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

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Organizations, Authors and Acknowledgments

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

Physicians for Social Responsibility (PSR) is a national organization of over 15,000 health care professionals and supporters which was founded in 1961. PSR works to address the public health effects of weapons of mass destruction, environmental degradation and community violence. With its international affiliate, International Physicians for the Prevention of Nuclear War, PSR received the 1985 Nobel Peace Prize for its efforts to eliminate nuclear weapons. The Greater San Francisco Bay Area and Los Angeles Chapters work to educate the medical community and the public about the linkages between environmental exposures and human health, and to encourage health professionals to participate in creating a sustainable and healthy environment. Members provide technical assistance and information on human health and environmental issues to citizens groups, health care providers, educational institutions and public policy makers.

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The California Public Interest Research Group (CALPIRG)

The California Public Interest Research Group (CALPIRG) is a non-profit, non-partisan public interest organization with over 70,000 members in California. Together with other state PIRGs across the country, CALPIRG has been at the forefront of the toxics movement for more than twenty years. The PIRG staff of attorneys, scientists, policy analysts, researchers and organizers have been instrumental in promoting the public's right-to-know about toxic chemicals and pressing government and industry to clean up and prevent toxic pollution. CALPIRG's Citizen Outreach Campaign reaches more than 250,000 households annually, and through its 7 campus chapters the organization helps to educate new generations of citizens and leaders.

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This report is the result of extensive collaboration among the four primary authors: Ted Schettler MD, MPH, member of Greater Boston PSR's Board of Directors; Gina Solomon MD, MPH, Co-Coordinator of the GSFBA Physicians for Social Responsibility Environmental Health Project and Senior Scientist with the Natural Resources Defense Council; Maria Valenti, Executive Director of Greater Boston PSR; and Jonathan Kaplan, MES Toxics Program Director of the CALPIRG Charitable Trust. Drs. Schettler and Solomon authored the major science sections of the report. Jonathan Kaplan researched and analyzed portions of the regulatory context and provided California-specific use and release data. All of the sections were reviewed extensively by project colleagues. Together, after numerous discussions with others, the authors developed a set of policy recommendations which they believe are entirely supported by material presented in the report.

Reviewers

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Contents

Executive Summary

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 and developmental effects are of concern because of important consequences for couples attempting to conceive and because exposure to certain substances during critical periods of fetal or infant development may have lifelong and even intergenerational effects.

Unfortunately, toxicological information is often incomplete. Animal testing usually looks at health effects using one chemical at a time. This strategy fails to provide information about interactive effects which may occur with exposure to more than one chemical. Moreover, animal tests often fail to examine for subtle, delayed, or difficult-to-diagnose conditions. Epidemiological (human) studies are often limited by inaccurate exposure assessments and incomplete information about health outcomes. Further complicating matters, the federal government is reducing its support for research and information analysis. Corporate funding is filling the void, providing an opportunity for bias in study design and data interpretation.

Some Chemicals Known, Some Suspected, as Reproductive Toxicants

Some of the specific synthetic chemicals or metals reviewed in this report are known to harm human reproduction or development. Lead and mercury, for example, disrupt brain development in the fetus. Solvent exposures are associated with spontaneous abortions in female workers. Several specific solvents have additional adverse effects — glycol ethers damage male reproductive function, and toluene causes birth defects at high levels of maternal exposure. Many Californians, particularly farm

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, detergents, cosmetics, and pesticides. While the full significance of some of these newly recognized or suspected reproductive and developmental toxicants is not yet clear, there is reason for concern about a wide range of chemicals and their potential effects on human health.

The Need for Policy Reform—Using Precaution as a Guide

Laws which regulate human and environmental exposure to hazardous substances generally take one of two possible approaches — "better safe than sorry" or "innocent until proven guilty." We believe that a "better safe than sorry," or precautionary approach, should guide risk management and regulatory decisions. This means that the issue of safety should be thoroughly considered before human and environmental exposures are permitted. No hazardous substance should be allowed to slip through the cracks because of a lack of information, time, or funding. Where there is some evidence of human or environmental toxicity, the precautionary approach demands that exposures be avoided or minimized.

Federal legislation which regulates pesticides and pharmaceuticals, for example, intends that manufacturers provide evidence of safety before a product is released for use — a seemingly cautious approach. But for many pesticides which were in use for years and "grandfathered" when EPA took over the pesticide registration process, safety studies are seriously inadequate. The special review process designed to address these deficiencies will not be complete for years. Moreover, despite the legislative intent, animal testing used to support an application for new pesticide registration currently fails to examine adequately for subtle and delayed toxicity. Furthermore, 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 (recent legislation would address the problem of cumulative pesticide exposures, though it remains unclear if the law can or will be effectively implemented). Finally, there is no comprehensive evaluation of the impact such chemicals may have on the environment generally.

For most industrial chemicals, however, there is no absolute requirement for advance demonstration of safety before the product enters the commercial market. For example, under the Toxic Substances Control Act, the only legislation which addresses chemicals not covered by other laws, the Administrator of the Environmental Protection Agency must have reason to believe that a substance poses unreasonable risk to health or the environment before proposing controls - i.e., the chemical is "innocent until proven guilty." Though the law states that the Administrator should have adequate data on which to base a decision, there are no standard testing protocols which are required before the chemical is released for use. And, with chemical manufacturers announcing more than 1,000 chemicals for production annually, the political and economic pressures to avoid thorough safety review are enormous. Appropriate screening and testing have never been practical possibilities under existing law. Moreover, industry has frequently abused "confidential business information" provisions in the legislation, effectively concealing the nature of industrial chemicals to which many people are exposed.

What Right-to-Know Data Reveal:

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

The federal Toxics Release Inventory (TRI) and the California Pesticide Use Reporting Program are two landmark laws that require public disclosure of chemical release by large manufacturing facilities and pesticide applicators, respectively. Each is based on the fundamental principle that individuals have the right to know the identity of substances to which they are or might be exposed. Because of the TRI, information is now available throughout the country about emissions of some toxic substances from selected industrial sources. In California, information about pesticide use is also available.

This report quantifies the use and release of 78 "listed chemicals" which have been identified as reproductive and developmental toxicants by government agencies or by weight of the evidence published in the scientific literature, as evaluated by the authors (see Table 1). In addition to this list, this report discusses the reproductive and developmental effects of additional chemicals for which use and release data are not available or for which the weight of evidence was not deemed sufficient for listing. For a variety of reasons, many chemicals are not adequately reported under the Toxic Release Inventory or the Pesticide Use Reporting Program.

Table 1: Chemicals Identified as Developmental and Reproductive Toxicants

2,4-DB	LEAD
2,4-D	LINDANE
ACEPHATE	LINURON
AMITRAZ	MALATHION
ANILAZINE	MANCOZEB
ARSENIC	MANEB
ATRAZINE	MANGANESE
BENOMYL	METAM SODIUM
BENZENE	METHOXYCHLOR
BROMACIL, LITHIUM SALT	METHYL BROMIDE
BROMOXYNIL	METHYLENE CHLORIDE (DICHLOROMETHANE)
CADMIUM	METRIBUZIN
CARBARYL	MOLINATE
CARBON DISULFIDE	MYCLOBUTANIL
CHLORPYRIFOS	N-METHYL-2-PYRROLIDONE
CHLORSULFURON	NALED
CYANAZINE	NITRAPYRIN
CYCLOATE	OXYDEMETON-METHYL
CYPERMETHRIN	PARATHION
DI(2-ETHYLHEXYL) PHTHALATE	PENTACHLOROPHENOL (PCP)
DIAZINON	PERCHLORETHYLENE (TETRACHLOROETHYLENE)
DICAMBA	PERMETHRIN
DICLOFOP	PHENOL
DICOFOL	PROMETRYN
DIENOCHLOR	PROPARGITE
DIMETHOATE	SIMAZINE
DIURON	STYRENE
ENDOSULFAN	TAU FLUVALINATE
EPTC	TEBUTHIURON
ETHYLENE OXIDE	TETRACHLORVINPHOS
FENBUTATIN-OXIDE	THIABENDAZOLE
FENOXAPROP ETHYL	THIOPHANATE-METHYL
FENOXYCARB	TOLUENE
FENVALERATE	TRIADIMEFON
FLUAZIFOP-BUTYL	TRICHLOROETHYLENE
FORMALDEHYDE	TRIFORINE
GLYCOL ETHERS	VINCLOZOLIN
HEXACHLOROBENZENE	XYLENE
IMAZALIL	ZIRAM

Environmental releases by California manufacturing facilities of chemicals with evidence of reproductive toxicity have declined substantially over the most recent five year period for which data are available. Emissions of these listed chemicals have declined 47% between 1991 and 1996, to 10.6 million pounds in the most recent year. However, the amount of these chemicals reported transferred offsite for recycling, treatment or disposal has increased, on average, over this time period, totalling 35.3 million pounds in 1996 (though transfers decreased from 1995 to 1996). Many of these transfers will inevitably re-circulate into the environment via leaking landfills, incinerator emissions or unsafe recycling practices.

Industries transferring and releasing the bulk of these chemicals include:

Fabricated metal products
Rubber and miscellaneous plastics
Petroleum refining
Transportation equipment

Toluene, styrene, glycol ethers, perchlorethylene and methylene chloride (also called dichloromethane) were all released in large amounts by California facilities. Toluene comprised 18% of total releases by manufacturing facilities. Several studies have demonstrated an increased risk of spontaneous abortion in women exposed to toluene in the workplace. The chemical 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.

Approximately half of all facility releases of listed developmental and reproductive toxicants occurred in two southern California counties –Los Angeles and Orange. In northern California, Santa Clara, Alameda, and Contra Costa ranked highest for releases of listed chemicals.

Relative to reported releases by manufacturing facilities, California pesticide applicators are using and releasing many more pounds of reproductive and developmental toxicants. Fifty eight million pounds of these pesticides were reportedly used in 1995. Furthermore, use of reproductive and developmentally toxic pesticides is increasing steadily, rising by almost 3 million pounds per year between 1991 and 1995. Numerous studies suggest that pesticide exposure is widespread and a high percentage of the population currently carries pesticide residues in body tissues and fluids.

Like total California pesticide use, the bulk of use for those chemicals identified as reproductive and developmental toxicants occurs in agriculture. Agricultural pesticide use poses high exposure risk to farmworkers and may also be a source of significant exposure for those living in rural communities, consuming contaminated groundwater or eating pesticide residues on food. Approximately 40% of listed chemicals applied as pesticides were used on carrots, cotton, strawberries and almonds in California.

Listed pesticides were also used extensively for non-agricultural applications. Over three million pounds were applied in and around buildings in California in 1995. In a recent CALPIRG survey, half of 46 California school districts – representing one in four of all California school children – reported using pesticides identified by U.S. EPA as reproductive and/or developmental toxicants in schools and on school grounds.

As expected, the bulk of these chemicals are used in the Central Valley, the nation's agricultural epicenter. Highest using counties include Fresno, Kern, Imperial, Monterey, Tulare, Merced, San Joaquin, Stanislaus, Kings, and Riverside counties.

To the degree that right-to-know laws have contributed to the decrease in emissions they have been useful for protecting public health. However, their ultimate validity rests in their recognition of the public's right-to-know, irrespective of incentives they provide for reducing toxicant use and releases. Such laws ensure that the public has the information required to make policy decisions and give individuals access to information they may need to protect themselves. We support efforts to expand each of these laws to include chemical use information; add additional industries and hazardous substances; and to make the data more readily available and understandable to the general public. We also encourage greater use of the Pesticide Use Reporting Program, both to encourage pesticide use reduction and generate demand for improving this under-utilized resource.

Policy Recommendations

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

1. Minimization of Chemical Use and Exposure

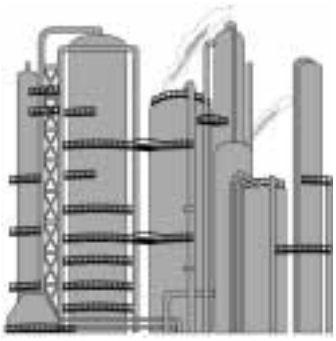
Strategies to eliminate unnecessary use, switch to safer alternatives, and a goal of zero-discharge of toxic chemicals should inform our decision-making.

2. The Precautionary Principle

The burden of proof must be placed on the industrial producer to prove that their chemicals are safe for use, rather than on the government or the public to prove that human health is being harmed.

3. Right-to-Know, Right-to-Education, Right-to-Training

We believe that all members of the public, both in and outside of the workplace, have the right to be fully informed about the chemicals that they are likely to come in contact with and the potential health hazards associated with those chemicals. Adequate information and education is essential for responsible personal and public decision-making where chemical exposure and proliferation may occur. Finally, disclosure has proven to be a highly effective tool in creating incentives for pollution prevention.



Introduction

Though it has been known for decades and, in some instances, centuries, that harmful health effects may result from environmental exposures, cancer often dominates the public agenda, receiving the most attention. There is, however, ample reason for concern about other health outcomes which may be subtle, delayed, difficult to diagnose, and not easy to link causally to specific exposures. Non-cancer effects include neurotoxicity, adverse effects on the immune system, reproduction and development, and injury to other individual organs. Reproductive and developmental toxicity are of concern not only because of important consequences for couples attempting to conceive but also because exposure to certain substances during critical periods of fetal or infant development may have lifelong and even intergenerational effects.

This report is the result of a collaboration between public health professionals, environmental organizers, and policy advocates. It is designed to raise awareness about known and suspected threats from reproductive toxicants in our environment and to provide a resource to help inform citizens, the medical community, advocacy groups, policy makers, growers, and industry. It is our hope that it will help to bring about changes necessary to minimize human exposures to potentially harmful substances.

In some cases there is compelling evidence of a cause-and-effect relationship between exposure to certain substances and reproductive or developmental disorders such as infertility, spontaneous abortions, and structural or functional birth defects. In others, the science is less clear, but a developing body of evidence is suggestive. Often, crucial missing information makes it impossible to draw definitive conclusions. These data gaps may result from incomplete animal toxicity testing and epidemiological studies which are inadequate or inconclusive. Information about human exposure to potentially toxic chemicals is also severely limited. Excessive workplace exposures are often unmeasured and unreported. Estimates of the use, release, and exposure to many chemicals with endocrine-disrupting potential are unavailable.

But important information is also missing because of inadequate attention to the relationship between human health and the environment. A comprehensive awareness of that relationship requires that one understand an illness not just as an individual condition but also as a public health concern. Because medical education is generally deficient in addressing the link between human health and the physical environment, health-care personnel are often ill-equipped to recognize, much less treat, illnesses with environmental causes. We need to address these important deficiencies in medical education and research. Medical practice from an expanded public health perspective offers additional insights and opportunities. It does not shy away from using appropriate political action as a tool for protecting human health.

Yet even as this report demonstrates examples of major information deficiencies, public funds for medical and scientific research are being reduced. Increased corporate funding is helping to fill the void, and in the process, influencing the fundamental nature of studies and raising the possibility of inappropriate bias in the presentation of data. In this report, for example, we describe how commercial corporate interests caused the intentional suppression of information about the spermatotoxic effects of a pesticide (DBCP) when pesticide regulation was under the control of the US Department of Agriculture. As a result, hundreds of agricultural workers were sterilized. Successful recent efforts to reduce EPA funding will not only limit the agency's oversight and enforcement capacity but also its research agenda and potential to broaden the scope of existing right-to-know requirements.

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 developmental physiology, a brief review of basic principles of reproductive toxicology, and general discussions of epidemiology and animal toxicity testing introduce what follows. These sections will be useful to some — unnecessary for others. As the reader will quickly see, it is virtually impossible to address the reproductive toxicity of all substances to which humans are potentially exposed. With over 75,000 synthetic chemicals currently in commercial use, and an estimated 1,000-2,000 newly introduced each year, the task is enormous. In many cases, their health effects are unstudied and unknown. Consequently, the reviews of solvents, metals, and pesticides focus on substances to which many people are regularly exposed and provide examples of the strengths and weaknesses of current toxicological information and investigation. We have included a section on endocrine disruptors as a subject of considerable recent concern which demonstrates the limits of our understanding of an important mechanism of toxicity.

Each section concludes with a summary of the weight of evidence implicating the substance of concern as a reproductive toxicant. We have consciously omitted any discussion of the reproductive risks of alcohol, tobacco, drug use, and radiation. These hazards are well known and are repeatedly and adequately described elsewhere. Their absence from this document does not imply a lack of concern.

The risk of an adverse health effect depends on more than the presence of a hazardous substance. One must also be sufficiently exposed. All too often accurate assessments of human exposure are simply unavailable making the likelihood of harm impossible to estimate. The federal Toxics Release Inventory and the California Pesticide Use Reporting Program data begin to address that problem by requiring some industries and pesticide users to report their releases of listed chemicals. Part IV of this report, “The California Picture,” includes an analysis of relevant data from those sources. Though use and release of hazardous substances does not necessarily imply broad human exposure, the limited reporting requirement begins to document and quantify the possibility, and in many cases, likelihood of exposure. As such, these data are an important first step.

Elsewhere the substances of concern might be different as other states may have industrial operations peculiar to their region. But the medical literature reviews and discussion of right- to-know legislation will continue to be of assistance to those not familiar with the material. Those who find the introductory material elementary should move directly to other sections of the document which may be read as stand-alone pieces. Consider the rich bibliographies and list of available resources at the end of the document for additional information.

In this document we have identified a pattern of continuing exposure to some known, highly-likely, or suspected

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.

Part I

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.

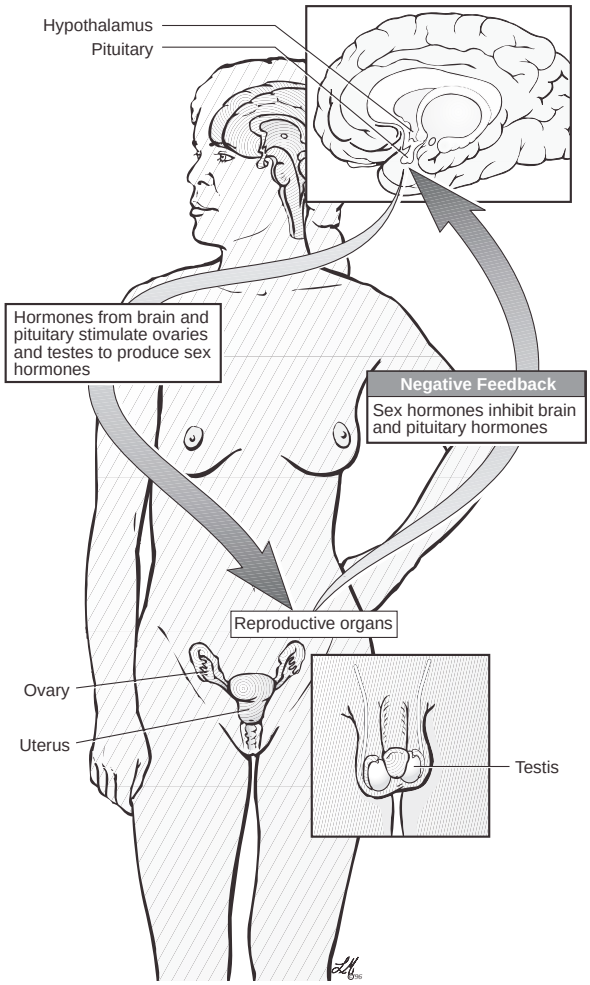


Figure 1 — A negative feedback loop in hypothalamic-pituitary-gonadal (HPG) hormonal communications tends to keep sex hormones at constant levels. In males, the feedback loop is always negative. In females, it fluctuates between negative and positive.

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 testosterone. LH is directly responsible for testosterone production by Leydig cells. FSH enhances the effects of LH on the Leydig cells and also interacts with Sertoli cells which are necessary for sperm production.

To maintain normal hormone levels, rising amounts of testosterone cause a decrease in LH secretion from the pituitary forming a negative feedback loop. Sertoli cells themselves produce *inhibin*, a hormone which reduces FSH production, forming a similar negative feedback loop.

In women, a pulsatile release of GnRH controls production and release of FSH and LH from the pituitary. Estrogen production in the ovary depends on FSH and LH stimulation. When estrogen reaches a particular critical circulating level for 36 hours, the feedback loop switches from negative to positive, and a surge of LH and FSH secretion leads to ovulation.

The resulting *corpus luteum* in the ovary secretes progesterone and estrogen, once again suppressing FSH and LH secretion from the pituitary. If fertilization fails to occur, levels of FSH and LH again begin to rise, recruiting a new set of follicles for development for the next menstrual cycle.

Prolactin is another pituitary hormone with a wide range of actions. Its primary and best known role is maintenance of milk production by the breast during lactation. Its secretion is spontaneous and does not require stimulation from the hypothalamus. In fact, inhibition of prolactin secretion is maintained by a chemical (*dopamine*) reaching the pituitary from the hypothalamus. Although all the functions of prolactin are not well understood, it is also involved in testosterone production by the Leydig cells in male mammals. Elevated levels of prolactin may be associated with diminished FSH and LH secretion causing disorders of ovulation or infertility.

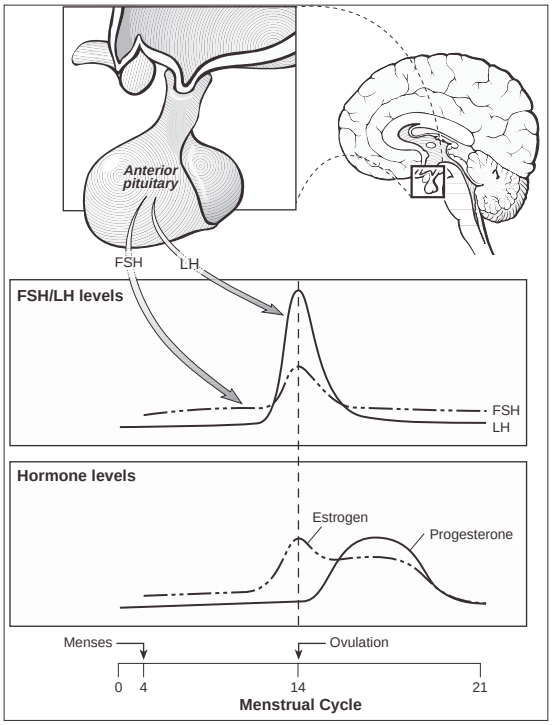


Figure 2 — Pituitary and ovarian hormone levels fluctuate throughout the female menstrual cycle showing both negative and positive feedback loops. FSH (follicle stimulating hormone) and LH (luteinizing hormone) are from the pituitary, estrogen and progesterone from the ovaries.

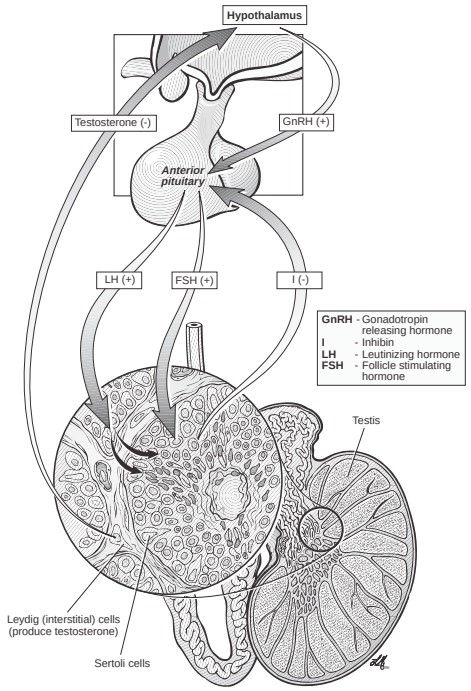


Figure 3 — Negative feedback loops characterize the male hypothalamic-pituitary-gonadal system.
I = inhibin; GnRH = gonadotropin-releasing hormone;
+ = stimulate; - = inhibit

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).

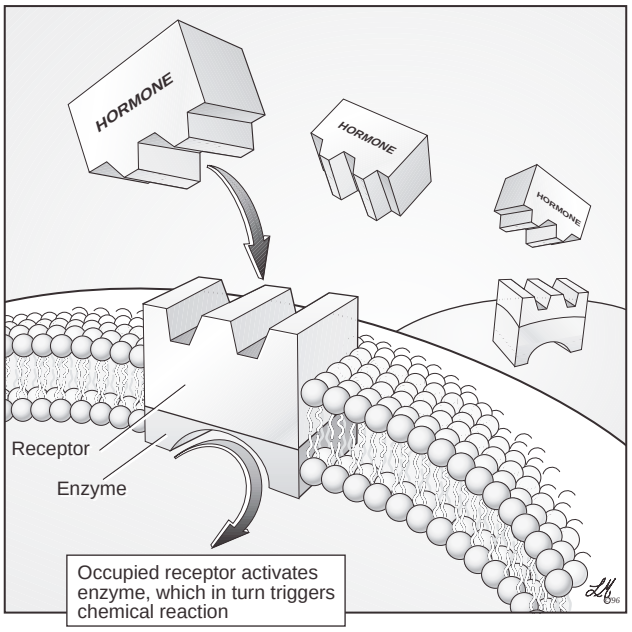


Figure 4 — The lock-and-key model of hormone-receptor interaction necessary for a hormone to trigger biochemical activity in a cell.

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 (*Leydig cells*), and 3) those that protect and nourish the developing sperm. The latter, known as *Sertoli cells,* help to form a *blood-testis barrier* which isolates the developing sperm from harmful substances which might be circulating in the blood.

Unlike females, males continue to produce sperm throughout their lifetime provided the immature germ cells (*stem cells*) remain healthy. Immature sperm mature in seminiferous tubules in the human in about 70 days. A convoluted tubule, the *epididymis,* transports sperm away from the testis over about 6 days.

Normal Fetal Development

General Principles

- *As cells divide in embryonic development, each becomes progressively more committed to a particular fate.*
- *As each cell becomes more committed, it loses its ability to develop in other ways.*

The newborn infant consists of millions of cells which come from a single cell — the fertilized egg. These cells are of many different types which, hopefully, have arrived at the right place at the right time, functioning normally. This extraordinary series of events is accomplished by the following strategies.

Early in development, each cell is flexible and capable of developing in a variety of ways. For example, the heart, kidney, and intestine all develop from the same primitive cell type. At an early stage of embryonic development, each of the primitive cells still has the capacity to develop into each of the three organs. Later in development, as the cells continue to divide and become more specialized, that capacity is lost. A cell committed to dividing along the lines of kidney cells can no longer switch back to develop in heart or intestinal directions. The very young embryo, therefore, is often less susceptible to structural birth defects than to lethal damage. If a chemical or physical injury does not kill it, it may still be able to develop into a normal infant since the cells still have considerable flexibility and damage can be repaired.

Formation of Organs *(Organogenesis)*

- *Different organs form at different times during gestation.*
- *The functions of organs, as well as their structures, may develop over prolonged periods of time.*
- *Humans develop a blood-brain barrier by six months of age which helps to protect the brain from toxic exposures. However, until that time the brain is vulnerable.*

Formation of organs begins early in gestation. However, not all parts of the body are formed at the same time. For example, development of the eye and brain begins early; the palate and genitals begin to form days later. Many structures and functions — for example, the brain, immune system, or the development of particular biochemical enzyme systems important for the metabolism of toxicants and drugs — continue to mature throughout pregnancy and well after birth.

Sexual differentiation of the body and brain begins early. Male sexual development results from hormonal suppression of female characteristics.

Normal Brain Development / Sexual Differentiation

1. The period of time necessary to complete basic brain nerve connections extends from the first part of pregnancy until several years after birth. This long period of brain development results in a long period of vulnerability to toxic exposures which cross the placenta during pregnancy and those which occur during infancy and early childhood — through breast milk, food, inhalation, skin absorption, etc. The brain has limited repair capacity. Unlike some other organs, the injured brain is not capable of replacing injured cells though it is able, in some instances, to shift functions to uninjured areas.

2. Sexual differentiation of the brain also takes place during fetal development. The very early embryo has the capacity to develop into a male or female child but under the influence of sex hormones, the brain permanently takes on male or female characteristics, influencing the hypothalamic-pituitary-gonadal connections and full sexual development.

3. Development of the hypothalamus is critical during the fetal period and early years of life. The hypothalamus secretes its hormone-regulating chemicals through blood vessels directly into the pituitary. During development, it sets the life-long baseline levels of those hormone regulators — much like a thermostat sets the temperature in a room. There may be fluctuations of hormone levels around the baseline, but the baseline itself is not re-adjusted.

4. The *blood-brain barrier* differs among embryos, newborns, and adults. The adult brain is partially protected from toxic substances by a blood-brain barrier which keeps many chemicals circulating in the blood from coming into contact with the brain tissue. However, the embryo has no blood-brain barrier in any portion of the brain. It is not complete until about 6 months of life in humans (3 weeks in rats). Even then, the hypothalamus has no blood-brain barrier — it is never protected throughout life. It remains vulnerable.[1]

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.

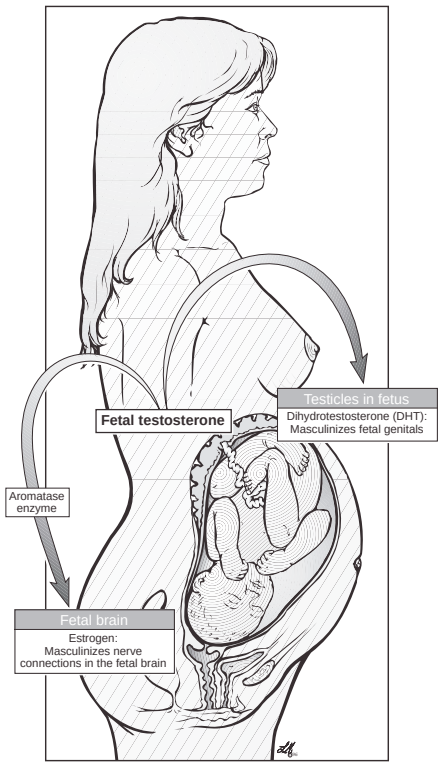


Figure 5 — Testosterone from the fetal testes is chemically altered in two ways. It is converted by an enzyme to estrogen, necessary, along with testosterone, for masculinizing the male fetal brain. It is also converted by a second enzyme to DHT, required for further male genital development.

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.

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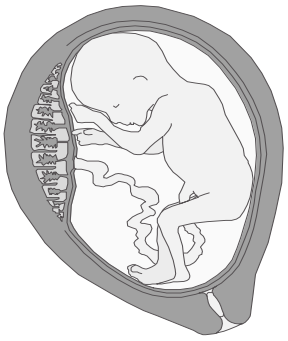
Chapter 2

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 infant life varies considerably, even among mammalian species.[1] Since actively growing and dividing cells are more vulnerable to chemical or environmental injury than resting cells, the "window(s) of vulnerability" will also vary among species. Translation of animal data to humans must be done with care.

Sites of Action

Individual reproductive toxicants may exert their adverse effects directly or indirectly on any of the organs or biochemical processes discussed above. This includes not only the ovaries or testes but also the brain, pituitary, and processes of communication among them.

Toxic Effects on the Ovary

- *The ovary has two essential functions — egg production and hormone synthesis.*
- *Either of these may be disrupted by toxic environmental exposures.*
- *Menstrual disorders, infertility, or developmental defects in offspring may result.*

Any of the basic cell types in the ovary may be damaged by environmental exposures, interfering with either of the two basic ovarian functions — hormone synthesis and egg production.

In humans, *malfunction of ovulation* results in abnormalities of the menstrual cycle or reduced fertility. These, of course, may have causes other than toxic exposures. Since every woman is born with all of the follicles and eggs that will be available throughout her reproductive life, any toxicity which results in egg or follicular destruction may result in premature menopause.

Egg or follicular toxicity is difficult to detect since there are always significant numbers of follicles which degenerate in each menstrual cycle. Even in animal studies where the ovaries are microscopically examined after exposure of the animal to a possible ovarian toxicant, it is difficult to determine if an excess number of follicles has been lost.

Abnormalities of hormone production may result from *damage to cells in the ovarian follicles* before ovulation or from exposures after ovulation leading to abnormal function of the corpus luteum. Recalling that the primary role of the corpus luteum is to produce the hormones necessary for implantation of the fertilized egg in the uterus and for early development of the placenta and fetus, *abnormal luteal function* may result in very early spontaneous abortion. Examples of substances which interfere with corpus luteum function include estrogens and estrogen-like compounds, which suppress progesterone production, and polycyclic aromatic hydrocarbons, which are found in cigarette smoke or in the products of fuel combustion.

Toxic agents which interact with *genetic material* on chromosomes in the egg may result in congenital abnormalities, inheritable disorders in future generations, developmental delays, or even cancer in offspring.

Toxic Effects on the Testes

- *Testicular toxicants may decrease sperm counts, cause infertility, or alter hormone production.*
- *There is some evidence that toxic environmental exposures may be responsible for an increased incidence of testicular cancer.*

Chemicals toxic to the testes may decrease sperm counts or damage sperm, cause infertility, and alter hormone production. As in the ovary, each of the various cell types of the testes is a potential target for environmental exposures. *Leydig cell toxicity* results in decreased testosterone production. *Sertoli cell toxicity* indirectly lowers sperm counts since these cells are necessary for the health of immature sperm. A toxicant which reduces the number of Sertoli cells formed during fetal development results in permanently lower sperm counts.[2]

The *blood-testis barrier* may be disrupted. This barrier results, in part, from tight connections between Sertoli cells and when intact, is able to protect *immature sperm* from toxic exposures. Its breakdown may result in sperm damage. In sufficient quantity, toxicants like lead, cobalt, and cadmium are harmful to the *blood vessels* in the testes, also causing damage to the Leydig cells and seminiferous tubules.[3] As sperm cells mature through progressive stages of development, susceptibility to toxicity varies.

Much about sperm production and function and cellular interactions in the testes is not well understood. Toxicity studies usually examine both the number and quality of sperm. The form (*morphology*) and movement of sperm

are important factors though toxicologists are not in full agreement about which is most predictive of abnormal fertility or pregnancy outcome in humans.
As with the egg, toxic effects on the *genetic material* of the sperm may result in pregnancy loss or inheritable disorders. There are reports of associations between paternal occupational exposures and congenital anomalies, cancer, and developmental abnormalities in offspring.[4]

There is also emerging evidence that fetal exposures to chemicals which have hormone-disrupting properties may predispose an individual to the development of testicular cancer years later. We discuss this more fully in Chapter 7 (Endocrine Disruptors) along with other delayed health effects.

Toxic Effects on Hypothalamo-Pituitary-Gonadal (HPG) Connections

Normal function of the testes or ovaries is dependent on intact HPG hormonal communications. Toxicants which interfere with function of the hypothalamus or pituitary gland may cause malfunctions which resemble those associated with direct toxicity to the ovaries or testes.
Examples include toluene and other organic solvents, a wide variety of pharmaceutical drugs, marijuana, and environmental agents which possess hormone-like activity.

Developmental Toxicology

Toxic Effects on the Developing Embryo/Fetus

■ *Developmental toxicants may result in fetal death, altered growth, and structural or functional abnormalities.*

Fetal effects of toxic exposures vary widely, from *death* to *altered growth.* Visible deformities (for example, cleft lip/palate) or those detectable on additional physical examination (for example, many types of congenital heart disease) or at autopsy represent structural *developmental defects*. The causes are often obscure. In humans, it is estimated that about 50% of major malformations are due to genetic or inheritance abnormalities; 3-4% to a specific, identifiable toxicant; and over 40% to unknown causes.[5]

Functional developmental defects are not necessarily visible but result from abnormal hormonal or biochemical processes which affect the way that various organs work. A normal appearing brain, pituitary, or thyroid gland may actually function abnormally because of a fetal toxic exposure or genetic abnormality. For example, fetal or infant lead exposure may interfere with mental function for years. In animal studies, small exposures to dioxin during a critical time of fetal life permanently alter certain hormone levels.[6] Concern about functional developmental defects has increased considerably as modern industrial society has increased the menu of potential toxicants to which large populations are exposed and as better understanding of the mechanisms and evidence of toxicity has evolved.

Developmental neurotoxicity, one kind of functional damage, has become an important subject of study. Some chemicals with only a temporary or weak effect on the brain in adults may have permanent effects on the developing brain, influencing intellectual function, sexual differentiation, and behavior.

The number of *hormone receptors* may be permanently increased or decreased by chemical exposures during fetal life or infancy. Fetal exposure to hormones or hormone-mimics at levels which have no effect on adults may set lifetime baseline levels of hormone production at inappropriate levels.

Similarly, fetal environmental exposures may influence the development and competence of the *immune system* with implications for the entire life of the offspring.

