductive success and development of wildlife by interfering with sex hormones. Humans are intentionally or inadvertently exposed to EDs in the workplace, home, community, or during medical care. Evidence of adverse health effects is overwhelming in some instances but only suggestive in others.

As early as the 1930's, studies in laboratory animals demonstrated estrogenic properties of a number of synthetic chemicals. Among them was bisphenol-A, now widely used in some plastics, resins, and dental sealants.[1] Estrogen-like effects of the pesticide DDT in chickens were reported in 1950. In 1962, Rachel Carson's *Silent Spring* alerted the world to the harmful effects of pesticides on wildlife reproduction. She described a cascade of events resulting in contamination of the food chain, decline of egg survival, and destruction of populations of songbirds. Though unrecognized as hormone disruption at the tixT*[(decline of egg sur)-mcrine dis

on the surface of cells. In turn, a series of “second messengers” initiates a cascade of events inside the cell resulting in biochemical changes.

excess of females. These effects correlate with levels of persistent organic pollutants like PCBs and DDT.

- Seal populations have markedly declined in portions of the Wadden Sea in the Netherlands. Fish from the area of decline are contaminated with higher levels of PCBs and pesticides than those from other areas. Captive seals fed fish exclusively from the contaminated area were less able to reproduce and had altered estrogen levels compared to seals fed less contaminated fish over a two year period.[33]

Human Health Effects

There is little disagreement that wildlife have suffered reproductive and developmental abnormalities as a result of exposure to EDs and that DES is an important example of an endocrine-disrupting chemical in humans. There is less agreement about the importance to human health of exposure to "weaker" EDs. But the increasing incidence of endocrine-related cancers, genital abnormalities, and an apparent decline in sperm counts remain unexplained. Scientists from various disciplines are increasingly concerned that environmental contaminants are the common thread tying these conditions together.

Carcinogenesis

There is no doubt that diethylstilbestrol (DES) caused the unusual vaginal cancers seen in some young women exposed to the drug as fetuses. Some investigators suspect that exposures to endocrine disruptors may also contribute to development of breast, prostate, and testicular cancer. In each case there are fragments of inconclusive evidence to support that concern. The mechanisms by which toxicants may foster development of each of these malignancies and the nature and timing of the relevant exposure(s) are matters of considerable debate and research interest.

One hypothesis consistent with current understanding of carcinogenesis proposes that hormone levels, environmental exposures at critical times in development, and genetic susceptibility interact to create the conditions for development of cancer. According to this view, pre-cancerous changes resulting from early molecular, biochemical, and cellular events are transformed, sometimes much later, into recognizable cancer.

Breast cancer

- *Breast cancer incidence has steadily increased in the U.S. over several decades.*
- *Hormonal effects on the breast are complex and vary with age, stage of cellular dif ent decline ,e-cane ea B0edh6erous cin*

widely throughout the environment.[41 42 43 44 45] Breast milk contains a large number of these contaminants in complex mixtures, and some studies show that breast feeding reduces the risk of developing breast cancer in pre-menopausal women.[46 47] If true, risk reduction could be attributable to low estrogen levels during the period of breast feeding, decreasing chemical concentrations by elimination in breast milk, or some combination of the two.

A variety of environmental contaminants mimic, block, or influence the levels of estrogen, progesterone, and prolactin. Whether breast cancer in adults may be initiated by fetal, pre-pubertal, or young-adult exposures to hormonally-active chemicals is unknown, but if so, the timing of the exposure may be as critical the nature of the chemical. Since studies of women with breast cancer are rarely able to determine the timing and magnitude of exposures with accuracy, this important question remains difficult to answer. Studies which do not account for important time windows of vulnerability may miss causative relationships if they exist.

Several studies suggest that breast cancer is related to tissue levels of organochlorines, like DDT, its by-product DDE, or PCBs.[48 49 50 51] In one study, for example, investigators compared PCB and DDE levels in stored blood specimens from 58 women who developed breast cancer with levels in the blood of women who were healthy. They found that DDE levels were significantly higher in women with breast cancer.[52] Another study of 150 women with breast cancer, with equal representation of Caucasians, African-Americans, and Asians, showed no correlation with DDE or PCB blood levels. However, when just the Caucasian and African-American women were included in the analysis, there was an increased risk of breast cancer for the women with the highest levels of DDE.[53] Several other studies show no relationship between organochlorine levels in breast tissue or blood and the risk of breast cancer, and the matter is unresolved.[54 55 56] If there is some relationship between chemical exposures and breast cancer risk, it may be that DDE or PCBs are only relatively crude markers for a more relevant exposure, explaining the discrepancy in study results.

There is also considerable debate about the role of estrogen metabolites as a contributor to breast cancer risk.[57] Various chemicals, including atrazine and organochlorine pesticides, alter the metabolism of estrogen, in some cases leading to an excess of a metabolite which itself is strongly estrogenic. It has been suggested that this is a mechanism by which environmental contaminants may increase breast cancer risk.[58]

Prostate cancer

- *Some animal studies show that fetal exposures to estrogenic substances can cause changes in the prostate which resemble early cancer.*
- *Fetal exposures to estrogenic substances increase the response of the prostate to further estrogenic exposures after birth.*
- *In humans, cancerous changes in the prostate sometimes occur quite early in life.*

Prostate cancer is a common disease of older men, found frequently in those who die of other causes. Deaths from prostate cancer have increased over the past 30 years, suggesting that the disease has increased in frequency more than can be explained by better screening alone. In the U.S. prostate cancer is responsible for about 40,000 deaths per year.[59] It is rare in men of Asian origin and more common in African-American males than Causcasians. Its natural history is variable as some tumors behave much more aggressively than others despite treatment.

Factors which contribute to the development of prostate cancer are not well understood. However, there are suggestions that both naturally-occurring estrogens and syn-

mice exposed to diethylstilbestrol (DES) only as fetuses also exhibit greater expression of an estrogen-responsive gene (c-fos - one of the genes responsible for cell division) when given estrogen after birth. There are estrogen-responsive sites in the prostate in dogs, monkeys, and humans as well.[62 63 64] These observations demonstrate the capacity of estrogenic agents to increase cell proliferation and cell division in the prostate, at least in part by altering gene expression.

A parallel line of reasoning holds that the products of estrogen metabolism may be significant. Estrogen can be transformed into metabolites (e.g., 4-hydroxy estradiol) which are sources of free radicals, short-lived fragments which can damage cellular proteins and DNA.[65 66] Although there are mechanisms which are constantly at work identifying and repairing damaged DNA, these mechanisms may fail, due to either rapid cell division, which overloads repair capacity, or reduced repair capacity associated with aging, and cancer may result. Moreover, as men age, estrogen levels rise relative to testosterone. This may be an important factor in the later development of prostate cancer.

In an autopsy study of 152 men 10 to 49 years old who died from other, unrelated causes, detailed microscopic examination of their prostate glands revealed cancer in 34% of all men between ages 40-49, and 27% of men ages 30-39. In addition, cellular changes which may progress to cancer or, alternatively, be evidence of susceptibility to cancer, were found in 9% of the 20-29 age group. [67] These results show that unrecognized prostate cancer sometimes begins quite early in life and is a disease of men much younger than previously thought.

Whether or not fetal exposure to estrogenic substances contributes to susceptibility to later development of prostate cancer in humans remains unclear, but the question obviously deserves further study. DES sons have not shown an increased incidence of prostate cancer, but sufficient time may not have passed for an increased risk to become apparent.

Testicular cancer

■ *There has been a dramatic increase in testicular cancer in the past 50 years.*

■ *At least some cancerous changes in the testes probably take place in fetal or infant life.*

The incidence of testicular cancer has increased dramatically, and it is now 2-4 times more common in industrialized countries than it was 50 years ago. However, it is still a relatively uncommon disease with an overall annual incidence of about 4-5/100,000 men. Testicular cancer is sometimes seen in infants but has its peak incidence in young adult men.[68] It is the most common malignancy in men 25-35 years old. Caucasians are more than twice as likely to develop this cancer as African-Americans. It may arise from any of the cell types found in the testes, but more than 90% of cases develop from germ cells (immature cells which will develop into sperm).

In a recent review of the possible role of sex hormones in the development of testicular cancer, the authors conclude that, despite uncertain mechanisms, cancerous changes of immature sperm cells "take place most probably during early fetal life. In this phase of development, germ cells are vulnerable to the influence of maternal hormones and other environmental agents."[69] The young cancer cells probably remain dormant until puberty when hormonal changes stimulate their growth.

Several pieces of epidemiological and laboratory evidence support this conclusion. Testicular cancer is more likely in those with undescended testicles, a condition seen in DES sons. The fetuses and newborn of mice exposed to estrogen during pregnancy have testicular and germ cell abnormalities which look like precursors to cancer.[70] First-born male children have an increased risk of testicular cancer, and first pregnancies are associated with higher estrogen levels than subsequent pregnancies.[71 72]

Evidence linking in utero DES exposure with later development of testicular cancer is conflicting, with some studies finding a strong association and others finding none.[73 74] This discrepancy may result from two study-related problems. It is often difficult to determine the timing and amount of DES used in pregnancies years before a study, making exposure assessment problematic. Moreover, though the incidence of testicular cancer has increased, it is still relatively uncommon, and studies of small numbers of DES-exposed males are statistically unlikely to identify cases of cancer. It is, therefore, not likely to be productive to concentrate exclusively on

DES sons to help resolve the role of estrogenic substances in the development of testicular cancer. Considering the laboratory and epidemiologic evidence

have been a significant increase in hypospadias and undescended testicles over the past few decades.[86] There was a doubling of the frequency of undescended testicles in England and Wales from 1962–1981. Similar increases were reported in Sweden and Hungary.[87] A doubling of hypospadias rates in the U.S. in the 1970's and 1980's has also been reported.[88] There is now considerable concern that falling sperm counts, increasing incidence of undescended testicles, hypospadias, and testicular cancer may be linked to fetal exposures to endocrine-disrupting chemicals.

2. Though food contains naturally-occurring phytoestrogens, some actually behave as estrogen antagonists in the presence of naturally-occurring estrogens. It is too sim-

Endocrine Disruptor Profiles

Many different and widely distributed man-made chemicals have the potential to interfere with normal hormone action. There are also naturally-occurring sub-

with higher dioxin levels had higher amounts of LH and FSH and lower amounts of testosterone than a control group from the neighborhood.[127] These results must be interpreted with caution since it was a cross-sectional study (all measurements of dioxin, testosterone, and gonadotropins were done on the same blood specimen making it difficult to determine cause-and-effect relationships), but the results are consistent with the effects of dioxin in animal studies.

In 1977, an industrial accident in Seveso, Italy released large amounts of dioxin, contaminating the environment and exposing local residents. From 1977–1984 there was

which may have resulted from fetal malformations. Children of exposed women have not been examined for subtle structural or functional developmental deficits.[130]

In Times Beach, Missouri, an area contaminated with dioxin-containing oil which had been spread on roads for dust control, there was no apparent increased risk of fetal deaths or low birth weight babies.[131] There was, however, a 2–3 fold increase in risk of nervous system defects and undescended testicles though this was not statistically significant. However, because of the small sample size, only a 6-fold increase in risk would have been found significant.

Investigators in the Netherlands found that higher dioxin levels in breast milk correlate with lower thyroid hormone levels in breast-feeding infants.[132] This finding is particularly important since the correlation appears at current levels of ambient dioxin exposure. Moreover, in pre-term and low birth weight babies, decreased thyroid hormone in the first weeks of life is associated with increased risk of neurological disorders, including the need for special education by age nine.[133] Though the thyroid hormone levels in the Netherlands study were still in the normal range, it is possible that the observed changes might influence infant development. This will require further research.

Summary

Animal studies confirm a wide range of reproductive and developmental effects of dioxin in different species, some occurring at low exposure levels. They include changes in hormone levels, fertility, sexual behavior, litter size, ability to carry pregnancies to term, birth defects, learning disabilities, and endometriosis.

Human studies designed to examine reproductive or developmental effects of dioxin exposure have produced mixed results. The studies are often limited by inadequate exposure information, incomplete recognition of health outcomes, or low power to detect rare events, and they virtually always lack an unexposed control population. Nevertheless, there is now sufficient evidence to conclude that dioxin is probably a cause of some birth defects. There is also evidence that testosterone levels are depressed in occupationally-exposed workers, and thyroid hormone is depressed in infants exposed at ambient levels through breast feeding.

Polychlorinated biphenyls (PCBs)

- *Are members of a family of chemicals with a wide range of toxicity and various mechanisms of action.*
- *Are no longer manufactured in the U.S. but continue to present a problem because of environmental persistence and continued leaking from discarded electrical equipment in which they were widely used.*
- *Have adverse reproductive effects in many different species.*
- *May mimic estrogens and interfere with thyroid hormone function.*
- *Are associated with decreased birth weight and delayed brain development in humans.*

The reproductive and developmental health effects of PCBs have been studied in a variety of animal species. (Table 2) Some of the reproductive effects occur after exposures that are considerably higher than any currently likely for humans in the U.S., though wildlife are at much greater risk because of their specialized diets. Of particular concern is the apparent neurotoxicity of some PCBs which cause reduced learning capacity and altered behavior after low levels of exposure during the period of brain development.

Studies of the estrogenic influence of two types of PCBs on sexual differentiation in turtles demonstrate a synergistic interaction.[139] The sex of turtles, like many other reptiles, is determined by the incubating temperature of the fertilized egg. For most turtles, low temperatures produce males, while higher temperatures produce females. PCBs with estrogenic activity, applied to turtle eggs, can cause female development in eggs incubated at male-producing temperatures. Certain PCBs synergize with minor alterations in temperature to cause more dramatic sex reversals than would be predicted by simply adding the PCB effect with the temperature change effect. The same phenomenon occurs with small amounts of PCBs in combination.

Epidemiological Studies

Since PCBs have been banned in the U.S. and many other parts of the world, there is little opportunity to study their toxic effects in the occupational setting where exposures might be expected to be high. However, a preban study of mothers potentially exposed PCBs in an electrical capacitor manufacturing plant showed a small but significant decrease in the birth weight of infants. [155]

Table 2
Reproductive and developmental toxicity of PCBs - animal studies[140]

Health effect	Species
Reduced fertility[141]	male rats exposed during lactation
Failure to conceive and abortion[142]	monkey
Reduced progesterone levels[143]	monkey
Estrogenic activity (stimulate uterine growth)[144]	rat
Prolonged estrus cycle[145]	monkey
Developmental toxicity [146 147]	
Prolonged gestation [148]	rats and mice
Low birth weight; reduced litters and infant survival[149]	monkeys and rats
Reduced litter, infant survival and delayed neuromuscular development[150]	rats (maternal dosing at 10 microgms/kg on every 2nd day from 9-19 of pregnancy)
Decreased thyroid function [151]	rat fetus
Birth defects	mouse (cleft palate - like dioxin)
Altered sexual differentiation[152]	turtle
Reduced visual discrimination, increased activity level[153]	rat
Increased locomotor activity [154]	rat, monkey, mice
Maze learning difficulties	rat, mouse, monkey

Summary

PCBs exert a range of adverse effects on reproduction and development, many of which are similar to the effects of dioxin. Two tragic accidental poisoning incidents in Japan and Taiwan demonstrated these effects in humans. Despite a 20-year ban on U.S. production, PCB exposures at current ambient environmental levels appear to impair intellectual and motor development of children in a dose-related fashion. Laboratory animal testing shows similar results. The environmental persistence of these chemicals and their tendency to bioaccumulate ensures continued exposure for years to come.