Principles of Abnormal Development of the Fetus

Several principles of *teratology* (the study of abnormal development) provide a basis for understanding the toxicity of individual or mixtures of chemicals.[7]

1. *Abnormal development may result in death of the embryo or fetus, altered growth, malformation, or functional disorders.*

2. *Susceptibility to abnormal development depends on the genetic makeup of the embryo and its interaction with the environment — that is, some embryos are more vulnerable than others.*

3. *The ability of toxicants to cause abnormalities varies with the stage of fetal development at the time of exposure.*

a) Some toxicants are lethal to an embryo at one stage

of development but cause structural or functional deficits at other stages. Some are able to cause structural defects in offspring even when the mother is exposed at the time of fertilization or pre-implantation (animal studies with hormones and ethylene oxide.)[8] Recent studies demonstrate that there may actually be multiple periods of particular susceptibility to developmental harm in particular organs.[9]

b) The exposure level (dose) of toxicant required to harm the embryo or fetus may change with the stage of development.

4. *Each teratogenic agent may act via one or more specific mechanisms on developing cells and tissues to initiate abnormal development.*

5. *Access of a potential toxicant to developing tissues depends on the nature of the toxicant.*

a) In order for an environmental exposure to directly affect a developing fetus, it must be able to cross the placenta. Most maternally administered substances have the potential to cross the placenta but at varying rates depending on the chemical nature of the agent.[10]

b) A reproductive toxicant may only exert its adverse effects if it is first absorbed, ingested, inhaled or otherwise internalized and makes its way to a target tissue. If it is not blocked or metabolized into a harmless substance, if it is present in sufficient quantity, and if the timing and duration of the exposure is correct, it may then exert an adverse effect.

c) The target tissue may or may not be able to repair the damage.

6. *Manifestations of abnormal development increase in degree as dosage increases.*

These include the entire spectrum of possible harmful effects. Some are subtle or delayed and occur with small exposures at critical times during development.

A Spectrum of Health Effects in Reproductive and Developmental Toxicology: What to Look For

- *A reproductive toxicant may cause reduced fertility or infertility, menstrual abnormalities, or miscarriage.*
- *A developmental toxicant may cause fetal death, malformations, growth alterations, or functional deficits in the offspring.*
- *Studies of developmental toxicity are difficult to design since some harmful effects are not immediately apparent and testing is complex.*

There is a range of possible health effects caused by exposure to potential reproductive toxicants. They are not always easy to identify or study. *Infertility* or reduced fertility may result from maternal, paternal, or couple-dependent factors. Investigating the cause in any couple requires assessment of each of these. Following fertilization of the egg, pregnancy loss (*miscarriage*) is a common adverse outcome. Studies show that up to 35-50% of *all* pregnancies may result in spontaneous abortion. Early miscarriages are frequently unrecognized even by the mother who may believe that she is only experiencing a slightly delayed menstrual period.[11]

Possible harmful *developmental effects* of toxic exposures include prematurity, malformations, retarded growth, mental retardation, metabolic and immunologic abnormalities, altered behavior and sexual differentiation, cancer, and infant illness or death.

Death of the Fetus — A Wide Range of Causes.

It is useful to distinguish between early and later fetal death since the causes are often different. One scheme defines spontaneous abortion as death of a fetus of less than 500 grams or 20-22 weeks gestation — stillbirth as death of a fetus over 500 grams.[12] Studies designed to determine the frequency of spontaneous abortion using very sensitive hormone measurements show that up to 50% of all pregnancies result in spontaneous pregnancy loss. Many of these are unrecognized. Genetic studies indicate that the most common cause of recognized early loss is fetal chromosome abnormalities. As the pregnancy progresses, other causes become more common and include maternal genital tract abnormalities, maternal illness, immunological abnormalities, and toxic exposures. The wide range of possible causes makes it difficult to attribute any particular spontaneous abortion or stillbirth to a toxic exposure with certainty.

Manifestations of Reproductive and Developmental Toxicity Studies: Female-, Male-, or Couple-Related Endpoints

Female	Menstrual cycle irregularities, hormone abnormalities
Male	Semen and hormone abnormalities
Couple	Infertility, increased time-to-pregnancy, pregnancy loss (spontaneous abortion, stillbirth), retarded intrauterine growth, birth defects, developmental defects

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.

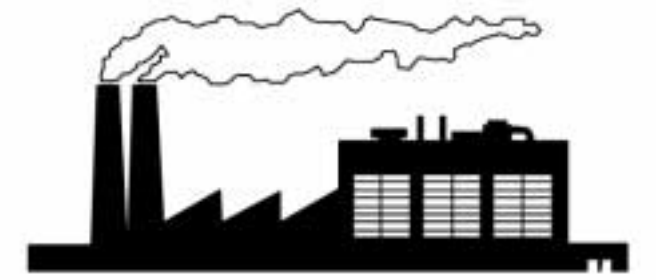
Functional abnormalities resulting from events during pregnancy may not be obvious to visual inspection or initial physical examination of infants — in fact, they may not become apparent for years. A registry of birth defects which depends on reports of abnormalities within a short time after birth is 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 Toxicity Studies

Many substances will show some evidence of reproductive or developmental toxicity to animals if large amounts are given. The question then is whether or not those results have any relevance to human exposures at lower levels. This is particularly problematic with *long-term, low-dose* human exposures which begin in the uterus and continue through the reproductive years.

The answer to the dilemma is not obvious. Throughout the intricate processes of the menstrual cycle, egg and sperm production, fertilization, implantation, and growth and development of the fetus, there are specific and often *short time intervals* when there may be *particular susceptibility* to *low-dose exposures*, undetected if studies are not designed to reveal them. Furthermore, if reproductive or developmental testing does not include careful examination for neurological, behavioral, or immunological changes in test animals a chemical may inappropriately be classified as safe for human exposure. In recognition of these uncertainties, the EPA and FDA continue to make important modifications to their animal testing protocols for pesticides and pharmaceuticals. But there are still significant data gaps. Many pesticides widely used for decades have had little developmental toxicity testing.[13] There is also disagreement or uncertainty about interpretation of test results. The emphasis continues to be on chemical-by-chemical analysis rather than examination of cumulative and multiple exposures which characterize the real world.

For most industrial and consumer-product chemicals, including many which are pervasive in the environment, the information is sketchy at best.[14] Many have had no reproductive or developmental testing.



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Additional Reading

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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 purposes is done only with single chemicals. This approach ignores interactive properties among substances that may significantly alter their toxicity. Exposure to mixtures of chemicals from multiple sources more accurately characterizes the real world in which humans and animals live. Scattered through this document are several examples of health effects of such interactions.

Dose-Response Considerations

- *The dose of a potential reproductive or developmental toxicant has three important characteristics — the amount, timing, and duration of exposure.*
- *Exposures of short duration may be important if they occur at critical "windows of vulnerability" or if they are repetitive and the chemical is stored in the body.*
- *Different doses of a particular toxicant may produce different health effects.*
- *The dose necessary to cause a specific health effect may change substantially depending on the developmental stage of the fetus.*
- *For reproductive and developmental health effects, regulatory agencies attempt to identify the threshold dose below which no harmful effects are likely.*

The amount, timing, and duration of exposure are critical to the ability of a potential toxicant to cause harmful effects. Each must be considered in toxicity studies of specific chemicals. Critical "windows of vulnerability" often make a developing fetus exquisitely sensitive to small amounts of a toxic substance — amounts which have no detectable effects at other times. Chemicals that are maternally stored extend the time frame of concern. They may have harmful effects on the fetus or infant long after maternal exposure. Examples are lead, stored in maternal bone but released during pregnancy, and PCBs, stored in fat tissue but delivered to a nursing infant in milk.

Large exposures of a potential toxicant may cause one type of health effect — smaller exposures, another. For example, large lead exposures cause lowered sperm counts in men. Pregnant women may experience spontaneous abortions or stillbirths. Lower maternal exposures do not interrupt the pregnancy but interfere with brain development of the child. Each of these health effects will have its own dose-response curve.

In developmental toxicology, the time when developmental commitments of embryonic cells are irreversible helps to determine the likelihood, degree, and type of damage from an exposure. Early exposures, if not lethal to an embryo, may be repairable. As an example of the

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 reproductive and developmental toxicants in our environment. In order to better understand a discussion of possible health effects of exposure to various chemicals, it helps to be familiar with the strengths and weaknesses of some of the different types of human studies that are done to assess these health effects.

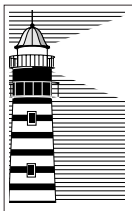
Epidemiology is the study of the patterns and causes of disease in human populations. It is useful for investigating associations between exposures and outcomes or in pinpointing groups at increased risk of an outcome. Because epidemiology studies populations, not individuals, it is of little use in predicting an outcome for a particular person. Thus, it is possible to say that exposure to organic solvents increases the risk of spontaneous abortion by 2-5 fold, but it is usually not possible to say whether a particular spontaneous abortion in an exposed woman was due to solvent exposure or to other factors.

It is important to remember that most adverse reproductive and developmental outcomes (infertility, spontaneous abortion, birth defects, menstrual problems, etc.) have multiple causes and that some of these causes are still unknown. Epidemiology tries, and often fails, to tease apart multiple associations, to clarify how much each is likely to be causal, and how much each contributes to the overall burden of the disease in the population.

Epidemiologic studies can have great difficulty attributing *causation*. Studies will generally report an *association* between a specific exposure and a certain outcome. For example, there is a clear association between exposure to lead and learning and behavioral problems in children. An association such as this could be due to chance, to other unmeasured exposures (confounding), or to bias (see below). Alternatively, it may represent cause and effect. The only way to move from saying that two factors are associated to saying that one causes the other is by repeated studies over time in animals and humans that yield a consistent, biologically plausible result, the finding of an appropriate time sequence with the exposure clearly coming before the effect, and results of a sufficient magnitude to be persuasive.

Table 1
Summary of Types of Epidemiologic Studies

Time:	Past	Present	Future
Case-Control:	Exposure<----------	Outcome	
Prospective Cohort:		Exposure---------->	Outcome
Retrospective Cohort:	Exposure---------->	Outcome	
Cross-Sectional:		Exposure & Outcome	



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 widely used chemicals – those produced or imported at volumes exceeding a million pounds per year – fail to meet internationally accepted minimum testing requirements outlined by the Organization for Economic Cooperation and Development (OECD).[3] As detailed in the table below, widely used chemicals lack testing in every category of health risk:

Type of health risk	Percent of chemicals tested
immunotoxicity	14%
neurotoxicity	33%
carcinogenicity	37%
toxicity to reproduction	47%
developmental toxicity/teratogenicity	~60%
genetic toxicity	~79%

Even for high-volume chemicals that are known to be released into the environment (because they are covered under the Toxics Release Inventory (TRI) , and shown as being released on TRI reports), the ignorance problem was conspicuous: 51% of such chemicals lacked minimum screening data in the public record. Because of the right-to-know focus on TRI chemicals, it might have been expected that they, at least, would have had preliminary health screening tests completed.

This finding underscores an important point: even though TRI chemicals have all been found to have at least one potential hazard already (a condition of making the TRI list), more than half haven't had basic screening for other health hazards.

Other studies stimulated by EDF's Toxic Ignorance report, both by U.S. EPA and by the chemical manufacturing industry itself, have confirmed EDF's results.

1. This spotlight is taken from excerpts of: Environmental Defense Fund, Inc, Environmental Health Program, Toxic Ignorance, The Continuing Absence of Basic Health Testing for Top-Selling Chemicals in the United States, published by the Environmental Defense Fund, 1997.
2. National Research Council. Toxicity Testing. Washington DC, National Academy Press, 1984.
3. Only includes OECD's criteria for "Toxicity Data," namely acute toxicity, repeated dose toxicity, genetic toxicity (in vitro), genetic toxicity (in vivo), reproductive toxicity and developmental toxicity/teratogenicity. This list does not include chemicals that may lack testing for environmental behavior and ecotoxicity. OECD. SIDS Manual (Second Revision): Screening Information Data Set Manual of the OECD Programme on the Cooperative Investigation of High Production Chemicals. Paris, France, May, 1996. Ch. 1, p. 3.

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.

The Ideal Study

The ideal study needs to be tailored to the question to be answered and to the particular outcome and exposure of interest. Rare outcomes (such as particular, unusual birth defects) are easier to study using the case-control approach involving selection of a group of children with the birth defect and a healthy comparison group and working backward to try to estimate exposures. A cohort study would require following huge numbers of exposed and unexposed people over many years to see if some of them might bear children with the rare defect.

Conversely, if the exposure, rather than the outcome, is rare, then a cohort study would be more suitable. For example, a study of whether cadmium exposure increases the risk of spontaneous abortion would be better designed if it followed a cohort of cadmium-exposed workers than if it identified groups of women with and without spontaneous abortions. In the latter case, it would be fairly unlikely that any of the women would report cadmium exposure during pregnancy. In addition, a cohort study may allow accurate measurement of exposure rather than estimates based on a reconstruction or on a questionnaire. Cohort studies may also be better at detecting a subtle association between a particular outcome and an exposure.

Sometimes there is no ideal study and each of the current epidemiologic methods is ill-suited to the situation or fraught with pitfalls. For example, investigation of a community where residents perceive a cluster of birth defects can be frustrating to all concerned. Case-control studies in this type of situation often are unable to assign people to exposed and unexposed groups with any degree of certainty. The result is usually random exposure misclassification and a negative study. Similar pitfalls await a retrospective cohort study in such a community. A prospective cohort study that accurately assessed exposure would be expensive, take years to complete, and would not be able to include the birth defects which had already occurred in the community — those which triggered the residents' concern in the first place. Thus no type of epidemiologic study is perfectly suited to answer questions about perceived clusters of a disease in a community.

Statistical Significance

Depending on the degree to which a particular exposure contributes to a particular outcome, a study may need to involve a large group of people. For example, to detect a real risk of spontaneous abortion which is 20% greater in a group of exposed vs. unexposed women in an industrial setting, the study group would have to be much larger than if the risk were increased by 80%. Therefore, a small study that finds no effect from an exposure may have failed to detect an effect because of insufficient numbers of study subjects (known as lack of *statistical power*), not because the chemical actually has no effect.

Discussions of epidemiologic studies often focus on whether or not the results are *statistically significant.* The conventional, though arbitrary, definition of statistical significance is that the result found in the study would be expected to occur by chance alone less than 5 times out of 100. This is often written in statistical shorthand as $p<.05$.

There are two important things to recognize about statistical significance. Clusters of adverse outcomes, such as birth defects, in certain towns or in certain factories can occur by chance alone. Distinguishing these flukes of chance from clusters due to a chemical exposure may be very difficult. The other important point is that epidemiologic studies are very conservative by design. A study may find a striking, consistent association between an exposure and an outcome, but if it is possible for that association to occur by chance alone, even only 6 to 10 percent of the time, it is still reported as not statistically significant and is often dismissed as if there is no evidence of an association. This dismissal of essentially positive results as if they are negative is a result of convention in the field of epidemiology and is due to a decision that it is better to miss an association that really exists than to claim an association that does not really exist.

It is important to keep in mind that humans are usually exposed to a great many substances in the workplace and

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.

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Part II

Chapter 4

Heavy Metals

- *Lead is a developmental toxicant at very low doses.*
- *Organic mercury is toxic to the developing brain.*
- *Inorganic mercury may lead to spontaneous abortions and birth defects.*
- *Cadmium is toxic to male reproduction and to the placenta in animals.*
- *Arsenic may lead to spontaneous abortion and stillbirth.*
- *Manganese may damage the developing brain and interfere with male reproduction.*

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, while some animal studies suggest that chromium and nickel damage fetal development.[1] Other metals such as tellurium, gallium, and indium, which have only recently come into widespread use as a result of high-tech applications, have some early indications of reproductive and developmental toxicity. These metals pose a potential hazard for future generations which cannot yet be quantified. For the purposes of this review, we will concentrate on the effects of lead, mercury, cadmium, arsenic and manganese.

Lead causes infertility in exposed males and spontaneous abortion in women exposed at high levels. Strong evidence suggests that lead exposure also leads to subtle neurological effects, developmental delays, and behavioral abnormalities in otherwise normal-appearing children. Mercury was responsible for two major epidemics of spontaneous abortion and birth defects in human populations. Organic mercury compounds cause brain damage to the developing fetus and result in microencephaly (small brain), cerebral palsy, and mental retardation.

The reproductive effects of cadmium, arsenic and manganese, by contrast, have not been well studied in humans. In animals, cadmium damages the testes and interferes with sperm production, and may interfere with normal lung development and predispose to respiratory distress syndrome in the newborn. Some evidence suggests that cadmium is toxic to the human placenta, and may thereby lead to spontaneous abortions and birth defects. Arsenic causes a characteristic set of malformations in lab animals exposed at high levels. In addition, some human studies suggest that arsenic exposure may lead to spontaneous abortion and stillbirth and may affect neurological development, particularly the development of hearing. Manganese is an important metal because it is a new gasoline additive and may be even more widespread in the environment in the future. Animal studies and a few human studies indicate that manganese may interfere with hormone production and damage reproductive function in men. In addition, manganese is toxic to the fetal brain.

Lead

- *Causes infertility in men, and spontaneous abortion at high doses*
- *Causes developmental delay and behavioral problems in children at very low doses*

Uses and Routes of Exposure

In its natural state, lead is found only in the earth's crust. Humans have mined and used lead ore for thousands of years, resulting in lead pollution of water, air and soil. Lead is now found in the bodies of all living things on the planet, and throughout the environment, including the polar ice caps. Most current environmental exposures to lead in this country come from lead paint exposures, though people are also exposed through the water supply, usually from leaching of lead from pipes. Additional sources of exposure include lead glazed pottery, certain medicinal and cosmetic preparations which are used by a variety of ethnic groups, and food grown in contaminated soil. Some occupations and hobbies often involve exposure to lead (see table 1). The phase-out of lead in gasoline and the end of the use of lead solder in commercial food canning have greatly reduced lead exposures

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).

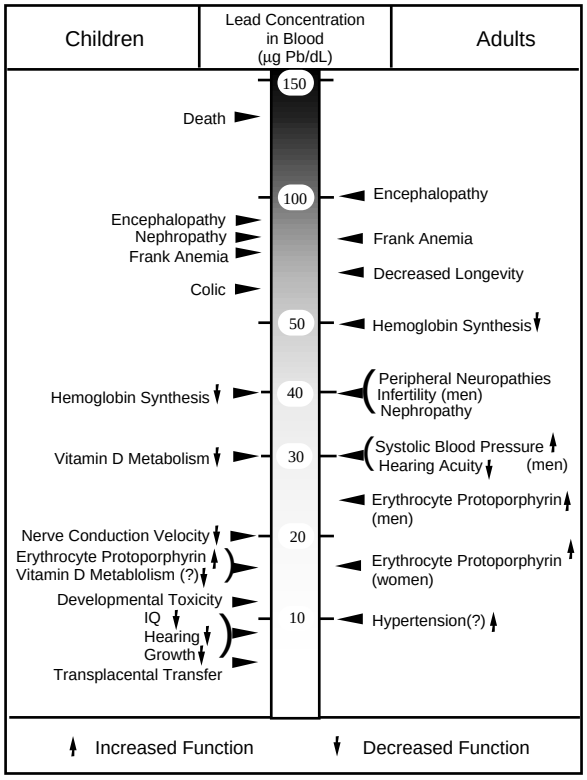


Table 2: Health Effects of Lead at a Range of Doses

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 1990 governmental study stated that "every pregnancy potentially represents a risk if the mother has a blood lead level of 10 µg/dl or higher." The authors estimated that 4.4 million women of childbearing age have blood lead levels over 10 µg/dl and projected that in the next ten years over 4 million fetuses would be at risk because of maternal lead exposure in the United States.[7] The EPA has listed 10 µg/dl as the maximum acceptable blood lead level for fetuses and young children, and the Centers for Disease Control recommends action to monitor and lower lead levels in children with higher levels. Almost 22% of African-American children one to two years old currently have blood lead levels over 10 µg/dl.[8]

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.[21] Though this study was small and the results were not statistically significant, it suggests that early lead exposures may affect subsequent reproductive ability, not surprising given what we know about lead storage in bone.

Effects at Low Doses

The most worrisome effect of lead at exposure levels close to the U.S. average is developmental toxicity to the fetus, which may permanently affect neurologic and behavioral development. There is an apparent relationship between rising blood lead levels and pre-term delivery, low birth weight, and fetal growth retardation.[22 23] This relationship is evident down to blood lead levels under 10 µg/dl. While one study demonstrated an association between minor birth defects and umbilical cord blood lead levels, overall there is little evidence that lead causes birth defects.[24] The main effects of lead on the fetus are as a growth retardant and as a neurologic toxicant.

Lead has long-term effects on behavior and intelligence in infants born to mothers with blood levels of 10-25 µg/dl. Developmental delays in lead-exposed children persist at least until five years of age. One study followed children into adulthood and found a seven-fold increased risk of non-graduation from high school, and a six-fold increased risk for reading disability in children exposed to lead as toddlers.[25 26 27] Though not all studies have found an effect on mental development at these low doses, the studies which have were well-conducted and persuasive. Several recent reviews of the literature have concluded that lead exposure, even at blood lead levels at or below 10 µg/dl, is linked with impaired neuro-behavioral development, low birth weight, and intrauterine growth retardation.[28 29] A recent report also found that lead in bone, a measure of lifetime exposure, is significantly correlated with aggressive and delinquent behavior in eleven year old boys.[30] Effects of lead on the brain appear to occur both after prenatal and post-natal exposure. Monkeys exposed from birth to doses of lead that maintain their blood lead level at 15 µg/dl showed increased distractibility, inappropriate responses to stimuli, and difficulty in changing response strategy.[31] The evidence is persuasive that lead has subtle harmful effects on brain development even at quite low levels.

Summary

Lead is a well-recognized reproductive and developmental toxicant. In workers with high occupational exposures, lead diminishes fertility and causes spontaneous abortion. Lower lead levels have not been well studied for their possible effects on the male reproductive system or on pregnancy in the partners of exposed males. Low lead levels result in fetal developmental delay, prematurely, and lasting deficits in concentration, learning and behavior among children exposed in utero. There is no evidence of a threshold dose below which these effects do not occur. Despite the reduction of lead use in this country, the continued use of leaded gasoline around the world, the persistence of lead in soil, and the continuing problem of lead paint in houses make the effects of lead certain to persist in this country and to worsen worldwide over the coming years.

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]

Elemental mercury is only a significant hazard when inhaled, but the vapor pressure is low, so it can be inhaled at room temperature. For this reason, a broken thermometer should be disposed of by sweeping, not vacuuming, the mercury. The heat of the vacuum cleaner vaporizes the mercury into the air. People may be exposed to mercury in the air from waste incinerators burning batteries, switches, fluorescent bulbs, or medical waste, or from oil or coal burning, since mercury is a contaminant of these fuels.[34] Once elemental mercury is in the body it passes easily into the brain and across the placenta to the fetus.

Organic Mercury

Organic mercury exposure resulted in two large epidemics of mercury poisoning in recent history. One episode, in the area around Minamata Bay in Japan, occurred in the 1950's (see spotlight), and the second series of outbreaks occurred in Iraq in the late 1950's, early 1960's, and early 1970's, when grain imported for planting was treated with organic mercury to retard fungal growth. Instead of being planted, the grain was used for bread-making, and thousands of people were poisoned. Although adults were affected, the main victims of the exposure in both epidemics were children exposed before and after birth.

Organic mercury selectively damages the developing brain. In the outbreaks of poisoning described above, infants had cerebral palsy, mental retardation, incoordination, weakness, seizures, visual loss, and delayed development.[35 36 37 38] Often a child exposed to organic mercury appeared fairly normal at birth, with only slight abnormalities of reflexes and muscle tone, but later had seizures, long delays in learning to walk and talk, and severe clumsiness. At lower dose levels, the only observed effects were abnormal muscle tone and reflexes and mild developmental retardation when re-tested at an older age.[39] The doses involved in these outbreaks were 10–100 fold greater than doses most

Table 3 Profile of the Three Major Forms of Mercury

Elemental Mercury Vapor	**Inorganic Mercury**	**Organic (Methyl) Mercury**
Used in dental fillings, thermometers, batteries, switches, florescent bulbs.	Found in electrical equipment, some fungicides, antiseptics, and medications, and in skin-lightening creams.	Fungicide in paints.
A contaminant in coal and oil; used in gold mining and chlorine manufacture.		
Emitted by waste incinerators, oil and coal burning.		Other forms of mercury are transformed into this in the environment.
Absorbed through the lungs. Poorly absorbed if swallowed.	Not usually inhaled. Absorbed slightly through the skin or if swallowed	Rapid absorbtion if swallowed. Some absorption via lungs, skin.
Crosses the placenta. Enters the brain.	Does not enter the brain or cross the placenta easily.	Crosses the placenta, enters the brain, is found in breast milk.

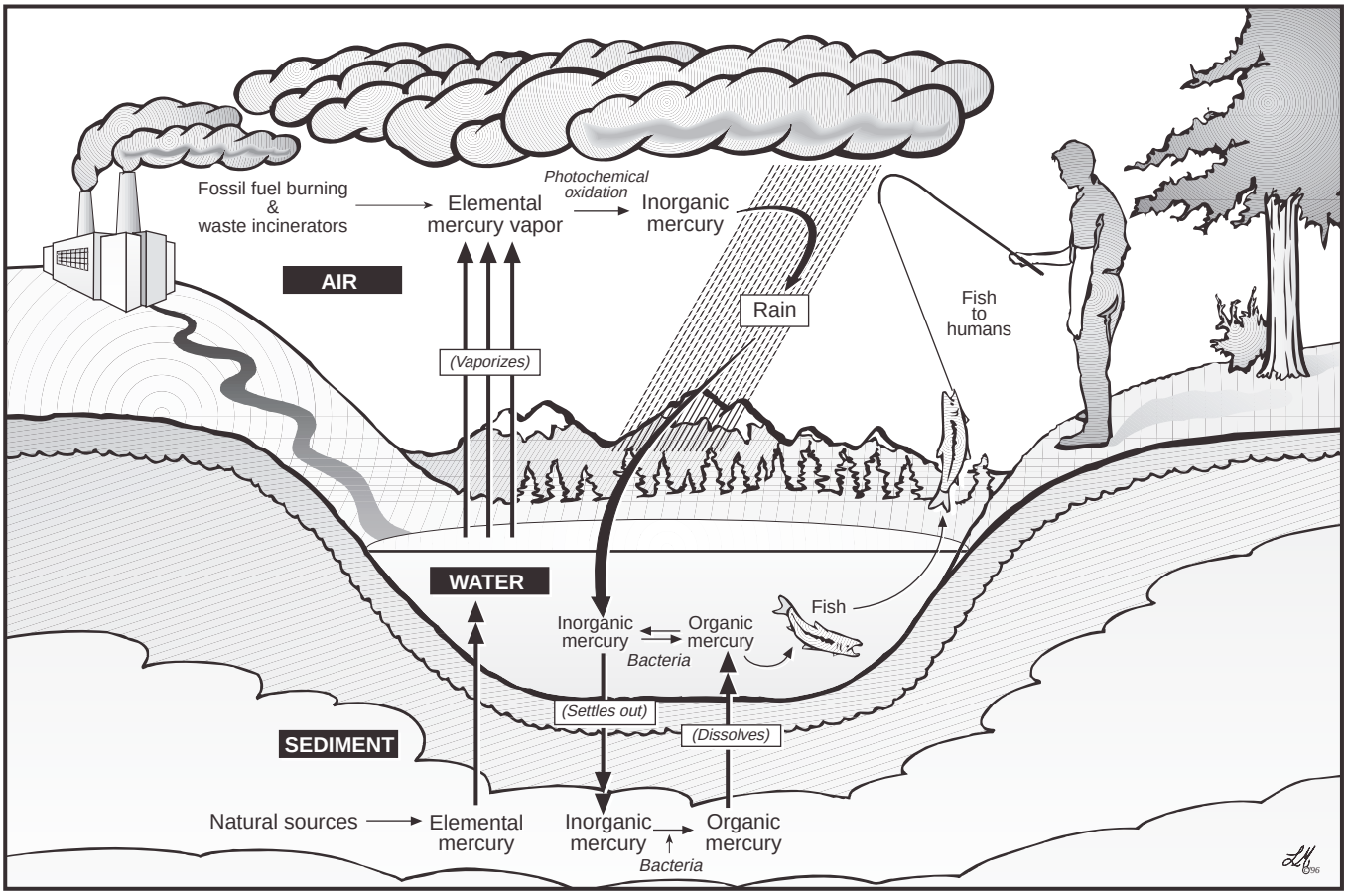


Table 4: The Cycle of Mercury in the Environment

fish consumers are exposed to today.

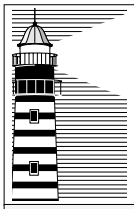
Health effects of organic mercury are similar in animal studies and in human populations, and mercury is one of the best understood developmental toxicants. Organic mercury interferes with cell division and migration of cells in the developing brain. Studies in mice have shown that cells in the developing brain stop in the middle of cell division when exposed to organic mercury.[40] In addition, methyl-mercury binds to DNA and interferes with the copying of chromosomes and production of proteins, processes which are essential to life.[41]

Two major ongoing studies of people who eat a lot of fish, one in the Seychelles Islands, and one in the Faeroe Islands, are attempting to evaluate the low dose effects of methyl mercury on brain development. Preliminary results are conflicting, with the Seychelles study showing little or no effect, and the Faeroe study showing subtle but significant impairment of brain function.[42] [43] [44] Based on an Iraqi study, the U.S. EPA projected that the highest chronic exposure to mercury tolerable without likely health effects is 1.0 µg/kg body weight/day, and on that basis set a reference dose (RfD) of 0.1 µg/kg/day. The RfD is the dose that is expected to be without any health effect even if exposure persists at that level over a lifetime.

Elemental and Inorganic Mercury

Elemental and inorganic mercury have more conflicting evidence of adverse effects. These forms of mercury do not appear to affect the developing brain like organic mercury does. While animal studies indicate that elemental mercury can damage male fertility, men occupationally exposed to elemental mercury vapor did not have any apparent decrease in fertility compared to a group of unexposed men, nor did their children have a greater risk of malformations.[45] [46] [47] A different study of exposed male workers found a two-fold increased risk of spontaneous abortion among their wives.[48]

Animal studies have shown that elemental mercury can be toxic to the fetus.[49] Studies in women, mostly dental assistants, have found conflicting results as to whether elemental mercury increases the risk of spontaneous



Spotlight on Mercury in Minamata Bay: The Dangers of Bioaccumulation

During the 1950s, many residents living around the Minamata Bay in Japan developed a disturbing neurological disorder. These people suffered symptoms ranging from numbness of the extremities and tremors to paralysis, blindness, deafness, and even coma. Many children born during this period suffered from cerebral palsy, mental retardation and microcephaly, a condition in which the brain is not fully developed.

It was several years before the cause of this mysterious outbreak was discovered. A nearby factory regularly discharged mercury into Minamata Bay. Inorganic mercury was not thought to be a serious health threat because it is poorly absorbed in the intestine of fish, animals, and humans. At that time, few people suspected that bacteria living in the sediments of wetlands and estuaries have the ability to transform inorganic mercury into the much more hazardous organic mercury. Organic mercury is easily absorbed by the intestine, and over time, mercury accumulated in the fish.

Because organic mercury has the ability to bioaccumulate in animals, the levels of organic mercury in fish can be up to 100,000 fold greater than the levels in the water. The people in the area depended on fish from the bay as a food source, and as they consumed the fish, the mercury accumulated in their bodies and moved easily across the placenta and into the fetal brain.

Chemicals which persist in the environment and bioaccumulate in the food chain can be especially hazardous to people. Humans are "top predators" because we eat animals and fish which in many cases are themselves carnivores. This means that we consume a dose of persistent toxic chemicals equivalent to that contained in all of the creatures eaten by the animal which we eat. It might have been easy to believe that the amount of mercury dumped into the bay was insignificant and would have quickly been diluted in the ocean. But because it entered the food chain, the mercury concentrated hundreds and thousands of fold and ended up ultimately in the bodies of the families living around Minamata Bay.

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

In summary, mercury is a known developmental toxicant which is particularly dangerous in the organic (methyl) form. It primarily affects the developing brain, causing anything from mild developmental delays to severe cerebral palsy, blindness and seizures. Organic mercury may pose a developmental danger to fetuses exposed at only slightly elevated levels of maternal fish consumption.

Elemental mercury and inorganic mercury have less clear-cut reproductive and developmental effects on humans. Nonetheless, all mercury compounds should at this time be considered reproductive and developmental toxicants.

Cadmium

- *Toxic to male reproductive function and causes birth defects in animals.*
- *Toxic to the human placenta.*
- *Damages the developing lung, may predispose to infant respiratory distress syndrome.*

Uses and Routes of Exposure

Cadmium is toxic to the testes in animals at fairly low doses, and also concentrates in and damages the placenta. In comparison to lead and mercury, however, the effects of cadmium on human reproduction and development are poorly understood. Animal studies suggest an increased risk of structural birth defects, and also suggest an association between cadmium exposure and delayed lung development, with a possible increase in respiratory distress syndrome of the newborn.

People can be exposed to cadmium at work or through

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 in the skeletons of a group of stillborn infants was found to be 10 times greater than levels in the bone of a comparison group of normal infants.[66]

Structural Birth Defects

Animal and human studies are conflicting regarding structural birth defects. Animals exposed to cadmium show birth defects, possibly due to damage to the placenta. Defects include decreased weight gain, abnormalities in the bony skeleton, damage to the central nervous system, and facial malformations. The particular effect which occurs depends on the timing of the cadmium dose during gestation.[67] In humans, two studies have reported a slight decrease in birthweight in infants of women exposed to cadmium during pregnancy, but one other study failed to confirm that effect; all three studies found no increase in congenital malformations.[68]

Other Adverse Effects on the Fetus

There is evidence of neurological effects, such as impaired reflexes and changes in activity level in the offspring of exposed animals.[69] In one case, young rats exposed to cadmium during gestation had abnormally low levels of two essential metals, copper and zinc, in their brains, were less active than normal rats, and behaved poorly in neuropsychological testing.[70] In another study, prenatally exposed rats showed significant decreases in birth weight and growth rate, as well as hyperactivity and delays in development of instinctive cliff avoidance and swimming behaviors.[71] No human studies have been done in this area.

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.[73] Inorganic arsenic at very low doses is an essential trace element for some animals, but at higher doses is considerably more toxic, as its reputation as a tool of poisoners suggests.

The primary commercial use of inorganic arsenic is in wood preservatives, accounting for over two thirds of commercial arsenic use. Arsenic treated wood is resistant to decay and is widely used for outdoor building purposes. Agricultural chemicals account for most of the remaining commercial use.

Ingestion is a major route of arsenic exposure. In some areas, naturally occurring arsenic contaminates groundwater supplies.[74 75 76] Inorganic arsenic may also be ingested in nutritional supplements containing dolomite and bone meal, as well as in certain folk medicines.[77] Glassmaking and metal smelting are other sources of arsenic exposure. Finally, although the production of inorganic arsenic pesticides for use on food crops has been banned by the E.P.A., existing stores of these pesticides may still be used.

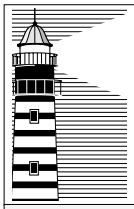
Distribution in the Body

Inorganic arsenic is well absorbed in the gastrointestinal tract, from the lungs, and to a lesser degree through the skin. [78 79] Animal studies have shown that arsenic distributes readily from the mother to the fetus and to all organs in the body. [80 81] In addition, these studies suggest that the placenta may selectively concentrate arsenic, though any effect this may have on the developing fetus has not been assessed. Limited evidence from human studies appears to show that arsenic distributes similarly in humans.[82] Finally, arsenic transfers into the milk of cows, goats and humans. [83 84]

Adverse Effects on the Fetus

High dose exposure to arsenic has adverse effects on fetal development in animals. A distinctive pattern of malformations including dose-related effects on brain and spinal cord development, malformed or missing eyes, failure of development of the kidneys and reproductive organs, and certain skeletal malformations has been consistently reported.[86 87 88] In addition to malformations, arsenic causes significant reductions in litter size, increased intrauterine death and postnatal mortality, as well as growth retardation.[89 90] Finally, one study in mice suggested that maternal exposure to arsenic may lead to cancer in offspring.[91]

People living in an area with arsenic contaminated drinking water had increasing risk of spontaneous abortion and stillbirth with higher levels of arsenic in the water. [92]



Spotlight on Arsenic in Wood Products

A family of eight living in a rural area of Wisconsin developed a series of health problems over a period of three years. [85] Their symptoms included recurrent rashes, respiratory problems, fatigue, muscle cramps, and diminished sensation in the hands and feet. Symptoms were worst in the winter and spring.

The two infants in the family suffered worse effects than other family members. These children, who frequently crawled about on the floor wearing only diapers, had red, peeling skin, bruising, bleeding, and seizure disorders. In addition, the children became completely bald. One of the children was born prematurely and suffered recurrent severe pneumonia.

Health care workers suspected an environmental source for the family's illness. Biological monitoring revealed high arsenic levels in the hair and fingernails of all family members. Investigation of the home revealed high levels of arsenic in and around their wood-burning stove, the primary source of heat in winter. In fact, the father had been burning plywood scraps from a nearby construction site in the stove, scraps which had been treated with chromium copper arsenate, a common wood preservative.

Although we cannot be sure that all of the health effects that this family suffered are directly due to arsenic exposure, case reports such as this are important sources of information about the health effects of environmental exposures. When evaluated along with animal studies, we can begin to draw connections between controlled, experimental studies and real life exposures. Cases such as these suggest areas for further research and also suggest ways to avoid such exposures in the future.

Two case control studies found less clear evidence of arsenic's effects on the fetus, one suggesting a link between arsenic exposure and a particular heart defect, and the other showing a small but not statistically significant association between arsenic levels and spontaneous abortion. [93 94] Finally, a series of studies conducted on workers and residents exposed to smelter emissions in Sweden reported a variety of adverse reproductive outcomes including spontaneous abortion, low birth weight, and malformations. [95 96 97 98] Because the smelter emissions contained a combination of arsenic, lead, cadmium, and mercury, it is impossible to assess what role arsenic played in the outcomes.

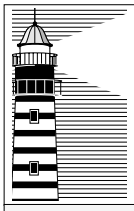
Neurologic Problems

A small but worrisome body of evidence suggests that arsenic may affect neurologic development. Mice exposed to arsenic before birth made more errors in learning a path through a maze.[99] In another study, rats were given arsenic from 2 to 60 days of age, while neurological development was still occurring. One hundred days after treatment, they had both changes in behavior and in levels of neurotransmitters in the brain.[100 101]

Two human studies have reported that arsenic exposure may lead to hearing loss in children.[102] In one case, over 12,000 infants in Japan were accidentally poisoned with inorganic arsenic in dry milk. Fifteen years later, many of these children showed disturbances of central nervous system function, including severe hearing loss in 18% of the 415 children examined in follow-up studies. In another study, children living near a coal-fired power plant in Czechoslovakia which emitted large amounts of arsenic were found to have higher than expected rates of hearing loss.

Summary

In its inorganic forms, arsenic is highly toxic, widely used and widely distributed in the environment. It is easily absorbed and distributed throughout the body, passing readily into the fetus, concentrating in the placenta, and passing into breast milk. A characteristic set of malformations occur in animals exposed to high levels of arsenic. Human studies have been limited both in number and clarity, but suggest a connection between arsenic exposure and spontaneous abortion and stillbirth. A small number of animal and human studies suggest that arsenic may have effects on neurologic development, particularly affecting hearing. Though further study is needed, there is evidence indicating that arsenic may be a significant reproductive and developmental toxicant.



Spotlight on Manganese in Gasoline

A new octane enhancer and anti-knock agent was developed in the 1970's for use in gasoline. This compound, methylcyclopentadienyl manganese tricarbonyl (MMT) was used for a brief period in the late 1970's during the oil crisis. Since then, it has been added to gasoline in Canada, where it was recently banned, but has not been used in the United States. The U.S. EPA refused to approve of MMT for sale in this country until there was further investigation of the possible health effects. The Ethyl Corporation, however, challenged the EPA in court and in 1995 won the right to add MMT to fuel sold in this country.

The court ruling allowing addition of MMT to gasoline stated that, under the Clean Air Act, the EPA may only concern itself with MMT's effect on automobile pollution control systems and can not prevent use of MMT on the basis of possible toxicity to humans. The Ethyl Corporation, the winner in this case, was founded in the 1920's to market tetraethyl lead, the infamous gasoline additive which led to dangerous lead exposure to the U.S. population and which was phased out and finally banned as recently as December 31, 1995.

This manganese additive may now be present in the gasoline sold throughout the country, except in regions where reformulated gasoline is required. MMT is known to be extremely toxic at high doses. At low doses, the effects are unknown and essentially unstudied. Many scientists are concerned that manganese may have subtle adverse neurologic effects, particularly in children, and that we may be witnessing a development similar to the original addition of lead to gasoline in the 1920's.

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 is now being added to gasoline as an anti-knock agent.

Toxicity to Adults

At high doses, such as found in some workplaces, manganese causes a degenerative neurologic condition similar to Parkinson's disease. This disease, known as manganism, begins as a loss of appetite, apathy, fatigue, leg weakness and pain. It progresses steadily and the final stages include an expressionless, mask-like face, difficulty initiating movements, a shuffling walk, and tremors. Inhalation of manganese produces an inflammatory reaction, increasing susceptibility to pneumonia and bronchitis.[103]

Effects on Male Reproduction

Studies in mice and rats have found that male animals exposed to manganese during fetal development, at doses below those which caused other toxic effects, have retarded growth of the testes.[104] Further investigation revealed that testosterone concentrations are reduced in the exposed animals. Oral administration of manganese oxides to infant animals leads to accumulation of manganese in the hypothalamus and the pituitary. These two important regions of the central nervous system control a variety of hormonal systems including the production of reproductive hormones such as testosterone. The researchers who conducted these studies suggest that manganese may interfere with the male reproductive system by damaging hormone production.[105]

This research is supported by similar findings in a human study. Workers exposed at levels averaging one fifth of the allowable workplace exposure limit had significantly fewer children during the period of exposure compared to similar unexposed workers.[106] A subsequent

study in which workers were exposed at slightly lower levels, however, found no effect on birth rates.[107] Another study in male workers exposed to levels within the allowable workplace limits found effects on hormone levels.[108] Both prolactin and cortisone levels were significantly higher among exposed workers, suggesting the potential for interference with reproductive processes.

Absorption and Distribution in the Fetus or Newborn

In adult animals, only a tiny proportion of a manganese dose (about one quarter of 1%) enters the brain of the animal. In the newborn animal as much as 4% of a dose of manganese enters the brain.[109] To compound the problem, the newborn lacks the ability to eliminate manganese from its body.[110] In addition, absorption of manganese through the gastrointestinal tract is greatly increased in the newborn and in pregnant women; the newborn rat absorbs 70% of an oral manganese dose, while the adult absorbs only 2%.[111] Finally, manganese is known to pass from the mother to the infant across the placenta and in breast milk.[112]

Fetal Development

Mice exposed to manganese by one-time injection had growth retarded fetuses with a high proportion of exencephaly, a birth defect in which the skull does not close. There was also an increase in fetal death. All of these effects occurred at the lowest doses tested, but doses were high compared to likely human exposures.[113] Another study in mice reported an increase in late resorptions, similar to spontaneous abortions, and delay in development of the bony skeleton at levels below those causing toxicity to the mothers.[114] Animals exposed prenatally to a very low-dose mixture of six metals, including manganese, cadmium, and lead, displayed severe growth retardation, suggesting a synergistic effect of various toxic metals in combination.[115]

The only human studies evaluating birth defects involve the population of a small island off the coast of Australia where major natural manganese deposits contaminate water and food. Preliminary surveys of this exposed population revealed a higher-than-expected number of stillbirths and an apparent excess of the deformity clubfoot.[116] It is unclear, however, if these observed outcomes are due to the manganese exposure or to other factors.

Neurologic Toxicity

Significant chemical changes in the brain and abnormalities in neurologic development have been reported in exposed infant animals. Reports have included reduced production of dopamine and excess of acetylcholine, important neurologic transmitters which must be maintained in delicate balance for normal function of the brain. These animals also have significantly lower activity levels and less exploratory behavior than unexposed animals, suggesting a neurotoxic effect.[117] [118]

The population of the island off the coast of Australia with environmental exposure to manganese contains a large group of people with severe neurologic problems. One neurologic syndrome has its onset in infancy and progresses very slowly for a few years before remaining stable for a lifetime. It consists of weakness and muscle atrophy in the legs leading to abnormal walking, or in severe cases, inability to walk or even sit up without assistance. All of these children also have club foot, scoliosis of the spine and some other mild abnormalities of the joints and skin, but they are intellectually fairly normal.

A second syndrome occurs later in life, and consists of clumsiness, unsteadiness, staggering, tremor, weakness, and an expressionless face. This second syndrome is very similar to the Parkinsonian syndrome previously described in workers exposed to manganese as adults. No other human studies exist on the possible neurologic effects of manganese in the developing fetus.

Summary

Although manganese is an essential mineral at low doses, overexposure may pose a hazard to human reproduction and development. It is likely that infants may experience overexposure to manganese at levels that are harmless to adults, and animal studies show evidence of growth retardation in fetuses, damage to the testes and sperm in young males, and some birth defects. There is evidence of neurologic damage to infants, which is not surprising, as manganese is known to be toxic to the brain even in adults. Though human studies are lacking, there is enough information to be concerned about the effects of manganese and to require further human studies before exposure increases from the addition of MMT as a gasoline additive.

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Chapter 5

Organic Solvents

- *Widely used.*
- *Many cause spontaneous abortions.*
- *Some damage male fertility.*
- *Several may lead to birth defects.*
- *Some evidence that certain childhood cancers may be related to parental solvent exposure.*

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 even show an increased risk of spontaneous abortion among wives of men exposed to solvents. Solvents may increase the risk of certain structural birth defects in humans, particularly those of the central nervous system, urinary system, heart, lip and palate. This area urgently needs further research. There is also one important study suggesting that solvent exposure may predispose to preeclampsia, or toxemia of pregnancy. Finally, defects of the central nervous system and childhood cancers of the brain and urinary tract, as well as leukemia, may occur in offspring of exposed parents, particularly fathers, at rates two to three times that of the general population. This contradicts previously accepted wisdom that only maternal exposures affect the fetus and child.

Solvents are characterized by their ability to dissolve other substances. They are generally liquids, and can be water-based or hydrocarbon (petroleum)-based. The hydrocarbon- based solvents are known as organic solvents. Because of their tendency to evaporate at room temperatures many organic solvents are also known as volatile organic compounds (VOCs). Organic solvents are used in an enormous variety of products. The most widely used organic solvents fall into several categories with varying possible reproductive toxicities (see Table 1).[1]

Table 1
Categories of Organic Solvents Suspected of Having Reproductive Effects

Aromatic hydrocarbons —	Benzene, toluene, xylene, styrene, phenol
Aliphatic hydrocarbons —	Hexanes, octane
Chlorinated derivatives —	Trichloroethylene, perchlorethylene, 1,1,1-trichloroethane, methylene chloride (dichloromethane), chloroform, carbon tetracholride
Alcohols —	Ethanol
Aldehydes —	Formaldehyde
Glycol Ethers —	Ethylene glycol monomethyl ether, ethylene glycol monoethyl ether acetate
Complex solvent mixtures —	Gasoline

People may be exposed to solvents at work in electronics, health care, dry cleaning, auto repair, laboratories, painting, and numerous other occupations. Household exposure to solvents may come from paints, strippers, glues, magic markers, cosmetics, correction fluids, and some cleaning agents. Pesticides frequently contain solvents as "inert" ingredients. Solvents contaminate drinking water in some areas, and airborne exposure may occur from dry cleaning shops or other facilities which emit large

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

Institute of Occupational Health.[5] In the Finnish studies, the biological measures were supplemented with questionnaire information about exposures.

Women who suffered a spontaneous abortion were consistently two to four times more likely to have been exposed to organic solvents during pregnancy.[6, 7, 8, 9] Similar studies performed in the U.S. have come up with almost identical results. A group of California women who had a spontaneous abortion were over three times more likely to report having been exposed to organic solvents at work compared with a group of otherwise similar women who had normal births.[10] Semiconductor workers and laboratory workers who are exposed to solvents also have an increased risk of spontaneous abortion.[11, 12, 13, 14] Specific solvents mentioned include perchlorethylene (PCE), trichloroethylene (TCE), glycol ethers and aliphatic solvents, but almost all the women were exposed to complex mixtures.[15] The human studies on solvent exposure and spontaneous abortion are presented in Table 2.

Structural Birth Defects

■ *Birth defects, particularly of the central nervous system, heart, urinary tract, lip, and palate, are more likely in children of solvent-exposed women.*

A variety of birth defects have been reported in association with organic solvents. These include cleft palate and lip,[29] cardiovascular malformations,[30] abnormalities of the abdominal muscles,[31] and central nervous system defects.[32] Some of these studies are case-reports or case-series (a group of case reports presented together). Others use various birth defects registries to identify children born with certain types of defects and attempt to contact and interview the mothers about exposures during pregnancy.

One interesting report noted a cluster of infants born with heart abnormalities in a neighborhood near Tucson, Arizona. The same area had groundwater contaminated with the solvent trichloroethylene, and trace amounts of dichloroethylene and chromium. Investigators found a

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 times more likely
			Cleft lip/Palate	2.2 times more likely
		Carbon tetrachloride	CNS	3.8 times more likely
			Cleft lip/Palate	3.6 times more likely
		Perchlorethylene	Cleft lip/Palate	3.5 times more likely
Finland[37]	Case-Control	Various	CNS, Cleft Palate	5.5 times more likely
Finland[38]	Case-Control	Various	CNS	Increased***
Finland[39]	Case-Control	Various	Cleft lip/Palate	4.5 times more likely
Finland[40]	Case-Control	Various	CNS	No increase
France[41]	Case-Control	Various	Cleft lip/Palate	8 times more likely
			Gastrointestinal	12 times more likely
			CNS	No increase
Europe[42]	Case-Control	Glycol Ethers	Cleft lip/Palate	2 times more likely
Canada[43]	Case-Control	Toluene/Aromatics	Urinary Tract	3.8 times more likely
Finland[44]	Case-Control	Various	Cardiac -VSD	1.5 times more likely
Finland[45]	Case-Control	Various	Cardiac - VSD	1.4 times more likely
Massachusetts[46]		Trichloroethylene	CNS	
Maryland[47]	Case-Control	Various	Cardiac	1.6 times more likely
Arizona[48]	Cohort	Trichloroethylene	Cardiac	3.0 times more likely*

*In a case-control study this means that mothers of babies with this birth defect were 3 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 3 times more likely to have a baby with this defect.
***No odds-ratio provided
NS =not statistically significant, all other results statistically significant at the 0.05 level
VSD = Ventricular Septal Defect (a particular heart malformation)
CNS = Central Nervous System (brain)

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 study showed a 25%-50% decrease in fertility among women occupationally exposed to organic solvents. This apparent effect on fertility was particularly strong among women working in dry-cleaning, and those exposed to halogenated hydrocarbons such as perchlorethylene.[49] A more recent study found a 75% increased risk of infertility in women occupationally exposed to volatile organic solvents.[50] The results of this study are strengthened by the fact that it looked only at women with medically diagnosed infertility, but because researchers relied on subjects' memory to assess exposure, the results may have been biased toward finding an association.

An investigation of a New Jersey population exposed to solvent-contaminated drinking water revealed an association between exposure to certain solvents, particularly the trihalomethanes and carbon tetrachloride, and low birth weight and small size for gestational age.[51] This was supported by a similar study in Iowa focusing on chloroform in drinking water.[52] People in New Jersey living adjacent to the top listed Superfund toxic waste site, which emitted airborne volatile solvents for nearly a decade, were found to have a five-fold risk of having a low birthweight baby during the period of greatest contamination. These families also had twice the risk of having a premature infant.[53] Solvents implicated in this study included benzene, bis (2-chloroethyl) ether, methylene chloride, 1,2-dichloroethane, ethylbenzene, 4-methyl-2-pentanone, toluene and xylene. This study is quite persuasive because most likely sources of bias would tend to result in underestimating a true effect. A North Carolina study looking at trihalomethanes in drinking water and miscarriage, preterm birth, and low birth weight failed to find any consistent association.[54] This study did not look for full-term births who are small for gestational age and did not consider exposures from showering. In summary, there is some evidence of an association between solvent exposure and smaller full-term babies, with conflicting evidence on the more nonspecific finding of low birth weight.

One well-designed prospective study showed a four-fold increased risk of pre-eclampsia, also known as toxemia of pregnancy, in women exposed to solvents.[55] Pre-eclampsia is a potentially life-threatening condition of late pregnancy consisting of hypertension, protein in the urine, generalized swelling (edema), and eventual seizures if untreated. Solvent exposure can lead to kidney injury, a presumed cause of pre-eclampsia.[56]

Reproductive Effects in Men

- *Solvent-exposed men may father children with low birth weight or congenital defects.*
- *Glycol ethers affect fertility and damage male reproduction.*

The effects of most solvents on men are not clearly understood and research findings in this area have been contradictory except regarding the short-chain glycol ethers. Animal and human studies on the glycol ethers indicate that they damage testicular function, lower sperm counts and can cause infertility. In animals, short-chain glycol ethers lead to testicular atrophy (see glycol ethers profile).[57]

There is some consistency in the finding that offspring of solvent exposed men face increased risk of birth defects and low birth weight. Male spray painters and body shop workers have twice been shown to be at increased risk of fathering a low birth weight baby.[58 59] Children of solvent-exposed men may also have an increased risk of birth defects including anencephaly (partial or complete absence of a brain).[60 61] One rare birth defect, the Prader-Willi syndrome (consisting of mental retardation, obesity, muscle weakness, and poor testicular or ovarian function) has been associated with paternal exposure to hydrocar-

bons, and appears to be due to a chromosomal deletion transmitted by the father.[62] This is an important finding because it was previously believed that only maternal exposure could lead to adverse effects in the fetus.

An assessment of sperm quality among men exposed to perchlorethylene in dry cleaning found differences in sperm shape and swimming ability, but no overall difference in sperm count compared to an unexposed group.[63] Painters exposed to mixed solvents have increased rates of sister chromatid exchange, a chromosome abnormality. This finding is a measure of toxicity to genes on the chromosome and may imply a risk of birth defects in offspring.[64] Two studies have shown slight increases in spontaneous abortion in wives of solvent-exposed men.[65] [66] Two others did not find any increased risk to wives but one of these two did find an increased risk of infertility in these couples.[67] [68]

Childhood Cancer

■ *Solvents may increase risk of neurological and urinary cancers, and leukemia in children of exposed parents.*

Fifteen of twenty studies which looked at parental solvent exposures and childhood brain tumors found an association between the two, though the finding was statistically significant only in ten.[82] [83] [84] The association was strongest when the father's job involved exposure to gasoline, trichloroethylene, methylethylketone, or freon.[85] [86] Childhood cancers of the urinary tract show a similar association. All eight studies on this topic showed elevated risk of these cancers in offspring of solvent-exposed parents, though only four had statistically significant effects.[87] [88]

The third childhood cancer showing an association with parental exposure is childhood leukemia. Parental exposure to gasoline has been particularly implicated in this malignancy.[89] [90] This is not surprising because of the known association of benzene, a constituent of gasoline, with adult leukemia. Several studies of childhood leukemia, however, have pointed to other solvent-exposed occupations, including spray-painting and beauty shop work.[91] Thus there is some consistent preliminary evidence that solvent exposures to either parent may result in an increased risk of neurological and urinary cancers, and acute leukemias in their children.[92] [93]

Table 4:
Male Exposure and Adverse Reproductive Effects of Solvents

Location	Study Type	Solvent	Defect	Result
U.S[69].	Cross-Sectional	Perchloro-ethylene	Semen quality	Mixed
U.S.[70]	Cross-Sectional	Toluene, mixed solvent	Sister-chromatid exchange	Positive*
U.S.[71]	Cross-Sectional	Glycol ethers	Semen quality	Positive
U.S.[72]	Cross-Sectional	Glycol ethers	Semen quality	Positive
U.S.[73]	Cross-Sectional	Glycol ethers	Semen quality	Mixed
Finland[74]	Case-Control	Organic solvents	SAB in wives Birth defects	2.7 times more likely 1.0 time more likely NS
Finland[75]	Case-Control	Various unspecified	SAB in wives	2.7 times more likely*
U.S.[76]	Cohort	Glycol ethers	SAB	2.4 times more likely NS
U.S.[77]	Retrospective Cohort	Perchlorethylene	SAB Infertility	Negative 2.5 times more likely NS
U.S.[78]	Retrospective Cohort	Various unspecified	Low-birth weight Other effects	1.6 times more likely Negative
Sweden[79]	Retrospective Cohort	Toluene, mixed solvent	Low-birth weight Other effects	Positive Negative
U.S.[80]	Case-Control	Various unspecified	Anencephaly	2.5 times more likely
U.S.[81]	Case-Control	Various unspecified	Prader-Willi Syndrome	1.9 times more likely

*No odds-ratio or risk-ratio provided
NS =Not statistically significant, all other results statistically significant at the 0.05 level
SAB = Spontaneous abortion

Spotlight on

Childhood Leukemia in Woburn, Massachusetts

In the 1970's, residents of Woburn, Massachusetts became concerned about a large number of cases of childhood leukemia in their community. In May of 1979, two of the wells supplying drinking water to part of the town were found to be contaminated with trichloroethylene, perchlorethylene, and chloroform, which leached into the well water from nearby toxic waste sites. Though the wells were promptly closed, they had supplied some portion of the town's water intermittently for 15 years.[94]

Subsequent investigations confirmed a cluster of leukemia in children under the age of 15 in the eastern section of town. In a town of that size only six cases of childhood leukemia would be expected over twenty years based on national rates of disease. Woburn had 28 cases in that time period. Extensive investigation has failed to reveal any other reason for the excess of leukemia.[95] The exposed community also had an increased risk of certain birth defects, particularly structural defects of the face and brain. Finally, exposure to the contaminated well water was associated with childhood diseases of the urinary tract and the lungs.[96]

Chlorinated solvents cause cancers in laboratory animals, and the time-period of exposure to the well water fits with what we know about the time-course of leukemia after chemical exposures. The increase in stillbirth fits with other epidemiological studies which found an increased risk of spontaneous abortions in women exposed to solvents. Though there are still many questions about what happened in Woburn to lead to this tragedy among the children, the evidence implicating solvent exposure is quite persuasive.

Solvents in the water supply are a hazard even to those who drink bottled water. Over half of the exposure to solvents in drinking water comes from inhalation and absorption through the skin in the shower or bath.[97]

Overall Assessment of Epidemiologic Studies

A large body of epidemiological literature addresses the question of whether organic solvents may have adverse reproductive effects in humans. Though some studies have failed to show any increased risk of adverse reproductive outcomes,[98 99] the negative studies are a very small minority.[100 101] There is consistent evidence that solvents raise the risk of spontaneous abortion among exposed women by two to four fold. There are two studies which even show an increased risk of spontaneous abortion among the wives of men exposed to solvents.

The evidence for structural birth defects in children of exposed women is also fairly consistent for defects of the central nervous system, heart, lip and palate. This area urgently needs further research. Though there is only one study on preeclampsia, the study was well designed, and the conclusions are persuasive. Organic solvents should be considered among the potential causes of preeclampsia.

There is a very disturbing body of evidence suggesting that defects of the central nervous system and childhood cancers of the brain and urinary tract, as well as leukemia, may occur in offspring of exposed parents, particularly fathers, at rates two to three times that of the general population. This contradicts previously accepted wisdom that only maternal exposures affect the fetus and child.

Most of the studies discussed above concern solvents generally, and only a few have identified specific possible culprits. The following sections focus on certain solvents that may be particularly responsible for some of the reproductive effects summarized above.

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

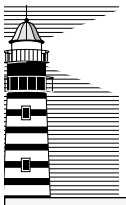
Benzene has long been recognized as a known cause of cancer in humans. Though its effects on reproduction and development have been less well studied there is evidence in both animals and humans that benzene also interferes with these processes.

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.



Spotlight on

Water Disinfection Byproducts: A Complex Mixture and a Public Health Dilemma

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 water to produce disinfection byproducts (DBPs), a mixture of volatile chemicals, including chloroform and trihalomethanes. People can be exposed to DBPs from drinking the water, or through inhalation or skin absorption during showering or swimming.[117] Levels in indoor air rise any time hot water is run in the house.[118] Some bottled water has also been shown to contain DBPs, while some types of water filters can remove these compounds.

Only limited information is available on the effects of DBPs on human reproduction and development. Two cases of pre-eclampsia, a complication of pregnancy, were reported in laboratory workers exposed to chloroform at 6 to 20 times the recommended exposure limit, a level which caused liver problems in other exposed workers.[119] More worrisome, perhaps, are studies which show a possible link between chlorinated drinking water and developmental problems in infants. In an Iowa study, researchers found a connection between maternal exposure to chloroform in drinking water and both low birth weight and intrauterine growth retardation.[120] Another study found correlations between trihalomethane exposure and reduced birth weight, small size for gestational age, central nervous system defects, cleft palate, and heart defects.[121] A second more limited study found only a slight association with increased miscarriage at high levels of exposure. Unfortunately, the exposure measure was the number of glasses of water drunk per day, which is subject to recall problems and overlooks exposure from showering.[122] Researchers in Massachusetts linked exposure to chlorinated water to an increase in stillbirths, while researchers in Italy found a connection with small body and skull size as well as an increased risk of neonatal jaundice. [123] [124]

In animals, DBPs have caused reduced birth weight, heart malformations, and spermatotoxicity.[125] [126] [127] It is not clear how to translate the high dose effects seen in animals into the low dose combinations found in water supplies.

Drinking water contaminants illustrate the complex mixtures that people are exposed to every day. These chemicals are present at low levels - far lower than any routinely evaluated in animal studies. Yet there is some evidence that they may have health effects, perhaps through interactive effects, or because a certain constituent is toxic even at low doses during fetal life. Because of the health benefits of water chlorination, changes need to be implemented with great care. Improved filtration of water, use of chloramine, or ozone disinfection are among the possible alternatives. People should not have to choose between the risk of infectious disease and the risk of adverse pregnancy outcomes.

Formaldehyde

■ **Uses**	Resins for particle board, plywood, insulation, and table tops. Used in rubber production, film manufacture, leather processing, dye production, cosmetics, hospitals and embalming.
■ **Routes of Exposure**	Occupational: Manufacturing jobs, foam installation, funeral homes, hospitals, and laboratories. Environmental: Motor vehicle exhaust, wood stoves, cigarette smoke, and emissions from resins; cosmetics.
■ **Reproductive Effects**	Animals: Damages reproductive organs at high doses. Humans: Menstrual disturbances and increased risk of spontaneous abortion.

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.

Formaldehyde damages the testes of rats after high dose exposure, resulting in declines in sperm production, motility, and viability as well as testicular degeneration.[129] [130] [131] Mice which inhaled near lethal doses of formaldehyde had degenerative changes in the uterus and ovaries.[132] Rats exposed to high levels of formaldehyde had disturbances of the estrus cycle, an effect which could have been due to stress from the irritant effects.[133]

Formaldehyde crosses the placenta in mice, and fetal animals eliminate it more slowly than adults.[134] However, even at doses which were highly toxic to the mothers, formaldehyde did not affect fetal size or increase the rate of malformations in mice, although it did slightly decrease litter size.[134] No malformations were reported in rats after inhalation exposure, but there was a slight increase in the length of gestation and an increase in average fetal weight.[136] Finally, beagles fed formaldehyde showed no physical effects on the mothers or pups and no behavioral effects after birth.[137]

Although the animal evidence is ambiguous and generally negative, several human studies suggest reason for concern. Almost half of a group of women working in formaldehyde exposed occupations reported having menstrual disorders, compared to less than ten percent of women in unexposed occupations[138]. Another study also found increased rates of menstrual disturbances, though other factors may have been involved.[139] Cosmetologists, who are often exposed to formaldehyde, have an increased rate of spontaneous abortions.[140] Finally, lab workers exposed to formalin, a water- formaldehyde mixture, had more than a three fold increased risk of spontaneous abortion.[141]

In summary, there is evidence of menstrual abnormalities with formaldehyde exposure, consistent with animal evidence of disturbed estrus and ovarian injury, although the latter studies were at high dose levels. Human studies have not looked at testicular function, although high-dose animal studies indicate a possible effect. Further study is also needed to confirm the observation of increased risk of spontaneous abortion which was seen only in the human studies.

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.

N-Methyl-2-Pyrrolidone (NMP)

■ **Uses**	Microelectronics, petroleum production, paints, paint strippers, and cleaners; production of resins such as Kevlar, wire-coating, graffiti removal; topical veterinary products, cosmetics; under consideration as an absorption enhancer for topical pharmaceuticals for human use.[187]
■ **Routes of Exposure**	Occupational: In labs, semiconductor work, and factories. Environmental: Paints, strippers, graffiti removers, and cosmetics.
■ **Reproductive Effects**	Animals: Fetal resorptions, stillbirth, and low birth weight.

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 fashion is fairly convincing. On the basis of the animal evidence, NMP should be considered fetotoxic in humans.

Perchlorethylene (PCE)

■ **Uses**	Dry cleaning, vapor degreasing, machining, auto paint, assembly plants, and electroplating.
■ **Routes of Exposure**	Occupational: In dry cleaning and facilities using degreasers. Environmental: Near dry cleaners, manufacturing and repair shops;[200, 201] from recently dry cleaned clothes;[202] drinking water contaminant in some areas.[203]
■ **Reproductive Effects**	Probably increases the risk of spontaneous abortion by two to five fold in those exposed at workplace levels; may increase the risk of infertility in both men and women; concentrates three fold in breast milk and can lead to jaundice in infants.

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 cleaners' wives were twice as likely to report unsuccessfully attempting to get pregnant for more than 12 months or seeking medical care for infertility.[205] However, both groups had similar numbers of pregnancies, and both had fertility rates above the national average. Women exposed to PCE in dry cleaning shops were found to take twice as long as an unexposed group to become pregnant.[206] In another study, women seeking care at an infertility clinic were almost three times more likely to report exposure to dry cleaning chemicals than were women without fertility complaints.[207] This study may suffer from recall bias.

Two studies found that exposure to PCE increases the risk of spontaneous abortion by two to five fold.[208, 209] Two others also found an increased risk of spontaneous abortion but the finding was not statistically significant, while one failed to find an association between PCE exposure and spontaneous abortion.[210, 211, 212] There was no increased risk of spontaneous abortion among the wives of PCE exposed men.[213] A study of solvent exposure in drinking water found a weak association between PCE exposure and oral cleft defects,[214] but there is currently little other evidence that PCE exposure increases the risk of birth defects.[215]

PCE may pose a risk to the newborn. A significant case report concerned a nursing mother who visited her husband at a dry-cleaning plant during his lunch breaks. Their six-week old infant who never entered the plant developed liver damage and jaundice which resolved after cessation of breast feeding. After a 30 minute plant visit the mother had detectable PCE in her blood, and levels in her breast milk were over three times greater than in her blood.[216] Exposure modeling indicates that women occupationally exposed to PCE at levels below the workplace standard, and women living in apartments over dry-cleaners, may have enough PCE in their breast milk to risk health damage to their infants.[217]

Animal studies have shown that PCE can cross the placenta and enter the developing fetus. A few studies in chickens and rodents showed decreased survival, decreased fetal body weight, and increased resorption of fetuses.[218] Most animal studies showed no effect on development and no increase in malformations.[219]

Overall, animal testing on the reproductive effects of PCE has not demonstrated significant reproductive toxicity, while human studies have shown toxic effects including spontaneous abortion and possible effects on human fertility. The presence of PCE in breast milk is a very worrisome finding, as this solvent is classified as a possible human carcinogen, and infant exposures during breast feeding could lead to harmful effects later in life.[220]

Phenol

■ **Uses**	Synthesis of resins, nylons, plasticizers, aspirin, and herbicides; disinfectant and analytical agent; by-product of leather tanning, timber products manufacture, pulp and paper production, textile manufacture, and iron/steel production.
■ **Routes of Exposure**	Occupational: In factories and laboratories. Environmental: Contaminated drinking water, emissions from wood and gasoline combustion; in some consumer products including disinfectants, mouth wash, and medicated skin products.
■ **Reproductive Effects**	Animals: Reduced fetal weight, sperm chromosome damage, possible changes in the estrus cycle. Humans: Infant jaundice.

Summary of Studies

Despite phenol's widespread usage in consumer products, information concerning its effects on reproduction and development is limited. The few animal studies show mixed results. In one study, pregnant rats inhaled phenol at levels which humans might encounter occupationally and suffered increased fetal and neonatal loss.[221] Other researchers injected rats with phenol on specific days of gestation. They found no evidence of birth defects or increases in fetal resorptions but did find fetal weight reduction in rats treated with the highest dose.[222] In another set of experiments conducted in both mice and rats, phenol exposure led to low birth weights at doses at which the mothers showed no evidence of harm.[223, 224]

Two other studies are harder to interpret. In one continuous breeding study several generations of mice were constantly exposed to phenol. The researchers found a dose-related increase in damage to sperm cell chromosomes in all generations of offspring.[225] It was not clear whether paternal, maternal, or fetal exposures led to the effect. However, the fact that there was a marked increase in chromosome damage at even the lowest levels of exposure is concerning. Finally, a study looking at the effects of phenol inhalation on female rats found changes in the estrus cycle, the rodent equivalent of the menstrual cycle.[226] In this case, the dose was so high that these changes may have been simply due to the general toxicity of phenol.

In humans, phenol is produced naturally in the intestine, and the human body seems able to process low levels without difficulty.[227] There are, however, reports of newborns developing jaundice as a result of exposure to phenol in disinfectant detergents used in hospitals.[228, 229] This implies that newborns are particularly sensitive to phenol exposure, a question which needs further examination.

Phenol is widely distributed in the environment, and widely used in a range of products and processes. Animal evidence suggests that phenol may damage chromosomes and lead to fetal toxicity, and several human case reports indicate that low level exposures to phenol may result in infant jaundice. Given these facts, phenol urgently needs further study to determine what its impacts on humans may be.

Styrene

■ **Uses**	Reinforced plastics manufacture, polystyrene manufacture, polyester resins, and rubber manufacture.
■ **Routes of Exposure**	Occupational: Various manufacturing jobs, boat building, fire fighting. Environmental: Burning of plastic and polystyrene; common water contaminant; leaches from polystyrene cups in small amounts; and present naturally in cinnamon.[230]
■ **Reproductive Effects**	Very conflicting evidence; possibly toxic to testicular function; may affect menstrual function; and may interfere with the endocrine system.

Summary of Studies

Styrene has been studied extensively in animals and humans. Two animal studies suggest an effect on hormone function. Rats exposed to styrene vapor at levels much lower than those allowed in the workplace showed a lengthening of their estrus cycle.[231] In another study, investigators removed one ovary from each experimental rat, then exposed half of the group to styrene orally. Normally, after removal of one ovary, the other ovary will grow in size as it takes over responsibility for hormone production. In the exposed rats, the remaining ovary did not grow to compensate for the loss, suggesting an effect on hormonal function in rats.[232]

One animal study using levels of styrene vapor ten fold lower than the allowable workplace average showed significant increases in embryonic death, but another study did not confirm this finding.[233, 234] Injection of styrene into chicken eggs consistently causes developmental abnormalities in the chicks.[235] These studies are the only ones which suggest that styrene might cause birth defects. Evidence that styrene may affect development and behavior comes from a study of rats exposed to low levels of styrene vapor for seven weeks after birth. These rats had significantly reduced weight gain and delayed ear and tooth development. The exposed rats displayed a dose-related reduction in exploratory and avoidance behavior.[236]

Human studies, for the most part, have not found a consistent effect on reproduction and development.[237] The largest human epidemiological studies were performed in Finland, and these generally found no significant effect of styrene exposure on pregnancy outcome.[238, 239, 240. 241] A series of Russian studies found an association between styrene exposure and self-reported menstrual abnormalities.[242] A small study in Italy found greater menstrual irregularity and reduced fertility in women occupationally exposed to styrene, but any conclusions are limited by the small sample size.[243] Similar studies in Finland and the U.S. did not find any effects of styrene on menstrual function.[244] Interestingly, a small study of women occupationally exposed to styrene found significantly elevated levels of the hormone prolactin and elevated levels of human growth hormone.[245] Elevated prolactin levels can lead to menstrual dysfunction and could explain the findings of abnormal menstrual cycling in women workers and abnormal estrus cycling in rats.

There is conflicting evidence on whether styrene affects male fertility. One group of styrene-exposed workers had a significantly lower proportion of normal sperm than a comparison group who sought care at an infertility clinic.[246] A styrene-based chemical, styrene maleic anhydride, is under consideration for use as a male contraceptive.[247] Animal studies on the effects of styrene on the testes are conflicting, with some studies showing reduced sperm counts and changes in the microscopic appearance of the testes, and other studies finding no effect.[248] Researchers have found an increase in damage to DNA in both human and rat testicular cells exposed to styrene in vitro.[249]

In summary, studies on the reproductive toxicity of styrene have been extraordinarily conflicting. The evidence for an effect on male testicular function is strongest, but needs further study. Despite a large number of studies, there is no clear answer to whether styrene affects female menstrual function, though this would not be surprising in light of evidence that the solvent may affect the endocrine system in rats and humans.

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 hormonal and reproductive function.

In summary, toluene increases the risk of spontaneous abortion in exposed women. High doses of toluene in humans, though not in animals, have been associated with a syndrome of severe congenital defects. One study found hormone suppressive effects in exposed men. More research needs to be done on the possibility of hormone suppression in humans from toluene exposure. Based on the current evidence, toluene is currently regulated by the state of California as a developmental toxicant.[266]

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]

TCE exposure is widespread in this country, but human and animal studies of possible health effects have shown conflicting results. Given the associations of other solvents with spontaneous abortions, this finding with regard to TCE is plausible and should be taken seriously. The consistency of the animal and human studies showing an increase in heart defects from TCE exposure prior to and during pregnancy is of great concern, and implies a hazard that requires further action.