Alkylphenols

- *A family of widely used chemicals, some of which have estrogen-like activity.*
- *Cause decreased testicular size, reduced sperm counts, and feminization of males in some animal studies*

Alkylphenols are industrial chemicals used in detergents, paints, pesticides, plastics, food wraps, and many other consumer products. Hundreds of thousands of tons of these chemicals are produced annually. Much ends up in sewage treatment works and is discharged to surface water.[163] Some alkylphenols accumulate in sewage sludge, and others remain dissolved in water. Alkylphenols may contaminate drinking water and food, leaching from plastics used in food processing and wrapping.[164 165] Some members of this family of chemicals are estrogenic.

In a laboratory in which estrogen-sensitive breast tumor cells were being studied, investigators discovered that the plastic (polystyrene) used to make test tubes for routine laboratory procedures contained a substance which behaved like estrogen. They identified it as nonylphenol, a member of this family of chemicals, extracted it from the test tube plastic, and demonstrated its ability to cause estrogen-sensitive cells to grow both in tissue culture and in the uterus of rats.[166] Other laboratory studies confirm estrogen-like properties of these chemicals in fish, bird, and mammalian cells.[167] Male fish raised in water near sewage outflows contaminated with alkylphenols are feminized. They produce a female protein, vitellogenin, found in egg yolks. Some have genitals of both sexes.[168] Whether these abnormalities in river fish should be attributed entirely to alkylphenols or to estrogen from human urine is still a matter of debate.

Alkylphenols which are estrogenic bind to the estrogen receptor. Most are individually much less potent than estrogen when studied in tissue culture or adult animals. However, in one of the first studies which looked at the effects of these chemicals on animal development, investigators gave pregnant rats water containing octylphenol or octylphenol polyethoxylate (both chemicals are members of the family of alkylphenols).[169] The doses used were estimated at less than 10 times human exposure levels, though human exposure to alkylphenols has never been accurately measured. Male rats exposed as fetuses and during the first three weeks of life through

nursing showed decreased testis size and decreased daily sperm production. The exposure period was chosen to cover the entire period of Sertoli cell development in the rat. In all species that have been studied, the number of Sertoli cells determines the size of the testes and sperm production. In men, the corresponding period of Sertoli cell development extends for several years, providing a longer window of opportunity for toxicity. However, there is no information about the effect of alkylphenols on humans.

Bisphenol-A

- *A major component of some plastics and epoxy resins used in dental sealants, plastic containers, and in the lining of food cans.*
- *Leaches out of sealants, plastics, and resins contaminating food and saliva.*
- *Causes estrogenic effects in animal studies at exposures near current human exposure levels.*

Bisphenol-A is a major component of polycarbonate plastics, epoxy resins, and flame retardants. More than a billion pounds of bisphenol-A are produced annually in the U.S., Europe, Japan, Taiwan, and Korea.[170] Polycarbonate plastics are among the largest and fastest growing markets. Epoxy resins made of bisphenol-A are used to coat the inside of food cans, as dental sealants, and in a variety of dental, surgical, and prosthetic devices. Laboratory tests show that bisphenol-A and related chemicals leach out of polycarbonate containers or the epoxy coating on the inside of food cans, particularly when the container is heated in order to sterilize the contents.[171 172] These same chemicals are found in saliva after dental treatment with sealants, sometimes years after the original application.[173]

Bisphenol-A and related chemicals attach to the estrogen receptor, exerting estrogenic effects.[174 175] Bisphenol-A stimulates the growth of estrogen-responsive breast cancer cells in cell cultures, though it binds about 2000 times less avidly to the estrogen receptor than estrogen in those studies.[176 177] When fed to rats, bisphenol-A also behaves like estrogen and stimulates prolactin production, but here it is only 100–500 times less active than estrogen - ten times more potent than would have been predicted from the cell culture studies.[178]

Previous research has shown that, in mice, small increases in serum estrogen levels during fetal life are related to enlargement of the prostate in adulthood. In one study, investigators fed pregnant mice 2 and 20 microgms bisphenol-A/kg on days 11–17 of gestation. Each of these doses resulted in significantly enlarged prostates in adult male offspring.[179] The larger of the two exposures also resulted in reduced sperm production.[180] These doses are near estimated ranges of human exposure to this chemical, raising questions about the relative safety of the various uses of bisphenol-A.[181 182]

There have been no studies of the effects in humans exposed to bisphenol-A.

Phthalates

- *The most abundant man-made chemicals in the environment.*
- *Contaminate the food supply.*
- *Have reproductive and developmental toxicity at a variety of exposure levels.*
- *Are testicular and ovarian toxicants and have estrogen-like activity in some cases.*
- *Interact synergistically with other common environmental contaminants.*

Phthalates are the most abundant man-made chemicals in the environment.[183] They are used in construction, automotive, medical, and household products, clothing, toys, and packaging. Over one billion pounds of 25 different phthalate compounds are produced annually in the U.S.[184] In their largest single application they serve as plasticizers for polyvinylchloride (PVC). Like alkylphenols, phthalates may leach out of packaging material into food. Plastic wraps, beverage containers, and the lining of metal cans all may contain phthalates. Phthalates volatilize during their manufacture and use and disperse atmospherically. The two most abundant, di-2-ethyl-hexyl phthalate (DEHP) and di-n-butylphthalate (DBP), are found in soil, in fresh, estuarine, and ocean water, and in a variety of fish, including deep sea jellyfish from more than 3000 feet below the surface of the Atlantic.[185] All phthalates tend to accumulate in fat tissue though some may be broken down and excreted from the body. They are easily absorbed through the skin.

The acute toxicity of phthalates is low. Large amounts must be given in animal studies to cause death or immediate health effects. However, some are reproductive and

DDT (and metabolite DDE)	Androgen antagonist.[202]
Methoxychlor	Estrogenic; metabolite interferes with sexual development, reproduction,

Spotlight on

LAKE APOPKA / DICOFOL

Foods containing hormonally-active chemicals

Pyrethroids

Pyrethrin and synthetic pyrethroid insecticides are heavily used in home and agricultural pesticide products. Studies of fluvalinate, permethrin, and resmethrin in cell cultures demonstrate that they bind to the androgen receptor in competition with testosterone, exerting an anti-androgen effect.[200]

Triazine herbicides

The triazine herbicides, atrazine, simazine, and cyanazine, are heavily used in large agricultural areas in the U.S. and are under special review by the EPA. Atrazine contaminates large groundwater aquifers used as drinking water in many parts of the country. Among toxicologic concerns are the endocrine disrupting properties of this widespread contaminant. Depending on the experimental design of animal studies, atrazine may have either estrogenic or anti-estrogenic effects.[201] It also causes breast cancer in one strain of rats.

Dithiocarbamate fungicides

Dithiocarbamates are heavily used fungicides with several produced in excess of a million pounds per yea. These chemicals are metabolized in animals and the environment into ethylene thiourea (ETU), a known mutagen, teratogen, and carcinogen as well as an anti-thyroid compound.

References:

0. Dodds EC, Lawson W. Molecular structure in relation to oestrogenic activity. Compounds without a phenanthrene nucleus. Proc Royal Soc London, Series B. 125:222-232, 1938.
1. Burlington H, Lindeman VF. Effect of DDT on testes and secondary sex characters of white leghorn cockerels. Proc Soc Exp Biol Med. 74:48-51, 1950.
2. Colborn T, Dumanoski D, Myers JP. Our Stolen Future. Dutton, Penguin Books, New York. 1996.
3. Estrogens in the Environment, ed. McLachlan JA. Elsevier Science Publishing Co. Inc., 1985
4. Guillette LJ, Gross TS, et al. Developmental abnormalities of the gonad and abnormal sex hormone concentrations in juvenile alligators from contaminated and control lakes in Florida. Environ Health Perspect 102(8) 680-688, 1994.
5. Tillet DE, Ankley GT, Giesy JP, et al. Polychlorinated biphenyl residues and egg mortality in double-breasted cormorants from the Great Lakes. Environ Toxicol Chem 11:1281-1288, 1992.
6. McMaster ME, Portt CB, Munkittrick KR, Dixon DG. Milt characteristics, reproductive performance, and larval survival and development of white sucker exposed to bleached kraft mill effluent. Ecotoxicol Environ Safety 23:103-117, 1992.
7. Rajpert-De-Meyts E., Skakkeboek NE. The possible role of sex hormones in the development of testicular cancer. Eur Urol 23:54-61, 1993.
8. Chilvers C, et al. Apparent doubling of frequency of undescended testicles in England and Wales 1962-81. Lancet i: 330-332, 1984
9. Jackson MB et al. Cryptorchidism: an apparent substantial increase since 1960. BMJ, 293: 1401-1404, 1986.
10. Paulozzi LJ, Erickson JD, Jackson RJ. Hypospadias trends in two US surveillance systems. Pediatrics 100:831-834, 1997.
11. Kimmel CA. Approaches to evaluating reproductive hazards and risks. Environ Health Perspect 101(Suppl 2):137-143, 1993.
12. US General Accounting Office: Reproductive and Developmental Toxicants. Washington DC, US General Accounting Office, October 1991.
13. Giusti RM, Iwamoto K, Hatch EE. Diethylstilbesterol revisited: A review of the long-term health effects. Ann Int Med 122(10):778-788, 1995.
14. Herbst AL, Scully RE. Adenocarcinoma of the vagina in adolescence: a report of 7 cases including 6 clear-cell carcinomas (somonter20nteescend3045e.7d-14

body burdens in experimentally exposed animals. Environ Health Perspect 103(9):820-831, 1995.
27. Gibbs PE, Pascoe PL, Burt GR. Sex change in the female dog-whelk, Nucella lapillus, induced by tributyl tin from antifouling paints. J Mar Bio Assoc UK 68:715-731, 1988.
28. Purdom CE, Hardiman PA, Bye VJ, et. al. Estrogenic effects of effluents from sewage treatment works. Chem Ecol 8:275-285, 1994.
29. Jobling S, Sheahan D, Osborne JA, et al. Inhibition of testicular growth in rainbow trout (Oncorhyncus mykiss) exposed to alkylphenolic chemicals. Environ Toxicol and Chem 15:194-202, 1996.
30. Guillette LJ, Crain DA, Rooney A, Pickford DB. Organization versus activation: The role of endocrine-disrupting contaminants (EDCs) during embryonic development in wildlife. Environ Health Perspect 103(Suppl 7):157-164, 1995.
31. Fry M. Reproductive effects in birds exposed to pesticides and industrial chemicals. Environ Health Perspect 103(Suppl 7):165-171, 1995.
32. Fox GA. Epidemiological and pathobiological evidence of contaminant-induced alterations in sexual development in free-living wildlife. In: Chemically-Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection. ed. Colborn T, Clement C. Princeton Scientific Publishing Co. Princeton NJ, 1992.
33. Reijnders PJH. Reproductive failure in common seals feeding on fish from polluted coastal waters. Nature 324:456-457, 1986.
34. Parker SL, Tong T, Bolden S, et al. Cancer statistics. CA Cancer J Clin 65:5-27, 1996.
35. Telang NT, Katdare M, Bradlow HL, Osborne MP. Estradiol metabolism: an endocrine biomarker for modulation of human mammary carcinogenesis. Environ Health Perspect 105(Suppl3):559-564, 1997.
36. Williams' Textbook of Endocrinology. 8th ed. Ed:Wilson JD, Foster DW. WB Saunders, Philadelphia, 1992.
37. Toniolo PG, Levitz M, Zeleniuch-Jacquotte A, et al. A prospective study of endogenous estrogens and breast cancer in post-menopausal women. J Natl Cancer Inst 87:190-197, 1995.
38. Adlercreutz H, Gorbach SL, Goldin BR, et al. Estrogen metabolism and excretion in oriental and caucasian women. J Natl Cancer Inst 86:1076-1082, 1994.
39. Liehr JG. Hormone-associated cancer: mechanistic similarities between human breast cancer and estrogen-induced kidney carcinogenesis in hamsters. Environ Health Perspect 105(Suppl 3):565-569, 1997.
40. Wolff MS, Weston A. Breast cancer risk and environmental exposures. Environ Health Perspect 105(Suppl 4):891-896, 1997.
41. Labreche FP, Goldberg MS. Exposure to organic solvents an breast cancer in women: a hypothesis. Amer J Indust Med 32:1-14, 1997.
42. Morris JJ, Seifter E. The role of aromatic hydrocarbons in the genesis of breast cancer. Med Hypotheses 38:177-184, 1992.
43. Mutti A, Vescovi PP, Falzoi M, et al. Neuroendocrine effects of styrene on occupationally exposed workers. Scand J Work Environ Health 10:225-228, 1984.
44. Alessio L, Apostoli P, Feriolo A, Lombardi S. Interference of manganese on neuroendocrinal system in exposed workers. Biol Trace Element Res 21:249-253, 1989.
45. Lucchi L, Govoni S, Memo M, et al. Chronic lead exposure alters dopamine mechanisms in rat pituitary. Toxicol Lett 32:255-260, 1986.
46. Newcomb PA, Storer BE, Longnecker MP, et al. Lactation and a reduced risk of premenopausal breast cancer. N Engl J Med 330:81-87, 1994.
47. Yuan JM, Yu MC, Ross RK, et al. Risk factors for breast cancer in Chinese women in Shanghai. Cancer Res 48:1949-1953, 1988.
48. Wolff MS, Toniolo PG, Lee EW, et al. Blood levels of organochlorine residues and risk of breast cancer. J Natl Cancer Inst 85(8); 648-652, 1993.
49. Mussslo-Rauhamaa H, Hasanen E, Pyysalo H, et al. Occurrence of Beta-hexachlorocyclohexane in breast cancer patients. Cancer 66:2124-2128, 1990.
50. Falck F, Ricci A, Wolff M, et al. Pesticides and polychlorinated biphenyl residues in human breast lipids and their relation to breast cancer. Arch Env Health 47(2): 143-146, 1992.
51. Dewailly E, Dodin S, Verreault R, et al. High organochlorine body burden in women with estrogen-responsive breast cancer. J Natl Cancer Inst 86:232-234, 1994.
52. Wolff MS, Toniolo PG, Lee EW, et al. Blood levels of organochlorine residues and risk of breast cancer. J Natl Cancer Inst 85(8); 648-652, 1993.
53. Krieger N, Wolff MS, Hiatt RA, et al. Breast cancer and serum organochlorines: a prospective study among

white, black, and Asian women. J Natl Cancer Inst 86:589-599, 1994.
54. Unger M, Kiaer H, Blichert-Toft M, et al. Organochlorine compounds in human breast fat from deceased with and without breast cancer and in a biopsy material from newly-diagnosed patients undergoing breast surgery. Environ Res 34:24-28, 1984.
55. Ahlborg UG, Lipworth L, Titus-Ernstoff L, et al. Organochlorine compounds in relation to breast cancer, endometrial cancer, and endometriosis: an assessment of the biological and epidemiological evidence. Crit Rev Toxicol 25(6):463-531, 1995.
56. Hunter DJ, Hankinson SE, Laden F, et al. Plasma organochlorine levels and the risk of breast cancer. N Engl J Med 337(18):1253-1258, 1997.
57. Safe S. Is there an association between exposure to environmental estrogens and breast cancer? Environ Health