Xylene

■ **Uses**	Paints, lacquers, varnishes, insecticides, in rubber, plastic, and leather manufacturing, an ingredient in gasoline.
■ **Routes of Exposure**	Occupational: Various manufacturing jobs, painting and varnishing. Environmental: Home use of paints, lacquers, varnishes, gasoline exposure, and water contamination.
■ **Reproductive Effects**	Animals: Toxic to the fetus, may cause certain birth defects, may interfere with endocrine function; Humans: Association with spontaneous abortions.

Summary of Studies

Some animal studies involving xylene are particularly troubling because of the toxicity and birth defects at low doses. One study found lethal effects at late stages of fetal development, abnormal bleeding, abnormalities in development of the skeleton, and growth retardation in rats exposed by inhalation to levels between 50 and 500 mg/m^3.[298] The workplace standard is 435 mg/m^3 for eight hours.[299] Higher-dose animal studies have found increased fetal resorptions, fetal death, delayed fetal development and low birth weight.[300, 301, 302, 303] An interesting study exposed rats to xylene alone, or to xylene and aspirin. The xylene alone was found to be somewhat toxic to the embryo, inhibiting normal growth. When xylene and aspirin were combined the effects were much more serious, with dramatic fetal toxicity and malformations, particularly of the skeletal system and the kidneys.[304] Aspirin is known to cause birth defects, and it appears that xylene may act synergistically to worsen this outcome.

Prenatal xylene exposure may lead to changes in development and behavior.[305] Rat pups exposed prenatally at fairly low levels showed a decrease in brain weight, delay in reflex development, and impairment in tests of neuromotor ability, learning and memory. The effects were most marked in the female pups.

Two important studies looked at the effects of xylene on sex hormones. Rats exposed to high levels of xylene have significantly lower blood levels of progesterone and 17ß estradiol, two of the hormones responsible for regulating the female reproductive cycle.[306] In addition, xylene prevents ovulation in rats.[307] Alterations in maternal hormone levels may be responsible for the toxicity to animal embryos.

There have been few human studies of the reproductive toxicity of xylene. One early investigator reported five cases of a rare birth defect called caudal regression in mothers exposed to solvents; this defect involves incomplete development of the pelvic region and legs. Of nine reported cases of this rare defect, five mothers were exposed to solvents. In a companion study, the investigator exposed chicken embryos to xylene, and found many deformities. About half of the deformities included "rumplessness."[308] Other human studies found a five-fold increase in spontaneous abortions in women exposed to xylene.[309] Mothers of children born with central nervous system defects were also more likely to have been exposed to aromatic solvents, particularly xylene, during pregnancy.[310]

In summary there is evidence of toxicity and neurodevelopmental effects in the rat fetus at inhaled levels

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.

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Chapter 6

Pesticides

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 those which are not defined by the manufacturer or EPA as active. About 2,500 inert ingredients are present in 20,000 pesticide formulations. "Inerts" may assist in the transport of the active ingredient to the target pest; give certain properties to the final recipe useful in mixing and application; or affect the length of time the product remains active in the environment.

Many so-called "inert" ingredients are also highly toxic. A recent study by the Northwest Coalition for Alternatives to Pesticides indicates that over 650 "inert" ingredients have been identified as hazardous by federal, state, or international agencies.[4] Almost 400 inert ingredients are now or have been used as the active ingredient in pesticides. In addition, 209 are hazardous air or water pollutants, 21 have been classified as carcinogens, and 127 are occupational hazards. Many have been identified by more than one statute or agency. For example, the "inert" ingredient naphthalene is a pesticide active ingredient, a hazardous air pollutant under the Clean Air Act, and a priority pollutant under the Clean Water Act. Some "inert" ingredients penetrate protective clothing, increasing skin contact with the active ingredient. Many "inerts" penetrate the skin, carrying active ingredients along and increasing the risk of toxic effects. "Inert" ingredients often comprise over 90% of the final product formulation.

Until recently, the EPA did not require that the names of the "inert" ingredients be listed on any pesticide label, accepting manufacturers' claims that the identity of the "inert" was a "trade secret". However, in 1994 the

Northwest Coalition for Alternatives to Pesticides charged that the EPA wrongfully accepted claims of confidentiality without first determining that the "inerts" were actually trade secrets. A federal district court ruled that pesticide manufacturers must disclose information about "inerts" in the six different products which were at issue. Though the ruling did not apply to all pesticide products, the EPA is now faced with having to apply the court decision more broadly.

Pesticide fate and transport

The distribution and life history of pesticides in the environment is largely determined by the chemical and physical properties of each agent. Of particular interest are:

- *Environmental persistence*—indicates how long it takes for a pesticide to break down in soil, sunlight, surface or groundwater, or indoors (see Table 1);
- *Water solubility*—determines the degree to which a pesticide will run off in rainwater or be transported into groundwater (see Table 1);
- *Volatility*—determines evaporation into the air and transport through the atmosphere;
- *Soil binding*—influences environmental persistence and runoff into water bodies;
- *Tendency to bioaccumulate*—indicates how much the concentration of a pesticide is likely to build up in a living organism over time.

Some pesticides persist for long periods, tightly bound to soil particles, while others readily evaporate and are dispersed over great distances through the atmosphere. They may be biodegraded by soil organisms and sunlight or persist unchanged as they cycle through ecosystems. Several organochlorine pesticides which have been banned for years in the US are so persistent that they are still detected in homes and residents continue to be exposed.[5] Sprayed pesticides drift to nearby land and water. Applications from airplanes are sometimes windblown many miles. Some pesticides bind to water droplets and are commonly found in fog and rainwater.[6] Pesticide atmospheric dispersion is global and penetrates the food chain at all levels.

Pesticides which persist in the environment and accumulate in living organisms tend to concentrate at the top of the food chain. For example, some organochlorine pesticides are dispersed worldwide, contaminating oceans, sediments, bottom-dwelling clams, mussels, sea urchins, and fish.[7] Persistent pesticidal and non-pesticidal organochlorines, along with other long-lasting and fat-soluble chemicals, concentrate in the fat tissue of marine mammals. Inuit mothers, whose diet at the top of the Arctic food chain is rich in marine mammal fat, have the largest known body burden of organochlorines, some of which are pesticides. They pass these chemicals on to their developing fetuses and nursing infants.[8]

Table 1
Pesticide Persistence and Solubility

Pesticide	Persistence	Solubility
Herbicides		
Atrazine	60-100 d	33 ppm
Bromoxynil	11 d	0.08 ppm
Cyanazine	12-108 d	170 ppm
Dicamba	8-25 d	8,310 ppm
Diuron	30-400 d	42 ppm
Molinate	12 d	800 ppm
Insecticides		
Acephate	3-6 d	650,000 ppm
Chlorpyrifos	11-141 d	2 ppm
Cypermethrin	7-82 d	0.004 ppm
Diazinon	3-13 d	60 ppm
Parathion	7-30 d	12 ppm
Carbaryl	7-28 d	50 ppm
Endosulfan	4-200 d	0.32 ppm
Dicofol	16-60 d	0.8 ppm
Lindane	400 d	7 ppm
Methoxychlor	7-180 d	0.1 ppm
Permethrin	6-106 d	0.006 ppm
Fungicides		
Mancozeb	7-139 d	6 ppm
Vinclozolin	14 d	3 ppm
Pentachloro-phenol	50 d	14 ppm

Persistence—soil half-life, in days. The amount of time required for the pesticide to break down to 1/2 of its initial concentration. Large ranges indicate variability in half-life depending on soil type, pH, aerobic or anaerobic conditions.

Solubility—high solubility means that the pesticide is more likely to be carried by water throughout the environment and into groundwater aquifers. (ppm = mg/L)

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 different sources.*
- *Population monitoring demonstrates generally widespread pesticide exposure, though infants, children, and farm workers are often excessively exposed.*
- *Routes of exposure include skin contact, inhalation, and ingestion.*

Pesticides contaminate air, soil, food, and water, and a focus on only one source will seriously underestimate total human and environmental exposure levels. Unfortunately, with only a few exceptions, accurate pesticide use and exposure information, necessary for studying health effects, is not routinely collected.

Skin absorption, inhalation, and ingestion are each important potential routes of exposure. Fat-soluble chemicals, purposely or accidentally applied to the skin, are readily absorbed into the body. The type of spray equipment, spray velocity, and pesticide volatility determine the extent of inhalation exposure.[10] Even when pesticides are used as recommended, exposures may be excessive.

The largest number of chemicals and the highest concentrations are often found in household dust, compared to air, soil, and food.[11] In a study of air and surface residues after chlorpyrifos (an organophosphate pesticide) had been used for indoor flea control according to directions, total absorbed doses for infants were estimated at up to 5 times the no-observable-effect level.[12] Another study found chlorpyrifos levels peaking on furniture, toys, and other indoor surfaces 36 hours after the pesticide had been applied to the floor of a room with subsequent ventilation according to directions.[13] The researchers concluded that skin contact, ingestion, and inhalation were likely to cause unsafe exposures to children playing in the room. Some chemicals banned years ago, like chlordane and aldrin, are still present in recent testing of indoor air and carpet dust.[14]

Pesticide ingestion from food depends on dietary patterns and details of food preparation. Infants and children consume more fruits and vegetables, such as apples, bananas, tomatoes, and squash, per unit of body weight than adults. Children also have less variety in their diets than adults. Consequently, young children are sometimes excessively exposed to pesticide residues on those foods. Moreover, banned or restricted pesticides are exported in large quantities by U.S. manufacturers. In 1990, for example, U.S. pesticide manufacturers exported over 465 million pounds of pesticides, and of those, 52 million pounds were banned, restricted, or unregistered for use in the US.[15] Some are returned as residues on the billions of pounds of fruits and vegetables imported into the U.S. annually and are not routinely tested for by the Food and Drug Administration. Finally, many allowable pesticide food residues - “tolerances” - are not currently set at levels protective of public health. Under the new Food Quality Protection Act, U.S. EPA is now required to revisit and evaluate over 9,000 tolerances (see Part III).

Occupational exposure is of great concern for many people. Nationally, at least half of the millions of farm workers in the U.S. come into direct contact with farm chemicals.[16] [17] Product-labeling requirements which emphasize the need for protective clothing or equipment may be the only regulatory safeguard against excessive exposure to farm chemicals. Yet, in warm climates, these are often intolerable because of the heat and are rarely used.[18] For an estimated five million migrant and seasonal farmworkers, most of whom belong to an ethnic minority, the extent of pesticide exposure and resultant health effects are largely unknown.[19] [20] Children living in homes near sites of agricultural pesticide use are likely to be exposed to pesticides that are not registered for residential use. Levels of pesticides in their homes are higher than in homes more remote from agricultural operations.[21]

In order to estimate the extent of pesticide exposure in the general population, and as part of the 1994 National Health and Nutrition Examination Survey III (NHANES III), urine samples were collected from about 1,000 adults selected from a broad spectrum of the US population.[22] Specimens were analyzed for 12 different chemical com-

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 monitored for pesticide exposures and a variety of health outcomes including cancer and reproductive effects. The results of this study will not be available for years.

Tables 2 and 3 summarize many of the available epidemiological studies. Collectively, the studies demonstrate a range of adverse reproductive outcomes, primarily among agricultural workers.

Spontaneous abortions and time-to-pregnancy

A number of studies report an increased incidence of miscarriages and stillbirths among women agricultural workers (Table 2). Though useful, these types of studies have inherent limitations. For example, when agricultural occupation is used as a surrogate for pesticide exposure there is always the possibility of exposure misclassification and underestimation of the true risks. Some of these studies rely on maternal interview for health effects data and are subject to recall bias which may tend to exaggerate the risks. Those studies that use hospital discharge summaries to document the outcome and occupation avoid recall bias but include only those women who were treated in a hospital. Self-reports of spontaneous abortions are likely to underestimate their true incidence when they occur early in pregnancy and often go unrecognized. Consequently, these studies must be interpreted with knowledge of their limitations. But, considered collectively, there appears to be an increased risk of spontaneous abortion in women occupationally exposed to pesticides which may be up to 5 times the risk in control groups.

An investigation of a group of Indian men employed as pesticide mixers and sprayers in cotton fields showed that their wives also experienced more miscarriages and stillbirths than a comparison group.[26] The men used a variety of pesticides, often without the use of protective equipment.

In the Netherlands, investigators studied time-to-preg-

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, this study is limited by its ecologic design. That is, there was no attempt to determine whether individual women whose offspring suffered from retarded growth were drinking more of the contaminated water than women whose children developed normally. More detailed exposure assessment will be required in a future study to resolve the matter.

In summary, the magnitude of increased risk of birth defects resulting from pesticide exposure is uncertain because of inadequate exposure assessment and incomplete or inaccurate reporting of defects. Nevertheless, taken as a whole, the weight of evidence from these studies supports the conclusion that birth defects are more likely in the children of parents exposed to pesticides before or during pregnancy.

Table 2 Studies of spontaneous abortion or fetal death (including stillbirth) in women* with agricultural occupation and potential pesticide exposure

Exposure	Reproductive outcome	Observed effect
agricultural occupation[28]	spont. abortion	1.3 times more likely**
agricultural occupation[29]	spont. abortion	2.8 times more likely
agric. or horticultural occ. >30 hrs/wk. beginning of preg[30]	spont. abortion	no effect
gardener[31]	spont. abortion	no effect
grape garden spraying-(both parents)[32]	spont. abortion	5.5 times more likely
floriculture[33]	spont. abortion, stillbirth	2.2 times more likely
ethylene oxide[34] (hospital worker)	spont. abortion	more than 2 times more likely
agric work >30 hr/wk for at least 2 wks at beginning of preg; pesticide exposure est. by interview later[35]	stillbirth without major malformation	3.1 times more likely
agric. or horticultural occ. at any time of preg.	stillbirth without other	5.7 times more likely
male pesticide mixers and sprayers[37]	spont. abortion stillbirth	1.7 times more likely 3.3 times more likely

* women exposed to pesticides except where otherwise noted

** more likely than in a control group in the study

Childhood Cancer

Childhood cancer is the second leading cause of death of children between 1 and 14 years of age in the US. The incidence of childhood cancer has been steadily increasing over the past 20 years, most markedly for leukemia and brain tumors.[56] Fortunately, more effective treatments have reduced the mortality from these diseases. Epidemiological studies of environmental factors which may contribute to childhood cancer are limited by small numbers of cases, making it difficult to achieve statistical significance (see Chapter 3). Nonetheless, a number of studies demonstrate an increased risk of these malignancies with parental occupational pesticide exposure or home use of pesticides.

A review of the published literature which examines the link between pesticide exposure and childhood brain cancer finds 8 of 9 studies showing an increased risk with three reaching statistical significance.[57] Of particular concern are the residential use of pesticide bombs and no-pest strips during pregnancy where the risk of brain cancer may be increased 5-6 fold.[58] This study also reported a strong association with childhood use of lice shampoo (lindane) and childhood contact with pesticides used on pets.

Five of nine studies found an increased risk of childhood leukemia with parental occupational exposure to pesticides.[59] Increasing frequency of home or garden use of pesticides was also reported associated with an increasing risk of childhood leukemia.[60] Of particular note are studies performed within the Children's Cancer Group Epidemiology Program. Participants diagnose and treat more than 90% of childhood cancer in the U.S. providing an opportunity to design studies with substantial statistical power. Completed studies of this program consistently find a statistically significant association between reported pesticide exposure and childhood acute myeloid leukemia.[61]

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

Several investigations have examined the effect of pesticides on chromosomes of exposed agricultural workers. Analysts usually study lymphocytes from the blood, and if chromosomal damage is found, similar damage may be occurring in other cells including sperm, raising concern about mutations and inheritable disorders. In a group of floriculture workers in Argentina who were using organochlorine, organophosphate, and carbamate pesticides, the frequency of some types of chromosomal abnormalities was 4 times higher than in a control population.[67] Similarly, lymphocytes from a group of pesticide-exposed workers in Hungary showed a 31% increase in damaged cells when compared to controls.[68] Pyrethroid pesticide exposure in a group of dealers and workers in Syria was associated with up to 3 times the frequency of chromosome breaks compared to controls.[69]

Summary

In summary, spontaneous abortions, delayed pregnancies, birth defects, retarded intrauterine growth, some childhood cancers, spermatotoxicity, and chromosome damage are associated with exposure to pesticides in a number of epidemiological studies. Many of these studies have found the association in agricultural workers, but several find an increased risk in the general population. Because exposure assessment and monitoring of adverse health outcomes are rarely precise, the magnitude of risks is difficult to determine precisely. Moreover, other factors may also influence the risks in agricultural work. But, recalling that more than 80% of families surveyed in Missouri in 1989 used pesticides during pregnancy and that large numbers of the general population have pesticide residues in their urine, obvious concerns are raised by this body of evidence.

Though animal testing with single chemicals drives the regulatory process, these epidemiological studies should not be ignored. Real-world exposures to pesticides appear to have adverse effects on human reproduction and development in some occupationally exposed or particularly susceptible groups. These data are essential to agricultural workers, employers, consumers, regulators, and pesticide manufacturers for making more health-protective choices.

Animal evidence

Unlike requirements for many other industrial chemicals, the current pesticide registration process is intended to ensure that every active ingredient proposed for manufacture and use will be subject to a standard battery of animal tests. There are, therefore, considerable toxicological data available for newly proposed pesticides. However, historically, regulators did not require rigorous toxicological evaluation of pesticides before allowing their commercial use. Consequently, for some widely used chemicals, the data are sparse - inadequate to meet current standards, not to mention proposed refinements.

For example, many pesticides have not been adequately tested for a range of developmental effects. Moreover, new understanding of subtle and delayed expressions of toxicity, such as developmental neurotoxicity and endocrine disruption, indicates that re-evaluation of

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 pesticide classes. Many of the approximately 600 active ingredients currently in use are not mentioned, but this does not imply that they have no important reproductive toxicity. Our intent is to review the reproductive and developmental toxicity of some commonly used, high volume chemicals.

Organophosphates and Carbamates

Insecticide	Uses
acephate	vegetables, peanuts, tobacco, forests, ornamentals
chlorpyrifos	fruit, vegetables, nuts, cotton grain, ornamentals, turf
diazinon	fruits, vegetables, tobacco, forage, field crops, nematodes in turf, seed treatment, fly control
dimethoate	fruits, vegetables, grain, tobacco, cotton, ornamentals
malathion	fruits, vegetables, ornamentals
naled	ornamentals, poultry houses, kennels, food processing plants, mosquito control
tetrachlorvinphos	fleas, ticks, mites, houseflies, animal feed larvicide
carbaryl	fruits, vegetables, forage and field crops, nuts, ornamentals, lawns, forests

Reproductive Effects
Vary among individual agents and include fetal deaths, abnormal sperm, abnormal ovarian follicles and eggs, hormonal changes, DNA damage, birth defects, neurobehavioral disorders

Organophosphates, originally designed as nerve warfare agents, are widely used in many pesticide products. Most are much less toxic than the original chemical weapons though acute toxicity is still their most commonly recognized adverse effect. Organophosphates and carbamates work through slightly different mechanisms to inhibit the destruction of a naturally-occurring neurotransmitter, acetylcholine. They accomplish this by destroying or disabling the enzyme, cholinesterase, responsible for metabolizing the transmitter into an inactive form. The result is over-expression or runaway transmission of nerve impulses along certain nervous system pathways. Symptoms of acute intoxication include excessive salivation, tremors, muscle twitching, nausea, vomiting, and diarrhea. Large exposures may lead to convulsions and

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

Organochlorines

Insecticide	Uses
dicofol	mite control on fruit, vegetable, ornamental, field crops
endosulfan	fruits, vegetables, coffee, tea, forage and field crops, grains, nuts, ornamentals, tobacco
lindane	seed and soil treatment, nurseries, tree farms, tobacco, human louse control
methoxychlor	fruit and shade trees, vegetables, dairy and beef cattle, home gardens, around farm buildings
dienochlor	shrubs, trees, and in greenhouses.

Reproductive Health Effects

Endocrine disruption, including effects on estrogen, androgens, prolactin and thyroid hormone, fetal loss, and reduced sperm counts in animal tests

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.

Table 5
Reproductive/developmental effects of organochlorine pesticides in animal tests

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]	• RfD 0.0003 mg/kg/day
	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]	
endosulfan	Estrogenic as shown in a large number of animal and other laboratory studies (see Chapter 7).	RfD 0.006 mg/kg/day
	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]	
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]	RfD 0.005 mg/kg/day (low confidence due to lack of definitive chronic toxicity studies)
	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 a residual effect from previous treatment.[108]	
	In the female rat exposure is associated with abnormal estrus cycle, inhibited luteal function, blockage of implantation, reduced fertility and litter size.[109]	
	In the male rat exposure is associated with elevated prolactin levels, suppression of Leydig cell function (some at 25 mg/kg/day). Associated with aggressive behavior in male rat offspring.[110]	
dicofol	Used in the U.S. since 1955, dicofol has been "grandfathered" for continued use as new testing requirements evolved and thereby escaped any thorough assessment of its toxicity.	
	Manufactured from and contaminated with DDT.[111] This not only complicates toxicity testing but provides ongoing release of DDT into the environment where dicofol is used. Currently the EPA requires manufacturers to use techniques which minimize DDT contamination.	
	Exposure to kestrels by oral intake leads to eggshell thinning, feminization of male embryos, abnormal submissive behavior in male offspring, and impaired reproductive capacity of the offspring after they mature.[112 113]	
	Lake Apopka (Florida) male juvenile alligators which were exposed to dicofol contaminated with DDT, along with other pollutants associated with agricultural activity, had significantly depressed testosterone levels, abnormal testes, and small penises when compared to control animals from another lake.[114]	
	Prenatal exposure alters behavior in rat offspring (10 mg/rat, days 4-15 of pregnancy).[115]	

Pyrethrins / Pyrethroids

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 products, mosquito control
permethrin	broad spectrum for wide range crops, home gardens, nurseries,termites, greenhouses

Reproductive Health Effects
In animal tests some pyrethoids decrease offspring weight, increase fetal losses, and cause delayed brain development.

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-

Table 6
Pyrethrins / pyrethroids

cypermethrin	Decreases offspring wgt at 5 mg/kg/day (rat); decreases brain neurotransmitter receptors in offspring when given day 5-21 pregnancy at 15 mg/kg/day; delays maturation of cerebral cortex at 3-6 wks of age.[119] Developmental delays (rat) (day 5-21 of preg. at 15 mg/kg/day).[120]	RfD 0.01 mg/kg/day – high confidence
fenvalerate	Decreases brain enzymes in offspring when given day 5-21 of pregnancy (rat) (10mg/kg/day).[121]	RfD 0.025 mg/kg/day – high confidence
permethrin	Liver and eye abnormalities in offspring at lowest dose tested (25 mg/kg/day) in a three generation study (rat)[122]	RfD 0.05 mg/kg/day – high confidence
resmethrin	The reference dose (RfD) for resmethrin is established on the basis of its reproductive toxicity in a 3-generation rat study.[123] The effects at the lowest dose tested (25 mg/kg/day) included an increased incidence of stillborn offspring and decreased body weight at weaning.	RfD 0.03 mg/kg/day – high confidence

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]

Table 7 Fungicides

dithiocarbamate fungicides (maneb, nabam, zineb, mancozeb, thiram)	Maneb and mancozeb cause birth defects or fetal death after fairly high levels of maternal exposure (rat) (500-1300 mg/kg/day during 11 days of pregnancy or inhalation of 500 mg/m3/day for 6 hrs./day during 5 days of pregnancy).[129 130 131] Birth defects include brain abnormalities (rat/hamster). Birth defects following exposure to maneb in the egg with some studies showing lower limb deformities (chick).[132 133] Zineb, maneb, and mancozeb are also toxic to sperm and damage the testes at fairly high exposure levels (rat).[134 135] Birth defects after single dose on day 11 or 13 of preg (rat) (>0.5 gm/kg needed).[136] Blocks LH surge and interferes with ovulation;[137] testicular toxicant at 5 mg/kg/day (rat).[138]	RfD 0.005 mg/kg/day – low to medium confidence
benomyl	Birth defects and testicular toxicity (rat/rabbit).[139 140 141] Damage to testicles, Sertoli cell toxicity and sperm toxicity (rat). [142]	RfD 0.05 mg/kg/day Listed under Prop 65
thiabendazole	Fetal death, birth defects above 60 mg/kg/day during 9 or more days of pregnancy (rat). [143 144]	RfD 0.1 mg/kg/day
vinclozolin	Feminization of male offspring exposed in utero (rat) [145]	
iprodione	Increased abortions at 60 mg/kg/day throughout pregnancy (rabbit)[146]	RfD 0.042 mg/kg/day – high confidence

Herbicides

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.
molinate	control of weeds in rice paddies.
EPTC	control of annual grassy weeds, perennial weeds, some broadleaf weeds in beans, legumes, potatoes, corn, and sweet potatoes.

Reproductive Health Effects

In animal studies, spermatotoxicity, fetal losses, decreased fetal weight, birth defects. In humans, evidence of birth defects and spermatoxicity

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-acetic acid, otherwise known as 2,4-D, is widely used by commercial appliers and homeowners to kill weeds. A mixture of 2,4-D and another member of this class, 2,4,5-T, is known as Agent Orange and was sprayed as a defoliant over vast areas of Vietnam during the 1960's and early 1970's. This mixture was inevitably contami-

Table 8
Triazines

atrazine	Causes birth defects when pregnant rats are dosed at 70 mg/kg/day on days 6-15 of pregnancy (rat).[150] Inhibits some estrogen-induced responses.[151 152] Accelerates the onset of breast tumors in one strain of rats but not in another, suggesting that it may also have an estrogenic effect (rat).[153.] Decrease in male offspring weight in 2nd generation at 25 mg/kg/day; skeletal birth defects at 70 mg/kg/day (rat) [154] Androgen antagonist: Interferes with receptor formation and testosterone conversion.[155] Increased fetal death at 75 mg/kg/day (rabbit).[156]	RfD 0.035 mg/kg/day
cyanazine	Fetal toxicity at 2 mg/kg/day (rabbit). Birth defects at 25 mg/kg/day (rat).[157]	RfD - withdrawn
simazine	Testicular toxicity, spermatotoxicity (sheep) (1.4 mg/kg/day). [158] Birth defects, decreased fetal weight (rat) (200 mg/kg/day).	RfD 0.005 mg/kg/day - high confidence

Table 9
Chlorinated Phenoxy herbicides

2,4-D	Increase in the offspring mortality at 50 mg/kg/day for 3 months before mating and throughout gestation (rats).[165]	RfD under review
diclofop	Fetal losses, birth defects including reduced bodywieghts and abnormalities of the urinary tract (rat) (5 mg/kg/day).[166] Increased offspring mortality occurred at 5 mg/kg/day in a 3-generation rat study.	
dicamba	Offspring with less weight gain, reduced fetal body weight, increased fetal loss (preg. rabbits given 10 mg/kg/day) Heart abnormalities in offspring, skeletal malformations (rat).[167] [168]	RfD 0.03 mg/kg/day

nated with dioxin as a result of the production process. Consequently, epidemiological studies intended to reveal the health effects of exposure to this class of chemicals have had to contend with the potential contribution of dioxin to the observed results.

In animal studies, 2,4-D causes toxicity to the blood, liver, and kidneys at 5 mg/kg/day.[160] Larger doses are necessary to elicit reproductive toxicity. Musculoskeletal, nervous system, urinary system, and head and face abnormalities appear at still higher doses in animal tests.

In a study of male farm sprayers exposed to 2,4-D as determined by measuring residues in their urine, significantly lower sperm counts and increases in abnormal sperm were seen in the exposed group when compared to controls.[161] This study has been criticized by a pesticide industry-sponsored review of the toxicity of 2,4-D for failing to describe how samples were handled and how controls were selected.[162] Yet, an epidemiological study in Minnesota showed significantly higher rates of birth defects among the offspring of pesticide appliers and the general population in areas of the state with highest use of chlorophenoxy herbicides and fungicides.[163] The increase was most pronounced for infants conceived in the spring, the time of highest herbicide use.

2,4-D and other chloro-phenoxy herbicides are under review by the EPA primarily because of concern about carcinogenicity. In particular, there is a body of evidence indicating a relationship between exposure to these chemicals and development of malignant lymphoma.[164] However, there are also studies which show no relationship, and it is unlikely that this controversy will be resolved anytime soon.

Substituted urea herbicides

Linuron and diuron are of a chemical class called substituted urea herbicides, which work by inhibiting photosynthesis. In rats given linuron (RfD - 0.002 mg/kg/day - high confidence) during pregnancy at doses of 6.25 mg/kg/day, pup weights and survival were reduced. Rabbits show the same adverse effects at 5 mg/kg/day. Rabbit offspring also show evidence of skull abnormalities.[169]

Diuron causes decreased body weight in offspring of a 3-generation reproduction study in rats and rib abnormalities in a teratology study. Both diuron and linuron are listed as developmental toxicants subject to TRI reporting.[170]

Other herbicides

Bromoxynil (RfD 0.02 mg/kg/day – medium confidence) is a nitrile herbicide that inhibits photosynthesis in the target weed. It is on the California Proposition 65 list of reproductive toxicants. In rats, this herbicide causes fetal toxicity and rib abnormalities in offspring at 35 mg/kg/day. [171] In rabbits, it causes brain, eye, and skull defects at 30 mg/kg/day.[172]

Metribuzin is a selective herbicide that, in rabbits, causes maternal and fetal toxicity when given at 45 mg/kg/day during days 6-18 of pregnancy. In rats, abnormalities of the spinal column and decreased pup body weight occur at 85 mg/kg/day. The EPA lists metribuzin as a develop-

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

Since 1982, at least 19 Californians have died from methyl bromide exposure, hundreds have become sick and thousands of residents from Fresno to Oxnard have been evacuated because of methyl bromide accidents. A highly toxic pesticide which is known to cause birth defects, methyl bromide is used across California to grow strawberries, grapes and other high-value crops. It is injected into the soil before planting crops and kills most living organisms. The gas can also drift into local homes, schools and neighborhoods, causing serious public health concerns.

In 1993 and 1995, Castroville residents were poisoned when methyl bromide drifted into their homes from a neighboring strawberry farm. In 1996, a day care center in Ventura relocated after neighbors complained of illnesses from methyl bromide use in a nearby strawberry field. In Watsonville, some 265 Amesti Elementary School students stayed home from school in September 1997 after the strawberry farm across the street was sprayed with methyl bromide. Amesti parents and teachers are now protesting to prevent future fumigations near the school.

Although public outcry has been great, state officials have done little to protect Californians from this hazardous pesticide. Methyl bromide is listed under California's 1984 Birth Defects Prevention Act (S.B. 950), which requires pesticide manufacturers to submit health impact studies on their chemicals. If the studies are not submitted on time, state agencies are required to de-register the pesticide. Methyl bromide manufacturers missed two deadlines for submitting the required studies, in 1991 and again in 1996, yet the chemical has never been de-registered.

In January 1996, Governor Wilson convened a Special Session of the state legislature to stop an impending ban on methyl bromide because of the missed 1996 deadline. Under pressure from agricultural lobbyists, the legislature extended the registration of methyl bromide until December 1997, giving pesticide manufacturers a third deadline to submit the required health studies. After thirteen years of delay, methyl bromide producers submitted the final toxicity studies in December 1997. The State's Department of Pesticide Regulation is currently reviewing these studies, and communities throughout the state continue to press for de-registration of this dangerous pesticide.

lower sperm counts and sperm with diminished motility.[182] [183] Sperm maturation is affected but recovers over a period of days to months when the EDB is removed from the diet. Agricultural workers exposed to EDB have also had decreased sperm counts, decreased viable and motile sperm, and increased numbers of abnormally shaped sperm when compared to an unexposed group.[184] Most uses of EDB have been cancelled, but groundwater contamination persists in some areas.

Ethylene oxide

Ethylene oxide (EtO) is a highly toxic, explosive chemical and is usually kept in tightly closed, automated systems with little opportunity for worker exposure. However, improperly operated or malfunctioning sterilizing systems in hospitals may result in brief but significant exposures. The hazards of EtO are widely known. Most hospitals, for example, are equipped with elaborate sterilizing systems, continuous EtO monitors, and gas recovery systems. Less-toxic alternatives are gradually replacing EtO in some hospitals.

EtO is a potent chromosome toxicant, causing mutations and other forms of damage even at low and intermittent exposure levels. Animal studies demonstrate that EtO is carcinogenic and causes harmful reproductive effects. Rats inhaling small amounts of the gas during and after mating produce smaller litters with lower birth weights.[185] EtO exposure has lowered the sperm counts of monkeys exposed to small amounts 7 hrs/day, 5 days/week, for 2 years[186] and has produced sterility in male mice.[187] Chromosome damage insufficient to cause fetal death may result in genetic damage transmissible to the next generation. Given to mice intravenously at doses thousands of times above occupational standards, EtO causes birth defects in offspring.[188] A study of hospital sterilizing staff in Finland demonstrated a significant increase in miscarriages among those exposed to EtO when compared to those unexposed.[189]

Methyl bromide

In 1993, California used nearly 15 million pounds of methyl bromide, mostly for soil fumigation.[190] Like other fumigants, it is extremely toxic and must be used with great care. Furthermore, methyl bromide is also a major depleter of the stratospheric ozone layer, with phase out called for in the Montreal Protocol. However, the Clinton administration has led a successful effort to shift the cut-off date for production and use of methyl bromide from 2001 to 2010 with provisions for "essential uses" after that date. Similarly, elected officials in California have delayed regulation of this chemical (see

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 effects were noted in reproductive success or tissue examination of parents or offspring.[194] Methyl bromide is listed in California as a known reproductive hazard.

Metam sodium (sodium s-methyldithiocarbamate)

Methylisothiocyanate (MITC) is the major breakdown product of metam sodium in organisms and in the environment. In animal tests, symptoms of acute toxicity of MITC include vomiting, diarrhea, weakness, and skin and eye irritation.[195] Short periods of inhalation of large amounts lead to convulsions and death. Smaller exposures over longer periods of time cause toxicity to the intestine, liver, kidneys, and ovaries. In rats, metam sodium causes adverse reproductive and developmental effects at doses of 10 mg/kg/day given on days 6-15 of pregnancy.[196] Some fetal deaths are seen at this dose with an increase in birth defects in surviving offspring at higher levels of exposure. Spinal column defects, brain swelling with hydrocephalus, umbilical hernias, and delayed skeletal development are observed in rats and rabbits.

Summary

Many active pesticide ingredients have reproductive and developmental toxicity at some level of exposure. Differing for each chemical, the threshold for health effects is often substantially higher than any likely human exposure but may be within or close to levels actually experienced by more heavily exposed groups. Some pesticides with clear evidence of reproductive toxicity in humans have been restricted or banned from use. Others are undergoing further study and continue to be used. The US EPA has listed 68 pesticide active ingredients as having enough evidence of reproductive and/or developmental toxicity to require Toxics Release Inventory reporting.

There are numerous opportunities for human exposure to pesticides. In general, infants and children experience higher exposures to some pesticides than adults on a body-weight basis and are more vulnerable to any potential developmental effects, many of which are unknown or understudied. Occupational exposures pose risks to the health of millions of agricultural workers and their families.

Epidemiological studies show that occupational exposures to pesticides are associated with spontaneous abortions, infertility, spermatotoxicity, chromosome damage, and birth defects. Some studies in the general population show associations between pesticide exposure and birth defects or childhood cancer. Other developmental abnormalities, including neurobehavioral disorders, have not been adequately examined in human studies. This is an important data gap.

The EPA reviews animal studies for evidence of a range of health effects in an attempt to establish “safe” human exposure levels. This process does not take into account epidemiological evidence of harmful effects at current exposure levels and does not require examination of non-chemical alternatives for pest control where possible. The pesticide registration process is described more fully in Part IV.

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Chapter 7

Endocrine Disruptors

Introduction

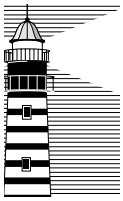
Hormones are chemical messengers which circulate in the blood and regulate many critical biological functions through intricate signalling mechanisms. Endocrine disruptors (EDs) are chemicals which mimic or block hormones or otherwise interfere with normal hormone activity, often at extremely small doses. 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 time, that mechanism of toxicity for some chemicals later became clear. In the 1970s scientists began to discuss hormone interference as a risk associated with widespread environmental contaminants of other types. In 1996, *Our Stolen Future* brought current scientific understanding to the general public, contributing to a broader debate about the health and environmental effects of a diverse group of chemicals.[2]

Early discussions focused on the estrogenic effects of environmental contaminants, but recent research extends concerns to anti-estrogens, androgens or anti-androgens, and some that interfere with thyroid hormone, cortisone, and others.[3] The reproductive and developmental success of birds, fish, reptiles, and other wildlife species has been impaired where they have been sufficiently exposed to endocrine disrupting chemicals.[4 5 6] Abnormalities include indeterminate sex, feminization of male animals, inability to successfully reproduce, and birth defects.

As more detailed understanding of the biological effects of EDs emerges, investigators have begun to study the potential relationship between exposure to these chemicals and a series of alarming human health observations. The incidence of breast, prostate, and testicular cancer has increased in this country and other parts of the world during the past several decades.[7] From 1962–1981 there was a doubling of the frequency of undescended testicles in England and Wales.[8 9] The rate of hypospadias, an abnormal opening of the urethra on the underside of the penis rather than at the tip, doubled in the U.S. during the 1970s and 1980s.[10] There is increasing agreement that sperm counts in some regions of the world have fallen substantially and, in some instances, approach levels which predict infertility.[11] The federal government reports that more than 2 million couples are involuntarily childless.[12] And a tragic 20-year human experiment with a synthetic estrogen, diethylstilbestrol (DES), begins to explain how fetal exposures may result in serious health effects years later. (see Spotlight)

Nevertheless, there is considerable controversy over the degree to which humans are threatened. Some argue that there is no persuasive evidence of health effects at current environmental exposure levels in the general population. They focus on the lack of a proven causal



Spotlight on

Diethylstilbesterol (DES)

From 1950-1971 diethylstilbestrol (DES), a synthetic estrogen with a chemical structure considerably different from naturally-occurring estrogen, was used in an attempt to prevent spontaneous abortions in women. An estimated 5-10 million Americans were exposed to DES during pregnancy (DES mothers) or in the uterus (DES daughters or sons).[13]

No harmful effects of DES exposure were suspected until 1970 when a rare form of vaginal cancer was reported in six young women, ages 14-21, who had been exposed to DES in the uterus.[14] Previously, this disease had occurred almost exclusively in older women, but it is now known to be caused in younger women by exposure of the developing fetus to DES. The risk for developing vaginal cancer from birth to age 34 is estimated to be 1 in 1000 to 1 in 10,000 for women exposed in the uterus - accounting for thousands of cases in the U.S. alone.

Later studies demonstrated that DES daughters often have abnormalities of their reproductive organs, reduced fertility, and unfavorable pregnancy outcomes including ectopic pregnancies, miscarriages, and premature birth, as well as immune system disorders. DES sons are more likely to have small and undescended testicles, abnormal semen, and hypospadias.[15] DES mothers have a breast cancer risk about 35% greater than those not exposed.[16] Animal studies in mice and monkeys show that prenatal DES exposure may result in masculinization of parts of the female brain and feminization in males.[17] Several studies in humans suggest similar results.[18]

Some DES daughters and sons are now in their mid-20's. Many do not know that they were exposed in the uterus. Their health status requires careful attention. As yet there is no definite evidence for adverse health effects in the offspring of those who themselves were exposed to DES in the uterus (DES grandchildren). However, since many are still young, it is too early to draw final conclusions, and the issue is not resolved.

DES is an example of an estrogenic chemical which causes reproductive and developmental abnormalities, immune system malfunction, and cancer in some people exposed as fetuses.

link between chemical exposures and human health observations. But this troubling issue is not easily dismissed by a prove-it-to-me response. Throughout the world humans and wildlife are exposed to chemicals which, under certain circumstances, clearly alter hormone levels and function, sometimes with disastrous results. Often, however, the long-term effects of those changes at the individual or population level are unknown and difficult to predict. Better understanding depends on further research. Consequently, as with other public health and environmental concerns, how or whether to respond in the face of cause-and-effect uncertainty emerges as a more general policy question.

Endocrine disruption has gained the attention of lawmakers. In 1996 Congress passed the Food Quality Protection Act and amended the Safe Drinking Water Act, including in each statute a requirement that the EPA develop a screening and testing program for the estrogenic effects of food-use pesticides and drinking water contaminants. The laws also allow the EPA administrator to consider other hormone disrupting properties of these chemicals. In response, the EPA convened the multi-stakeholder Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) to develop recommendations for the screening and testing program.

This chapter will describe the biological features of EDs, along with wildlife and human health observations. A discussion of the endocrine-disrupting potential of specific chemicals follows a summary of the current policy debate.

Mechanisms of Action

The body produces many different hormones. Each has its own receptor on the surface or inside of cells. To exert its effect, a hormone attaches to a receptor much like a key fits into a lock. Under normal circumstances, this attachment initiates a cascade of events resulting in a biochemical reaction or chemical production in the cell. Endocrine disruptors may interfere in several different ways.

Hormones generally fall into three categories depending on their chemical structure: steroids, polypeptides, and amino acids. Sex hormones from the ovaries and testes and cortisone from the adrenal glands are examples of steroids. Thyroid hormone is a polypeptide. The receptors for these types of hormones are on the inside of cells. Hormone-receptor complexes are transported to the nucleus where they attach to DNA and trigger genetic activity resulting in various gene products. Some neurotransmitters, such as those from the hypothalamus, are simple amino acids or peptides and attach to a receptor

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

For some hormones, such as human chorionic gonadotropin, as few as 0.5-5% of receptors in a cell must be occupied for full activation of response. For others, higher levels of receptor occupancy are needed.[19]

Endocrine disruptors may interfere with hormone function in a variety of ways:

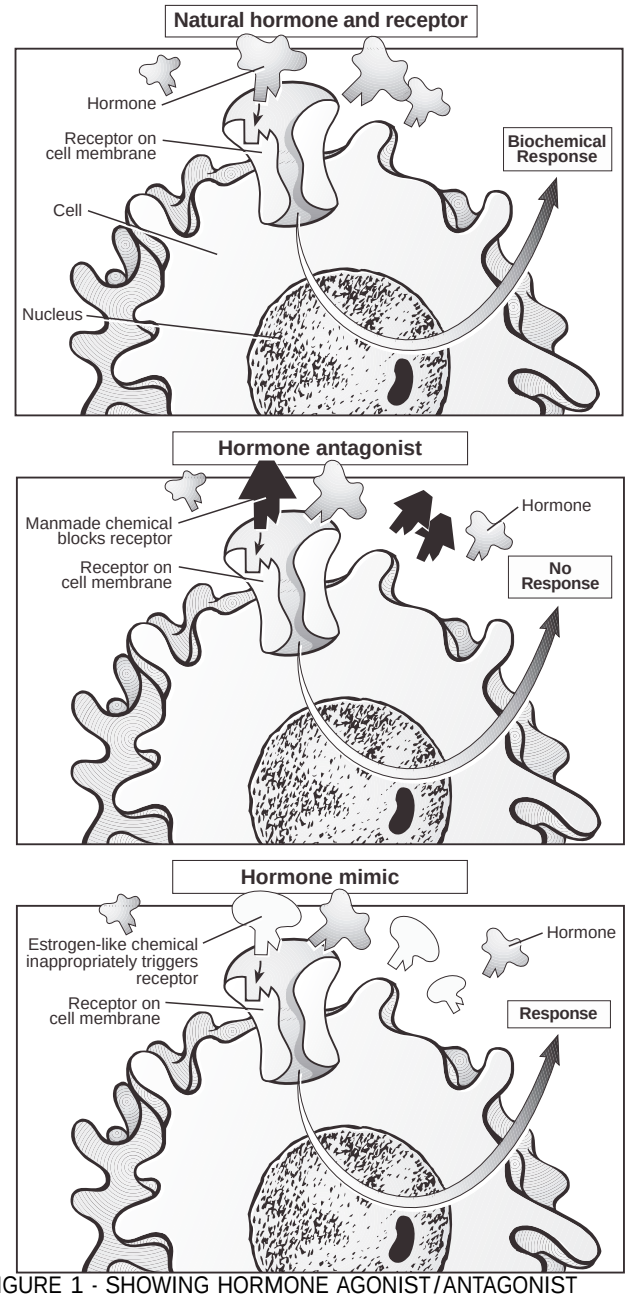


FIGURE 1 - SHOWING HORMONE AGONIST/ANTAGONIST

1. An ED may mimic or block a naturally-occurring hormone. If a chemical is similar enough to the natural hormone, it may occupy the binding site on the receptor and trigger the same sequence of events as the natural hormone - a hormone mimic causing a hormone-like effect. In some instances, it may occupy the receptor but not be similar enough to initiate a biochemical response. By attaching, however, it effectively blocks the receptor from occupancy by the natural hormone, acting as a hormone antagonist. (Figure 1)

2. Hormones are transported through the circulation largely attached to carrier proteins. EDs may alter the levels of these carrier proteins or interfere with hormone attachment. Most naturally-occurring estrogen and testosterone, for example, is bound to sex hormone binding globulin (SHBG), confining the hormones to the blood stream and limiting the amount of free hormone available to cells. The degree to which a hormone binds to a receptor, therefore, depends, in part, on the concentration of carrier proteins like SHBG. However, the hormone-SHBG combination also appears to be able to influence cellular activity from the cell surface under certain conditions.[20]

Thyroid hormone exists in two forms, T3 and T4, and is bound to several different proteins including thyroid hormone-binding globulin, transthyretin, and albumin. Only T4, bound to transthyretin, is able to enter the developing fetal brain where the T4 is then converted to T3, essential for normal brain development. Any chemical contaminant which interferes with the level of T4 or its attachment to transthyretin has the potential to disrupt normal brain development.

Little is known about interactions of most chemicals with hormone-binding proteins, but a few man-made and naturally-occurring chemicals have been studied. For example, some pyrethroid insecticides displace testosterone from SHBG, and phytoestrogens from plants stimulate SHBG production.[21] [22] Some polychlorinated biphenyls (PCBs) displace T4 from transthyretin, potentially disrupting thyroid hormone delivery to the developing brain.[23]

3. Exposures to EDs may interfere with hormone production, and fetal or infant exposures permanently alter baseline levels of hormones in some circumstances. For

example, in rats, dithiocarbamate fungicides suppress signaling required for the ovulatory surge of luteinizing hormone (LH) from the pituitary. As a result, hormone production by the ovary is disrupted.[24] Rats exposed to small amounts of dioxin at critical times of pregnancy give birth to male offspring with permanently lowered testosterone levels.[25]

4. The number and kinds of hormone receptors normally fluctuate, subject to various hormonal or chemical influences. Some EDs inappropriately increase or decrease the number of hormone receptors in various organs of the body. Estrogen and estrogen-mimics, for example, readily induce the formation of estrogen and progesterone receptors. In fact, the induction of progesterone receptors in the uterus is often used in laboratory tests as a measure of the potency of an estrogenic agent.

The Health Effects of Endocrine Disruptors

Hormones, circulating in extremely low concentrations, are essential to normal reproduction and a critical component of the signaling mechanisms that orchestrate development. In general, developing organisms are more susceptible to the effects of EDs than adults. Fetal or infant exposures may cause a range of health effects including abnormalities of reproduction, growth and development, impaired function of the immune and nervous systems, and cancer. This diversity emphasizes the fundamental nature of the processes potentially affected by these chemicals. Moreover, effects of EDs may not be apparent for years or only in future generations, complicating attempts to study any link to early exposures in humans or wildlife. Functional abnormalities are not always easy to identify. Since they may not be apparent for years, these effects are difficult to attribute to exposure during pregnancy or infancy.

Universal exposures often make it difficult or impossible to identify unexposed comparison populations. Some ED chemicals have already accumulated in humans, domestic animals, and wildlife at levels which are near or above those which cause biological effects.[26] Additional exposures, though small, may be of great importance. These features argue for the re-design of toxicity studies used to determine the safety of chemical exposures to humans and wildlife.

Wildlife Health Effects

A variety of invertebrates, reptiles, birds, fish, and mammals have been adversely affected by EDs. The following examples illustrate the diversity of health effects:

- Various types of snails exposed to environmental levels of tributyl tin, an anti-fouling additive used in marine paint on ships, develop a condition called imposex in which affected female snails have irreversibly superimposed male sex characteristics.[27]
- Hermaphroditic fish are found in rivers below sewage treatment plants in Great Britain. Vitellogenin, a protein normally synthesized by female fish in response to estrogen, is utilized as a yolk protein to nourish the developing fish. Male fish have vitellogenin levels similar to gravid females in some rivers.[28] Laboratory tests show that nonylphenol, an alkylphenol used in detergents and surfactants and found in effluent, behaves as an estrogen mimic and induces vitellogenin formation and testicular inhibition in male trout.[29] However, it is not entirely clear which chemical or combination of chemicals in the sewage effluent mixture is responsible for the observations in river fish. Some investigators believe that estrogens from the urine of women taking birth control pills also contribute.
- Alligators and red-eared turtles in Lake Apopka in Florida are demasculinized after exposure to a mixture of chemical contaminants including the pesticide, dicofol. (see Spotlight) There are no normal male turtles in Lake Apopka. All hatchlings have either normal appearing ovaries or are intersex.[30]
- Gulls breeding in the Puget Sound and Great Lakes regions show evidence of eggshell thinning and reproductive tract abnormalities with feminization of male embryos. In some instances, populations have declined and sex-ratios are skewed.[31] These areas are contaminated with mixtures of DDT, PCBs, and polycyclic aromatic hydrocarbons, each of which may cause the observed effects. Birds from these areas and from locations far more remote from industrial activity show elevated tissue levels of contaminants.
- Great Lakes gulls and terns, as well as some western gulls, have, within the past several decades, shown supernormal egg clutches and female-female pairing.[32] Gulls in these colonies also show excessive chick mortality, birth defects, and skewed sex ratios, with an

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 differentiation, and presence or absence of hormone receptors.*
- *Several studies implicate environmental exposures in the development of breast cancer.*

Breast cancer incidence has increased in the U.S. over several decades. Today, one in eight or nine women will develop this cancer in her lifetime, resulting in over 44,000 breast cancer-related deaths annually.[34] The causes of breast cancer are not well understood but may include early biochemical and cellular events that increase susceptibility or cause changes that are later transformed into full-blown malignancy.[35] The breast in males and females is quite similar until the pre-pubertal period when female breast development begins. This is a time of rapid cell proliferation and differentiation, dependent on interactions of estrogen, progesterone, prolactin, and growth hormone.[36] Estrogen and prolactin levels at this time regulate the number of estrogen receptors in breast tissue. Hormonal effects on the breast are complex and vary with age, stage of cellular differentiation, and presence or absence of hormone receptors.

There is considerable evidence that the total lifetime exposure to estrogen influences the likelihood of developing breast cancer. High serum or urine levels of estrogen, early onset of menstruation, delayed menopause, and delayed first-child bearing are all risk factors for breast cancer.[37] [38] There are two parallel pathways by which excess estrogen or estrogenic environmental contaminants may increase breast cancer risk. The first is through increased proliferation of estrogen-responsive cells, and the second is through direct DNA damage by estrogen metabolites.[39]

Although environmental exposures may affect breast cancer risk, radiation exposure and alcohol are the only well-established links.[40] However, a considerable amount of interest and research is focused on other environmental contaminants as possible contributors, including organochlorine compounds, solvents, metals, and polycyclic aromatic hydrocarbons, which are products of combustion spread

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 synthetic estrogenic toxicants may play a role. As with breast cancer, the evidence follows two parallel pathways, one of which emphasizes the cell-proliferative function of estrogenic agents and the other the cell-damaging effects of estrogen metabolites.

First, studies in mice show that estrogenic exposures during fetal life increase prostate weight in adult animals.[60] This has been demonstrated with estrogen, DES, bisphenol-A, and octylphenol. Also in mice, estrogenic exposures during the first three days of life initiate cellular changes in the adult resembling those associated with prostate cancer.[61] The abnormal cells have features, such as enlarged nuclei and abnormal organization, which are often identified as pre-cancerous in other tissues. Moreover, when compared with unexposed mice, male

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 as a whole, most investigators agree that a link to estrogenic compounds must be examined closely.[75]

Falling Sperm Counts, Undescended Testicles, Hypospadias

- *A series of studies indicates that human sperm counts and the quality of semen have declined substantially over the past several decades.*
- *Recent studies show considerable geographic variation in sperm counts.*
- *There is concern that falling sperm counts, increasing incidence of undescended testicles, hypospadias, and testicular cancer may have a common cause that fetal exposures to endocrine-disrupting chemicals may explain each trend.*

In recent years there has been considerable controversy about sperm-count trends in the general population. In a review and analysis of 61 papers published in the medical literature between 1938 and 1991, the authors concluded that there had been a substantial decline in semen quality over the past 50 years.[76] They excluded all studies of men from infertility clinics in order to avoid possible bias. Furthermore, they excluded any studies in which sperm counts had been done by methods not available during earlier years. Their analysis of the world's literature showed a 42% decline in sperm count from 113 million sperm/cc of semen to 66 million sperm/cc. This report sparked intense debate, including disagreement over the appropriateness of the authors' statistical methods.[77 78] A re-analysis of the same data, using several different statistical techniques, confirmed the original conclusions but showed that the decline was seen in the U.S. and Europe but not in non-Western countries, though the data for the latter are limited. This review of some 61 studies concluded that sperm counts have declined in the U.S. at a rate of 1.5% per year and 3.0% in European nations.[79] Even within the U.S., there appears to be considerable geographical variation.[80] Future research will need to account for this variable and search for explanations.

A review of 20 years of sperm-bank data from a single laboratory in Paris showed that, in 1351 healthy men who were fathers, there was a yearly decline in the average sperm count and motile, normal-appearing sperm for donors of a given age.[81] The sperm count declined by 2.1% per year over the 20-year period. This analysis took into account the period of sexual abstinence of the donors, a variable which influences sperm counts in individuals, and has the advantage of using data from a single laboratory.

An analysis of data from 577 semen donors collected over 11 years in a laboratory in Scotland showed that a later year of birth was associated with a lower number of sperm and lower number of motile sperm in the ejaculate. When men born in the 1970's were compared with men born in the 1950's, the total number of motile sperm was reduced by 25%.[82]

Other studies have not confirmed a decline.[83 84] However, different statistical techniques were used in the analyses making comparisons difficult. For example, the Paris and Scottish studies compared the sperm counts of donors of the same age, while those finding no decline aggregated all donors for a given year and corrected for an average age. This latter technique runs the risk of missing a decline within each age group from year to year which may be a more sensitive indicator of changes than an average across all age groups.

There are significant challenges inherent in any study of sperm donors since there is considerable daily variation in sperm numbers, even in the same individual. An autopsy study of Finnish men was designed to circumvent this limitation. Investigators compared the quality of sperm production in 1991 vs. 1981 by post-mortem microscopic examination of the testes of 528 men, showing that there had been a decline in the percentage of men with normal, healthy sperm production from 56% in 1981 to 27% in 1991.[85] There was a decrease in the average weight of the testes, a decrease in the size of the seminiferous tubules, and an increase in the amount of fibrous tissue. The investigators accounted for differences in age, weight, and history of smoking, alcohol, and drug use. Their results support the conclusion that there has been a significant decline in the quality of human semen in the past several decades.

Along with a decline in sperm counts, there also appears to

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.

Behavioral and Learning Abnormalities

Fetal and neonatal exposures to some environmental agents also adversely affect neurological and intellectual development. For example, it has been known for some time that lead and mercury are neurological toxicants. However, they are not toxic through endocrine-disrupting mechanisms at likely levels of human exposure. But, more recent studies suggest that some behavioral and learning abnormalities, as well as general impairment of intellectual function, may result from endocrine disruption.

Intellectual development in children is impaired after fetal exposure to PCBs.[89] One theory holds that this is explained by PCBs' interference with thyroid hormone function during critical periods of fetal brain development. Thyroxine, a form of thyroid hormone necessary for normal brain development, is decreased after exposure to PCBs and dioxin.[90 91] In addition, some PCBs compete for binding to the thyroid receptor or thyroid transport proteins, and thyroxine must be attached to transthyretin in order to enter the fetal brain. PCBs may also increase the metabolism of thyroid hormone. Any of these mechanisms may interfere with brain development.

Reported thyroid disrupting properties of other industrial chemicals raise concerns that they might also adversely affect normal development.[92 93 94] Among the challenges facing investigators is the recognition of adverse effects due to minor changes in thyroid status during fetal development since neurological and behavioral effects are often difficult to measure.

This sparse but growing body of evidence of the neurological effects of some endocrine-disrupting chemicals furthers concern about their contribution to learning disabilities and behavioral abnormalities in the general population, but complete understanding is still a distant goal. Though some studies show that social behavior may be influenced by prenatal chemical exposures, others show that social deprivation at birth can lead to exaggerated responses to chemical exposures later in life.[95] The complex interaction of early social factors, genetics, lifelong metabolic pathways, stress hormone levels, and chemical exposures requires considerable additional research for understanding.

The Debate

There are those who believe that concerns about environmental hormone-disrupting chemicals are much ado about nothing.[96] Though we know that the function of various hormones may be altered by some chemicals under certain circumstances, much of the general debate centers around the importance of low-dose exposures. Those who believe that these substances are unlikely to be important at current exposure levels often refer to the following:

1. The low potency of man-made chemicals, when compared to naturally-occurring hormones, makes their role minor and insignificant. (DES is an exception. It is generally agreed to be "strong.")
2. Exposures to estrogenic chemicals naturally present in foods (phytoestrogens) are much larger than exposures to synthetic man-made chemicals with estrogenic action.
3. Feedback loops are resilient and easily able to adjust for minor fluctuations in hormone levels.
4. Man-made estrogenic and anti-estrogenic chemicals tend to balance each other.

These observations are misleading for several reasons:

1. A chemical may interfere with hormone function in a variety of ways. Comparing the strength of receptor binding of a synthetic chemical with that of a natural hormone is important but tells nothing about other previously-discussed factors which may contribute to hormone disruption, including:

a) alterations in hormone metabolism
b) distribution, storage, or bioaccumulation of a synthetic chemical,
c) effects on carrier proteins, like SHBG and albumin,
d) interaction with the hypothalamic-pituitary-gonadal axis.

2. Though food contains naturally-occurring phytoestrogens, some actually behave as estrogen antagonists in the presence of naturally-occurring estrogens. It is too simplistic to conclude that a comparison of the receptor-binding capacities of two chemicals in a test tube will predict how each will behave in an intact organism. Moreover, man-made chemicals with endocrine-disrupting potential may be metabolized, stored, or protein-bound in the body in very different ways from naturally-occurring substances to which humans and wildlife have been exposed throughout their evolution. Comparisons of synthetic with naturally-occurring chemicals must be made carefully.
3. Although adult feedback loops may be resilient, this argument ignores evidence of the exquisite sensitivity of the developing organism to minor hormone fluctuations at critical times in fetal life. The thresholds and sensitivities of adult feedback loops are set during development and may be permanently altered by small fetal exposures. For example, dioxin has developmental effects at levels well below those causing adult toxicity. 17-alpha estradiol (a close relative of 17-beta estradiol, the naturally-occurring form of estrogen) is relatively inactive in adults but causes tumors in mice when given to newborns.[97]
4. The argument that man-made hormone mimics and antagonists will balance each other out is not based on any evidence. There are specific chemicals which interact competitively with hormone receptors, but given multiple mechanisms of hormone disruption, to postulate a net effect of zero is purely speculative.

Conclusions

Humans and wildlife are exposed to a large number of naturally-occurring and man-made chemicals capable of mimicking, blocking, or otherwise interfering with the endocrine system. They interact in complex ways with each other, food constituents, naturally-occurring hormones, receptors, and carrier proteins and may disturb a wide range of reproductive and developmental events.

These chemicals are found in air, soil, food, water, and human and wildlife flesh throughout the world, in plastics, food wraps, cosmetics, baby bottles, detergents, and pesticides. Only about 3,000 man-made organic compounds out of an estimated 60,000 in drinking and waste water and sewage sludge have been identified.[98] A random screen of 20 of these chemicals showed 9 of them to interact with the estrogen receptor.[99] We are likely, it seems, to be exposed to large numbers of unidentified and unstudied chemicals, many of which may have endocrine-disrupting activity.

Animal, laboratory, and epidemiological studies demonstrate adverse health effects resulting from exposure to endocrine-disrupting chemicals and clarify the importance of timing as well as magnitude of dose. Small exposures during critical windows of vulnerability may cause lifelong changes in reproductive function and development. Though estrogenic or estrogen-antagonistic effects of some of these chemicals have been known for years, interference with the function of other hormones including androgens, thyroid hormone, insulin, cortisone, and neurotransmitters is now apparent.

There are documented world-wide increases in a number of diseases or conditions of the reproductive system in infants, children, and adults which may be linked to early exposures to hormonally-active chemicals. For some the connection is clear. For others there is limited evidence of environmental cause. Several hormone-related cancers have also increased in frequency in recent decades. Biologically plausible hypotheses suggest ways in which they may be related to exposure to endocrine disrupting chemicals during periods of susceptibility. Consistent findings of delayed psychomotor development of children exposed to PCBs in the uterus come from several sources. Possible relationships between neurobehavioral disorders and chemical exposures are incompletely understood and are under investigation.

When entire populations of humans and wildlife are exposed, the consequences of a population-wide effect, even if subtle or difficult to detect in individuals, may be profound. For example, there are important social and economic consequences of small population-wide shifts in behavior patterns, learning capacity, or sperm counts. Very little population-wide change is needed to markedly increase the need for special education or demand for fertility services. It will take many years to acquire more thorough understanding of the importance of widespread, low-dose, multi-chemical exposures through fetal life, infancy, growth and development. Meanwhile, the world's populations of humans and wildlife participate in the ongoing experiment.

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 substances produced by plants and fungi which have estrogenic or anti-estrogenic effects. Total exposure to combinations of chemicals from all sources will influence their biological effects and cannot be predicted by simply adding doses and responses. The following sections review some of the chemicals known to have endocrine-disrupting activity.

Dioxin

- *Is a by-product of a variety of industrial processes and incineration of waste.*
- *Persists for years in the environment and tends to bioaccumulate in the fat tissue of animals and humans where it remains for years*
- *Is present in humans in amounts at or near those known to cause metabolic and immune changes in laboratory animals.*
- *Is present in breast milk at levels which expose infants to substantially higher levels than adults.*
- *Interferes with the production or activity of enzymes, hormones, other growth factors.*
- *Adversely affects reproduction, growth, and development through a variety of mechanisms.*

Dioxins are among the better known and studied EDs. They are a family of related compounds differing in the number and position of chlorine atoms on the basic underlying structure. The toxicity of each member of the family varies considerably and is usually described relative to the most toxic. Together, they demonstrate several different mechanisms of hormone-disrupting action and have diverse biological effects.

Dioxin results from heating mixtures of chlorine and organic compounds in industrial processes, such as the bleaching of paper pulp, production of some pesticides, or during incineration of chlorine-containing materials. Because many consumer products contain chlorinated organic compounds (e.g., polyvinyl chloride), municipal, medical, and hazardous waste incinerators are leading dioxin sources. It is not easily broken down in the environment, accumulating in soils and sediments and biomagnifying as it passes up the foodchain. Dioxin bioaccumulates in fat tissue with an estimated half-life in humans of approximately seven years.

There may be significant regional variations depending on local industrial activity, but dioxin is widely spread around the globe. Beef, pork, fish, shellfish, animal and human milk are the major sources of human exposure. Because breast milk has a high fat content, nursing infants are actually exposed to higher daily amounts of dietary dioxin than most adults and may receive more than 10% of their anticipated lifetime exposure during this particularly vulnerable period of mental and physical development.[100]

Since 1991, dioxin has been under critical review by the EPA after the American Paper Institute and the Chlorine Institute campaigned to convince regulators that dioxin was not nearly as dangerous as previously thought.[101] Their claims were based on a recount of tumors in a 14-year-old industry-sponsored rat study. Pressure from industry and environmentalists has been intense, revealing the highly political nature of the interpretation of scientific findings as well as the regulatory response intended to flow from them.

The extensive six-year EPA review documents a wide range of health effects which result from exposure to dioxin, some of which occur at extremely low exposure levels, and provides important information about dioxin sources. Though there is some variation with geographical location and diet, many people have dioxin levels which are at or near those known to cause harmful effects in animal studies.[102]

Animal studies

In animal studies dioxin has a wide range of health effects which differ among the fetus, newborn, and adult. Some are only apparent with large doses, but cancer, immune system toxicity, and reproductive and developmental effects (Table 1) occur at low levels of exposure. Dioxin causes the liver to produce metabolic enzymes at exposures of 1-10 picogms/kg/day, a level similar to daily adult human exposures. (A picogram is one-trillionth of a gram.) These enzymes, in turn, alter the metabolism of hormones and other endogenous or exogenous chemicals. Enzyme induction occurs at levels which also cause immune system toxicity in mice and

reproductive effects in rats.[23] In rats, thyroid tumors occur at doses as low as 1400 picogm/kg/day.[103]

There is considerable variability in the toxicity of dioxin among adults of different animal species but much less among fetuses and infants, particularly with respect to the sensitivity of offspring to developmental effects. For example, adult hamsters are several thousand times more resistant to dioxin toxicity than adult guinea pigs.[104] But the hamster fetus is only 10 times more resistant to dioxin than the guinea pig fetus. Similarly, early life stages of fish and birds are more sensitive to dioxin toxicity than adults.[105 106] From these data one might suspect that dioxin toxicity in human fetuses would be similar to that in fetuses of other species, even if human adults were relatively resistant.

Sufficient exposure to dioxin during pregnancy causes prenatal mortality in the monkey, guinea pig, rabbit, rat, hamster, and mouse. The response is dose related, and there is a species difference. Monkeys and guinea pigs are the most sensitive followed by rabbits, rats, hamsters, and mice, which are the most resistant. In these species the maternal dose necessary to cause prenatal mortality ranges from 1-500 microgms/kg (cumulative dose). The timing of maternal exposure is just as important as the magnitude of the dose, often demonstrating a window of vulnerability. In the guinea pig, for example, prenatal death is caused by a single dose of 1.5 microgm/kg on day 14 of pregnancy, whereas later in pregnancy, larger amounts are needed.[107]

Similarly, a single low maternal dose of dioxin at a critical time in pregnancy may cause permanent developmental effects in male offspring, including altered sexual differentiation of the brain.[108] On day 15 of a typical 21-day pregnancy in rats, most organs are formed but the HPG (hypothalamic-pituitary-gonadal) axis is just beginning to function. The critical period of sexual differentiation of the brain extends from late fetal life through the first week of post-natal life. A single low maternal dose of dioxin (0.16 microgm/kg) on that day of pregnancy reduces male testosterone levels, delays descent of the testicles, decreases anogenital distance (making them more female-like), and reduces prostate weight and sperm production in offspring.[109] It also demasculinizes their sexual behavior in the months that follow. A single maternal dose of just 0.064 microgms/kg on day 15 of pregnancy causes a 43% reduction in sperm production in male offspring.

Dioxin does not attach to the estrogen receptor, yet it causes both estrogenic and anti-estrogenic activity in different tissues of the body. Both dioxin and PCBs attach to another intracellular receptor, called the Ah-receptor, whose function is not otherwise fully understood. (Unlike dioxin, some forms of PCBs also attach to the estrogen receptor.) The occupied Ah-receptor is transported into the nucleus of a cell where it attaches to DNA, influencing the activity of genes which, in turn, regulate chemical production. By this mechanism, dioxin indirectly influences estrogen activity. Its anti-estrogenic effects, which seem to predominate, may result from : a) causing the cells to produce an enzyme which metabolizes the body's normal estrogen or b) decreasing the number of estrogen receptors available for normally-occurring estrogen.[110 111]

Epidemiological Studies

In the "Ranch Hands" study, reproductive histories of men who sprayed Agent Orange in Vietnam from 1962-1971 were examined beginning in 1978 in an attempt to see if exposure to dioxin might have had adverse effects in their children.[125] Agent Orange is a mixture of two herbicides, almost always contaminated with dioxin. Dioxin in the blood of participants was measured years after exposure and an attempt was made to estimate earlier levels from those results. An increase in all nervous system defects in offspring was found. However, increases in spina bifida and cleft palates were too few to allow formal statistical analysis. One finding that is difficult to explain was an increased risk for spontaneous abortion, all birth defects, and specific developmental delays in the low- but not the high-dioxin exposure group.
Another study of Vietnam veterans found that opportunity for Agent Orange exposure was associated with an increased risk of spinal cord abnormalities (spina bifida) and cleft palates in offspring.[126] The National Academy of Sciences has concluded that there is limited but suggestive evidence of a relationship between paternal Agent Orange exposure and spina bifida in offspring.

In a study of 248 chemical production workers in New Jersey and Missouri, investigators found that workers

Table 1
The reproductive and developmental toxicity of dioxin - animal studies

Health effect	Species (dose)
Reproductive toxicity	
Decreased fertility, litter size (offspring are sensitive to even lower doses as they reproduce - a second generation effect)	rats (0.1 microgm/kg/day) [112]
Inability to carry pregnancies to term Estrogen levels are suppressed	monkeys (50 ppt dietary dioxin) [113]
Endometriosis[114]*	monkeys (5-25 ppt dietary dioxin) [115]
Decreased testis weight, sperm production, fertility	adult rats (65 microgm/kg), mice - in monkeys when given in doses sufficient to reduce feed intake and/or body weight.[116 117 118]
Lower testosterone levels	rats - 15 microgms/kg[119]
Developmental toxicity	
Embryo mortality** , ***	rainbow trout embryos - LD50, 0.4 microgms/kg egg wgt. juvenile rainbow trout - LD50, 10 microgm/kg body wgt. fertilized lake trout eggs - LD50, 65 picogms/g egg wgt. chicken embryo - LD50, 0.25 microgm/kg egg wgt. [120]
Congenital heart defects	chickens - eggs treated with 1 picomol/egg[121]
Reduced size of the thymus gland and altered blood counts, altered immune system	most laboratory animals at a range of doses depending on species[122]
Cleft palate formation and enlarged kidneys	mice -doses which are not maternally toxic, e.g., 1-4 microgm/kg on day 6-15 pregnancy[123] (Other species as well but at higher doses)
Learning disability (impaired object learning - not spatial learning.)	monkeys - 5-25 ppt in maternal diet [124]

* Three of 7 female monkeys exposed to 5 ppt dietary dioxin (43%) and 5 of 7 animals exposed to 25 ppt dietary dioxin (71%) had moderate to severe endometriosis after 4 yrs of exposure followed by 10 yrs. of no exposure. The frequency of disease in a control group was 33%.

** The LD50 is the concentration of dioxin which will kill (lethal dose) 50% of those exposed. A microgm. is one millionth of a gram. A picogm. is one trillionth of a gram.

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 a marked increase in the female to male birth sex ratio among those most heavily exposed.[128] Almost twice as many girls as boys were born during those years. Over the next ten years the ratio began to return to normal. The mechanism by which dioxin may have this effect on sex determination is unclear. In this same population, there was no increase in the rate of birth defects, as determined from a birth defects registry, when compared to an unexposed population.[129] However, in this study the number of children of mothers with the highest likelihood of exposure was too small to assess specific categories of birth defects. Other limitations include possible exposure misclassification and unrecognized spontaneous abortions

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]

Spotlight on

PCBs and Rice Oil Contamination

From 1929-1977 PCBs were manufactured and widely used in the U.S. in electrical transformers and capacitors, hydraulic fluids, plasticizers, and adhesives. They were banned from most uses in the U.S. because of environmental persistence, bioaccumulation, and toxicity. However, they remain widely spread in the environment, and because of bioaccumulation, human and wildlife consumption of food contaminated with even small amounts of PCBs inevitably leads to gradual increases in total body stores. Ninety-four percent of fish collected nationwide show PCB residues at a average concentration of 0.53 ppm.[134] In marine mammals, amounts may be 30,000 to 60,000 times higher.[135] Inuit mothers in the Arctic have the highest known levels of PCBs in their milk as a result of a diet rich in marine mammal fat.[136]

PCBs and dioxin are related families of structurally similar chemicals. Each may have a different number of attached chlorine atoms, the number and position of which largely determines molecular shape and toxicity which varies dramatically with the different arrangements of atoms. Like dioxin, many PCBs attach to the Ah-receptor and have similar toxic effects. PCBs, however, also behave differently from dioxin. Some are capable of binding competitively to thyroid hormone carrier proteins. This interferes with transport of thyroid hormone which is essential for normal growth and development.[137] Also unlike dioxin, some forms of PCBs occupy the estrogen receptor, causing an estrogenic or anti-estrogen effect. In some instances estrogen-receptor binding is facilitated by metabolic alteration (hydroxylation) of one portion of the PCB molecule so that it more closely resembles a portion of an estrogen molecule. However, this metabolic transformation is not always necessary for estrogen-receptor binding.[138]

Japan and Taiwan resulted from consumption of PCB-contaminated rice oil. Since then investigators have monitored the people exposed, their pregnancies, and offspring.[156] The immune system of people exposed was affected so that they were more susceptible to infection and had decreased antibody levels. There were increases in prenatal deaths, retarded fetal growth, and infant mortality. Delayed brain development and behavioral abnormalities in the children exposed as fetuses persists years after the incident. They score lower on developmental testing, and their intellectual development lags behind. According to teachers, they are hyperactive and exhibit more behavioral problems than unexposed children.[157] Some believe that the toxic responses were not due to PCBs but to other toxic chemicals called polychlorinated dibenzofurans (PCDFs) which contaminated the PCB industrial fluid.[158]

One group of 212 children exposed to ambient levels of PCBs in the uterus or through breast milk has been followed in Michigan. In most cases, their PCB exposure increased with the amount of Lake Michigan fish that their mothers consumed before and during pregnancy. Those who were most highly exposed to PCBs as fetuses showed delayed or reduced psychomotor development and poorer performance on a visual recognition memory test.[159] When the data were analyzed to include only prenatal exposure (no exposure through breast milk) deficits investigators have reported results of neurological and intellectual testing of these children at 11 years of age. They found that prenatal PCB exposure was associated with lower IQ scores after controlling for other factors such as socioeconomic status.[160] The most highly exposed children were more than three times as likely to perform poorly on IQ tests and tests designed to measure their attention span. They were more than twice as likely to be at least two years behind in word comprehension in reading.