80.Fisch H, Goluboff ET. Geographic variations in sperm counts: a potential cause of bias in studies of semen quality. Fertil Steril 65:1044-1046, 1996.
81.Auger J, Kunstmann JM, Czyglik F, et al. Decline in semen quality among fertile men in Paris during the past 20 years. N Engl J Med 332(5):281-285, 1995.
82.Irvine S, Cawood E, Richardson D, et. al. Evidence of deteriorating semen quality in the United Kingdom: birth cohort study in 577 men in Scotland over 11 years. Brit Med J 312:467-471, 1996.
83.Fisch H, Goluboff ET, Olson JH, et al. Semen analyses in 1,283 men from the United States over a 25-year period: no decline in quality. Fertil Steril 65:1009-1014, 1996.
84.Paulsen CA, Berman NG, Wang C. Data from men in greater Seattle area reveals no downward trend in semen quality: further evidence that deterioration of semen quality is not geographically uniform. Fertil Steril 65:1015-1020, 1996.
85.Pajarinen J, Laippala P, Penttila A, et al. Incidence of disorders of spermatogenesis in middle-aged Finnish men, 1981-1991: two necropsy series. Brit Med J 314:13-18, 1997.
86Giwercman A, Carlsen E, Keiding N, Skakkebaek NE. Evidence for increasing incidence of abnormalities of the human testis: A review. Environ Health Perspect 101(Suppl 2): 65-71, 1993.
87.Anonymous. An increasing incidence of cryptorchidism and hypospadius? Lancet i:1311, 1985.

2,3,7,8-tetrachlorodibenzo-p-dioxin: Recent advances toward understanding the mechanism. Teratology 42:619-627, 1990.

108. Mably TA, Moore RW, Goy RW, et al. In utero and lactational exposure of male rats to 2,3,7,8-tetrachlordibenzo-p-dioxin. 2. Effects on sexual behavior and the regulation of LH secretion in adulthood. Toxicol Appl Pharmacol 114:108-117, 1992.
109. Mably TA, Moore RW, Peterson RE. In utero and lactational exposure of male rats to 2,3,7,8-tetrachlorodibenzo-p-dioxin: 1. Effects on androgenic status. Toxicol Appl Pharmacol 114:97-107, 1992.
110. McKinney JD, Waller CL. PCBs as hormonally active structural analogues. Environ Health Perspect 102(3): 290-97, 1994.
111. Birnbaum LS. The mechanism of dioxin toxicity: Relationship to risk assessment. Environ Health Perspect 102(Suppl9):157-63, 1994.
112. Murray FJ, Smith FA, Nitschke CG et al. Three-generation reproduction study of rats given 2,3,7,8- tetrachlorodibenzo-p-dioxin (TCDD) in the diet. Toxicol Appl Pharmacol 50:241-25, 1979.
113. Allen JR, Barsotti DA, Lambrecht LK, et al. Reproductive effects of halogenated aromatic hydrocarbons on nonhuman primates. Ann NY Acad Sci 320:419-425, 1979.
114. Barsotti DA, Abrahamson LJ, Allen JR. Hormonal alterations in female rhesus monkeys fed a diet containing 2,3,7,8-TCDD. Bull Environ Contam Toxicol 21:463-469, 1979.
115. Rier SE, Martin DC, Bowman RE et al. Endometriosis in rhesus monkeys (Macaca mulatta) following chronic exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Fund Appl Toxicol 21:433-441, 1993.
116. Kociba RJ, Keeler PA, Park GN, et al. 2,3,7,8-tetrachlorodibenzo-p-dioxin: Results of a 13 week oral toxicity study in rats. Toxicol Appl Pharmacol 35:553-574, 1976
117. McConnell EE, Moore JA, Haseman JK, et al. The comparative toxicity of chlorinated dibenzo-p-dioxins in mice and guinea pigs. Toxicol Appl Pharmacol. 44:335-356, 1978.
118. Chahoud I, Krowke R, Schimmel A, et al. Reproductive toxicity and pharmacokinetics of 2,3,7,8-TCDD. Effects of high doses on the fertility of male rats. Arch Toxicol 63:432-439, 1989.
119. Moore RW, Jefcoate CR, Peterson RE. 2,3,7,8-tetrachlorodibenzo-p-dioxin inhibits steroidogenesis in the rat

mental outcome at age 5 and 9 years in a national cohort of very preterm and/or very low birth weight infants. Pediatr Res 39:142-145, 1996.
134. Schmitt CJ, et al. National pesticide monitoring program. Residues of organochlorine chemicals in freshwater fish, 1980-81. Arch Environ Contam Toxicol 14:225-260, 1985.
135. Leifer, et al. Environmental Transport and Transformation of PCBs. EPA-560/5-83-025. 1983.
136. Dewailly E, Ayotte P, Bruneau S, et al. Inuit exposure to organochlorines through the aquatic food chain in arctic Quebec. Environ Health Perspect 101:618-620, 1993.
137. McKinney JD, Waller CL. Polychlorinated biphenyls as hormonally active structural analogues. Environ Health Perspect 102(3):290-297, 1994.
138. Fielden MR, Chen I, Chitten B, et al. Examination of the estrogenicity of 2,4,6,2',6'-pentachlorobiphenyl (PCB 104), its hydroxylated metabolite 2,4,2',4',6'-pentachloro-4-bephenylol (HO-PCB 104), and a further chlorinated derivative, 2,4,2',4',6'-hexachlorobiphenyl (PCB 155). Environ Health Perspect 105(11):1238-1248, 1997.
139. Crews D, Bergeron JM, McLachlan JA. The role of estrogen in turtle sex determination and the effect of PCBs. Environ Health Perspect 103(Suppl 7):73-77, 1995.
140. Battershill JM. Review of the safety assessment of polychlorinated biphenyls (PCBs) with particular reference to reproductive toxicity. Human and Experimental Toxicol 13:581-597, 1994.
141. Sager DB, Shih-Schroeder, Girard D. Effect of early postnatal exposure to polychlorinated biphenyls (PCB) on fertility in male rats. Bull Environ Contam Toxicol 38:946-953, 1987.
142. Barsotti DA, Marlar RJ, Allen JR. Reproductive dysfunction in Rhesus monkeys exposed to low levels of polychlorinated biphenyls (Aroclor 1248). Food Cosmetics Toxicol 14:99-103, 1976.
143. Muller WF, Hobson W, Fuller GB, et al. Endocrine effects of chlorinated hydrocarbons in Rhesus monkeys. Ecotoxicol Environ Safety 2:161-72, 1978.
144. Jansen HT, Cooke PS, Porcelli J, et al. Estrogenic and anti-estrogenic actions of PCBs in the female rat: in-vitro and in-vivo studies. Reprod Toxicol 7:237-248, 1993.
145. Barsotti DA, Marlar RJ, Allen JR. Reproductive dysfunction in Rhesus monkeys exposed to low levels of polychlorinated biphenyls (Aroclor 1248). Food Cosmetics Toxicol 14:99-103, 1976.
146. Tilson HA, Davis GJ, McLachlan JA, Lucier GW. The effects of polychlorinated biphenyls given prenatally on the neurobehavioral development of mice. Environ. Res. 18:466-474, 1979.
147. Agrawal AK, Tilson HA, Bondy SC. 3,4,3',4'-tetrachlorobiphenyl given to mice prenatally produces long term decreases in striatal dopamine and receptor binding sites in the caudate nucleus. Toxicol Lett 7:417-424, 1981.
148. White RD, Allen SD, Bradshaw WS. Delay in the onset of parturition in the rat following prenatal administration of developmental toxicants. Toxicol Lett 18:185-192, 1983.
149. Barsotti DA, Marlar RJ, Allen JR. Reproductive dysfunction in Rhesus monkeys exposed to low levels of polychlorinated biphenyls (Aroclor 1248). Food Cosmetics Toxicol 14:99-103, 1976.
150. Bernhoft A, Nafstad I, Engen P, Skaare JU. Effects of pre- and postnatal exposure to 3,3',4,4',5-pentachlorobiphenyl on physical development, neurobehavior and xenobiotic metabolizing enzymes in rats. Environ Toxicol Chem 13(10):1589-1597, 1994.
151. Collins WT, Capen CC. Fine structural lesions and hormonal alterations in thyroid glands of perinatal rats exposed in utero and by the milk to polychlorinated biphenyls. Amer J Pathol 99:125-142, 1980.
152. Crews D, Bergeron JM, McLachlan JA. The role of estrogen in turtle sex determination and the effect of PCBs. Environ Health Perspect 103(Suppl 7):73-77, 1995.
153. Holene E, Nafstad I, Skaare JU, et al. Behavioral effects of pre- and postnatal exposure to individual polychlorinated biphenyl congeners in rats. Environ Toxicol Chem 14(6):967-976, 1995.
154. Bowman RE, Heironimus MP, Barsotti DA. Locomotor hyperactivity in PCB-exposed rhesus monkeys. Neurotoxicology 2:251-268, 1981.
155. Taylor PR, Stelma JM, Lawrence CE. The relation of PCBs to birth weight and gestational age in the offspring of occupationally exposed mothers. Am J Epid 129:395-406, 1989.
156. Rogan WJ, Gladen BC, Hung KL., et al. Congenital poisoning by polychlorinated biphenyls and their contaminants in Taiwan. Science. 241:334-338, 1988.
157. Hsu C-C, Chen Y-C, Rogan WJ. Intellectual and behavioral development of Yu-cheng children. Chemosphere, 1991.
158. Safe, S. Toxicology, structure-function relationship, and human and environmental health impacts of polychlorinated biphenyls: progress and problems. Environ Health Perspect 100:259-268, 1992.
159. Jacobson JL, Jacobson SW. Effects of in utero exposure to PCBs and related contaminants on cognitive func-

tioning in young children. J Pediatrics 116(1); 38-45, 1990.
160. Jacobson JL, Jacobson SW. Intellectual impairment in children exposed to polychlorinated biphenyls in utero. N Engl J Med 335:783-789, 1996.
161. Gladen BC, Rogan WJ. Effects of perinatal polychlorinated biphenyls and dichlorodiphenyl dichloroethene on later development. J Pediatr 119:58-63, 1991.
162. Koopman-Esseboom C, Morse DC, Weisglas-Kuperus N, et al. Effects of dioxins and polychlorinated biphenyls

188. Heindel JJ, Gulati DK, Mounce RC, Russell SR, Lamb JC. Reproductive toxicity of three phthalic acid esters in a continuous breeding protocol. Fund Appl Toxicol 12:508-518, 1989.
189. Jobling S, Reynolds T, White R, et. al. A variety of environmentally persistent chemicals, including some phthalate plasticizers, are weakly estrogenic. Environ Health Perspect. 103(6): 582-587, 1995.
190. Lloyd SC, Foster PMD. Effect of mono-(2-ethylhexyl)phthalate on follicle-stimulating hormone responsiveness of cultured rat Sertoli cells. Toxicol Appl Pharmacol 95:484-489, 1988.
191. Davis BJ, Maronpot RR, Heindel JJ. Di-(2-ethylhexyl) phthalate suppresses estradiol and ovulation in cycling rats. Toxicol Appl Pharmacol 128:216-223, 1994.
192. Ema M, Itami T, Kawasaki H. Teratogenic phase specificity of butyl benzyl phthalate in rats. Toxicology 79(1):11-19, 1993.
193. Ema M, Itami T, Kawasaki H. Embryolethality and teratogenicity of butyl benzyl phthalate in rats. J Appl Toxicol 12(3):179-183, 1992.
194. Gulati DK, Barnes LH, Chapin RE, Heindel J. Final report on the reproductive toxicity of di(N-butyl)phthalate in Sprague-Dawley rats. NTIS Technical Report (NTIS/PB92-111996) 1991 Sept; 279pp.
195. Ministry of Agriculture, Fisheries, and Food Food Safety Directorate. Food surveillance information sheet No. 82, March 1996. London.
196. Ministry of Agriculture, Fisheries, and Food Food Safety Directorate. Food surveillance information sheet No. 83, March, 1996. London.
197. Jaeger R, Rubin R. Migration of a phthalate ester plasticizer from polyvinyl chloride blood bags into stored human blood and its localization in human tissue. NEJM 287:1114-1118, 1972.
198. Menzer RE. Water and soil pollutants. In: Casarett and Doull's Toxicology, The Basic Science of Poisons, 4th ed. Eds: Amdur MO, Doull J, Klaassen CD. McGraw-Hill, 1991.
199. Kelce WR, Monosson E, Gray LE. An environmental androgen. Recent Prog in Hormon Res 50:449-453, 1995.
200. Eil C, Nisula BC. The binding properties of pyrethroids to human skin fibroblast androgen receptors and to sex hormone binding globulin. J Steroid Biochem 35(3-4):409-414, 1990.
201. Connor K, Howell J, Chen I, et al. Failure of chloro-s-triazine-derived compounds to induce estrogen receptor-mediated responses in vivo and in vitro. Fundam Appl Toxicol 30:93-101, 1996.
202. Kelce WR, Stone CR, Laws SC et al. Persistent DDT metabolite p,p'-DDE is a potent androgen receptor antagonist. Nature 375:581-585, 1995.
203. Eroschenko VP, Cooke PS. Morphological and biochemical alterations in reproductive tracts of neonatal female mice treated with the pesticide methoxychlor. Biol Repro 42(3):573-583, 1990.
204. Gray LE, Ostby JS, Ferrell JM, et al. Methoxychlor induces estrogen-like alterations of behavior and the reproductive tract in the female rat and hamster: Effects on sex behavior, running wheel activity, and uterine morphology. Toxicol Appl Pharmacol 96(3):525-540, 1988.
205. Gray LE, Ostby JS, Ferrell JM, et al. A dose-response analysis of methoxychlor-induced alterations of reproductive development and function in the rat. Fund Appl Toxicol 12(1):92-108, 1989.
206. vom Saal FS, Nagel SC, Palanza P, et al. Estrogenic pesticides: binding relative to estradiol in MCF-7 cells and effects of exposure during fetal life on subsequent territorial behavior in male mice. Toxicol Lett 77:343-350, 1995.
207. Soto AM, Chung KL, Sonnenschein C. The pesticides endosulfan, toxaphene, and dieldrin have estrogenic effects on human estrogen-sensitive cells. Environ Health Perspect 102:380-383, 1994.
208. Sircar S, Lahiri P. Lindane (gamma-HCH) causes reproductive failure and fetotoxicity in mice. Toxicol 59(2):171-177, 1989.
209. Cooper RL, Chadwick RW, Rehnberg GL, et al. Effect of lindane on hormonal control of reproductive function in the female rat. Toxicol Appl Pharmacol 99(3):384-394, 1989.
210. MacLellan KN, Bird DM, Fry DM, et al. Reproductive and morphological effects of o,p'-dicofol on two generations of captive American kestrels. Arch Environ Toxicol 30(3):364-372, 1996.
211. Van den Berg KJ, van Raaij AGM, Bragt PC, Notten WRF. Interactions of halogenated industrial chemicals with transthyretin and effects on thyroid hormone levels in vivo. Arch Toxicol 65:15-19, 1991.
212. Van den Berg KJ. Interaction of chlorinated):1tions203r1091 -1DE 10.8 TD[(20e sexcerrten ith transto)lbureceptor-