Another group of children are followed in North Carolina and show similar results.[161] Transplacental and breast-feeding PCB exposures were determined by measuring maternal PCB levels at birth and in maternal milk. Children with higher transplacental exposure to PCBs consistently scored lower at 6 and 12 mos. of age on a psychomotor development test than children with lower exposures.

In the Netherlands, investigators found that higher levels of PCBs in breast milk were correlated with lower levels of thyroid hormone in mothers and higher TSH levels in nursing infants.[162] The subjects in this study were exposed to PCBs at ambient environmental levels.

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 developmental toxicants at a range of exposure levels. Phthalates also cause cancer in animal studies though there is debate about the relevance of this observation to humans because of metabolic differences in species.[186]

Some phthalates attach to the estrogen receptor and, in laboratory tests, behave as weak estrogens.[187] However, they vary considerably in potency. In descending order of estrogenicity, as measured by receptor binding in test tube experiments, they are butyl benzyl phthalate (BBP), dibutyl phthalate (DBP), diisobutyl phthalate (DIBP), diethyl phthalate (DEP), and diisononyl phthalate (DINP). DEHP showed no estrogenic activity in this study.

In animal studies, DEHP reduces fertility and testis weight more readily than DBP.[188] Phthalates are likely, therefore, to be toxic to the testes through some mechanism other than estrogenicity.[189] Research showing that phthalates, or breakdown products, interfere with the function of FSH may better explain testicular toxicity, since FSH is required for normal Sertoli cell maintenance in the testes.[190] Developing animals are much more susceptible to this effect than adults. Interference with FSH function might also account for altered estrogen levels and ovulation in rats exposed to DEHP.[191] At larger doses in rats (maternal diet 2% BBP) BBP is toxic to the fetus, causes spontaneous abortions, and birth defects.[192] [193] In multiple generation studies, the effects of DEHP on the second generation are greater than the first.[194] Virtually nothing is known about the chronic effects of long-term low-dose human or wildlife exposure.

The largest source of human exposure to phthalates is likely to be from food. Estimates of average dietary intake of all phthalates range from 0.1-1.6 mg/person/day.[195] The average intake from infant formulas is larger, estimated at 0.13 mg/kg body wgt/day for a newborn.[196] If the usual uncertainty factors for extrapolating risks from animals to humans were applied to the animal data showing adverse effects on the male reproductive system, this level of exposure is several fold larger than what would be considered a safe dose.
DEHP also leaches from the plastic of medical equipment and is found in the blood or tissues of people who have undergone blood transfusions or kidney dialysis.[197] Little is known about the metabolism, storage, and excretion of phthalates in humans. Because of the widespread presence of phthalates in water and sewage effluent, where concentrations range from nanograms to milligrams/liter, effects on fish and wildlife are also a concern.[198]

Pesticides

- *The organochlorines endosulfan, methoxychlor, dicofol, and lindane interfere with normal estrogen function.*
- *Wildlife and laboratory animals exposed to these chemicals in sufficient amounts have both reproductive and developmental abnormalities; males exposed in fetal life may be feminized; females have altered estrus cycles and hormone levels.*
- *Dicofol, pentachlorophenol, dinoseb, and bromoxynil interfere with thyroid function.*
- *Some pyrethrins and vinclozolin, pesticides currently in use, have anti-androgen activity resulting from androgen-receptor blockade.*
- *Humans may be exposed to these chemicals in their food, through spray drift, home pesticide use, and as medication (lindane, pyrethroids).*

A number of pesticides belonging to several classes have endocrine disrupting properties. These are summarized in Table 3 below. The reproductive and developmental toxicity of these chemicals are more comprehensively presented in Chapter 6.

Organochlorines

Some organochlorines have been banned from use in the U.S. because of environmental persistence and endocrine-disrupting properties. Laboratory animal and wildlife studies demonstrate a range of toxic effects, some of which are due to interference with normal endocrine function. They have other mechanisms of toxicity as well.

Vinclozolin

Vinclozolin is a fungicide used on fruits, vegetables, ornamental plants, and grass. It is degraded in soil or in plants into two by-products, also detected in rats treated with the fungicide.[199] Vinclozolin binds to androgen receptors and exerts an anti-androgen effect.

Table 3
Hormone Disrupting Effects of Selected Pesticides

DDT (and metabolite DDE)	Androgen antagonist.[202]
Methoxychlor	Estrogenic; metabolite interferes with sexual development, reproduction, and behavior of birds and mammals.[203 204 205]
	Increases aggressive behavior (mouse) (DDT, methoxychlor, or DES on days 11-17 of pregnancy) .[206] Note high doses of DES reduced effect.
Endosulfan	Binds to the estrogen receptor and in cell cultures, stimulates the growth of estrogen-sensitive breast cancer cells.[207]
Lindane	Accumulates in the ovarian follicles, fallopian tubes, and uterus of test animals. Most investigators conclude that lindane has anti-estrogenic properties.[208 209]
Dicofol	Causes feminization of male embryos, abnormal submissive behavior in male offspring, and impaired reproductive success (birds);[210] contaminated with DDT; strongly competes for binding site of the thyroid hormone.[211]
Pentachlorophenol (PCP)	Potent competitor for human transthyretin, binding to the protein twice as readily as the naturally-occurring hormone, thyroxine.[212]
	An estimated 64% of the U.S. population (1994) had PCP residues in their urine.[213] Lowers thyroid hormone levels significantly (rat).[214] Observations of the thyroid-disrupting effects of dicofol and PCP in animals raise concerns about their effect on the developing brain in humans. [215]
Vinclozolin	By-products of metabolism bind to androgen receptors and effectively block testosterone, causing feminization of male rats and other birth defects.[216 217] In the absence of testosterone, behaves as androgen, rather than anti-androgen.[218]
Cypermethrin	Significant decrease in anogenital distance but no change in sperm counts (exposure for last 7 days of gestation and male offspring for the first 30 days of life). [219]
Atrazine	Fewer testosterone receptors in prostrates of male offspring; altered enzyme activity in their pituitary glands of female offspring (rat) (17mg/kg/day during pregnancy) [220]
	Inhibits conversion of testosterone to dihydrotestosterone in their pituitary glands in exposed adult rats (130 mg/kg/day) [221] Alters the metabolism of naturally-occurring estrogen, resulting in a metabolite that is even more highly estrogenic.[222] Disrupts hypothalamic-pituitary regulation of ovarian function; interferes with biochemical conversion of testosterone and its interaction with the testosterone receptor in the prostate.[223 224 225]
Dithiocarbamates	Decrease in thyroid hormone (T4) levels and a corresponding increase in thyroid stimulating hormone (TSH) (rat/mouse).[226] A study of dithiocarbamate appliers and landowners in Mexico where the pesticide was used showed elevated TSH levels but no decrease in thyroid hormone levels.[227] In exposed animals, the resultant constant stimulation of the thyroid by TSH is thought to be the cause of an increase in thyroid cancers

Spotlight on

LAKE APOPKA / DICOFOL

Foods containing hormonally-active chemicals

Alligators and Dicofol

Lake Apopka in Florida showed a dramatic decline in its alligator population in the 1980's following a pesticide spill from the adjacent Tower Chemical Co. The pesticide mixture contained dicofol contaminated with DDT.[94] Investigators interested in the population decline collected alligator eggs from Lake Apopka and an uncontaminated lake, hatched them under identical circumstances, and studied the offspring. Within 10 days of hatching there was a 41% mortality of neonates from Lake Apopka compared to less than 1% from the other lake. Surviving female juvenile alligators from Lake Apopka had higher estrogen levels. Surviving males had testosterone levels almost four times lower than males from the uncontaminated lake. After leuteinizing hormone (LH) stimulation, Lake Apopka males showed markedly increased levels of estrogen compared to their counterparts. Their prenatal exposure to an environmental estrogen had programmed them to respond with a female hormone when stimulated.

Some Lake Apopka male alligators had abnormal genitals — males with testes but no penis and two with a penis-like structure but ovaries internally. Microscopic examination of Lake Apopka male testes showed numerous abnormalities. The results of this study are consistent with those of other animals exposed to similar chemicals — reduced hatchability, reduced offspring survival, demasculinization of males and superfeminization of females.

The former Tower Chemical Co. remains an EPA Superfund site.

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.

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Part III Regulations

A confusing set of laws grant regulatory agencies the responsibility for protecting human health and the environment from exposure to toxic chemicals. Here we provide an overview noting differences among the various types of exposures which each law addresses, highlighting those laws which are more precautionary and those which are not. We then address right-to-know legislation which has been somewhat effective in reducing harmful exposures.

Review of Applicable Legislation

The U.S. Environmental Protection Agency (EPA) has been given the authority and responsibility to regulate toxic air pollutants under the Clean Air Act (CAA), toxic water contaminants under the Clean Water Act (CWA), toxic wastes deposited in or on the ground under the Resource Conservation Recovery Act (RCRA), pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) which was amended by the Food Quality Protection Act (FQPA), and toxic chemicals generally under the Toxics Substances Control Act (TSCA).[1]

There are situations where two or more of the laws overlap. In other situations, EPA may share the authority to regulate with one or more agencies. For example, both the Occupational Safety and Health Administration (OSHA) and EPA have a responsibility to regulate worker exposure to harmful chemicals.[2]

Chemicals are regulated quite differently depending on their end use. Manufacturers of pesticides and pharmaceuticals are required to test the effectiveness and safety of their products prior to their review for registration purposes. In part the rationale for this requirement is that these products are developed specifically because they have biological effects. By placing the burden on the manufacturer to demonstrate the safety of the product prior to registration and marketing, the federal government has adopted a relatively precautionary approach to the regulation of these consumer products. Unfortunately, for pesticides, the testing is incomplete and not fully health-protective, yet the legislative intent is that the safety of all newly-proposed pesticide products be evaluated prior to marketing.

Most chemicals used by industry, however, do not undergo similar scrutiny. In fact, many manufacturers know little about the potentially harmful effects of their products and are not required, with rare exceptions, to study those effects in any detail. The maker of an adhesive product, for example, is primarily interested in creating a substance that will effectively bond materials together — and may overlook potential biological side-effects. The regulatory framework governing exposures to the vast majority of industrial chemicals and all cosmetics does not adopt a precautionary approach. Instead, the burden is placed on the government to demonstrate that there is reason to believe that the chemical is unsafe before proposing action to control exposures.

The Toxic Substances Control Act (TSCA)

The EPA has the authority to regulate industrial chemicals under the Toxic Substances Control Act of 1976 (TSCA). However, the sheer magnitude of this task (over 75,000 chemicals in the TSCA inventory and approximately 2,000 new chemicals added annually)[3], the design of the law, and political considerations have severely restricted that effort. Millions of people are involuntarily exposed every day to unknown amounts of industrial chemicals. Even in the occupational setting, where exposures may be the most consistent and concentrated, the level and pattern of exposure is often unknown.

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 test old chemicals as well as new, and it allows the agency to regulate those substances broadly, from halting production to requiring labeling. This is an aspect of TSCA's potential, however, which remains largely untapped given the volume of new chemicals constantly heading to market. In addition, the regulatory burden to require testing or labeling of a chemical is as onerous at that required to actually ban the chemical, effectively discouraging regulatory action altogether. Finally, TSCA contains record-keeping and reporting requirements, as well as broad confidentiality protection for manufacturers.[5]

Implementation of the Act has been weak and chemical manufacturers have been very successful in exploiting the confidential business information (CBI) provision allowing them to withhold data from the public. In addition, industry challenges of test rules and other decisions have been quite successful at delaying effective regulatory action. A report by the federal General Accounting Office found that while TSCA had resulted in 75,000 chemicals on the chemical inventory list, only nine chemicals have been controlled by EPA for posing unreasonable health risks.[6]

The Occupational Safety and Health Act (OSHAct)

Federal legislation designed specifically to protect workers on the job was passed in 1970. One of the threats to worker health that Congress intended the Occupational Safety and Health Act (OSHAct) to address was the harmful effects of toxic chemicals.[7] In recognizing the lack of accurate and comprehensive data about the effects of chemical exposures, Congress allowed the Occupational Safety and Health Administration (OSHA) to set toxic standards based on the best available evidence.[8] Supreme Court decisions interpreting the law have found that enforcement of a protective standard is appropriate, but only when it is necessary to avoid a significant health risk. Once again, the initial burden of demonstrating a significant risk is placed on the enforcing agency.[9] In practice, the result has been that OSHA has been slow to address occupational disease, and has been even slower to address reproductive hazards. In the cancer realm, OSHA has chosen to define a "significant health risk" as more than one excess cancer for every thousand workers exposed, making workers the least protected members of society from chemical carcinogens. The law also requires employers to make information available to their employees about potential toxic hazards they may encounter in the workplace. (See the following section for information about Material Safety Data Sheets.)

Federal Insecticide, Fungicide and Rodenticide Act

Pesticides are regulated under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). The regulation of pesticides is, in some respects, more stringent than that for other chemicals. The rationale is that pesticides are designed expressly to be toxic and are intentionally released to the environment. The result is that virtually all pesticides undergo some toxicity testing prior to marketing. Unfortunately, inadequate testing requirements, delays in implementation and the inherent difficulty of assessing and regulating thousands of pesticide products has left these chemicals inadequtely regulated:

- 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 to the EPA as well as to the state in which the facility is located. The data must also be made available to the public in a computerized "Toxics Release Inventory" (TRI), the first publicly accessible, on-line computer database ever mandated by federal law.

The law was passed despite opposition from both the chemical industry and the EPA. Environmental groups, labor organizations and grass roots activists campaigned for the law, recognizing the need for useful information on facilities' toxic waste generation. The tragic chemical accident at a pesticide factory in Bhopal, India in December 1984 provided context for the hotly contested congressional debate on the bill. Ultimately, the key TRI provision of the law was passed in Congress by a one vote margin (212-211).

Over the past ten years, the TRI has been heralded by industry and citizen activists as a major environmental achievement. Citizens groups have effectively used the

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.

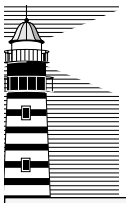
In practice, there are about 150 chemicals, mostly pharmaceutical products, listed as "known" reproductive toxicants in California. Many of the products which contain these chemicals must be labeled with a warning. Proposition 65 has had more far-ranging effects than might be predicted from the simple 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



Spotlight on

Pesticide Regulation in California: A Failure to Prioritize Public Health

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 permissible ambient level for methyl bromide exposure, for example, is 210 ppb averaged over a 24 hour period. In 1996, EWG detected 36 violations of the standard within a 12 hour period.[3] DPR dismissed the data and potential risk, stating that the 24 hour standard had not been violated. In 1997 EWG detected methyl bromide levels above the standard over a 24 hour period in two communities, Castroville and the Salsipuedes Elementary School in Watsonville.[4] In both cases, DPR dismissed EWG's data, downplaying the potential risk to those exposed, under the rationale that the 24 hour standard has a "100-fold built-in safety factor."

Years of grassroots campaigns by victims of pesticide drift has yet to prompt the agency to revoke a single pesticide permit.

Keeping Pesticides Out of California Well Water

The 1985 Pesticide Contamination and Prevention Act requires DPR to maintain a statewide database of wells sampled for pesticides and annually report detections and actions as part of a program to prevent any pesticides from migrating to ground water. Although the number of wells contaminated annually has declined dramatically, old, persistent and toxic pesticides such as sterility-causing DBCP and EDB were still found in hundreds of California wells in 1997 along with several newer pesticides, such as simazine.[5] To date, 94 pesticides have been found in 4,226 wells in California, in some cases as a result of legal, agricultural use[6] – a concern since as much as 90% of rural residents get their drinking water from wells.[7]

Inadequate Funding for Pesticide Alternatives

In 1989, the California Food Safety Act mandated that DPR provide funds for the research of alternative pest management practices "with an emphasis on projects that will result in the reduction of pesticide use, the use of safer pesticides, or minimizing pesticide residues." However, a recent report shows that only 2.6% of DPR's $40-50 million dollar budget goes towards research into alternatives.[8] In 1997, the agency advocated lowering the tax on pesticide sales and cutting its own budget.

References (from spotlight on preceding page)

1 AB 1807 , Legislative Counsel's Digest, (1)

2 Lifsher, M., Pesticide Control Agency is Stalling, Critics Say, The Wall Street Journal, March 5, 199, p.p. CA1-CA4.

3 Environmental Working Group, Toxic Farm Fumigants Drifting Into California Neighborhoods. Washington: Environmental Working Group Policy Memo, January 1996.

4 Environmental Working Group, Methyl Bromide Found in Air Near Watsonville Elementary School, San Francisco, CA, November 17, 1997.

5 Opportunities Lost, New Pathways Available, p. 11

6 California Environmental Protection Agency, Department of Pesticide Regulation, Sampling for Pesticide Residues in California Well Water, March 1997, p. v.

7 Pease, W., et al., Pesticide Contamination of Groundwater in California, California Policy Seminar, University of California, 1995, p. xiii

8 Chapa, G., et al., Opportunities Lost, New Pathways Available: The California Pesticide Mill Tax, The Department of Pesticide Regulation and the Potential for Pollution Prevention,î Pollution Preventio n Eucatin and Research Center Report, Los Angeles, CA 1997, p. 6, 11, 12

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.

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6. Dahl R. Can You Keep A Secret? Environmental Health Perspectives. 103:915;1995.
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8. Ibid.
9. Ibid at pg 409.
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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 bays and inland waters: the California Toxics Rule, 1997

Spotlight on

Fishing Rights and Reproductive Toxicants in the San Francisco Bay

Submitted by Communities for a Better

In 1992, an organizing survey by Communities for a Better Environment (CBE) discovered that thousands of people fish San Francisco Bay for food.

More than 100 persistent, bioaccumulative toxic chemicals are found in Bay fish that people eat.[1] A state health warning recommends that women of child bearing age eat less than a pound of Bay fish per month due to contamination with dioxin, PCBs, mercury, DDT, dieldrin and chlordane.[2] Subsistence fisher people – most of them low income people of color – report eating up to a pound of these fish every day. This exposure level exceeds those shown to cause developmental and neurotoxicity (slow learning) after exposure in utero,[3] and boost cancer risk significantly.

The response to this public health threat has been frustrated by industrial and waste disposal interests that discharge two billion liters of toxicant–laden waste water a day into the Bay,[4] and by anglers' relative lack of economic and political clout (low income anglers often lack access to medical attention). The health warning was all but hidden until anglers demanded posting it on fishing piers. Currently, the US EPA proposes to set water quality standards[5] at levels calculated to protect against carcinogens only if people eat a tiny 6.5 grams of fish per day — seventy times less than the amount subsistence fisher people actually report consuming.

In practical terms, EPA's proposal would fail to protect people who fish for food by allowing relatively more pollution to be discharged. Bay fisher people are now organizing to demand another choice besides hunger or exposure.

1. California Regional Water Quality Control Board. Toxic Contaminants in San Francisco Bay Fish, 1994.
2. Office of Environmental Health Hazard Assessment. Health Advisory about eating fish from San Francisco Bay, 1994.
3. See e.g., Schecter AJ. Abstract for Regional Water Control Board science workshop, May 7, 1997.
4 US EPA. Economic Analysis for the Proposed California Toxics Rule. S.F. Bay cancer and non-cancer assessment, 1997.
5. US EPA. Proposed water quality standards for California bays and inland waters: the California Toxics Rule, 1997.

Appendix 1

Material Safety Data Sheets

Material Safety Data Sheets (MSDS) are documents intended to address potential health hazards associated with exposure to chemical products. Requirements for MSDSs appear in several pieces of federal and state legislation.

Under the federal Occupational Safety and Health Administration (OSHA) Hazard Communication Standard (HCS), chemical manufacturers and importers are required to obtain or develop a MSDS for each hazardous chemical they produce or import and provide these MSDSs to distributors and employers.

Title III of the Superfund Amendments and Reauthorization Act of 1986 (SARA) requires businesses to covered by OSHA HCS to submit MSDSs to local emergency planners and responders, subject from there to public disclosure. Since 1987, the HCS applies to manufacturing and non-manufacturing businesses. Trade secret information is protected from disclosure except in specific emergency and non-emergency situations described in the standard.

Each MSDS is supposed to contain the following information:
a) chemical and common name, subject to trade restrictions; b) physical and chemical properties of the substance; c) physical and health hazards; d) possible routes

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-

Table 1
Profile of Listed Chemicals (1995)

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
TRIFORINE	40,858		X		X
ATRAZINE	38,140				X
METRIBUZIN	30,953		X		X
FENVALERATE	25,770				X
TRIADIMEFON	22,996		X		X
FLUAZIFOP-BUTYL	21,265		X		
CARBON DISULFIDE	20,100			X	
THIABENDAZOLE	18,574		X		X
ANILAZINE	17,912		X		
DICLOFOP	16,540		X		X
LEAD	16,428	24,219,948		X	X
IMAZALIL	13,699		X		
PARATHION	13,693				
DIENOCHLOR	10,009				X
TETRACHLORVINPHOS	7,489				X
BROMACIL, LITHIUM SALT	6,517		X		
CHLORSULFURON	6,172		X		
ETHYLENE OXIDE	5,315			X	X
TAU FLUVALINATE	5,230		X		X
TEBUTHIURON	4,817		X		
DI(2-ETHYLHEXYL) PHTHALATE	4,737	299,421			X
LINDANE	4,654				X
FENOXAPROP ETHYL	4,100		X		
FENOXYCARB	1,673		X		
METHOXYCHLOR	1,188				X
NITRAPYRIN	712	4,300	X		
PENTACHLOROPHENOL (PCP)	523	1,250			X
CADMIUM	259	5,800		X	X
HEXACHLOROBENZENE	5	11,171		X	

* Transfers to sewage treatment facilities are considered releases.
** Chemicals identified by U.S. Environmental Protection Agency as being developmental or reproductive toxicants. U.S. EPA, Federal Register, Vol. 59, No. 229,61436, November 30, 1994.
*** California Environmental Protection Agency, Chemicals Known to the State to Cause Cancer or Reproductive Toxicity, May 1, 1997.
**** Identified as a reproductive or developmental toxicant by definite or sugestive evidence as presented here by the authors.

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 other toxic chemicals that are not required to be reported under TRI, etc.

- Many facilities are exempted from reporting under the TRI, including oil wells, sewage plants and medical waste incinerators. Metal mines, coal processors, waste disposal facilities, solvent recyclers, oil and coal-fired utilities, chemical wholesalers, and petroleum bulk storage facilities were also exempted until this year and are not represented in the TRI data used in this analysis. These facilities will begin reporting in 1998.

The Pesticide Use Reporting System

California has one of the most comprehensive pesticide use reporting systems in the world. State regulation requires commercial pesticide applicators to report monthly pesticide use reports, including type, location, purpose and amount of pesticide used. Limitations

Table 2
Top 10 Listed Pesticides

Chemical	Use in 1995 (pounds)	Total Use 1991-1995	Percent of total (1995)
METHYL BROMIDE	17,565,348	86,846,299	31%
METAM SODIUM	15,274,166	48,160,556	27%
CHLORPYRIFOS	3,524,366	13,191,678	6%
DIAZINON	2,376,883	7,421,369	4%
PROPARGITE	1,813,831	8,217,409	3%
ZIRAM	1,638,866	8,011,555	3%
MOLINATE	1,427,055	6,934,038	3%
MANEB	1,309,283	3,649,097	2%
DIURON	1,073,681	5,384,913	2%
CARBARYL	858,369	4,129,896	2%

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.

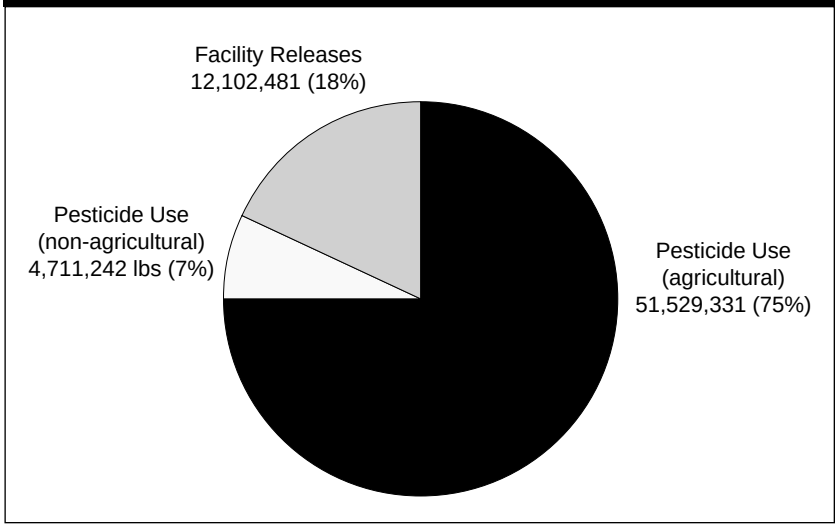
- Data entry errors may cause significant inaccuracy.

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.

Table 4
Frequency of Pesticide Use Among Applicators*

Amount used (lbs)	No. of growers	% of growers
1 - 100	10,074	41%
101 - 500	6333	26%
501 - 1,000	2472	10%
1,001 - 10,000	4481	18%
10,000 - 25000	552	2%
25001 - 50,000	226	1%
50,001 - 100,000	109	0%
100,001 - 500,000	64	0%
>500,001	1	0%

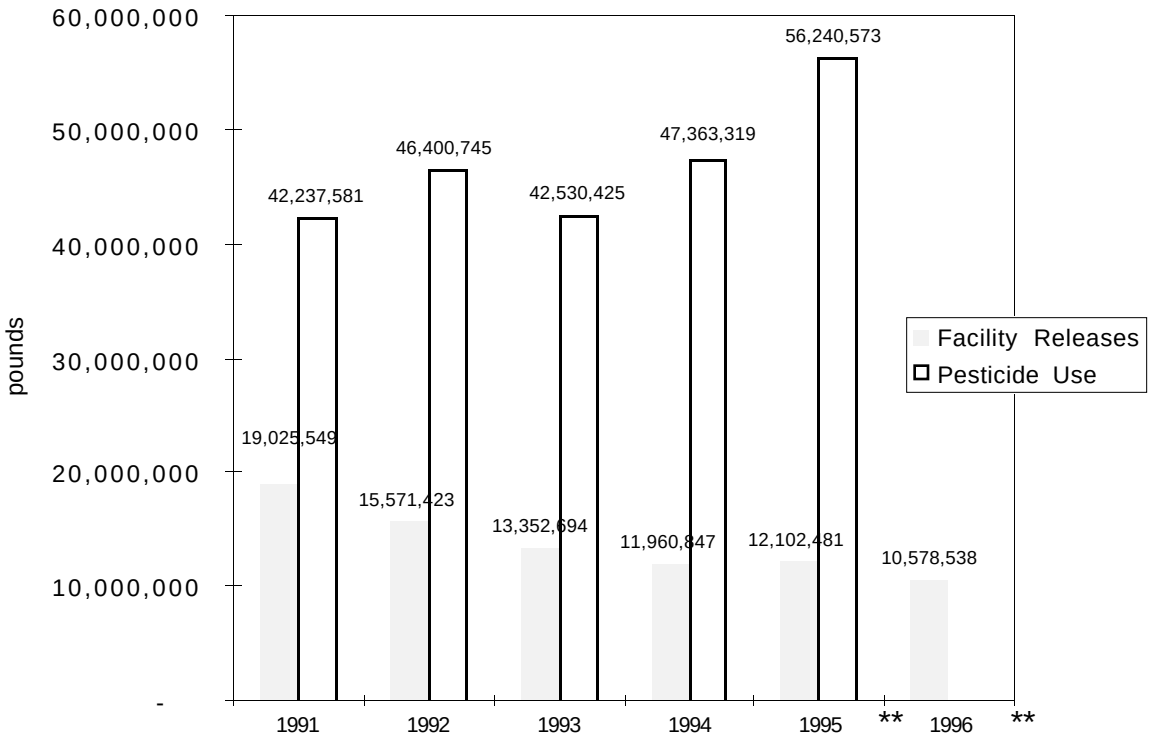
* "Applicators" here includes non-agricultural pesticide applicators

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 throughout the study period – both continue to be significant sources of released listed chemicals. For those chemicals that have been reported from 1991 through 1996, facility releases have declined every year, decreasing 47% or 8.9 million pounds. The regression line shows that release of these chemicals has decreased an average of 1.6 million pounds per year during the study period. However, some listed chemicals were added to the TRI law in 1995 and were first reported in that year. When these chemicals are added for 1995 and 1996 (they are included in Table 7) the over-all trend of reduced emissions is maintained, though at a slower rate; emissions then increased between 1994 and 1995.

Pesticide use, on the other hand, has gone up every year of the study period except 1993, rising 33% or 14 million pounds. The regression line indicates that use of listed pesticides has increased an average of 2.9 million pounds per year. Use of listed pesticides increased dramatically in the most recent data year, rising 9.5 million pounds in 1995.

Figure 2
Pesticide Use and Facility Releases of Listed Chemicals (1991-1996)*



* Transfers to sewage treatment facilities are considered releases.
** 1995 facility data includes 372,290 lbs of Listed Chemicals that were first reported in 1995; 1996 data includes 463,964 lbs of these newly reported chemicals.

Table 5
Top 20 Counties Using Listed Pesticides (1995)

Rank	County	Amount of use (lbs)	Percent of total
1	Fresno	8,884,513	16%
2	Kern	7,950,464	14%
3	Imperial	4,644,836	8%
4	Monterey	4,268,110	8%
5	Tulare	2,917,110	5%
6	Merced	2,370,526	4%
7	San Joaquin	2,104,021	4%
8	Kings	1,829,871	3%
9	Stanislaus	1,785,136	3%
10	Riverside	1,626,207	3%
11	Ventura	1,599,372	3%
12	Santa Barbara	1,551,087	3%
13	Sacramento	1,470,794	3%
14	Madera	1,234,269	2%
15	Butte	992,015	2%
16	Santa Cruz	958,775	2%
17	Sutter	895,776	2%
18	Los Angeles	886,091	2%
19	Yolo	868,906	2%
20	Colusa	749,507	1%

Use of Listed Pesticides (Non-Facility)

During the five year study period, over 234.7 million pounds of pesticides identified as developmental and reproductive toxicants (listed pesticides) were released in California. Use of listed pesticides increased 33%, mirroring total pesticide use in California which increased 31% from 1991 to 1995.[3] The increase in listed pesticides was driven by rising use of metam sodium, chlorpyrifos, diazinon, maneb, naled, propargite, mancozeb, cyanazine, molinate and permethrin. Use of metam sodium alone more than tripled during the study period, increasing nearly 10.4 million pounds. In 1995, metam sodium was used heavily on carrots (5,301,284 lbs); tomatoes (2,888,208 lbs); potatoes (1,448,609 lbs); cotton (1,213,651 lbs.) and for pre-planting activities (650,552 lbs.). As indicated in the table below, metam sodium and methyl bromide, both widely used fumigants, comprised nearly two thirds of all listed pesticide use in 1995.

Nearly 52 million pounds of listed pesticides were applied to 165 food crops. Crops receiving the most use of listed pesticides include carrots, cotton and strawberries. These three crops alone received nearly 30% of all listed pesticides used in 1995. Non-agricultural applications comprised 4.7 million pounds of listed pesticide use.

Structural pesticide control, which includes use in and around buildings, comprised the bulk of non-agricultural use (3.1 million pounds). Because the California use reporting system does not require comprehensive reporting for urban pesticide use, it is impossible to identify the types of buildings and structures where these chemicals were applied. Similarly, because use of over-the-counter pesticide products is not reported, we are unable to quantify the amounts of listed pesticides used in household products.

Anecdotal evidence, however, suggests that reproductive toxicants are frequently used in and around buildings where we spend most of our time –homes, offices, schools, apartment buildings, etc. A nine-month study of 238 families in Missouri in 1989 disclosed that 98% used pesticides at least once annually and two thirds more than five times per year. More than 80% used pesticides during pregnancy and 70% during the first six months of a child's life. Pesticide use in the home was most common (80%), followed by herbicide use in the

Table 6
Top Ten Applicators Applying Listed Pesticides

Rank	Name	County	Amount of use (lbs.)	Target Crops (Top Three)
1	D M Camp & Sons	Kern	529,682	carrots,potatoes, watermelons
2	Grimmway Enterprises Inc (DBA: Grimmway Farms)	Imperial	466,970	carrots
3	Britz Farms	Madera	410,140	uncultivated ag. area, alfalfa
4	Bolthouse Farms Inc, William	Kern	345,900	carrots
5	South Valley Inc	Imperial	343,646	carrots, lettuce, broccoli
6	Johnston Farms (DBA: Johnston, Dennis B)	Kern	330,656	potatoes, peppers, oranges
7	Bear Creek Production Co (DBA: Bear Creek Corp)	Kern	316,023	
8	Sun & Sand Enterprises	Riverside	263,562	peppers, cantaloupes, tomatoes
9	(The) Elmore Co	Imperial	259,915	carrots, cantalopes, potatoes
10	Ecco (or ECCO)	Imperial	258,697	carrots, potatoes, cantaloupes

yard (57%), and flea and tick control on pets (50%). According to a 1998 CALPIRG report, diazinon, dicamba, diuron, EPTC, fenoxycarb, methyl bromide, hydramethylnon, oxadiazon, simazine, and tebuthiuron – all identified by US.EPA as developmental or reproductive toxicants – were used in 52% of 46 surveyed California school districts.[4] Similarly, a cursory survey of San Francisco Bay Area hardware and gardening supply stores reveals that listed chemicals appear on the ingredients of at least 55 different over-the-counter products.[5]

Listed pesticides were used in all 58 California counties. As Table 5 indicates, central valley "farmbelt" counties received the bulk of listed chemical use. Fresno, Kern, Imperial, Monterey, Tulare, Merced and San Joaquin counties all received more than 2 million pounds of use. Alpine, Trinity, Sierra, and Inyo counties reportedly used negligible amounts of listed pesticides – 61, 120, 263 and 804 pounds, respectively.

Relative to the number of TRI reporting facilities, use of listed pesticides is spread between many more pesticide applicators – 24,312 reported using listed pesticides in 1995. The vast majority of these applicators report using relatively small amounts of pesticide. Combined, the bottom 85% (20,665) of all reporting applicators applied only 6.1 million pounds, little more than ten percent of all listed pesticide applications. At the high end, the top ten applicators report only 6.2% of total use. These numbers bear important implications for agricultural pollution prevention – use reduction by only the leading pesticide users will have limited overall impact.

The top ten applicators applying the greatest amounts of listed pesticides are presented in Table 6. In ranking pesticide applicators, it's important to realize that these businesses may provide important personal, community or even national benefits in terms of pest management, convenience, food production, jobs, etc. Growers, particularly, face tremendous pressures to use pesticides, including crop security, crop insurance requirements, "expert" advice from pest control advisors and inadequate access to alternative technologies and information. As noted above, the top ten applicators comprise only a small fraction of total pesticide use – 3.5 million pounds or

Table 7
Facility Releases of Listed Chemicals in California (1991-1996)*

Release	1991	1992	1993	1994	**1995	**1996
Air	16,398,071	13,504,613	11,478,226	10,301,094	10,021,555	9,471,474
Water	80,767	107,016	25,493	18,877	22,255	20,423
Underground injection	963	961	8,092	7,095	6,023	5,130-
Land	417,913	375,067	347,509	225,971	257,395	231,403
Sewage syst em	2,127,835	1,583,766	1,493,374	1,407,810	1,795,253	850,108
Facility Total	19,025,549	15,571,423	13,352,694	11,960,847	12,102,481	10,578,538

Table 8
Facility Transfers of Listed Chemicals (1991-1996)*

Transfer	1991	1992	1993	1994	***1995	***1996
Offsite recycling	24,537,485	21,685,354	28,404,495	28,197,927	27,769,360	24,590,767
Incineration	6,371,015	6,859,886	4,559,396	4,000,277	4,912,679	5,431,629
Offsite treatment	1,179,478	1,350,069	1,263,351	2,338,139	7,919,700	1,950,427
Transfer (other)	49,494	1,450	-	5	755	5
Offiste disposal	2,569,241	1,408,610	1,460,682	2,461,376	2,810,663	3,308,137
Facility Total	34,706,713	31,305,369	35,687,924	36,997,724	43,413,157	35,280,965

* Transfers to sewage treatment facilities are considered releases; they are not included in Table 8.