roidal hormone regulation in the rat. Toxicol Lett 71(9-25, 1994.
215. van Raaij JA, Frijters CM, Kong LW, et al. Reduction of thyroxine uptake into cerebrospinal fluid and rat brain by hexachlorobenzene and pentachlorophenol. Toxicol 94(1-3):197-208, 1994.
216. Gray LE, Ostby JS, Kelce WR. Developmental effects of an environmental antiandrogen: the fungicide vinclozolin alters sex differentiation of the male rat. Toxicol Appl Pharmacol 129(1):46-52, 1994.
217. Kelce WR, Monosson E, Gamcsik MP, et al. Environmental hormone disruptors: evidence that vinclozolin developmental toxicity is mediated by antiandrogenic metabolites. Toxicol Appl Pharmacol 126(2):276-285, 1994.
218. Wong C, Kelce WR, Sar M, Wilson EM. Androgen receptor antagonist versus agonist activities of the fungicide vinclozolin relative to hydroxyflutamide. J Biol Chem 270(34):19998-20003, 1995.
219. Ronis MJJ, Barger TM, Gandy J, et al. Anti-androgenic effects of perinatal cypermethrin exposure in the developing rat. Abstracts of the 13th International Neurotoxicology Conference. Hot Springs, AK, 1995.
220. Connor K, Howell J, Chen I, et al. Failure of chloro-s-triazine-derived compounds to induce estrogen receptor-mediated responses in vivo and in vitro. Fundam Appl Toxicol 30:93-101, 1996.
221. Babic-Gojmerac T, Kniewald Z, Kniewald J. Testosterone metabolism in neuroendocrine organs in male rats under atrazine and deethylatrazine influence. J Steroid Biochem 33:141-146, 1989.
222. Davis DL, Bradlow HL. Can environmental estrogens cause breast cancer? Scientific American 166-72, Oct.,1995.
223. Kniewald J, Osredecki V, Gojmerac T, et al. Effect of s-triazine compounds on testosterone metabolism in the rat prostate. J Appl Toxicol 15(3):215-218, 1995.
224. Cooper RL, Stoker TE, Goldman JM, et al. Atrazine disrupts hypothalamic control of pituitary-ovarian function. The Toxicologist 30:66, 1996.
225. Cooper RL, Stoker TE, Goldman JM, et al. Effect of atrazine on ovarian function in the rat. Reprod Toxicol 10(4):257-264, 1996.
226. Houeto P, Bindoula G, Hoffman JR. Ethylenebisdithiocarbamates and ethylenethiourea: possible human health hazards. Environ Health Perspect 103:568-573, 1995.
227. Steenland K, Cedillo L, Tucker J, et al. Thyroid hormones and cytogenetic outcomes in backpack sprayers using ethylenebis(dithiocarbamate) (EBDC) fungicides in Mexico. Environ Health Perspect 105:1126-1130, 1997.
228. Whitten Pl, Lewis C, Russell E, Naftolin F. Potential adverse effects of phytoestrogens. J of Nutrition. 125(3Suppl):771S-776S, 1995.
229. Whitten PL, Lewis C, Russel E, Naftolin F. Phytoestrogen influences on the development of behavior and gonadotropin function. Proc Soc Exptl Biol and Med. 208(1):82-86, 1995.
230. Levy JR, Faber KA, Ayyash L, Hughes CL. The effect of prenatal exposure to the phytoestrogen genistein on sexual differentiation in rats. Proc Soc Exptl Biol and Med. 208(1):60-66, 1995.
231. Whitten PL, Russel E, Naftolin F. Influence of phytoestrogen diets on estradiol action in the rat uterus. Steroids 59(7):443-449, 1994.
232. Whitten PL, Lewis C, Naftolin F. A phytoestrogen diet induces the premature anovulatory syndrome in lactationally exposed female rats. Biol of Reprod 49(5):1117-1121, 1993.
233. Faber KA, Hughes CL. Dose-response characteristics of neonatal exposure to genestein on pituitary responsiveness to gonadotropin releasing hormone and volume of the sexually dimorphic nucleus of the preoptic area (SDN-POA) in postpubertal castrated female rats. Reprod Toxicol 7(1):35-39, 1993.
234. Adlercreutz H. Phytoestrogens:Epidemiology and a possible role in cancer protection. Env Health Perspect 103(Suppl 7):103-112, 1995.

Remarkably, many of the chemicals to which workers and the public are regularly exposed have had no formal reproductive toxicity evaluation of any type. Some are chemicals which may have been in use for some time; others are newly proposed for commercial use and fail to trigger testing thresholds for reasons which are political, statutory, or bureaucratic rather than biological.[4] Among those which are subject to testing, there are often uncertainties about the adequacy of the testing protocol and its relevance to human experience.

TSCA was originally intended to act as a safeguard against harmful exposures to toxic chemicals. There is little doubt, however, that it has failed to ensure adequate protection of public health and the environment. The fundamental flaw in the Act is its "innocent until proven guilty" approach to chemical regulation. TSCA requires manufacturers to notify the EPA of the planned manufacture of a new chemical. The EPA Administrator can require testing of the substance by the manufacturer, but only if the EPA can make a formal determination that the chemical may pose an "unreasonable risk" or that the chemical will be produced in "substantial quantities" and may lead to "significant human exposure". If the agency fails to make a decision within 90 days, the chemical is presumed safe and may be manufactured.

The Act makes it possible for EPA to require industry to

- Many of the older pesticides were poorly tested by modern standards yet they remain on the market. The special review process designed to address these deficiencies will not be complete for years;
- Despite legislative intent, animal testing used to support an application for new pesticide registration currently fails to examine adequately for subtle and delayed toxicity.
- The registration process for pesticides does not account for interactive or cumulative effects of multiple exposures that individuals are likely to experience in real-world situations;
- There is no comprehensive evaluation of the impact such chemicals may have on the environment generally.
- Most existing levels of pesticides allowed on foods (tolerances) were not set to protect health but rather to reflect expected pesticide use patterns;
- EPA was required to consider the benefits of pesticide use prior to taking any regulatory action and it was as cumbersome for EPA to require a label on a product as it was for the agency to ban the product.

The Food Quality Protection Act

The strongest part of early pesticide law was the "Delaney clause" which banned any use of a pesticide when it was carcinogenic and accumulated on processed foods.[10] Unfortunately the Delaney clause did not address neurotoxicants, reproductive toxicants, and other hazardous pesticides, nor did it address pesticides on raw, non-processed foods.

In August 1996, Congress repealed the Delaney clause and passed the Food Quality Protection Act (FQPA) in an effort re-design pesticide regulation. The FQPA applies a risk assessment-based strategy to re-evaluate allowable pesticide residues on food. EPA is now required to consider pesticides which act by the same biological mechanism as acting cumulatively; look at all exposures to a given pesticide from all food, water, home, and other sources together when considering the total risk; and ensure that any pesticide tolerances adequately protect children. In addition, the FQPA has provisions requiring that EPA design a testing strategy to look for endocrine disruptive effects and to apply those tests to pesticides.

The FQPA is relatively new and it remains to be seen if it will adequately serve to protect the public against the hazards of pesticides. Early EPA decisions indicate that the law has not yet lived up to it's potential due to weak enforcement in the face of intense lobbying by the pesticide industry. Critics of the act believe implementation will not be possible for years, if at all.

Legislation Affecting Your Right-to-Know

While the virtual explosion of new chemicals into the marketplace of industrialized societies began a half century ago, it is only recently that citizens and workers have had meaningful access to information about the chemicals they may be exposed to on a daily basis. Even today, the quantity and quality of information provided to the public about toxic chemicals used or emitted in their neighborhoods remains inadequate.

The Toxics Release Inventory (TRI)

In 1986, Congress passed the Emergency Planning and Community Right-to-Know Act (EPCRA, or SARA Title III). The law, an amendment to the hazardous waste site Superfund law, requires the owners and operators of large manufacturing facilities to report their environmental releases (to land, air and water) and off-site transfers of certain toxic chemicals on an annual basis. This information must be submitted 77(oxico0(esoJT*e nning 1l6ois)
emain oanh3Do-s2u,(EEannual basirs and T*83cP)4li(-sit)]TJT*.p.EE

data in negotiations with industry and government officials, resulting in numerous success stories including: the early phase-out of ozone-depleting chemical use by factories in California and Massachusetts; funding for air toxics monitors in Ohio; greater regulation of toxic releases in Louisiana and North Carolina; the creation of an accident prevention plan in New Jersey; and the passage of toxics use reduction laws in Massachusetts, New Jersey and Oregon.[11] Even industry officials adamantly opposed to the law, have found the annual data releases to be an opportunity for positive public relations — if their company has achieved measurable reductions.

The list of chemicals that must be reported under TRI currently contains more than 600 entries. The list was most recently modified by EPA when 286 chemicals were added to TRI in November 1994. The addition of 152 of those chemicals to the list provoked a lawsuit by the Chemical Manufacturers Association (CMA). CMA argued that the federal agency had exceeded its authority in adding chemicals linked to chronic health effects such as birth defects and cancer. In August 1997 the federal court of appeals sided with EPA in determining that the agency had acted properly in expanding the list of chemicals.[12]

California's Proposition 65

The Safe Drinking Water and Toxic Enforcement Act was passed by California voters by a three to one majority as a ballot referendum (Proposition 65) in 1986. This law carries the right to know one step further than the TRI. Proposition 65 requires that anyone who, in the course of doing business, exposes someone to a chemical known to cause cancer or reproductive harm, must first warn the person exposed. Furthermore, the law forbids discharge of carcinogens or reproductive toxicants into sources of drinking water.

In practice, there are about 150 chemicals, mostly pharmaceutical products, listed as "known" reproductive toxicants in California. Many of the products which contain these chemicals must be labeled with a warning. Proposition 65 has had more far-ranging effects than might be predicted from the simple labeling requirement. In fact, many manufacturers have reformulated products to eliminate listed chemicals in order to avoid the competitive disadvantage of a warning label in the marketplace. Many of the reformulations have occurred nationwide because California represents such a large market for products that it makes financial sense for a company simply to change their entire product line. This nationwide reformulation occurred with many brands of nail polish when toluene was listed as a reproductive toxicant, and with brass faucets manufactured with lead that leached into water.

One particularly powerful aspect of Proposition 65 is the ability of any Californian to enforce the law. In fact, the high penalties for a violation and the fact that these penalties may be collected by anyone has created a powerful incentive for companies to comply.

Unfortunately, Proposition 65 is only as powerful as the list of chemicals which triggers the warnings. This list of known reproductive toxicants and carcinogens is compiled by the state, and has been subject to enormous political pressures. The result has been an extremely slow pace of listing. Many chemicals which have strong evidence of hazard, such as many discussed in this report, and many listed by U.S. EPA on the TRI due to reproductive toxicity, remain unlisted in California despite scientific evidence that they may pose a threat to public health. If the chemical is not formally listed, the labeling and drinking water provisions do not apply, and the public is not warned about the risk.

Toxics Use Reduction Acts (TURA)

In a few states, including Massachusetts, New Jersey, and Oregon, major industrial users of toxic materials are required to report not only their emissions of toxic chemicals, but their use of certain listed chemicals and their plans to reduce or eliminate their dependence on these materials. In Massachusetts, more than 900 chemicals are covered by this mandatory reporting law. The information reported by the facilities regarding the type and quantity of toxic chemicals they use, as well as what happens to those chemicals in the manufacturing process, is centrally reported and available to the public. Chemical use reporting enables tracking of toxic chemicals released as products – an enormous chemical stream that cannot currently be characterized under federal regulations. Companies are also required to produce plans which describe and evaluate various methods of achieving toxics use reduction. These are kept on site at the

The Department of Pesticide Regulation (DPR), within California EPA, is charged with protecting Californians from exposures to hazardous pesticides. Unfortunately, the history of the DPR's activites suggests that the agency has generally done a better job protecting the economics of agrichemicals, rather than protecting public health. The agency appears to have ignored or diluted the implementation of several landmark laws intended to protect Californians from pesticide proliferation:

The California Birth Defect Prevention Act of 1984

This law requires DPR to evaluate new and old pesticides for their potential to cause cancer, birth defects and other heath effects. The agency is required to cancel the registrations of those pesticides that are found to cause "significant adverse health effects," and, unlike federal law, the BDPA requires that the agency consider only health risk, and not risk-benefit balancing. Since implementation of the act, however, DPR has failed to move forward in a timely manner to fill important data gaps regarding the toxicity of widely used pesticides. Meanwhile, these poorly-studied chemicals remain in use in California. More importantly, in the last ten years the agency has not once eliminated the use of a single registered pesticide, except when pesticide registrations were voluntarily withdrawn by the manufacturer.