** 1995 facility release data includes 372,290 lbs of Listed Chemicals that were first reported in 1995; 1996 data includes 463,964 lbs of these newly reported chemicals.

*** 1995 facility transfer data includes 2,291,626 lbs of Listed Chemicals that were first reported in 1995; 1996 data includes 2,669,391 lbs of these newly reported chemicals.

Table 9
Top Ten Listed Chemicals Released by California Facilities (1991-1996)*

Rank	Chemical	1991	1992	1993	1994	1995	1996
1	TOLUENE	2,396,487	1,858,873	1,811,059	1,675,940	1,982,780	1,963,831
2	STYRENE	1,740,911	1,750,627	1,727,475	2,110,287	1,883,639	1,904,635
3	GLYCOL ETHERS	3,077,213	2,953,378	2,321,859	2,345,745	1,879,170	1,550,883
4	PERCHLORETHYLENE	2,842,848	2,233,393	1,683,122	1,079,459	1,487,558	1,379,108
5	METHYLENE CHLORIDE	3,961,897	2,849,994	2,152,962	1,363,565	1,206,341	999,334
6	XYLENE(S)	1,990,414	1,618,857	1,308,144	1,169,850	1,032,589	868,030
7	PHENOL	1,528,090	980,824	1,320,132	1,181,932	1,174,953	530,231
8	FORMALDEHYDE	413,500	359,184	322,007	546,019	651,376	487,289
9	MANGANESE	381,759	381,876	316,219	232,361	218,770	207,122
10	BENZENE	357354	262023	187445	129855	119452	94,035

*Transfers to sewage treatment facilities are considered releases.

6.2%. In the authors' opinion, however, those using the largest amounts of these chemicals have a proportionate responsibility to prevent exposures and pursue the implementation of safer alternatives.

Note that because growers often report pesticide use separately for each farm, a grower with farms scattered across the state would not be represented in the top ten users if none of his or her individual operations were among the ten largest users. Thus there may be other proprietors with multiple operations around the state who, in aggregate, use more pesticides than those applicators listed below. Evidencing this, Grimmway Enterprises, Britz Farms, Bolthouse Farms Inc. and Johnston Farms all reported also applying listed pesticides in counties other than those listed here, though in smaller amounts. Note also that many pesticide users reporting to California's Pesticide Use Reporting System do not provide adequate self-identification – over 2.8 million pounds of listed chemicals were reported by unidentifiable applicators.

Table 10
Top 20 Industries Releasing and Transferring Listed Toxicants (1996)*

Rank	Industry	Release(lbs)	Transfer	Total
1	PETROLEUM REFINING	1,352,781	44,260	1,397,041
2	METAL CANS	882,692	1,212,938	2,095,630
3	COMMERCIAL PRINTING, GRAVURE	863,133	22,299	885,432
4	PLASTICS PLUMBING FIXTURES	642,875	-	642,875
5	PLASTICS PRODUCTS, NEC	527,446	67,936	595,382
6	AIRCRAFT	434,476	390,353	824,829
7	PLASTICS FOAM PRODUCTS	410,138	-	410,138
8	MOTOR VEHICLES AND CAR BODIES	388,015	177,355	565,370
9	PLATING AND POLISHING	268,457	467,312	735,769
10	MINERAL WOOL	220,662	11,613	232,275
11	PETROLEUM AND COAL PRODUCTS, NEC	206,306	-	206,306
12	BOAT BUILDING AND REPAIRING	203,493	-	203,493
13	RECONSTITUTED WOOD PRODUCTS	198,603	-	198,603
14	GRAY AND DUCTILE IRON FOUNDRIES	191,473	30,715	222,188
15	PAINTS AND ALLIED PRODUCTS	185,900	702,441	888,341
16	MANUFACTURING INDUSTRIES, NEC	169,491	3,445	172,936
17	TRAVEL TRAILERS AND CAMPERS	168,723	2,500	171,223
18	HOUSEHOLD AUDIO AND VIDEO EQUIPMENT	148,732	2,307	151,039
19	BOLTS, NUTS, RIVETS AND WASHERS	146,714	43,729	190,443
20	AIRCRAFT PARTS AND EQUIPMENT, NEC	146,243	22,173	168,416

*Transfers to sewage treatment facilities are considered releases.

Facility Releases and Transfers

California industrial facilities released over 82.6 million pounds of listed reproductive and developmental toxicants between 1991 and 1996. The vast majority of these releases were to air – 71.2 million pounds comprising 86% of releases during this period. After releases to air, sewage treatment plants rank second as a destination for listed chemicals. Dumping toxic chemicals into

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)
	STYRENE		446,901	-	-
3	**CHEVRON USA PRODS. CO.**	**403,178**	EL SEGUNDO	LOS ANGELES	PETROLEUM REFINING
	BENZENE		5,390	-	1,915
	FORMALDEHYDE		23,000	-	-
	LEAD		113	6	990
	MANGANESE		13,980	710	1,900
	N-METHYL-2-PYRROLIDONE		330,000	-	-
	PHENOL		1,980	-	9
	PERCHLORETHYLENE		-	-	-
	TOLUENE		21,960	1	687
	XYLENE(S)		6,030	8	310
4	**CARPENTER CO.**	**394,000**	LATHROP	SAN JOAQUIN	PLASTICS FOAM PRODUCTS(1987)
	METHYLENE CHLORIDE		394,000	-	-
5	**NEW UNITED MOTOR MFG. INC**[12]	**388,015**	FREMONT	ALAMEDA	MOTOR VEHICLES AND CAR BODIES
	BENZENE		500	-	255
	GLYCOL ETHERS		213,000	5	150,500
	MANGANESE		250	-	250
	TOLUENE		32,750	5	8,850
	XYLENE(S)		141,500	5	17,500
6	**MOBIL OIL TORRANCE REFINERY**	**241,770**	TORRANCE	LOS ANGELES	PETROLEUM REFINING
	BENZENE		8,600	9,900	187
	PHENOL		370	160,000	-
	TOLUENE		8,500	27,000	1,989
	XYLENE(S)		4,400	23,000	1,058
7	**JACKSON VALLEY ENERGY L.P.**	**206,306**	IONE	AMADOR	PETROLEUM & COAL PRODUCTS, NE
	TOLUENE		206,306	-	-
8	**U.S. PIPE & FNDY. CO.**	**191,473**	UNION CITY	ALAMEDA	GRAY AND DUCTILE IRON FOUNDRIES
	LEAD COMPOUNDS		1,162	1	27,973
	MANGANESE COMPOUNDS		190,310	-	642
9	**AEROCHEM INC.**	**181,500**	ORANGE	ORANGE	AIRCRAFT
	METHYLENE CHLORIDE		14,400	-	3,600
	PERCHLORETHYLENE		167,100	-	310,000
10	**REYNOLDS METALS CO.**[13]	**175,036**	TORRANCE	LOS ANGELES	METAL CANS
	(TORRANCE CAN PLANT)				
	GLYCOL ETHERS		175,023	-	578
	MANGANESE		-	13	158,330

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 products, are an important source of styrene emissions into the environment.[11] Industries releasing the largest amounts of styrene in California include plastic plumbing fixtures (34%), plastic products (23%), boat building and repairing (11%) and travel trailer and camper manu-

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. Transferred chemicals may also be a source of exposure to workers and to community members at risk from chemical spills and accidents. Because of limitations of the Toxics Release Inventory, chemicals transferred into products disappear from the ledger and we have little information about listed chemicals transferred from facilities into our homes, schools, workplaces and communities as product.

Clearly, the chemical use and release reports reviewed in this section suggest that we have spread large quantities of reproductive and developmental toxicants throughout our urban and natural environment. Employees are at risk for significant exposure in the workplace. Consumers may be exposed during product use or disposal. Residents of communities in which listed chemicals are used or released may also be at risk. Readers can learn more about local use and release of listed chemicals from maps in the following section. The Resources Guide in this document may also be useful.

References

1 California Environmental Protection Agency, Chemicals Known to the State to Cause Cancer or Reproductive Toxicity, May 1, 1997. U.S. Environmental Protection Agency, Federal Register, Vol. 59, No. 229,61436, November 30, 1994. Note that no chemicals which are regulated as pharmacueticals under the Federal Food,Drug and Cosmetic Act are included in this analysis.

2 Working Note on Community Right to Know, United States Public Interest Research Group Education Fund, Washington D.C., May-June, 1997, p. 2.

3 Liebman, J, Rising Toxic Tide, Pesticide Use in California 1991-1995, Pesticide Action Network, San Francisco, CA, 1997, p. v.

4 Kaplan, J., Failing Health: Pesticide Use in California Schools, California Public Interest Research Group, 1998, p. 2. Note that hydramethylnon and oxadiazon are not included in this chapter because of low reported use.

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

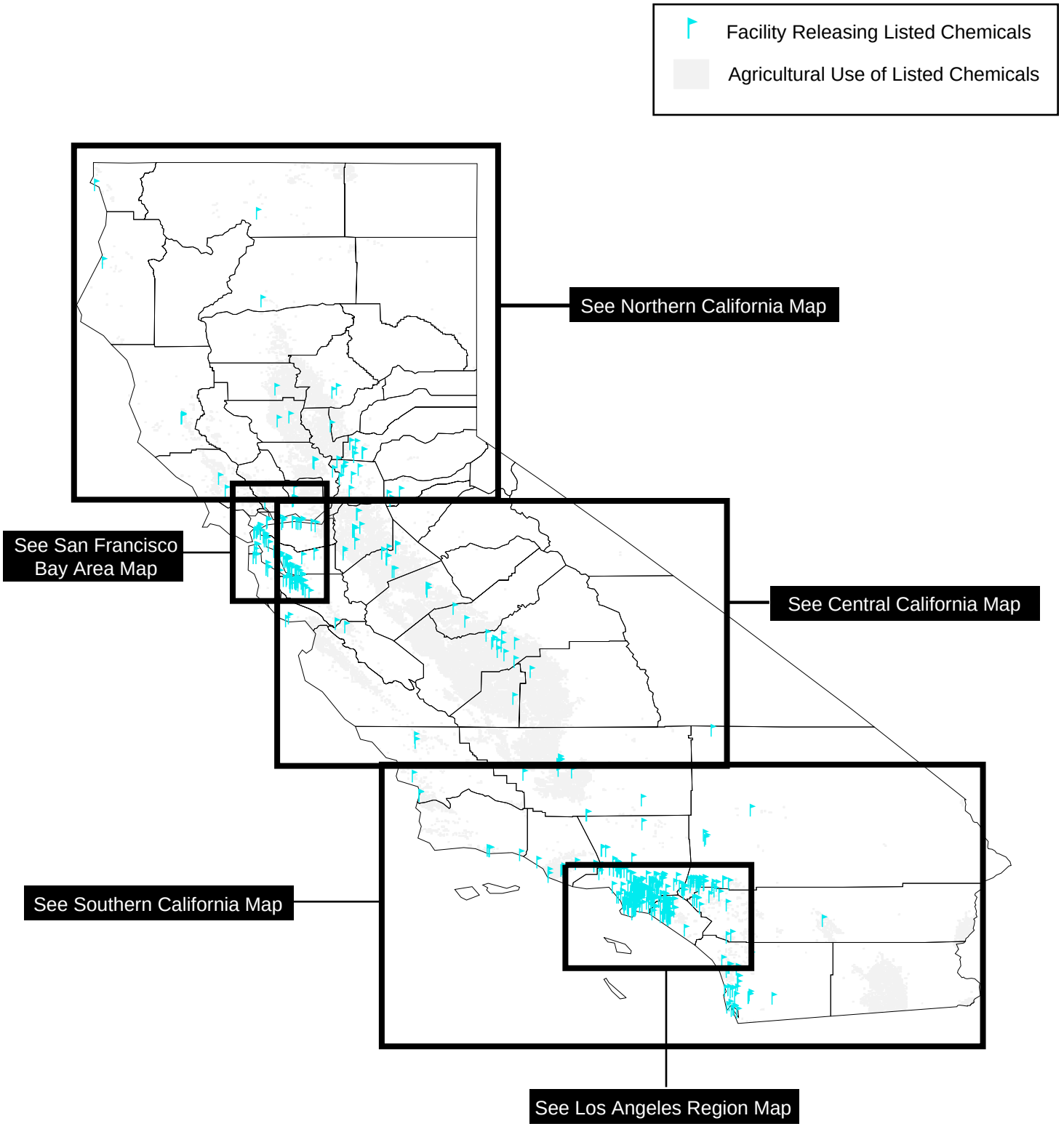
The maps in the following pages are intended to present a geographical thumbnail sketch of reproductive and developmental toxicant use in California. Regional maps provide bracketed intensity and location of listed pesticide use – those pesticides identified as Listed Chemicals throughout this report. 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:

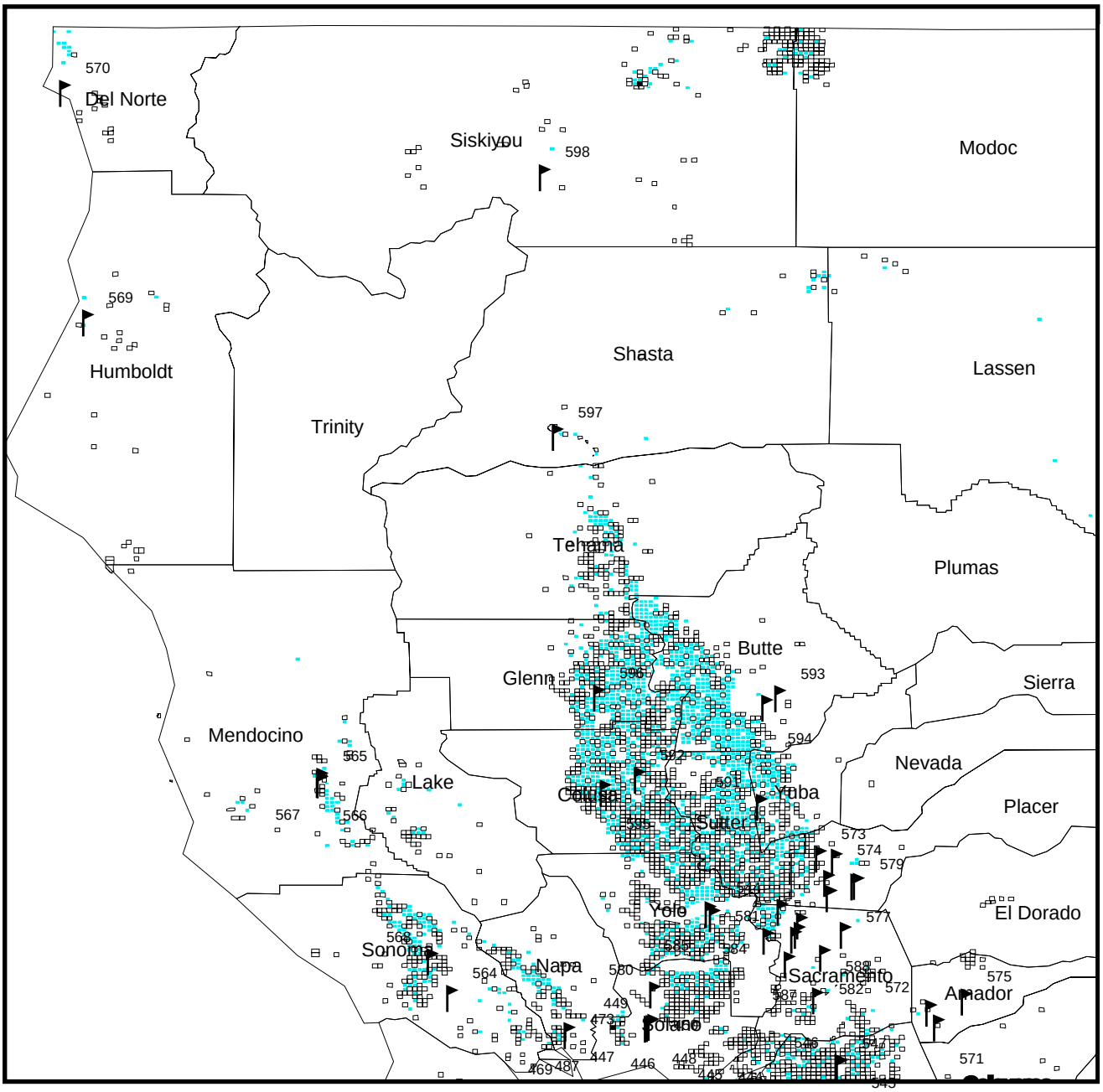
California Department of Pesticide Regulation, Pesticide Use Reporting Program, 1995;

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

Use and Release of Listed Chemicals in California (1995)

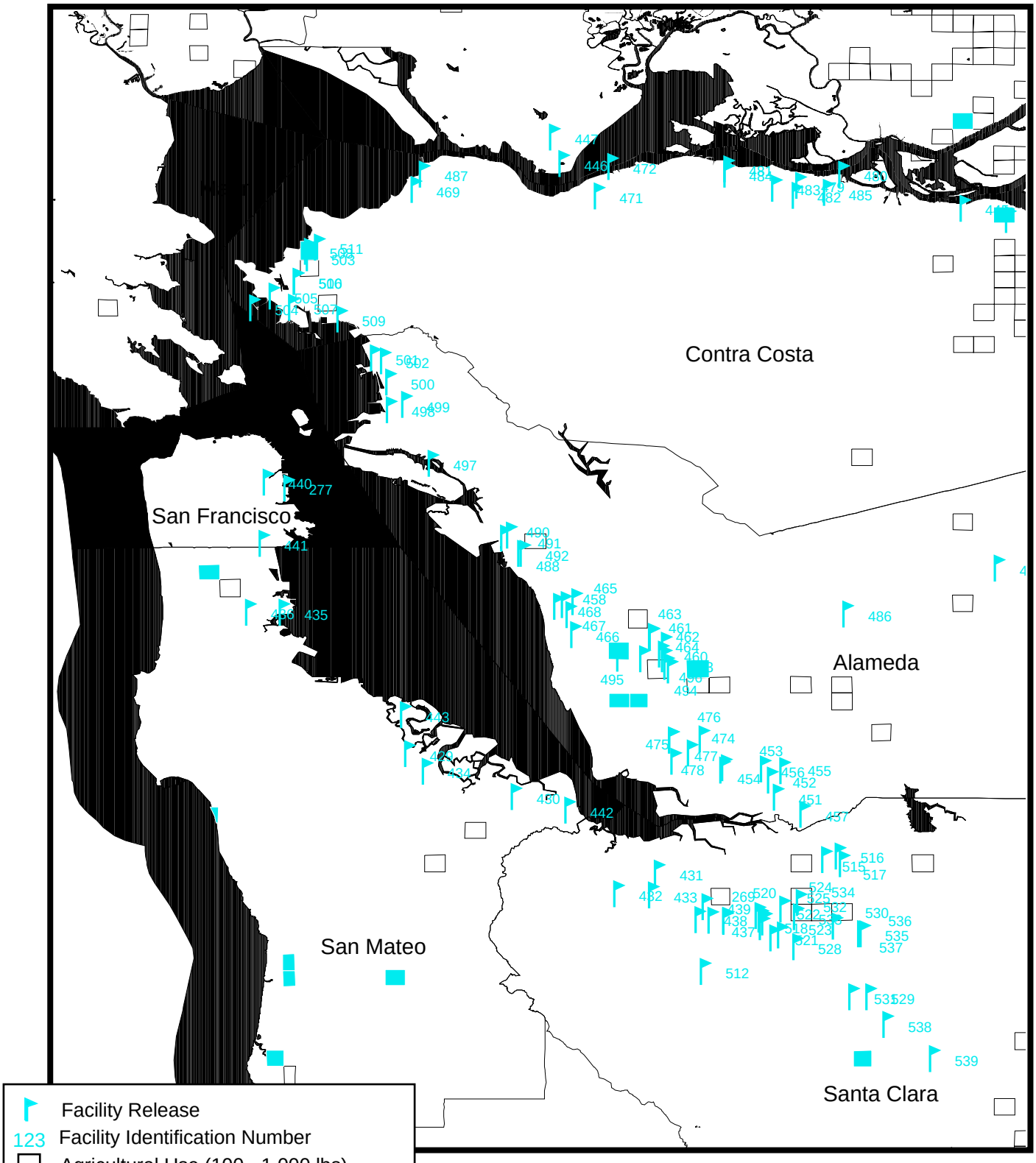


Use and Release of Listed Chemicals in Northern California (1995)

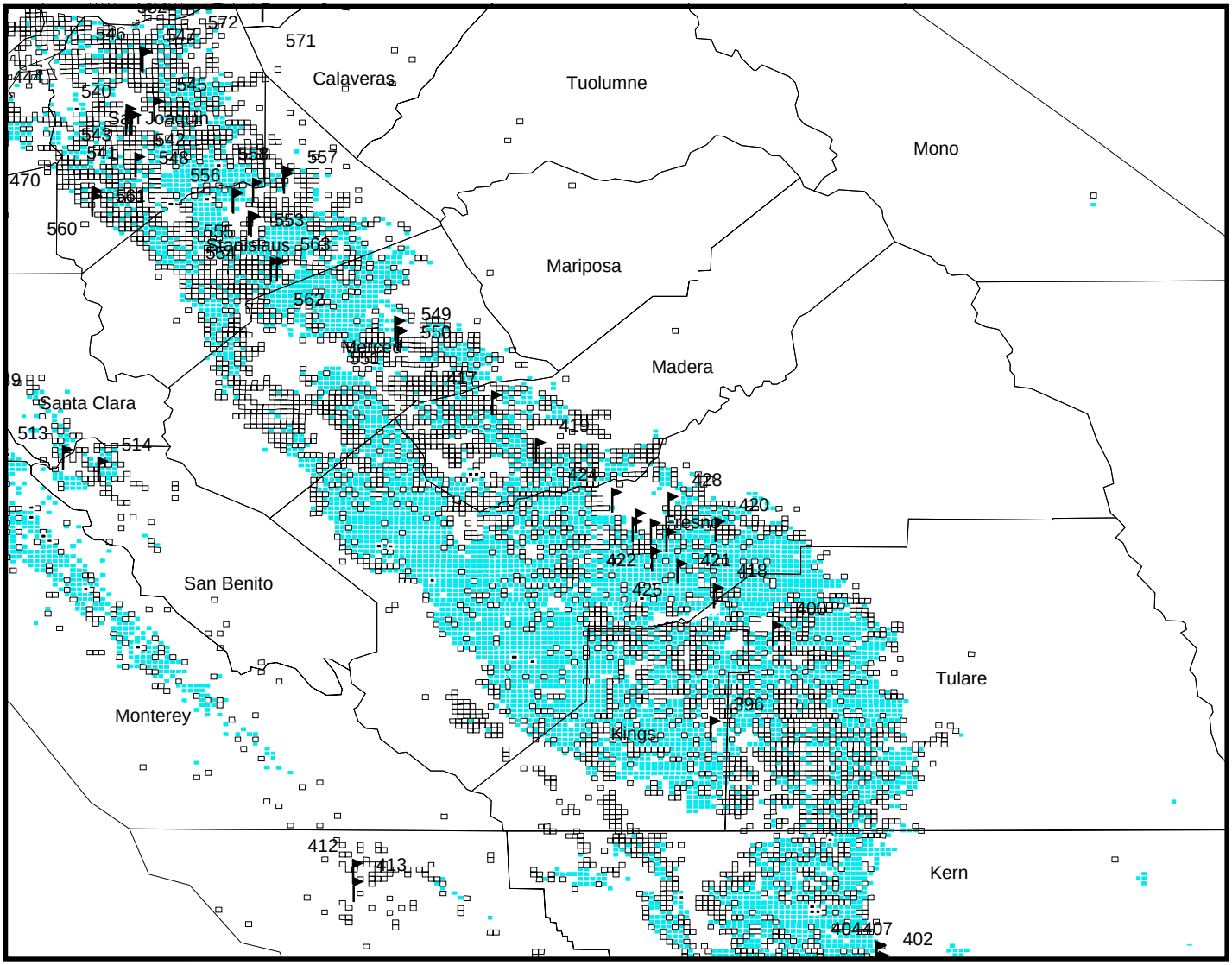


Facility Release
123 Facility Identification Number
Agricultural Use (100 - 1,000 lbs)
Agricultural Use (1,001 - 50,000 lbs)
Agricultural Use (50,001 - 200,000 lbs)

Use and Release of Listed Chemicals in the San Francisco Bay Area (1995)

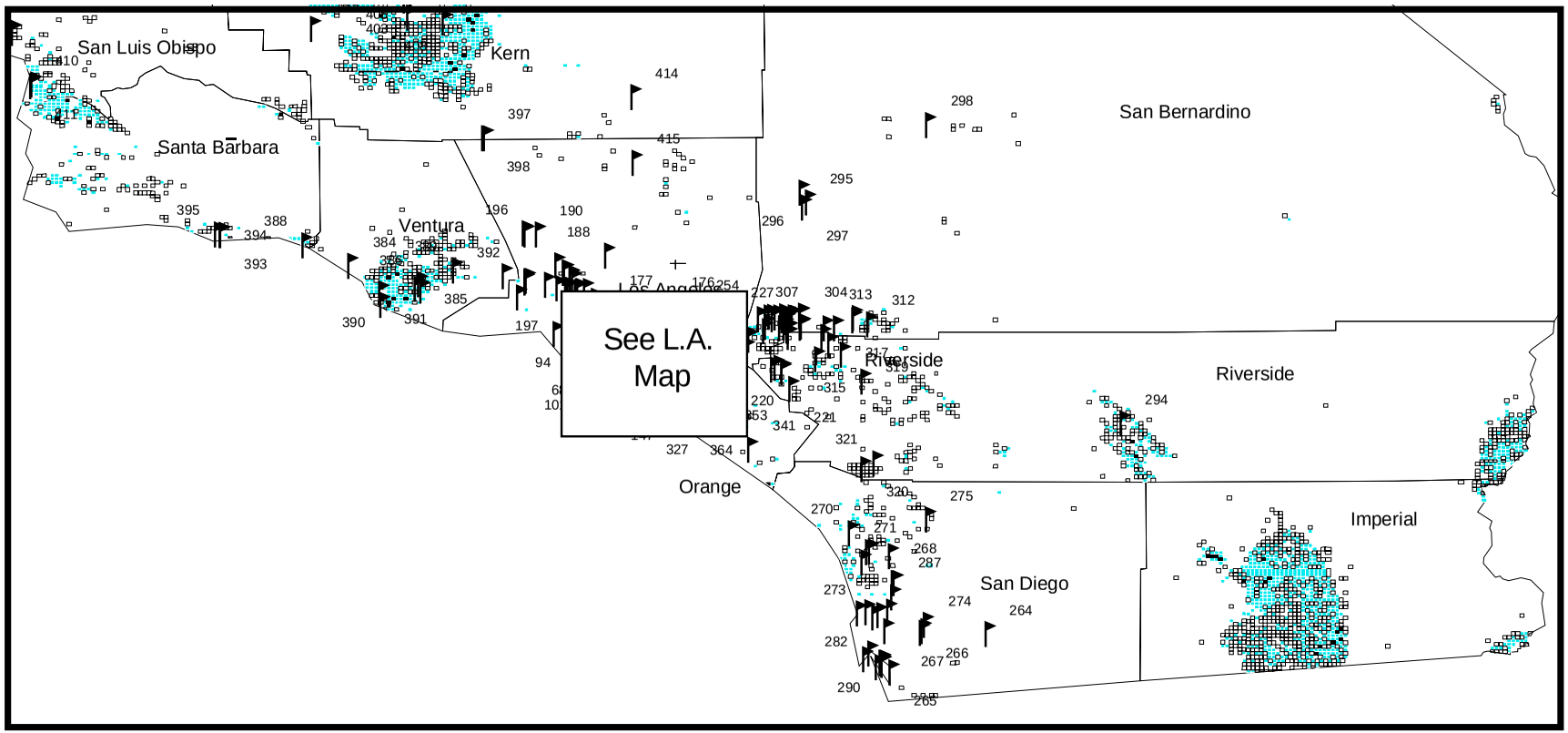


Use and Release of Listed Chemicals in Central California (1995)

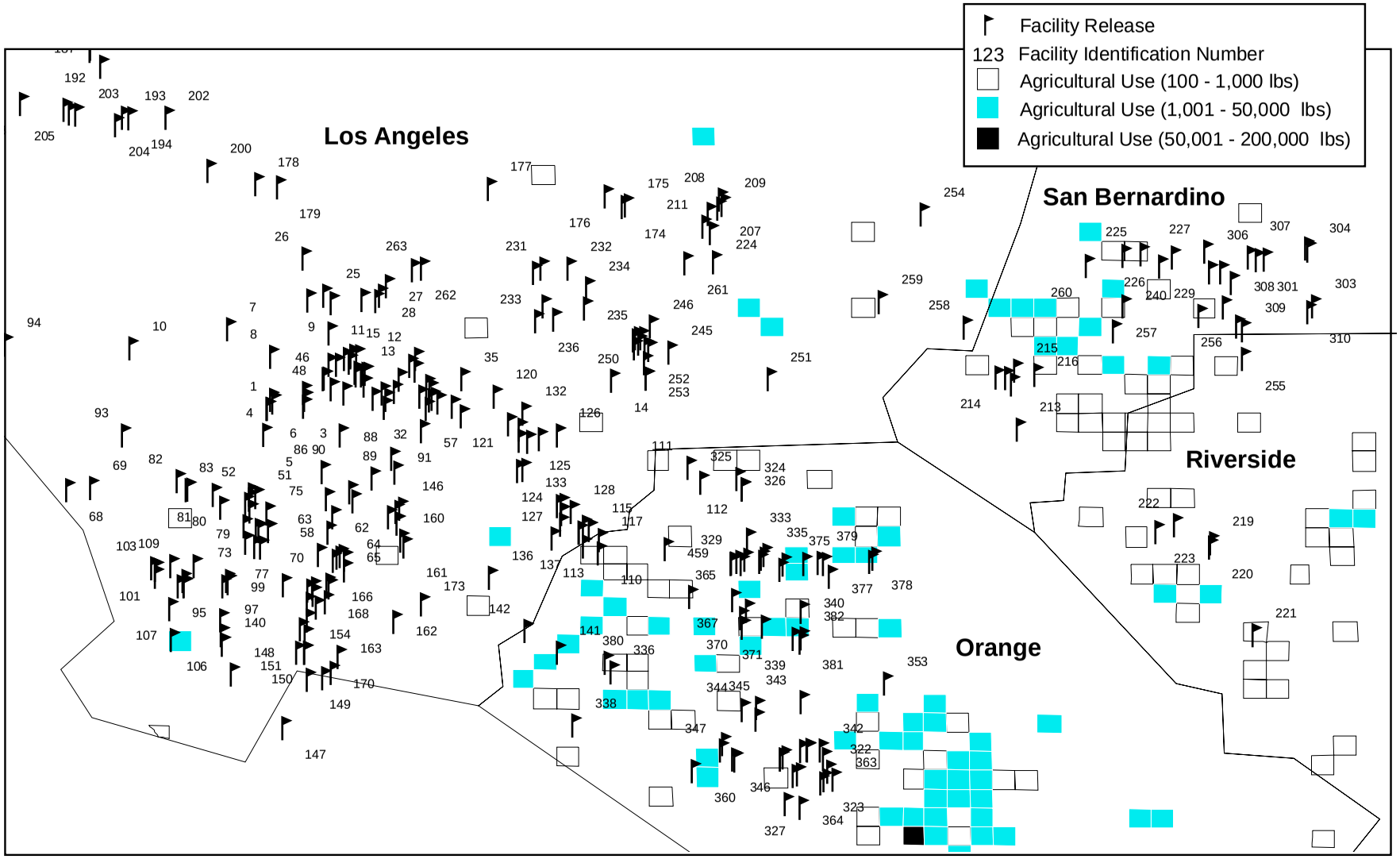


Facility Release
123 Facility Identification Number
Agricultural Use (100 - 1,000 lbs)
Agricultural Use (1,001 - 50,000 lbs)
Agricultural Use (50,001 - 200,000 lbs)

Use and Release of Listed Chemicals in Southern California (1995)



Use and Release of Listed Chemicals in the Los Angeles Area (1995)



MAP KEY: Facilities Releasing and Transfering Listed Chemicals

ID	RELEASE	TRANSFER	FACILITY	CITY
1	37,701	36,313	FABRI COTE	L.A.
2	29,800	3,200	STANDARD NICKEL-CHROMIUM	L.A.
3	29,057	937,730	LONZA INC.	L.A.
4	500	-	PERVO PAINT CO.	L.A.
5	28,040	-	JOHN BOYD DESIGNS	L.A.
6	6	7,708	U.S. RADIATOR CORP.	L.A.
7	11,335	-	SILVESTRI STUDIO INC.	L.A.
8	20,000	2,100	PALACE PLATING	L.A.
9	10	8,199	WESTERN BRASS WORKS	L.A.
10	2,000	4,620	SPRAYLAT CORP.	L.A.
11	12,042	51,468	SHERWIN-WILLIAMS DIVERSIFIE	L.A.
12	14,690	9,284	U.S. CAN CO.	L.A.
13	1,500	-	CARGILL FOODS INC.	CITY OF COMMERCE
14	250	-	JAMES RIVER CORP.	L.A.
15	71,630	891	BAUCHET INTL.	L.A.
16	19,000	-	CERTIFIED ENAMELING INC.	L.A.
17	13,947	10,151	AIR PRODS. & CHEMICALS INC.	L.A.
18	1,010	29,080	SURFACE PROTECTION IND. INC	L.A.
19	750	-	VIGORO IND. INC.	VERNON
20	530	602,226	BERG LACQUER CO.	L.A.
21	4	141	ALLIED-SIGNAL INC.	L.A.
22	-	-	DAVIS COLORS	L.A.
23	-	-	FOUR STAR CHEMICAL	L.A.
24	91	9,461	AMVAC CHEMICAL CORP.	L.A.
25	255	1,000	SMILAND PAINT CO.	L.A.
26	-	250	MISSION KLEENSWEEP PRODUCTS	L.A.
27	260	292	ARROWHEAD BRASS PRODS.INC	L.A.
28	-	-	CASTROL INDUSTRIAL N.A.	L.A.
29	-	-	MORTON INTL. INC.	L.A.
30	51,993	-	BOYD FURNITURE	COMMERCE
31	7,595	19,730	ASHLAND CHEMICAL INC.	L.A.
32	3,256	4,698	DUNN-EDWARDS CORP.	L.A.
33	2,876	-	KOP-COAT INC.	VERNON
34	1,755	82,589	ICI SINCLAIR	CITY OF COMMERCE
35	1,401	-	ELLAY INC.	COMMERCE
36	1,020	10,200	EPS INC.	CITY OF COMMERCE
37	209	5,458	KAISER ALUMINUM EXTRUDED	L.A.
38	129	55,897	GNB TECH. INC.	CITY OF COMMERCE
39	94	13	B. M. & CO.	COMMERCE
40	-	-	CASTROL INDUSTRIAL N.A.	L.A.
41	260	256,473	RAMCAR BATTERIES INC.	CITY OF COMMERCE
42	13,160	-	ANDERSON LITHOGRAPH CO.	L.A.
43	14,940	2,441	SANDBERG FURNITURE MFG.	L.A.
44	14,000	12,800	PUNCH PRESS PRODS. INC.	VERNON
45	3,257	849,230	GNB TECHS. INC.	VERNON
46	500	-	GRIFFITH MICRO SCIENCE INC.	L.A.
47	11	199,420	P. KAY METAL SUPPLY INC.	L.A.
48	10	-	LIQUID CARBONIC IND. CORP.	L.A.
49	-	5	LUBRICATING SPECIALTIES CO.	VERNON
50	500	-	GRIFFITH MICRO SCIENCE INC.	VERNON
51	211,650	7,050	WESLOCK NATL. INC.	L.A.
52	11,000	10,500	AL'S PLATING CO. INC.	L.A.
53	2,010	81,800	LYLE VAN PATTEN CO. INC.	L.A.
54	151	2,930	PRECISION SPECIALTY METALS	L.A.
55	169	7,451	RHONE-POULENC	L.A.
56	5	5	PACIFIC TUBE CO.	L.A.
57	8,645	775	MODEL PLATING CO. INC.	BELL GARDENS
58	-	-	FIBERNETICS	COMPTON
59	500	-	BALL IND.	COMPTON
60	14,309	-	JBI INC.	COMPTON
61	1,374	-	GROW GROUP INC.	COMPTON
62	897	-	CENTURY PLASTICS INC.	COMPTON
63	4	-	EME INC.	COMPTON
64	5	-	MANNER PLASTIC MATERIALS IN	RANCHO DOMINGUEZ
65	2,255	-	FLO-KEM PRODS.	COMPTON
66	963	-	CRAIN IND. INC.	COMPTON
67	765	-	DEMENNO/KERDOON	COMPTON
68	258,502	12,389	CHEVRON USA PRODS. CO.	EL SEGUNDO
69	246	25,160	INTERNATIONAL RECTIFIER	EL SEGUNDO
70	18,590	-	CORONET MFG. CO. INC.	GARDENA
71	12,747	114	KUSHWOOD CHAIR INC.	GARDENA
72	24,950	6,000	LILLY IND. INC.	GARDENA
73	23,670	2,676	A. B. PLASTICS CORP.	GARDENA
74	2,976	-	PERMALITE REPROMEDIA CORP.	GARDENA
75	500	2,238	INDEPENDENT INK INC.	GARDENA
76	255	1,318	IPS CORP.	GARDENA
77	13	101	MAJOR BRASS FOUNDRY INC.	GARDENA
78	8	10,392	DEUTSCH	GARDENA
79	22,200	-	STABOND CORP.	GARDENA
80	16,173	16,173	PB FASTENERS	GARDENA
81	1,430	-	EWC CO.	GARDENA
82	3,100	1,865	INTERPLASTIC CORP.	HAWTHORNE
83	51,910	776	NORTHROP GRUMMAN CORP.	HAWTHORNE
84	52,626	6,838	MYERS CONTAINER CORP.	HUNTINGTON PARK
85	-	-	COMMERCIAL ENAMELING CO.	HUNTINGTON PARK
86	3,148	399,996	MCWHORTER TECHS. INC.	LYNWOOD
87	2,214	-	W. W. HENRY CO.	MAYWOOD
88	1,879	160,967	LILLY IND. INC.	SOUTH GATE
89	15	4,033	TECHNI-CAST CORP.	SOUTH GATE
90	-	-	DIATEC ENVIRONMENTAL	SOUTH GATE
91	-	-	HUGHES BROTHERS	SOUTH GATE
92	-	250	SHULTZ STEEL CO. (SSC)	SOUTH GATE
93	250	750	ELECTROSTAR INC.	INGLEWOOD
94	5,114	34,137	GILLETTE CO.	SANTA MONICA
95	10	2,689	MARTIN BRASS FOUNDRY	TORRANCE
96	-	-	DEXOL IND.	TORRANCE
97	17,091	-	GERON FURNITURE INC.	TORRANCE
98	2,489	11,523	AMERICAN POLYSTYRENE CORP.	TORRANCE
99	6,600	1,400	R. R. DONNELLEY & SONS CO.	TORRANCE
100	7,908	429,980	DOW CHEMICAL CO.	TORRANCE
101	1,889	13	UNION CARBIDE CORP.	TORRANCE
102	-	-	C. P. HALL CO.	TORRANCE
103	372	-	UNION CARBIDE CORP.	TORRANCE
104	233,507	189,469	REYNOLDS METALS CO.	TORRANCE
105	1,474	21,532	ALLIED-SIGNAL INC.	TORRANCE
106	500	136,506	BACHEM INC.	TORRANCE
107	-	11,000	ALLIED-SIGNAL	TORRANCE