The California Toxic Air Contaminant Program of 1984

State laws passed in 1983 and 1984 mandated DPR (then the California Department of Food and Agriculture) to nominate potentially harmful pesticides to be included on an official list of "toxic air contaminants" and regulate these chemicals to the point *"at which no significant adverse health effects are anticipated."*[1] In 14 years, DPR has nominated only one pesticide suspected of being a possible toxic air contaminant, ethyl parathion, which had already just been banned by U.S. EPA.[2] Dozens of pesticides flagged as "high priority" candidates for listing continue to be used in California.

Pesticide Drift and Safe Exposure Levels

The agency has repeatedly dismissed monitoring data collected by a national non-profit environmental organization, the Environmental Working Group, even when the data flagged potentially significant public health risks. The state's

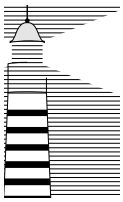
facility and are not available to the public, although summaries are filed with the state.

Rather than focusing on the more traditional "end-of-the-pipe" approach to environmental protection, toxics use reporting takes a preventive approach which encourages the public and private sectors to work cooperatively toward a solution to the problem of use and potential exposure to toxic chemicals. The increased access to chemical use data in certain states has provided an added incentive for businesses to reduce their reliance on hazardous substances. This incentive, coupled with the promise of cost savings, environmental benefits and assistance from state agencies has led to some successful results. These programs need to be introduced in California and at the federal level.

The limitations of some of our most important environmental laws, together with inadequate enforcement practices and the frequency with which new chemicals and pesticides are developed, have conspired to create an imperfect system of health and environmental protection. It is not surprising that a large number of chemicals fall through the cracks and avoid appropriate study and regulation.

References

1. Ashford NA, Caldart CC. Technology, Law, and the Working Environment. Massachusetts Institute of Technology, Van Nostrand Reinhold, NY, 1991, pg. 41.
2. Ibid.
3. Francis EZ. "Testing of environmental agents for developmental and reproductive toxicity" in: Developmental Toxicology, 2nd Edition., ed. Kimmel CA and Buelke-Sam J. Raven Press, Ltd., New York, 1994.
4. Dahl R. Can You Keep A Secret? Environmental Health Perspectives. 103:914-916; 1995.
5. Ashford NA, Caldart CC. Technology, Law, and the Working Environment. Massachusetts Institute of Technology, Van Nostrand Reinhold, NY, 1991, pg 195.
6. Dahl R. Can You Keep A Secret? Environmental Health Perspectives. 103:915;1995.
7. Findley R, Farber D. Environmental Law. 4th Edition. West Publishing Co.: St. Paul; 1995: pg 413.
8. Ibid.
9. Ibid at pg 409.
10. The Dalaney clause was embodied in the Food Drug and Cosmetic Act, legislation intended to compliment FIFRA.
11. Orum P, MacLean A. Progress Report: Community Right-to-Know. Washington, DC. July, 1992, pg 1-24
12. Cushman J. "Court Backs EPA Authority on Disclosure of Toxic Agents". The New York Times. May 2, 1996, sec A20.
13. California Regional Water Quality Control Board. Toxic Contaminants in San Francisco Bay Fish, 1994.
14. Office of Environmental Health Hazard Assessment. Health Advisory about eating fish from San Francisco Bay, 1994.
15. See e.g., Schecter AJ. Abstract for Regional Water Control Board science workshop, May 7, 1997.
16. US EPA. Economic Analysis for the Proposed California Toxics Rule. S.F. Bay cancer and non-cancer assessment, 1997.
17. US EPA. Proposed water quality standards for California



Spotlight on

Fishing Rights and Reproductive Toxicants in the San Francisco Bay

Submitted by Communities for a Better

of exposure; e) any established exposure limits; f) handling precautions; g) control measures; h) emergency procedures; i) date of MSDS preparation; j) the telephone number and address of manufacturer or importer; and k) whether the substance is listed as a carcinogen. Employers are permitted to rely on the information supplied by the manufacturer. They are not required to address inadequate MSDS information. The OSHA HCS requires that employees be informed about the standard, the location of hazardous chemicals in the workplace, and the availability and location of MSDSs.

Given the requirements for MSDSs and the intention that they be a significant source of information for workers and the public, the adequacy of information provided in these documents is important.

Concern over MSDS Accuracy & Accessibility

In a 1989 study focusing on reproductive and developmental hazard warnings, investigators from the University of Massachusetts analyzed MSDSs for glycol ethers and lead on file with the Central Massachusetts Department of Environmental Protection.[1] Each substance is a reproductive and developmental toxicant covered by both federal and and Massachusetts laws requiring disclosure of health hazards. They found that:

- Only 7% (1800/25,000) of the required facilities had submitted MSDSs to the DEP;
- 62% of the documents made no reference to effects on the reproductive system and were completely uninformative;
- Of the remainder, 41% mentioned or implied the reproductive target organ without specifying signs or symptoms; 28% referred only to developmental effects; 2% referred only to fertility effects; and 29% mentioned both fertility and developmental risks.

The authors noted that all descriptions of fertility effects pertained only to male workers, representing a gender bias.

In a 1993 study of 100 unionized manufacturing workers in Maryland, investigators learned that only about two-thirds of the health and safety information presented on MSDSs was understood by those workers.[2] Participants attributed their difficulties in understanding to wordiness, technical language, or confusing layout of the documents.

The investigators also describe a previous report OSHA in which MSDSs were found to be "accurate" or "partially accurate" with respect to health effects in only 37% of those sampled.

MSDSs are an important and legally required means for disseminating information to workers and the public about health hazards of chemical exposures. They are, however, of little or no value when incomplete, uninformative, in error, or difficult to understand.

References

1 Paul M, Kurtz S. Analysis of reproductive health hazard information on material safety data sheets for lead and the ethylene glycol ethers. Am J Indus Med. 25:403-4-15, 1994.

2 Kolp P, Sattler B, Blayney M, Sherwood T. Comprehensibility of material safety data sheets. Amer J Indust Med 23:135-141, 1993.

Part IV

The California Picture

Introduction

The previous sections of this report have largely been a summary of the reproductive health effects of several classes of chemical substances. But as individuals, health care providers, citizens groups, legislators, and policy makers consider this information in their states or communities, private and public decisions must be based on more specific data. We have stressed that the risk of harm depends on the likelihood of meaningful exposure as well as the potency or toxicity of a substance. Estimating likelihood of exposure requires knowledge about which chemicals are used in the workplace, home and community. Without this information, we are effectively disempowered from making our own personal and collective choices, leaving protection from hazardous exposures to others.

Regardless of whether a particular toxic chemical used or released in a manufacturing process can be linked to an actual human exposure or a particular observed health effect, it may rationally be a substance of real concern for workers, consumers, waste handlers, and local residents. For those who are intentionally, carelessly, or accidentally exposed, information about the nature of the exposure as well as possible health effects is of obvious practical importance. This section begins to address this need by presenting available information about the use and release of known, suspected, or possible reproductive and developmental toxicants in California.

About the Chemicals Reviewed

The list of chemicals included for analysis in this section is not likely to include all developmental and reproductive toxicants used and released in California. As discussed elsewhere in this report, numerous chemicals in commerce are inadequately studied and/or remain outside the jurisdiction of current use and release reporting regulations. Such chemicals would not be included for analysis here. Chemicals included for analysis are:

- Identified as reproductive or developmental toxicants, either by U.S. EPA, the State of California, or by definite or suggestive evidence as presented here by the authors;[1]
- Transferred offsite or released directly to the environment in an amount of 1,000 pounds or more by a California manufacturing facility; and
- Reported under the Federal Toxics Release Inventory or the California Pesticide Use Reporting System.

Note, there is considerable variability in the strength of the scientific evidence which leads us to include each substance on the list.

Furthermore, the exposure necessary to cause adverse health effects and the timing of that exposure varies considerably among chemicals. A reader concerned with the magnitude of risk from specific chemicals and facilities will need to bear in mind that confidence in the adequacy of toxicity data as well as the likelihood of significant exposure vary for the chemical, the facility, workers, and the general community.

About the Chemical and Transfer Release Data

The transfer and release data presented in this section derives from two data sources: The Federal Toxics Release Inventory (TRI) and the California Pesticide Use Reporting System (PUR). Each data source provides its own resources and limitations, which are only briefly dis-

Chemical	Release*	Transfer	U.S.EPA**	Prop65***	GAR****
METHYL BROMIDE	17,634,532			X	X
METAM SODIUM	15,274,171	12,550	X	X	X
CHLORPYRIFOS	3,524,366				X
DIAZINON	2,376,883		X		X
TOLUENE	1,982,780	2,489,700		X	X
STYRENE	1,883,639	926,621			X
GLYCOL ETHERS	1,879,467	1,252,739		X	X
PROPARGITE	1,813,831		X		
ZIRAM	1,638,866				X
PERCHLORETHYLENE (TETRACHLOROETHYLENE)	1,488,300	753,509			X
MOLINATE	1,427,126		X		X
MANEB	1,309,283				X
METHYLENE CHLORIDE (DICHLOROMETHANE)	1,206,063	1,326,633			X
PHENOL	1,174,953	235,269			X
XYLENE	1,098,981	8,464,676			X
DIURON	1,073,681		X		
CARBARYL	858,369				X
SIMAZINE	842,712		X		
MALATHION	826,757				X
FORMALDEHYDE	804,895	9,231			X
NALED	711,519		X		X
MANCOZEB	679,286				X
EPTC	666,432		X		X
CYANAZINE	647,335			X	X
DICOFOL	598,301		X		X
DIMETHOATE	596,791		X		X
24-D	570,365				X
ACEPHATE	481,759				X
PERMETHRIN	420,396				X
N-METHYL-2-PYRROLIDONE	372,212		X		X
MANGANESE	238,277	1,024,043			X
ENDOSULFAN	229,157				X
PROMETRYN	213,145		X		X
BENOMYL	197,050			X	X
ARSENIC	125,274	85,744		X	X
THIOPHANATE-METHYL	122,955		X		X
OXYDEMETON-METHYL	122,748		X		
BROMOXYNIL	119,837		X	X	
BENZENE	119,452	9,481		X	X
MYCLOBUTANIL	100,956		X		
CYPERMETHRIN	98,838				X
LINURON	85,931				X
FENBUTATIN-OXIDE	80,156		X		
AMITRAZ	77,198		X		
DICAMBA	59,477		X		X
2,4-DB	51,275			X	
VINCLOZOLIN	49,977		X	X	
CYCLOATE	49,897		X		
TRICHLOROETHYLENE	46,128	4,250			X

TRIFORINETR116(98,838)-30003(X)]TJET55.6(59,477)-14117 0 0 7 55.5 325.01 Tm8J7 0 0 7 55.5 505.75 m55654(TE-METH.75 E760OTR11[(-(X)]TM8NET55]TJETP0 m5R5]TJE

cussed here. This analysis uses the most recent officially released data years for both data sources: 1991-1995 for PUR data; 1991-1996 for TRI data.

The TRI requires manufacturers to report chemical releases and transfers for some 600 toxic chemicals. Several limitations apply:

- Manufacturing facilities that process or manufacture less than 25,000 pounds or otherwise use less than 10,000 pounds of a listed chemical are exempt from the reporting requirements.

- Any facility with fewer than ten employees is not required to report regardless of the quantity of chemicals used. Therefore, use and release information from individual dry cleaners, auto-body shops, or small laboratories, for example, many of which use listed toxicants, are not reflected in any of the tables which follow. For a given individual, exposure resulting from releases at a non-reporting facility may be greater than that from one required to report (see, for example, Spotlight on Dry Cleaning).

- Because the TRI does not require manufacturers to report chemical use in products, this analysis cannot include chemical use in the home, community, and workplace from cleaning products, solvent-based paints, adhesives, hobby or craft supplies, gasoline, and others.

- The 600 chemicals required to be reported under the TRI represent only about 1% of all chemicals in commerce.[2]

- Because of minimum threshold reporting requirements, certain highly toxic chemicals that are released or produced in small amounts, such as dioxin, PCBs, mercury, and other chemicals discussed in this document, are often exempted from reporting.

- Chemical releases and transfers submitted by manufacturers to the TRI may be vulnerable to "phantom" reporting changes – paper changes that are not in fact based on actual process changes. Apparent reductions, for example, may be attributed to different methods of emission/transfer estimation (chemical fate information is estimated, not measured), moving toxic chemicals into products (which are not subject to reporting requirements), moving toxic processes off site, substituting to

Table 3
Top 20 Uses of Listed Pesticides (1995)

Rank	Type of Use (1995)	Amount of use (lbs)	Percent of total
1	CARROTS	6,192,122	11%
2	COTTON	5,595,528	10%
3	STRAWBERRY	4,484,416	8%
4	ALMOND	3,618,604	6%
5	STRUCTURAL PEST CONTROL	3,145,066	6%
6	TOMATOES (PROCESSING/CANNING)	3,141,795	6%
7	LETTUCE	1,799,302	3%
8	UNCULTIVATED AGRICULTURAL AREAS	1,728,293	3%
9	SOIL APPLICATION (SEEDBEDS ETC.)	1,706,378	3%
10	GRAPES (WINE)	1,700,109	3%
11	POTATO (WHITE, IRISH,RED, RUSSET)	1,694,967	3%
12	RICE	1,525,774	3%
13	ALFALFA	1,437,937	3%
14	GRAPES	1,416,788	2%
15	ORANGE	1,315,927	2%
16	OUTDOOR CONTAINER PLANTS	1,203,818	2%
17	WALNUT (ENGLISH, PERSIAN)	1,004,301	2%
18	PEPPERS (FRUITING, VEGETABLE, BELL, CHILI, ETC.)	842,984	1%
19	RIGHTS OF WAY	798,937	1%
20	PEACH	796,798	1%

include:

- Over-the-counter pesticide use is not reported; pesticide applications by non-certified applicators are typically not reported.

- Applicators applying pesticides in a non-agricultural setting are exempted from reporting where pesticides were applied. This makes it impossible to differentiate, for example, the types and amounts of pesticides used in schools from those used in garages or cemeteries.

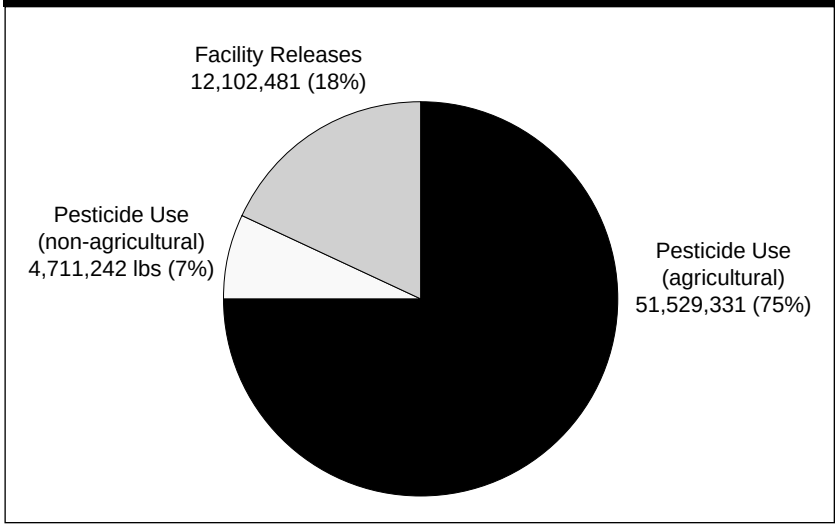
- Data entry errors may cause significant inaccuracy.

Release of Listed Chemicals in California

All told, California manufacturing facilities, agri-businesses and pesticide applicators released over 306.8 million pounds of listed reproductive and developmental toxicants in California from 1991 through 1995. These releases include agricultural and non-agricultural pesticide applications, direct releases from California facilities to land, air, water, underground injection and transfer from facilities to sewage treatment plants. An additional 10.6 million pounds were released by California manufacturing facilities in 1996.

As indicated in Figure 1, agricultural activity accounts for the single largest source of listed reproductive toxicants released to the environment in California, compris-

Figure 1.
Use and Release of Listed Chemicals (1995)*



*Transfers to sewage treatment facilities are considered releases.

ing 75% of all reported releases in 1995. Total pesticide use, including non-agricultural applications, comprised 56.2 million pounds, or 83% of all listed chemicals released in that year.

Over time, manufacturing facility releases have declined while pesticide use has increased substantially through-

yard (57%), and flea and tick control on pets (50%).

Table 11
Top 10 Facilities Releasing Listed Chemicals (1996)

Rank	Facility / Chemical	Total in lbs. (release + trans. to sewage treatment facility)	City / Release	County / Transfer (to sewage treatment facility)	Industry (SIC code) / Transfer (all other)
1	**QUEBECOR PRINTING,INC.**	**863,133**	SAN JOSE	SANTA CLARA	COMMERCIAL PRINTING, GRAVURE
	TOLUENE		831,051	10	21,573
	XYLENE(S)		32,062	10	726
2	**LASCO BATHWARE**, (DIV. OF TOMKINS INC.)	**446, 901**	ANAHEIM	ORANGE	PLASTICS PLUMBING FIXTURES(1987)

sewage treatment plant networks often results in a direct release to the environment because these chemicals typically find their way to coastal waters. Sewage treatment facilities are designed to monitor and treat municipal waste and often cannot treat toxic constituents dumped by industrial facilities. According to a recent CALPIRG study, 71% by weight of chemicals dumped into the sewage system in California are not monitored for or regulated by the sewage plants or the state.[6]

While reported facility releases have declined substantially between 1991 and 1996, transfers of listed chemicals have increased by 1.8 million pounds a year, on average, not including newly listed chemicals in 1995 and 1996. Although not directly released to the environment, transferred chemicals may threaten environmental or public health. Chemicals incinerated for energy reclamation, for example, may be transformed into new constituents that are as toxic or more toxic than the parent materials. Even incinerators with so-called "state-of-the-art" pollution control equipment fail to capture 100 percent of air emissions. The burning process may also free certain chemicals that were otherwise fairly well contained in the product. That which is not burned, including the remaining ash, is typically buried in landfills. All landfills leak, and over time, these polluting burial sites may imperil critical public drinking water supplies.

Chemicals transferred off-site for recycling may also find their way back to the urban or natural environment. For example, cadmium, mercury, lead, arsenic and other listed chemicals are often found in fertilizer products made from "recycled" hazardous wastes.[7] These chemicals may then accumulate in agricultural soils, potentially contaminating our food supply and ruining farmlands. While some hazardous waste recycling may be beneficial and can alleviate the need to produce and use more toxic chemicals, recycling or treating toxic chemicals is not a substitute for pollution prevention in terms of protecting public health and the environment.

Chemicals

Together, the top five chemicals ranked for releases by manufacturing industries in 1996 comprise 73% of total facility releases of listed toxicants. These include toluene, styrene, glycol ethers, perchlorethylene and methylene chloride. It is important to remember that these lists include only data from industries required to report (and does not include pesticide use). Even for those chemicals listed, the picture is not complete since many chemicals are also used and released in settings which do not meet threshold requirements. For instance, perchlorethylene is ranked fourth in California (See Table 9) in terms of chemical releases. Yet, dry cleaners, which use an estimated 15% of all perchlorethylene are not required to report their use or releases of the toxic material because they typically do not meet reporting criteria for number of employees or volume of emissions.[8] If dry cleaners and other industries not currently reporting were required to submit their data on use and releases, these figures would no doubt increase significantly.

Of all listed toxicants released by California facilities, toluene is the most heavily emitted. Toluene releases accounted for approximately 18% of all facility releases in 1996. This chemical is used in glues, coatings, inks, paint, cleaning agents and as a gasoline additive. California industries releasing the most toluene in 1996 include printing and publishing (42%), petroleum refining (12%) and furniture and fixtures manufacturers (11%). As discussed in Chapter 5, several studies have demonstrated an increased risk of spontaneous abortion in women exposed in the workplace; toluene is toxic to fetuses in animal studies at doses well below those causing maternal toxicity; and is known to the state of California to be a developmental toxicant.

Styrene is the second most widely released listed toxicant in California. Most of the chemical is reportedly transformed during the manufacturing process into polystyrene (styrene linked together in long chains). Most of the products made of polystyrene, however, also contain some unlinked styrene.[9] These products include packaging, insulation, fiberglass, pipes, automobile parts, drinking cups, other "food use" items, and carpet backing.[10] Emissions of styrene from these products or other building materials is considered a significant factor in indoor air pollution. In addition, municipal waste incinerators, the final resting place for many polystyrene prod-

facturing (8%) in 1996. Relative to toluene, the toxicity of styrene is less established (see Chapter 5).

Industries - Transfer and Release

When reported by broad industry categories, fabricated metal products (17% of total facility releases of listed chemicals), rubber and miscellaneous plastics (17%), petroleum refining and related industries (15%), transportation equipment (15%) and printing, publishing and allied products (8%) were lead releasers of listed chemicals in 1996. The top 20 specific industries releasing these chemicals are presented in Table 10, below. While these industries have been ranked for their direct releases of listed toxicants, offsite transfers may also pose a significant risk to human and environmental health (see discussion above).

Facilities - Release of Listed Chemicals

In 1996, 1388 facilities in California were required to report emissions and transfers of toxic chemicals under the Toxics Release Inventory; 592 released or transferred substantial quantities of one or more listed reproductive and developmental toxicants. The communities in California that host facilities using and releasing listed chemicals have, in many cases, experienced important benefits brought by those companies. They may be considered good neighbors by those who live nearby; many facilities, including some of those listed below, have already made progress in reducing emissions over recent years. That these manufacturers use or emit potentially harmful chemicals does not, in and of itself, negate these positive contributions.

Nevertheless, those facilities that continue to release high amounts of reproductive and developmental toxicants bear a unique responsibility to minimize exposures and develop safer alternatives. The top ten releasing facilities are listed in Table 11, below. Quebecor Printing released the greatest amount of listed toxicants in California in 1996. The company uses a high-quality printing process which requires intensive use of xylene and toluene based solvents -- chemicals that are required to control ink drying speed. Nearly all of its releases were to air. Georgia Pacific Resins Inc., maker of plastic plumbing products, ranks second in the state, largely due to releases of phenol and formaldehyde.

Note that the facilities presented in Table 11 were ranked for releases only, though chemical transfer data are also included. Ranking facilities by total release and transfer or transfer alone would have substantially changed this list.

Table 12
Facility Release of Listed Chemicals by County (1996)

Rank	County	Release (lbs)*	Transfer(lbs)
1	LOS ANGELES	3,727,800	12,658,417
2	ORANGE	1,627,069	11,462,938
3	SANTA CLARA	990,595	2,152,243
4	ALAMEDA	911,558	1,519,166
5	SAN JOAQUIN	504,535	90,920
6	SAN BERNARDINO	451,950	1,470,572
7	SAN DIEGO	304,716	242,623
8	CONTRA COSTA	279,485	1,358,356
9	AMADOR	237,736	-
10	RIVERSIDE	233,720	1,052,508
11	SACRAMENTO	218,562	154,957
12	SOLANO	160,583	912,224
13	BUTTE	143,173	1,500
14	GLENN	99,095	1,275
15	SANTA CRUZ	97,922	242,000
16	STANISLAUS	89,190	173,285
17	PLACER	69,401	97,000
18	MERCED	66,508	101,252
19	YOLO	63,669	-
20	COLUSA	49,520	10,326

*Transfers to sewage treatment facilities are considered releases.

Chemical Release by County

More than half of all facility releases of listed developmental and reproductive toxicants occurred in just three southern California counties, Los Angeles, Orange, and Riverside. In northern California, Santa Clara, Alameda, and Sacramento counties ranked highest for releases of listed chemicals.

Summary and Conclusions

The trends presented in this analysis indicate that pesticide use warrants invigorated scrutiny by policy makers for new opportunities in pollution prevention. Steady increases in reported use of pesticides identified as developmental or reproductive toxicants has out-paced decreases in releases of listed toxicants by manufacturing facilities, resulting in a net increase in the release of these chemicals in California from 1991 to 1995. Pesticide use comprises the bulk of total releases of these chemicals, dwarfing releases by manufacturing facilities by five

fold. As discussed elsewhere in this document, we have proliferated listed pesticides through our natural and urban environment, potentially causing exposures through the contamination of food, water, and air; and by use in our homes, offices, parks and schools.

A variety of theories have been forwarded by regulators and public interest organizations in an attempt to explain rising pesticide use. Theories include political and marketing influence by pesticide manufacturers, increasing chemical resistance by pests, climate change and changes in crop patterns. Most parties agree, however, that current laws and regulations do not seek to encourage pesticide use reduction, but rather focus on controlling pesticide exposure. As described in Part III (See Spotlight: California Pesticide Regulators Fail to Prioritize Public Health), political pressures also hamper enforcement of existing regulations. Given that much of our regulatory system does not attempt to advance safer alternatives, and that even existing regulations are thwarted with alarming frequency, we might reasonably expect continued proliferation of these chemicals under the status quo.

Releases by industrial facilities, on the other hand, have steadily declined over the five year study period, though reductions seem to have leveled off late in the period. Hopefully, reported reductions by industrial facilities represent actual progress in pollution prevention – better quality control, increased recycling, product substitution and changes in industrial processes – and are not merely "phantom" reductions as described above. To the extent that disclosure and reporting requirements under the TRI have provided incentives to reduce releases of listed chemicals, they appear to have been highly successful, perhaps providing an important lesson for pesticide use reduction. Relative to the Toxics Release Inventory, California's Pesticide Use Reporting System has been little used by regulators and public interest organizations and may bear untapped potential for creating incentives for reducing pesticides.

While releases of listed toxicants from facilities has declined, this success is only part of the story. Unlike facility releases, off-site facility transfers of listed toxicants have actually increased, on average, between 1991 and 1996, though transfers decreased in the most recent data year. As discussed above, these chemicals do not simply disappear, but often re-emerge into the environment, possibly from incinerator smokestacks, leaking landfills or ill-regulated recycling practices. Transfersfers d has

5 Kaplan, J., Van Loben Sels, C., Solomon, G., Broken Trust: How Cal-EPA has Kept Californians in the Dark about 66 Reproductive Toxicants, CALPIRG Charitable Trust, Natural Resources Defense Council, 1997, p. 8.

6 Ma, S., California: A Polluter's Paradise, California Public Interest Research Group Charitable Trust, November, 1997, p. 3.

7 Factory Farming, Toxic Waste and Fertilizer in California, 1990–1995, Environmental Working Group, Washington DC, 1998.

8 Toxicological Profile for Tetrachloroethylene: U.S. Dept. of Health and Human Services; Sciences International, Inc. August, 1995. p 155.

9 Styrene: Toxicological Profile; U.S. Department of Health and Human Services. Prepared by Life Systems, Inc. September, 1992. p 81.

10 Ibid.

11 Ibid.

12 Representatives of New United Motors (NUM) informed us that their estimated transfers for 1996 differ from values in U.S. EPA's TRI database. For the sake of consistancy, Table 11 presents the values as reported by the TRI database. NUM's corrected values differed significantly only for transfers of benzene (-220 lbs) and transfer of glycol ethers (+19,755 lbs) (changes are +- TRI values).

13 Representatives of Reynolds Metal informed us that their transfers of manganese for 1996 differs from the value in U.S. EPA's TRI database. For the sake of consistancy, Table 11 presents the value as reported by the TRI database. Reynold's corrected values for the Other Transfers of manganese is 138,093 lbs.

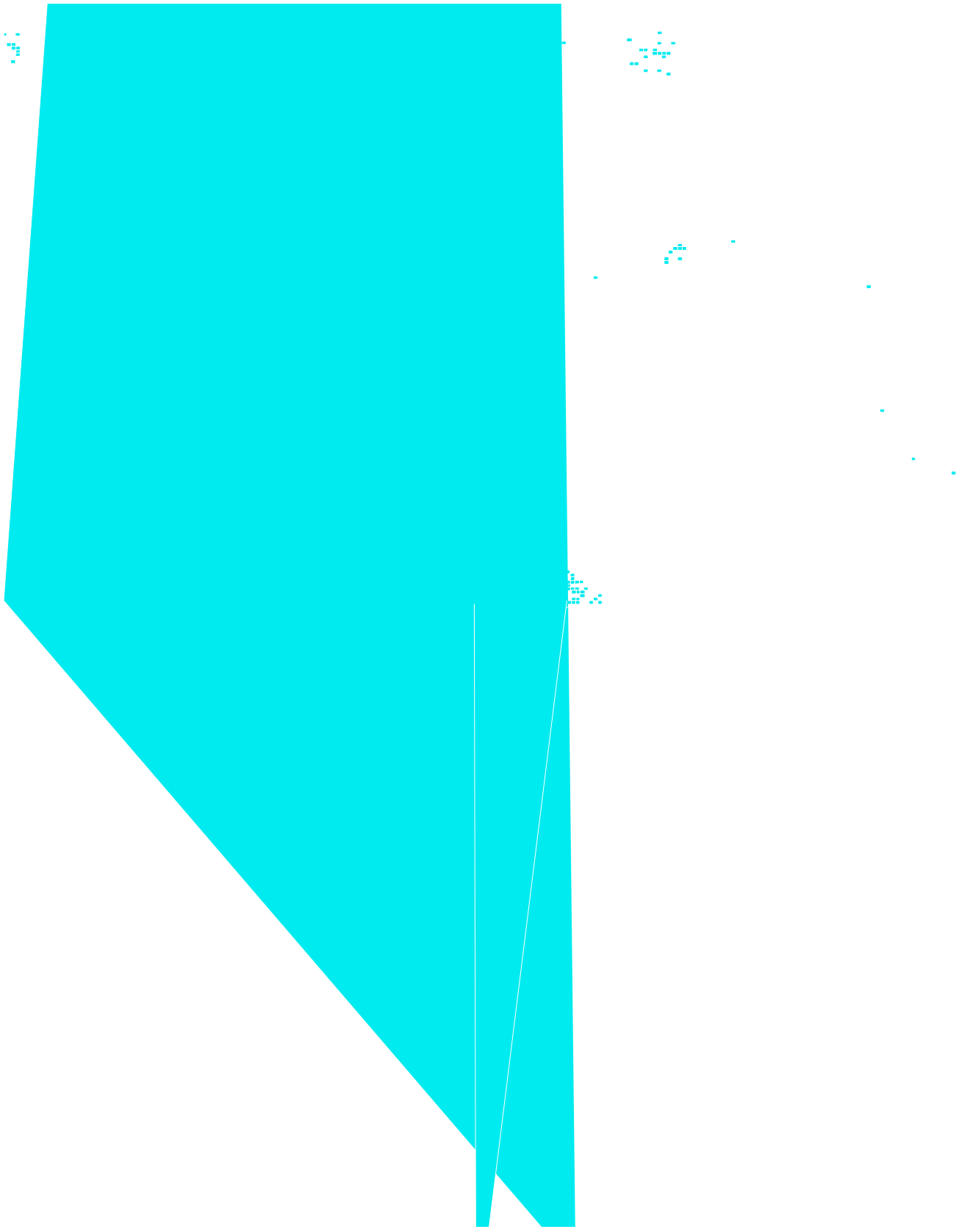
Appendix 1: Mapping Use and Release of Listed Chemicals

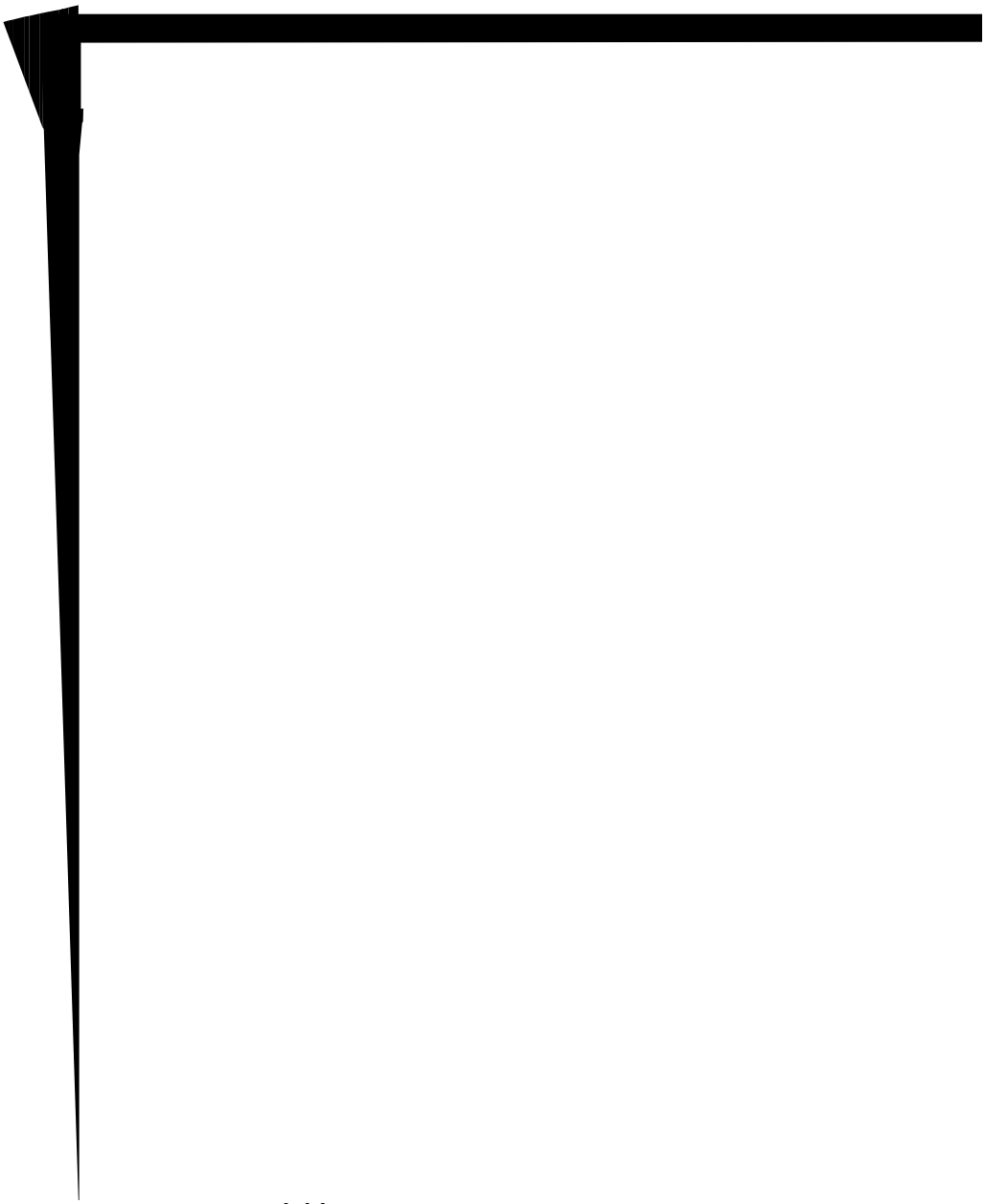
The maps in the following pages are intended to present a geographical thumbnail sketch of reproductive and developmental toxicant use in California. Regional maps provide bracketed intensity and location of listed pesticide use – those pesticides identified as Listed Chemicals throughout this report. Each square of pesticide use represents average reported use in a square mile (on average) and is presented to scale. Flags, denoting manufacturing facilities releasing Listed Chemicals, are positioned according to the reported latitude and longitude of the reporting facility. Because there are so many facilities on some maps, facility identification numbers (indexed below) may be missing or may appear near more than one flag. Facility identification numbers are referenced in a table beginning on page 143. All information about chemical use and release, release location and facility location is for 1995. Facility releases include all releases to air, water, land and transfers to sewage treatment centers (sewage treatment transfers have been subtracted from "Transfers" to avoid double counting).

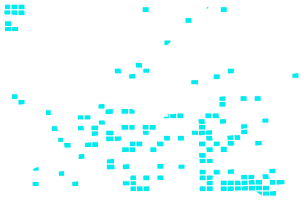
Sources:

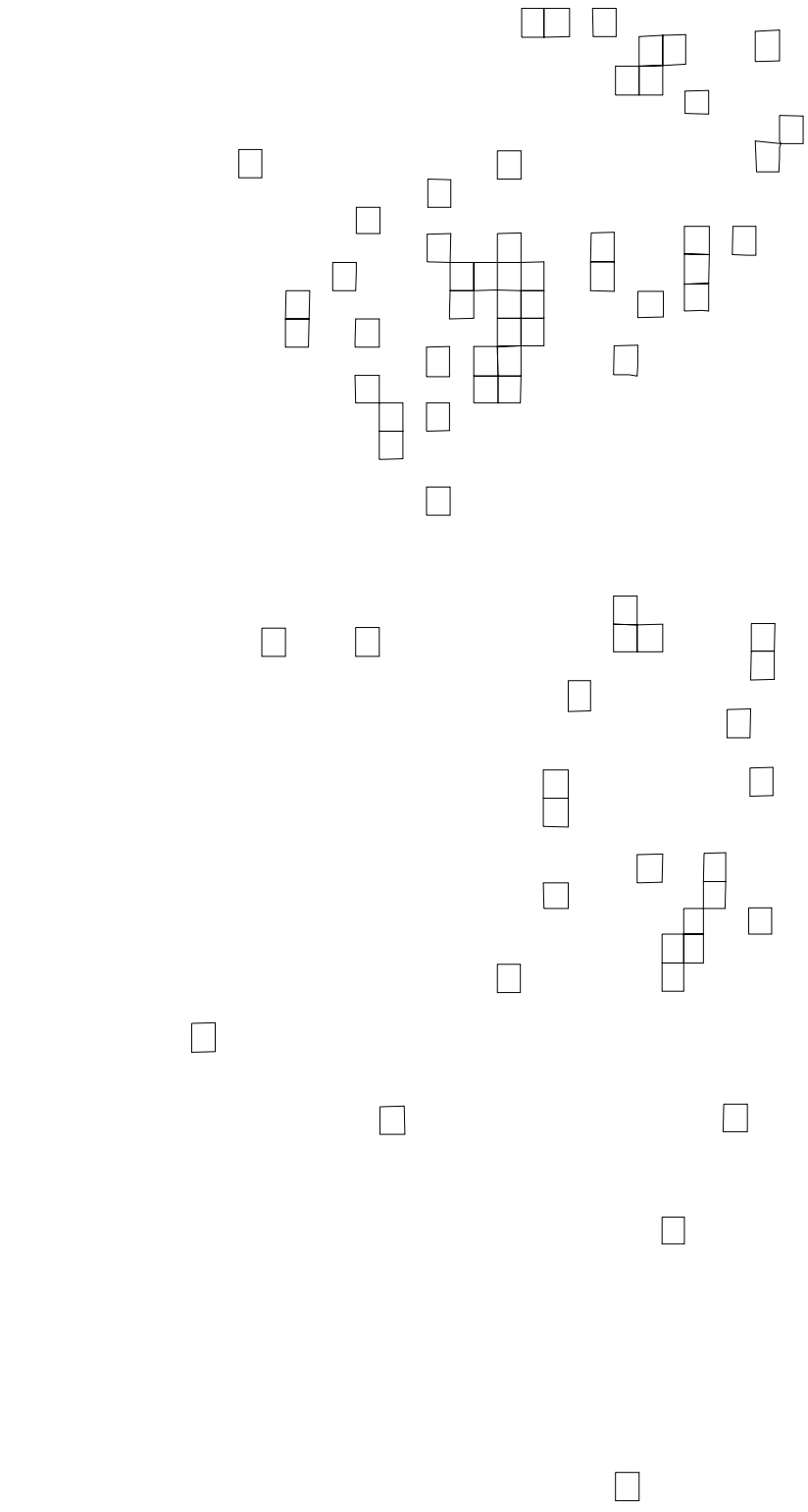
California Department of Pesticide Regulation, Pesticide Use Reporting Program, 1995;

Toxics Release Inventory 1995, made available by Right-to-Know Net, a project of OMB Watch and the Unison Institute









108	1,124	6,073	MAJOR PAINT CO.	TORRANCE
109	283,767	3,365	MOBIL OIL TORRANCE REFINERY	TORRANCE
110	11,839	-	KUSHWOOD MFG. INC.	BUENA PARK
111	3,668	-	REGAL CULTURED MARBLE INC.	LA HABRA
112	-	-	SHEPARD BROTHERS	LA HABRA
113	38,617	48,949	CROWN CORK & SEAL CO. INC.	LA MIRADA
114	63,670	62	XA CABINET CORP.	LA MIRADA
115	35,000	1,100	AMADA MFG. AMERICA INC.	LA MIRADA
116	26,116	14	BIZ & ASSOC.	LA MIRADA
117	750	2,836	BRENT AMERICA INC.	LA MIRADA
118	20	1,208	ROHM & HAAS CO.	LA MIRADA
119	6,300	5,450	LILLY IND. INC.	MONTEBELLO
120	115,010	3,570	ACTIVAR CO. INC.	PICO RIVERA
121	-	510	LUBRICATING SPECIALTIES CO.	PICO RIVERA
122	102,194	4,892	LEFIELL MFG. CO.	SANTA FE SPRINGS
123	33,000	4,700	PRECISION TUBE BENDING	SANTA FE SPRINGS
124	19,962	24,953	CONTINENTAL HEAT TREATING I	SANTA FE SPRINGS
125	3,100	-	FINE LINE PAINT CORP.	SANTA FE SPRINGS
126	2,640	10	PFI INC.	SANTA FE SPRINGS
127	893	-	GOLDEN W. REFINING CO.	SANTA FE SPRINGS
128	760	1,969,409	TROJAN BATTERY CO.	SANTA FE SPRINGS
129	500	-	CHEMIFAX	SANTA FE SPRINGS
130	250	-	CUSTOM CHEMICAL FORMULATORS	SANTA FE SPRINGS
131	142	344,093	TROJAN BATTERY CO.	SANTA FE SPRINGS
132	-	-	GLOBAL PROCESSING CO.	SANTA FE SPRINGS
133	5	1,100	BROWN-PACIFIC INC.	SANTA FE SPRINGS
134	750	-	WITCO CORP.	SANTA FE SPRINGS
135	63,699	75,350	POWERINE OIL CO.	SANTA FE SPRINGS
136	56,425	10,378	FOAM MOLDERS & SPECIALTIES	CERRITOS
137	30,261	-	FREDRICK RAMOND INC.	CERRITOS
138	9,030	125,900	VARIAN SAMPLE PREPARATION	HARBOR CITY
139	3,875	-	WARCO LABS. CO. INC.	HARBOR CITY
140	-	-	PRIME WHEEL CORP.	HARBOR CITY
141	24,800	2,300	ARROWHEAD PRODS. CORP.	LOS ALAMITOS
142	750	-	TOA MEDICAL ELECTRONICS USA	LOS ALAMITOS
143	706	37,900	IDEAL ROLLER CO.	PARAMOUNT
144	15	39,440	CERRO METAL PRODS. CO.	PARAMOUNT
145	-	-	R & S PROCESSING CO. INC.	PARAMOUNT
146	9,050	2,955	PARAMOUNT PETROLEUM CORP.	PARAMOUNT
147	27,900	139,100	TERMINAL ISLAND PLANT	TERMINAL ISLAND
148	112,395	8,916	UNOCAL	WILMINGTON

341	500	-	CLARK FOAM	LAGUNA NIGUEL
342	68,554	157,252	STEELCASE INC.	TUSTIN
343	16,012	-	JASCO CHEMICAL CORP.	SANTA ANA
344	5	5,327	SOLDER STATION ONE INC.	SANTA ANA
345	65,305	98,179	ARLON INC.	SANTA ANA
346	24,000	-	JACUZZI WHIRLPOOL BATH INC.	SANTA ANA
347	19,500	-	NEWPORT LAMINATES	SANTA ANA
348	4,122	23,923	MICROSEMI CORP.	SANTA ANA
349	2,866	-	MEDITERRANEAN YACHT CORP.	SANTA ANA
350	250	-	BAF IND.	SANTA ANA
351	11,900	5,100	EMBEE INC.	SANTA ANA
352	4,212	250	RICOH ELECTRONICS INC.	SANTA ANA
353	15,000	5,700	ASTECH MFG. INC.	SANTA ANA
354	35,653	-	BRISTOL FIBERLITE IND.	SANTA ANA
355	20,903	-	HOOD MFG. INC.	SANTA ANA
356	-	-	ALPHA METALS INC.	SANTA ANA
357	-	-	CHERRY TEXTRON	SANTA ANA
358	510	-	GALLADE CHEMICAL INC.	SANTA ANA
359	8,400	2,040	BASF CORP.	SANTA ANA
360	7,644	-	PROTOTYPE CONCEPTS INC.	FOUNTAIN VALLEY
361	510	31,375	DEFT INC.	IRVINE
362	-	6,184	RICOH ELECTRONICS INC.	IRVINE
363	-	-	BACON IND. INC. OF CA.	IRVINE
364	13,907	5,539	ELEXSYS INTL. INC.	IRVINE

460	125,132	97,642	REYNOLDS METALS CO.	HAYWARD
461	17,094	-	ACME FIBERGLASS INC.	HAYWARD
462	2,060	750	DEXTER PACKAGING PRODS. DIV	HAYWARD
463	-	-	SURTEC INC.	HAYWARD
464	-	-	DAVIS WIRE CORP.	HAYWARD
465	35,853	310,058	WHITE CAP INC.	HAYWARD
466	2,372	40	ROHM & HAAS CO.	HAYWARD
467	1,333	-	WASHINGTON CHEMICAL SALES O	HAYWARD
468	109	77,437	EKC TECH. INC.	HAYWARD
469	19,186	-	PACIFIC REFINING CO.	HERCULES
470	2,650	4,800	HEXCEL CORP.	LIVERMORE
471	38,973	8,661	SHELL MARTINEZ REFINING COM	MARTINEZ
472	34,156	404	TOSCO REFINING CO.	MARTINEZ

580	10,440	693,600	ALZA CORP.	VACAVILLE
581	24,500	-	FARMERS' RICE CO-OP. WEST	SACRAMENTO
582	500,351	5,657,819	GEORGIA-PACIFIC RESINS INC.	ELK GROVE
583	19,710	-	FORMICA CORP.	SUNSET WHITNEY RAN
584	63,669	-	LEER WEST INC.	WOODLAND
585	-	2,300	CALIFORNIA CASCADE WOODLAND	WOODLAND
586	3,181	-	CULTURED MARBLE PRODS. L.	SACRAMENTO
587	76,449	-	CAMPBELL SOUP CO.	SACRAMENTO
588	751	-	H. C. MUDDOX	SACRAMENTO
589	250	250	INTERMAG INC.	SACRAMENTO
590	162,956	25,785	U.S. AIR FORCE MCCLELLAN AI	SACRAMENTO
591	999	-	CHRISTY CONCRETE PRODS. INC	MARYSVILLE
592	-	7,652	PIRELLI CABLE CORP.	COLUSA
593	134,109	-	LOUISIANA-PACIFIC CORP.	OROVILLE
594	16	5	KOPPERS IND. INC.	OROVILLE
595	28,373	-	VIKING POOLS INC.	WILLIAMS
596	96,500	1,750	SCHULLER INTL. INC.	WILLOWS
597	21,540	-	SUNSET PLASTICS INC.	ANDERSON
598	-	750	J. H. BAXTER & CO.	WEED

As modern industrial society has evolved, we have developed the technology to manufacture more than 75,000

public and private funding sources and institutional affiliations of investigators and authors.

- Epidemiological Research — Aggressive research programs should be developed to address probable or possible reproductive and developmental toxicants. Human studies should include more emphasis on exposure assessment as well as health outcomes and should also investigate subtle developmental defects. Such studies, though complex, time-consuming, and expensive, are important and should be adequately funded.

Government / Regulatory

- Phase-Out Chemicals — The most dangerous reproductive hazards or the industrial processes that produce them should be phased out, especially those for which an alternative is available. Some examples are:

  1) Lindane (used for the treatment of lice) should be banned from direct use on humans and should be phased out of agricultural and forest use;

  2) Disincentives for the use of perchlorethylene in dry-cleaning should be developed, including gradually increasing fees on the chemical, while transfer to existing non-toxic alternatives is encouraged;

  3) Incineration of waste, both medical and municipal, should be avoided;

  4) Glycol ethers should be replaced by non-toxic alternatives.

- Right-to-Know — The public's right-to-know about exposure to, and potential toxicity of, chemicals used and released in their homes, communities, workplaces, and found in consumer products should be broadened because it is essential to public health. Expansion should include additional industries, more chemicals, lower reporting thresholds for extremely toxic chemicals, and chemical use data.

- Life Cycle Analysis — The economic costs of any product or substance must be based on a life cycle analysis including but not limited to direct and indirect costs to public health of extracting raw materials, manufacturing, transportation, storage, and disposal.

- Identification of Workplace Hazards — Material

or federal requirement.

- Voluntary Chemical Testing – Chemical manufacturers should generate and make publicly available com-

References

1. Healing Environmental Harm: Is There a Doctor in the House? Environmental Health Perspect 104(2) :150-153, 1996.

Part VI

Resources and Contacts – Where to Go From Here

Generations at Risk Resource Guide

There is no one comprehensive source for all information on a particular toxic hazard. It is important to remember that public agencies and private organizations may have very different goals and agendas, and that the way information is interpreted and presented must be analyzed and scrutinized for subjectivity and vested interest based on the stated goals of the agency or organization. The Internet is an excellent way to access information on many subjects. The following resources were selected based on currency and usefulness of information, as well as reliability to the best of our knowledge. It does not in any way constitute a complete list or imply an endorsement of any organization or product, but merely offers pathways for you to further your own research .

Notes: All World Wide Web addresses are preceded by http:// See other resources referenced at the end of individual chapters.

Federal Government Sources

United States Environmental Protection Agency (EPA)
401 M Street, SW Washington, DC 20460 (202) 260-7751 (Public Information Center) www.epa.gov There are 10 regional EPA offices throughout the country, call for the contact numbers. Access EPA (Publication number EPA 220-B-93-008), Government Printing Office (202) 512-1800. A guide to EPA's environmental services and databases. Provides phone numbers and contacts for EPA programs, libraries, and databases.

Selected U.S. EPA Internet sites:

www.epa.gov/epahome/r2k.htm - Excellent Community Right-to-Know page with links to food, air, water and land issues and databases such as the Toxics Release Inventory (TRI). Includes a link entitled "Concerned Citizens at the Workplace."

www.epa.gov/opptintr/tri - Toxics Release Inventory Homepage Database which provides information to the public about releases of toxic chemicals to the air, water and land from some manufacturing facilities EPA's Toxics Release Inventory User Support Service (TRI-US) helps citizens locate and access TRI data. Provides general information about the TRI and support for access to any of the data formats; comprehensive search assistance for the TRI on-line and CD- ROM applications; referrals to EPA Regional and state TRI contacts, libraries where TRI is available. (202) 260-1531, (202) 260-4659 FAX.

Federal Government Information Lines and Hotlines
(800) 638-2772 - Consumer Product Safety Commission Hotline.

(800) 535-0202 - Emergency Planning and Community Right-to-Know Hotline - Fact sheets on Toxics Release Inventory (TRI) state releases; includes state TRI contacts.

(800) 490-9198 - Environmental Publications and Information, National Center.

(800) 270-8869 - Food and Drug Administration's Office of Cosmetics and Colors Automated Information Line (202) 512-6000 - Government Accounting Office (GAO)-For copies of GAO reports www.gao.gov.

(800) 438-4318 - Indoor Air Quality Information Clearinghouse www.epa.gov/iaq/index.html Publications available free through the EPA IAQ Info Line include: The Inside Story: A Guide to Indoor Air Quality, April 1995 - (IAQ-0029) Carpet and Indoor Air Quality Fact Sheet, October 1992 (IAQ-0040) Indoor Air Pollution:An Introduction for Health Professionals, 1994 (IAQ-0052).

(800) LEAD-FYI - Lead Information Center, National - To obtain an information package (800) 424-5323 - To speak to an information specialist.

(800) 424-8802 - National Response Center Hotline - To report a chemical spill or a new hazardous waste site.

(800) 858-7378 - Pesticide Telecommunications Network - Provides scientific information on the toxicity and health effects of pesticides - Documents available include Citizens Guide to Pest Control and Safety and the EPA Catalog on Pesticide Publications

(800) 426-9346 - RCRA/Superfund Hotline - Information on solid and hazardous waste issues and Superfund sites.

(800) 426-4791 - Safe Drinking Water Hotline - Information on the Act and also on filters, state drinking water offices.

(202) 554-1404 - TSCA Hotline - Questions pertaining to the Toxic Substances Control Act. Or e-mail to tsca-hotline@epamail.epa.gov.

Other Federal Information Sources

Agency for Toxic Substances and Disease Control (ATSDR) U.S. Department of Health and Human Services (404) 639-6315, (404) 639-6315 FAX atsdr1.atsdr.cdc.gov:8080/atsdrhome.html Conducts public health assessments of waste sites, maintains health surveillance and registries, educates and trains on hazardous substances. Provides fact sheets on more than 100

development and enforcement related to air quality issues.

California Department of Toxic Substances Control, 400 P Street, Sacramento, CA 95812-0806, (916) 322-0476, www.cahwnet.gov/epa/dtsc. Regulates hazardous waste cleanup, storage, transportation, treatment, recycling and disposal.

California Office of Environmental Health Hazard Assessment, 601 North Seventh Street, Sacramento, CA 94234-7320, (916) 324-1945, www.calepa.cahwnet.gov/oehha/. Provides scientific evaluation of risk posed by hazardous substances to state and local government agencies. Implements the Safe

policy and public health implications of environmental hormones. Includes a section where you can submit questions on environmental hormones directly to the Centers experts.
http://www.tmc.tulane.edu/ecme/EEHome/default.html.

National Women's Health Network 514 10th Street, NW, Suite 400 Washington, DC 20004 (202) 628-7814 - Information Clearinghouse (202) 347-1168 FAX Women's health advocacy group. General women's health information and resource center. Publication available: Turning Things Around: A Woman's Occupational and Environmental Health Resource Guide, 1990. $9.95.

Pregnancy and Environmental Hotlines throughout the country maintained by Organization of Teratology and Information Services (OTIS) Free services that answer questions regarding pre-natal exposures 2128 Elmwood Avenue Buffalo, NY 14207 (716) 874-4747 There are over 30 members of OTIS. Referral to the hotline nearest you.

Chemical Alert: A Community Action Handbook. 1993. Edited by Marvin Legator and Sabrina Strawn. University of Texas Press. (512) 471-4032 Written for the citizen activist and medical professional, provides information on the health effects of chemicals and discusses strategies for communities to conduct their own health surveys. An update to the popular and very useful Health Detective's Handbook.

Designer Poisons. Marion Moses. Pesticide Education Center, San Francisco, CA, 1995.

Get to Know Your Local Polluter. 1993. Citizens for a Better Environment (CBE) (612) 824-8637, (612) 824-0506 FAX Provides a great example of how to use information on toxic chemicals in a way that produces results. The CBE model is one that is very adaptable to other locations.

Living Downstream. Sandra Steingraber. Addison Wesley, Boston, 1997.

Occupational and Environmental Reproductive Hazards:A Gal ri 0 79(,)3.

bers in California. CALPIRG addresses environmental, consumer and good government issues.

Californians for Pesticide Reform (CPR), 49 Powell Street, Suite 530, San Francisco, CA 94102 (415) 981-3939, www.igc.org/cpr. CPR is a coalition of over 100 California public interest organizations committed to reducing pesticide use. CPR serves as a clearing house for information and local organizing efforts and monitors state policy development.

CCHW (Center for Health, Environment and Justice) P.O. Box 6806 Falls Church, VA 22040 (703) 237-
CCHW Assistance and organizing on toxic hazards and

Pesticide Watch 116 New Montgomery Street #530 San Francisco, CA 94105 (415) 543-2627, (415) 543-1480 FAX For information on the "Model Cities Platform" to phase-out pesticides on schools, public lands and in public buildings.

Physicians for Social Responsibility– Bay Area Chapter, 228 Fulton St, #307, Berkeley, CA 94704, (510) 845-8395, (510) 845-8476 FAX, psrcassf@igc.org. Los Angeles Area Chapter, 1316 Third St. Promenade Suite B1, Santa Monica, CA 90401-1325, (310) 458-2694, (310) 453-7925 FAX, psrsm@psr.org. Conduct public education, research, and policy work related to environmental health issues. The national affiliate of the Nobel Prize-winning International Physicians for the Prevention of Nuclear War.

Right-to-Know Network (RTK Net) 1742 Connecticut Ave. NW Washington, DC 20009 (202) 234-8494, (202)234-8584 FAX www.rtk.net Established to empower citizen involvement in community and government decision- making. Provides free access to numerous databases including the TRI and IRIS, information on EPA enforcement actions and fines, chemical production, company pollution discharge permits, chemical effects, corporation environmental impacts, population statistics, and chemical accidents. Contains graphics files containing area maps, the CAMEO worst-case accident scenario modelling program, and discussion groups. RTK Net staff can assist. Excellent resource. Also, the Working Group on Community Right-to-Know. (202) 546-9707.

University of California Statewide Integrated Pest Management Program, University of California, One Shields Avenue, Davis, CA 95616-8621 www.ipm.ucdavis.edu. Provides summarized pesticide use data by chemical, year or site (target crop).

The most direct way to get information on company chemical hazards is from the company. However, many companies will not voluntarily provide sensitive environmental or business information. You may want to obtain information about the products the local company produces, its finances, or corporate officers.

Data: Where It is and How to Get It: The 1993 Directory of Business, Environment, and Energy Data Sources. Coleman/Morse Associates (410) 757-3197 Contains sections on understanding data, differences between good and bad data, as well as separate directories for business, environmental, and energy data.

Synthetic Organic Chemicals: United States Production and Sales. Government Printing Office (202) 512-1800 This publication is produced annually (through 1995) by the United States International Trade Commission and provides information about synthetic chemicals such as who manufactures the chemical, and for some, how much of it was produced and sold. Includes a directory of chemical manufactures with their addresses and phone numbers.

See also Material Safety Data Sheets and Hazardous Substance Sheets (See appendix 1 for an explanation).

California Occupational Health Program Hazard Evaluation and Information Service (HESIS) 2151 Berkeley Way, Annex 11, 3rd Floor Berkeley, CA 94704

Part VII

Index of Chemicals