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
149	89,622	-	ULTRAMAR INC.	WILMINGTON
150	45,119	2,100	TRMI	WILMINGTON
151	634	260	HUNTWAY REFINING CO.	WILMINGTON
152	196,731	-	UNOCAL L.A. REFY.	CARSON
153	10,034	-	NIKLOR CHEMICAL CO. INC.	CARSON
154	45	637	GEON CO.	CARSON
155	1,000	9,844	JOHNSON LAMINATING & COATIN	CARSON
156	-	-	OLDE TYME PRODS. INC.	CARSON
157	20,700	40	NORTHROP GRUMMAN CORP.	COMPTON
158	249,293	12,253	ARCO PRODS. CO.	CARSON
159	3,249	8,214	ZYNOLYTE PRODS. CO.	CARSON
160	41,086	747	TABC INC.	LONG BEACH
161	588	250	EDGINGTON OIL CO.	LONG BEACH
162	-	5	CERTIFIED ALLOY PRODS. INC.	LONG BEACH
163	46,000	2,300	CUSTOM FIBREGLASS MFG. C	LONG BEACH
164	16,374	500	WESTERN TUBE & CONDUIT CO	LONG BEACH
165	3,800	-	LONZA INC.	CARSON
166	270	1,675	ALFLEX CORP.	LONG BEACH
167	-	-	NALCO CHEMICAL CO.	CARSON
168	-	-	BARMET ALUMINUM CORP.	CARSON
169	500	250	EDOCO	LONG BEACH
170	525	2,750	J. H. BAXTER & CO.	LONG BEACH
171	47	-	TRMI	LONG BEACH
172	315	115	TRMI	WILMINGTON
173	54,690	68,141	DOUGLAS AIRCRAFT CO.	LONG BEACH
174	84,725	160,768	AVERY DENNISON	MONROVIA
175	36,400	22,275	3M	MONROVIA
176	4,215	468	MASK-OFF CO. INC.	MONROVIA
177	5	6,800	K. C. PHOTOENGRAVING CO.	PASADENA
178	1,361	6,375	COURTAULDS AEROSPACE INC.	GLENDALE
179	7,500	10,875	DRILUBE CO.	GLENDALE
180	132,446	250	AMERICAN NATL. CAN CO.	CHATSWORTH
181	7,910	26,800	FIBER RESIN CORP.	CHATSWORTH
182	-	-	CHATSWORTH PRODS. INC.	CHATSWORTH
183	76,799	4,680	HARMAN SPEAKER MFG.	NORTHRIDGE
184	255	5,800	BURBANK PLATING SERVICES CO	PACOIMA
185	51	3,825	PRICE PFISTER INC.	PACOIMA
186	255	-	MOC PRODS. CO. INC.	PACOIMA
187	7,327	8,273	M. A. HANNA COLOR	SAN FERNANDO
188	47,183	-	JOHANSON DIELECTRICS INC.	SYLMAR
189	32,000	25,000	VALLEY-TODECO	SYLMAR
190	1,320	-	KEYSOR-CENTURY CORP.	SAUGUS
191	20,500	-	NUPLA CORP.	SUN VALLEY
192	2,150	-	P. B. FIBERGLASS PRODS. INC	SUN VALLEY
193	-	-	FLAMEMASTER CORP.	SUN VALLEY
194	19,044	-	COLUMBIA SHOWCASE & CAB	SUN VALLEY
195	30,775	-	GRUBER SYS. INC.	VALENCIA
196	162,906	9,806	POLYCARBON INC.	VALENCIA
197	102,967	-	CATALINA YACHTS INC.	WOODLAND HILLS
198	3,597	-	VIBRA FINISH CO.	VAN NUYS
199	250	20,786	TECHNO COMPONENTS INC.	VAN NUYS
200	-	-	ALL METALS PROCESSING CO. I	BURBANK
201	9,000	16,218	QUALITY HEAT TREATING INC.	BURBANK
202	23,000	4,400	SENIOR FLEXONICS INC.	BURBANK
203	41,440	910	REMO INC.	NORTH HOLLYWOOD
204	26,300	5,600	E/M CORP.	NORTH HOLLYWOOD
205	3,500	-	AMERICH CORP.	NORTH HOLLYWOOD
206	9,067	-	ARMORCAST PRODS. CO.	N. HOLLYWOOD
207	2,390	5,410	RUBBER URETHANES INC.	AZUSA
208	2,255	10,077	VALSPAR CORP.	AZUSA
209	-	-	CALIFORNIA AMFORGE CORP.	AZUSA
210	-	28,521	TUBING SEAL CAP INC.	AZUSA
211	289	67,023	REICHHOLD CHEMICALS INC.	AZUSA
212	11,511	3,497	OPTICAL RADIATION CORP.	AZUSA
213	5	-	HIGGINS BRICK CO.	CHINO HILLS
214	6,608	-	HUSSMANN CORP.	CHINO
215	500	530	SHIELD PACKAGING OF CA INC.	CHINO
216	-	-	GENLABS	CHINO
217	-	1,518	TRUS JOIST MACMILLAN	CHINO
218	43,418	-	CLARK MFG.	CHINO
219	-	5	IMCO RECYCLING OF CALIFORNI	CORONA
220	28,523	2,852	SCHULLER INTL. INC.	CORONA
221	255	874,461	U.S. BATTERY MFG. CO.	CORONA
222	9,770	250	UNLIMITED PERFORMANCE PRODS	CORONA
223	20	-	GOLDEN CHEESE CO.	CORONA
224	10	207,287	MEDSEP CORP.	COVINA

225	12,100	48,900	WESTERN METAL DECORATING CO	RANCHO CUCAMONGA
226	10,335	46,590	AVERY DENNISON	RANCHO CUCAMONGA
227	811	20,532	BHP COATED STEEL COR	ANCHO CUCAMONGA
228	-	211,878	ROBERT MFG. CO.	RANCHO CUCAMONGA
229	8,506	4,496	CAL FINISHED METAL	RANCHO CUCAMONGA
230	4,861	-	ARLON MATERIALS	RANCHO CUCAMONGA
231	370	-	CROWN CITY PLATING CO.	EL MONTE
232	37	39,001	JAMES JONES CO.	EL MONTE
233	14,138	-	M. C. GILL CORP.	EL MONTE
234	4	-	VALLEY BRASS INC.	EL MONTE
235	43,255	5	MCCONNELL CABINETS INC.	EL MONTE
236	3,053	33,916	CARDINAL INDUSTRIAL FINISHE	SOUTH EL MONTE
237	750	-	SANTOSHI CORP.	SOUTH EL MONTE
238	6,238	3,950	VACCO IND.	SOUTH EL MONTE
239	500	779,120	TAMCO	RANCHO CUCAMONGA
240	44,253	-	GENERAL MARBLE CO.	GUASTI
241	12,940	740	SUNSET FIREPLACE FIXTUR	CITY OF INDUSTRY
242	1,769	1,479,820	QUEMETCO INC.	CITY OF INDUSTRY
243	250	714	W. L. CHAPMAN CO.	CITY OF INDUSTRY
244	32,226	-	BENTLEY MILLS INC.	CITY OF INDUSTRY
245	2,013	-	DIVERSEY CORP.	CITY OF INDUSTRY
246	276	3,746,300	GNB TECHS. INC.	CITY OF INDUSTRY
247	10	750	DEXTER CORP.	INDUSTRY
248	1,014	49,547	MACLIN CO.	CITY OF INDUSTRY
249	23,503	117,710	TENNECO PACKAGING	CITY OF INDUSTRY
250	250	-	OAKITE PRODS. INC.	CITY OF INDUSTRY
251	-	250	PLASTRON AN ACTION TECH.	CITY OF INDUSTRY
252	1,600	-	CAMCO CHEMICAL CO. INC.	LA PUENTE
253	16,005	20,300	KERN IND.	CITY OF INDUSTRY
254	-	14,342	LA VERNE METAL PRODS.	LA VERNE
255	110,250	750	METAL CONTAINER CORP.	MIRA LOMA
256	255	-	GRIFFITH MICRO SCIENCE INC.	ONTARIO
257	5	-	RYCOLINE PRODS. INC.	ONTARIO
258	46,292	-	CENTURY MARBLE CO.	POMONA
259	239	-	W. R. MEADOWS OF CALIFORNIA	POMONA
260	500	-	ALTAWOOD INC.	UPLAND
261	265	954,011	CONCORDE/INTERSPACE BATT	WEST COVINA
262	1,089	1,389	INTERNATIONAL EXTRUSION COR	ALHAMBRA
263	10	250	CROWN BRASS MFG. CO.	ALHAMBRA
264	50,000	755	ROHR INC.	CHULA VISTA
265	-	-	BANNISTER STEEL INC.	NATIONAL CITY
266	5,074	42	CHEM-TRONICS INC.	EL CAJON
267	20,022	3,600	CARPENTER TECH. CORP.	EL CAJON
268	5	500	TITLEIST & FOOT-JOY WORLDWI	ESCONDIDO
269	-	-	ZEP MFG. CO.	SANTA CLARA
270	5,331	-	HOBIE CAT CO.	OCEANSIDE
271	35,154	98,477	SIGNET ARMORLITE INC.	SAN MARCOS
272	2,150	1,930	NAPP SYS. INC.	SAN MARCOS
273	2,736	250	STRUCTRON CORP.	SAN MARCOS
274	11,600	-	CUSTOM CRAFT MARBLE	SANTEE
275	4,260	-	SURVIVAL SYS. INTL. INC.	VALLEY CENTER
276	14,000	-	GENERAL DYNAMICS CORP.	SAN DIEGO
277	12,595	-	SAN FRANCISCO DRY DOCKS	SAN FRANCISCO
278	500	1,500	SOUTHWEST MARINE INC.	SAN DIEGO
279	27,701	-	NUTRASWEET KELCO CO.	SAN DIEGO
280	998	-	PRO-LINE PAINT CO.	SAN DIEGO
281	750	9,829	FRAZEE IND.	SAN DIEGO
282	400	15,000	MULTIPLE PEPTIDE SYS.	SAN DIEGO
283	10	20,384	BACHEM INC.	SAN DIEGO
284	2,110	-	DEPOSITION TECHS. INC.	SAN DIEGO
285	37,557	32,383	TOPPAN WEST INC.	SAN DIEGO
286	600	38,200	ALCOA	SAN DIEGO
287	101	427,548	SONY ELECTRONICS INC.	SAN DIEGO
288	91	2,915	HERCO TECH. CORP.	SAN DIEGO
289	12,785	364	FLUID SYS. CORP.	SAN DIEGO
290	24,350	52,000	U.S. NAVY	SAN DIEGO
291	9,522	96	U.S. NAVY SAN DIEGO	SAN DIEGO
292	2,058	18	U.S. NAVY	SAN DIEGO
293	11,282	4,475	NATIONAL STEEL & SHIPBUILDI	SAN DIEGO
294	7,936	750	ARMTEC DEFENSE PRODS. CO.	COACHELLA
295	6,952	-	PACIFIC TANK LTD.	ADELANTO
296	75,496	1,541	AEROCHEM INC.	ADELANTO
297	17,019	-	MOLDED FIBER GLASS CO.	ADELANTO
298	4,133	85,148	U.S. MARINE CORPS	BARSTOW
299	20	37,600	ATLAS PACIFIC CORP.	BLOOMINGTON
300	11,273	99,435	MORTON INTL. INC.	COLTON
301	105,900	12,000	GOLD SHIELD FIBERGLASS INC.	FONTANA
302	25,800	186,000	VAN CAN CO.	FONTANA
303	2,073	2,073	CARLISLE COATINGS	FONTANA
304	1,242	1,389	SPECIALTY FINISHES CO.	FONTANA
305	210	-	HECKETT MULTISERV	FONTANA
306	-	1,500	VISTA METALS CORP.	FONTANA
307	-	3,120	WESTERN WOOD TREATING FONTA	FONTANA
308	673	45,988	AMERON	FONTANA
309	10,000	15,293	SIERRA ALUMINUM CO.	FONTANA
310	6,842	-	JAMES HARDIE BUILDING PRODS	FONTANA
311	808	-	TST INC.	FONTANA
312	15	242,882	TELEDYNE AIRCRAFT PRODS.	REDLANDS
313	24,000	-	SNOW PLASTICS INC.	SAN BERNARDINO
314	20	7,130	GO/DAN IND.	SAN BERNARDINO
315	11,250	-	SUPREME TRUCK BODIES OF CA	RIVERSIDE
316	23,883	28,410	DEVOE COATINGS CO.	RIVERSIDE
317	123	-	PARKS CORP.	RIVERSIDE
318	3,800	23,702	SIERRA ALUMINUM CO.	RIVERSIDE
319	8,629	-	NATIONAL R.V. INC.	PERRIS
320	3,195	83,664	INTERNATIONAL RECTIFIER HEX	TEMECULA
321	-	-	MEDICAL DESIGN CONCEPTS	TEMECULA
322	64,500	-	JACUZZI WHIRLPOOL BATH INC.	IRVINE
323	-	-	PACKARD-HUGHES INTERCONNECT	IRVINE
324	19,765	255	AUTOMOTIVE WHEELS INC.	BREA
325	141	-	LEFFINGWELL	BREA
326	-	-	AMERON PROTECTIVE COATINGS	BREA
327	15,176	-	KYOWA AMERICA CORP.	COSTA MESA
328	12,296	-	RESINART CORP.	COSTA MESA
329	10,005	-	PACIFIC SEACRAFT CORP.	FULLERTON
330	65	-	NELCO PRODS. INC.	FULLERTON
331	-	200	INX INTL. INK CO.	FULLERTON
332	-	-	FUTURE FOAM INC.	FULLERTON
333	27,000	-	PCA METAL FINISHING INC.	FULLERTON
334	1212	712,000	JOHNSON CONTROLS BATTERY	FULLERTON
335	68,486	20,669	KAYNAR TECHS. INC.	FULLERTON
336	20,777	2,041	BAZZ HOUSTON CO.	GARDEN GROVE
337	13,193	-	DOUBLE D ENTS.	GARDEN GROVE
338	3,984	52,216	COATINGS RESOURCE CORP.	HUNTINGTON BEACH
339	155,350	304,500	AEROCHEM INC.	ORANGE
340	28,600	99,301	AKZO NOBEL COATINGS INC.	ORANGE

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
365	2,486	8,172,158	DELPHI ENERGY & ENGINE	ANAHEIM
366	5	-	KESTER SOLDER	ANAHEIM
367	4,000	6,200	J & H DEBURRING	ANAHEIM
368	-	5,189	ESSEX GROUP INC.	ANAHEIM
369	132,462	106,050	KWIKSET CORP.	ANAHEIM
370	23,530	-	WEYERHAEUSER	ANAHEIM
371	-	-	ORANGE COUNTY COLOR GRAPHICA	ANAHEIM
372	14,850	-	ADVANCED SPA DESIGNS	ANAHEIM
373	510	40	NEVILLE CHEMICAL CO.	ANAHEIM
374	447,700	-	LASCO BATHWARE	ANAHEIM
375	7,700	-	WILLARD MARINE INC.	ANAHEIM
376	165,350	-	XERXES CORP.	ANAHEIM
377	11,382	548,421	SHERWIN-WILLIAMS DIVERSIFIE	ANAHEIM
378	10,984	9,300	CIBA COMPOSITES	ANAHEIM
379	57,000	880	QLP LAMINATES INC.	ANAHEIM
380	-	-	GOODWIN CO.	GARDEN GROVE
381	2,470	20,991	FIBERITE INC.	ORANGE
382	-	-	ORANGE COUNTY METAL WORKS	ORANGE
383	18,570	3,250	AC PRODS. INC.	PLACENTIA
384	750	-	APPLIED SILICONE CORP.	VENTURA
385	-	13,220	VITESSE SEMICONDUCTOR CORP.	CAMARILLO
386	336	5,188	CLAIROL INC.	CAMARILLO
387	76	35,633	3M	CAMARILLO
388	5	12,083	NUSIL TECH.	CARPINTERIA
389	4,923	6,734	KAVLICO CORP.	MOORPARK
390	1,177	7,631	PH CHEMICALS INC.	OXNARD
391	70,360	129,413	REICHHOLD CHEMICALS INC.	OXNARD
392	1,933	-	WAMBOLD FURNITURE	SIMI VALLEY
393	500	15,000	CHANNEL IND. INC.	SANTA BARBARA
394	2,267	23,480	MCGHAN MEDICAL CORP.	SANTA BARBARA
395	750	25,320	APPLIED MAGNETICS CORP.	GOLETA
396	25,836	-	CDR SYS. CORP.	CORCORAN
397	2,530	25,560	SYSTECH ENVIRONMENTAL CORP.	LEBEC
398	98	-	NATIONAL CEMENT CO.	LEBEC
399	5,506	-	U.S. DOE NAVAL PETROLEUM	TUPMAN
400	-	-	HELLER PERFORMANCE POLYMERS	VISALIA
401	8,050	-	KERN OIL & REFINING CO.	BAKERSFIELD
402	68,550	-	SAN JOAQUIN REFINING CO. IN	BAKERSFIELD
403	43,785	177	TEXACO REFINING & MARKETING	BAKERSFIELD
404	10,333	610	FLUID CONTAINMENT INC.	BAKERSFIELD
405	6,601	740	TEXACO REFINING & MARKETING	BAKERSFIELD
406	1,514	29	TEXACO REFINING & MARKETING	BAKERSFIELD
407	10	21,706	KW PLASTICS OF CALIFORNIA	BAKERSFIELD
408	-	250	PACIFIC WOOD PRESERVING	BAKERSFIELD
409	2,005	29,450	JBL SCIENTIFIC	SAN LUIS OBISPO
410	500	505	UNOCAL CORP. 76 PRODS.	ARROYO GRANDE
411	-	-	UNOCAL 76 PRODS. CO.	ARROYO GRANDE
412	1,510	250	CHEMRON CORP.	PASO ROBLES
413	5	64,390	ZURN IND.	PASO ROBLES
414	1,330	65,309	COURTAULDS AEROSPACE INC.	MOJAVE
415	59,389	-	REXHALL IND. INC.	LANCASTER
416	-	-	NORTH AMERICAN CHEMICAL CO.	TRONA
417	32,874	762	CERTAINTEED CORP.	CHOWCHILLA
418	-	-	BIOPRODUCTS INC.	KINGSBURG
419	250	-	FMC CORP.	MADERA
420	-	25,381	GENERAL CABLE CORP.	SANGER
421	255	-	FRESNO VALVES & CASTINGS IN	SELMA
422	499	3,855	FLOWAY PUMPS	FRESNO
423	-	-	WILBUR-ELLIS CO.	FRESNO
424	24,000	-	MODERN WELDING CO.	FRESNO
425	-	-	CREATIVE MARKETING & RESEAR	FRESNO
426	-	-	AG FORMULATORS INC.	FRESNO
427	-	-	KP IRON FNDY. INC.	FRESNO
428	505	5,414	DUNCAN ENTS.	FRESNO
429	5,818	250	PETERSON PRODS.	BELMONT
430	33,470	1,120	RAYCHEM CORP.	MENLO PARK
431	248	1,770	NASA AMES RESEARCH CNTR	MOFFETT FIELD
432	20,457	-	JASCO CHEMICAL CORP.	MOUNTAIN VIEW
433	5	512	RAYTHEON CO.	MOUNTAIN VIEW
434	-	-	PERFORMEX MACHINING CO.	SAN CARLOS
435	21,375	4,415	THE GLIDDEN CO.	SOUTH SAN FRANCISC
436	2,135	10,208	SIMPSON COATINGS GROUP INC.	SOUTH SAN FRANCISC
437	750	250	NCH CORP.	SUNNYVALE
438	250	16,600	ROHM CORP.	SUNNYVALE
439	24,014	-	ADVANCED MICRO DEVICES	SUNNYVALE
440	110	730	GLIDDEN CO.	SAN FRANCISCO
441	-	-	SCHLAGE LOCK CO.	SAN FRANCISCO
442	1,000	126,000	CATALYTICA BAY VIEW INC.	EAST PALO ALTO
443	550	25,000	PERKIN-ELMER CORP.	FOSTER CITY
444	630	40	DU PONT	ANTIOCH
445	25,670	21,692	WESTERN STEEL & TINPLATE IN	ANTIOCH
446	940	100	HUNTWAY REFINING CO.	BENICIA
447	76,306	2,148	EXXON CO. USA	BENICIA
448	58,027	118,800	BALL METAL CONTAINER	FAIRFIELD
449	19,142	250	AMERICAN NATL. CAN CO.	FAIRFIELD
450	701	-	CLOROX	FAIRFIELD
451	371,040	199,290	NEW UNITED MOTOR MFG. INC.	FREMONT
452	19,000	-	SEAGATE TECH. INC.	FREMONT
453	3,739	10	BORDEN CHEMICAL INC.	FREMONT
454	32,982	17,679	CROWN CORK & SEAL CO. INC.	FREMONT
455	49,950	-	TREND CIRCUITS INC.	FREMONT
456	750	189,421	READ-RITE CORP.	FREMONT
457	250	4,100	ADVANCED DIELECTRICS INC.	FREMONT
458	5,056	50,312	UNITED CAN CO.	HAYWARD
459	12,820	6,400	UNITED CAN CO.	FULLERTON

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
473	5	67,622	NAPA PIPE CORP.	NAPA
474	4,896	10,763	AMERICAN NATL. CAN CO.	NEWARK
475	4,104	-	C & C IND.	NEWARK
476	2,245	-	C & C IND.	NEWARK
477	95	3,129	OATEY CO.	NEWARK
478	-	-	CARGILL SALT CO.	NEWARK
479	25,290	718,628	DOW CHEMICAL CO.	PITTSBURG
480	15	70,824	SIGNODE WESTERN OPS.	PITTSBURG
481	-	250	GENERAL CHEMICAL CORP.	PITTSBURG
482	-	13,100	USS-POSCO IND.	PITTSBURG
483	10	250	DEXTER CORP.	PITTSBURG
484	-	123,400	CHEMICAL & PIGMENT CO.	PITTSBURG
485	125	19,230	ACME PACKAGING CORP.	BAY POINT
486	19	2,207	HULS AMERICA INC.	PLEASANTON
487	55,221	8,042	UNOCAL SAN FRANCISCO REFY.	RODEO
488	31,392	14,686	CROWN BEVERAGE PACKAGI	SAN LEANDRO
489	4,380	54,400	SILGAN CONTAINERS CORP.	SAN LEANDRO
490	135	190	W. R. GRACE & CO.-CONN.	SAN LEANDRO
491	-	6,000	INX INTL. INK CO.	SAN LEANDRO
492	500	8,244	TRIANGLE COATINGS INC.	SAN LEANDRO
493	185,017	60,400	U.S. PIPE & FOUNDRY CO.	UNION CITY
494	20,666	250	CROWN BEVERAGE PACKAGING IN	UNION CITY
495	-	-	SIKA CORP.	UNION CITY
496	11,013	6,988	ORCON CORP.	UNION CITY
497	6,425	6,504	CALIFORNIA/WASHINGTON CAN C	OAKLAND
498	1,505	1,295	SHERWIN-WILLIAMS CO.	EMERYVILLE
499	-	-	FLECTO CO. INC.	OAKLAND
500	1,500	84,310	COURTAULDS AEROSPACE	BERKELEY
501	505	18,950	PACIFIC STEEL CASTING CO.	BERKELEY
502	-	2,375	MACAULAY FNDY. INC.	BERKELEY
503	10,171	3,211	MYERS CONTAINER CORP.	SAN PABLO
504	37,555	9,480	CHEVRON USA PRODS.	RICHMOND
505	209	61	CHEVRON RESEARCH	RICHMOND
506	-	-	CHEVRON CHEMICAL CO.	RICHMOND
507	-	-	CASTROL N.A. AUTOMOTIVE INC	RICHMOND
508	1,441	3,949	MAGRUDER COLOR CO.	RICHMOND
509	20,176	15,074	ZENECA INC.	RICHMOND
510	26,000	8,420	CHEVRON CHEMICAL CO.	RICHMOND
511	9,696	32,000	COLORSTRIP INC.	RICHMOND
512	4,632	36,160	MICROMODULE SYS. INC.	CUPERTINO
513	33,150	-	TRICAL INC.	HOLLISTER
514	40	265	PACIFIC PAC INC.	HOLLISTER
515	33,811	428,906	READ-RITE CORP.	MILPITAS
516	1,425	24,007	COOK COMPOSITES & POLYMERS	MILPITAS
517	-	-	SCOTTS/SIERRA HORTICULTRUAL	MILPITAS
518	4,345	156	TC CO.	SANTA CLARA
519	1,934	-	MARBLED ELEGANCE INC.	SANTA CLARA
520	51	287,000	ZYCON CORP.	SANTA CLARA
521	-	5	WESTERN FORGE & FLANGE CO.	SANTA CLARA
522	51,605	2,276	OWENS CORNING	SANTA CLARA
523	126	314,600	ECS REFINING	SANTA CLARA
524	1,200	17,070	ANALOG DEVICES INC.	SANTA CLARA
525	5	85,950	INTEL CORP. D2	SANTA CLARA
526	17,592	202,000	SILICON SYS. INC.	SANTA CRUZ
527	114,143	-	SALZ LEATHERS INC.	SANTA CRUZ
528	2,062	478	UNITED DEFENSE L.P.	SAN JOSE
529	1,500	-	U.S. CELLULOSE CO. INC.	SAN JOSE
530	345	5,826	CARDINAL INDL. FINISHES INC	SAN JOSE
531	4,653	-	GLASFORMS INC.	SAN JOSE
532	838,055	15,158	QUEBECOR PRINTING SAN JOSE	SAN JOSE
533	4,179	93,535	VLSI TECHNOLOGY INC.	SAN JOSE
534	4,620	21,310	HEWLETT-PACKARD CO.	SAN JOSE
535	27,844	500	QUAZITE CORP.	SAN JOSE
536	250	10,285	ANDPAK-EMA INC.	SAN JOSE
537	1,578	-	ECOLAB INC.	SAN JOSE
538	43	-	SOUTH BAY CIRCUITS INC.	SAN JOSE
539	7,240	702,404	IBM CORP.	SAN JOSE
540	29,250	500	SIGMA CIRCUITS INC.	STOCKTON
541	40,200	47,100	SILGAN CONTAINERS CORP.	STOCKTON
542	1,475	-	VIKTRON CALIFORNIA	STOCKTON
543	250	28,000	PDM STROCAL	STOCKTON
544	-	-	DANA CORP.	STOCKTON
545	71	-	HYDRITE CHEMICAL CO.	STOCKTON
546	18,000	250	HOLZ RUBBER CO. INC.	LODI
547	6,162	2,167	PACIFIC COAST PRODUCERS	LODI
548	362,000	-	CARPENTER CO.	LATHROP
549	35,641	-	MALIBU BOATS WEST INC.	MERCED
550	23,164	-	FINELINE IND. INC.	MERCED
551	28,400	10,000	NORTH AMERICAN PACKAGING CO	MERCED
552	79	68,429	MODINE WESTERN-CENTRAL PACI	MERCED
553	14,143	250	CROWN CORK & SEAL CO. INC.	MODESTO
554	396	-	FABRICATED EXTRUSION CO. IN	MODESTO
555	250	-	LAMAR TOOL & DIE CASTING	MODESTO
556	-	80,726	COLUMBIA PACIFIC	MODESTO
557	7,750	4,500	UNITED CAN CO.	OAKDALE
558	255	-	A. L. GILBERT CO.	OAKDALE
559	57,100	87,200	SILGAN CONTAINERS CORP.	RIVERBANK
560	21,780	-	CELOTEX CORP.	TRACY
561	12,000	-	AMERON CONCRETE & STEEL PIP	TRACY
562	32,664	-	VARCO PRUDEN BUILDINGS	TURLOCK
563	11,822	861	INTERNATIONAL PAPER	TURLOCK
564	500	8,160	HOSOKAWA BEPEX CORP.	SANTA ROSA
565	6,083	81	PERFORMANCE COATINGS INC.	UKIAH
566	3,599	841	GEORGIA-PACIFIC RESINS INC.	UKIAH
567	-	29	LOUISIANA-PACIFIC CORP.	UKIAH
568	3,185	1,755	STANDARD STRUCTURES INC.	WINDSOR
569	12,600	-	LOUISIANA-PACIFIC CORP.	ARCATA
570	2,420	-	HAMBRO FOREST PRODS. CO.	CRESCENT CITY
571	125,854	-	JACKSON VALLEY ENERGY L.P.	IONE
572	-	-	H. C. MUDDOX	IONE
573	18,000	-	COLLEDGEWOOD INC.	LINCOLN
574	3,423	-	GLADDING MCBEAN	LINCOLN
575	27,227	-	GEORGIA-PACIFIC WEST INC.	MARTELL
576	9,200	347,000	NEC ELECTRONICS	ROSEVILLE
577	4,578	-	FOREMOST INTERIORS INC.	RANCHO CORDOVA
578	25,000	-	SIERRAPINE LTD.	ROCKLIN
579	8,310	-	PACIFIC MDF PRODS. INC.	ROCKLIN

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

Part V

Policy Recommendations

As modern industrial society has evolved, we have developed the technology to manufacture more than 75,000 man-made chemicals, many of which are toxic to humans, wildlife, and the environment generally. Most pose risks that are incompletely characterized. Society has previously made large mistakes by failing to fully study or understand the health or environmental effects of many of these chemicals.

Government, industry, the medical community, non-governmental organizations, and the general public each has a role to play in reducing use of, and exposure to, toxic substances.

Three fundamental concepts inform our policy recommendations. They are:

1. Minimization of Chemical Use and Exposure

In order to protect workers and the community, whenever possible, exposures to synthetic chemicals should be minimized. Strategies to eliminate unnecessary use, switch to safer alternatives, and a goal of zero-discharge of toxic chemicals should inform our decision-making.

2. The Precautionary Principle

The burden of proof should be placed on the industrial producer to prove that their chemicals are safe for use, rather than on the government or the public to prove that human health is being harmed. Given the potential magnitude of the health consequences resulting from exposures to tens of thousands of industrial chemicals, this is the most health protective risk management tool.

3. Right-to-Know, Right-to-Education, Right-to-Training

All individuals have a right to know the identity and potential health risks of substances to which they are exposed. When a substance is known or suspected to pose a health threat during its life cycle, all individuals, including workers, have a right to education and training to enable them to protect their health during exposures.

We have organized specific policy recommendations into the following categories:

- Medical and Scientific Community
- Government
- Industry
- Public
- Non-Governmental, Non-Profit Community

Implementation Strategies and Specific Recommendations

Medical and Scientific

- Patient Histories on Environmental Exposures — Medical histories and intake forms for all patients of reproductive age should include detailed documentation of occupational and environmental exposures.
- Patient and Staff Education Materials — Educational materials for patients and for health care workers should be created and disseminated to medical offices, clinics, and hospitals. These may include brochures and fact sheets on reproductive and developmental hazards.
- Medical School and Continuing Education — School curricula should include more environmental health material. Currently only about 6 hours of medical school training is devoted to environmental health.[1] Health care institutions should sponsor conferences and rounds focusing on environmental health hazards and encourage use of reproductive hazard consultation services and information sources.
- Registries — Existing birth defect registries should be current, comprehensive, accessible, and useful. New registries should be developed for other reproductive and developmental outcomes, including neuro-developmental effects.
- Public Funding and Disclosure — Public funding for environmental health research should be enhanced to assure a balanced and systematic research agenda. All reports and studies should include full disclosure of

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 Safety Data Sheets (MSDS) must be revised and improved. Reliable and complete MSDSs should be readily available to workers and consumers. Potential reproductive hazards should be clearly identified. Manufacturers who provide inaccurate or incomplete MSDSs should be subject to legal action.
- Consumer Product Labeling — Consumers must be given the opportunity to make informed decisions about the products or services they purchase. Product labels should be written in plain language, identify all ingredients, and clearly state the potential health effects related to exposure.
- Interagency Cooperation — Agencies throughout local, state, and federal governments involved in risk assessment or risk management should cooperatively interact to enable a more systematic approach to data collection and regulation.
- Toxic Substances Control Act (TSCA) — This law is fundamentally flawed by requiring that the EPA Administrator show that a chemical poses an unreasonable risk to health or the environment before proposing action to control exposures. This law should be amended to require that the manufacturer address health and environmental risks before commercial production is permitted. Substantive change and aggressive enforcement is required for this law to protect the public from toxic exposures which are not regulated by other means.
- Government Procurement — Federal, state, and local governments should implement policies that encourage the purchase of non-toxic and recycled products.

Industry

- Develop and Implement Pollution Prevention Strategies — Industrial users of toxic chemicals, including chemicals associated with human reproductive disorders, should adopt policies aimed at reducing their reliance upon and use of those substances.
- Voluntary Phase-out — As a precautionary measure to protect workers, consumers, and facility neighbors, businesses should move quickly to phase out the use of reproductive toxicants, especially where safer alternatives already exist. In situations where the transition to an alternative process or chemical substance is feasible, it is irresponsible for industry to wait for government action in order to stop using chemicals that may result in harm.
- Voluntary Disclosure — Industrial facilities should fully disclose all chemical hazards, releases, and transfers (as waste or product) without waiting for a state

or federal requirement.

- Voluntary Chemical Testing – Chemical manufacturers should generate and make publicly available comprehensive acute and chronic toxicity testing for their products.
- Worker Involvement — Facility management should involve workers in the development of plans to reduce their use of toxic chemicals. Workers should be given unrestricted access to Material Safety Data Sheets (MSDS) which should be displayed where workers may review them without having to go to their supervisor. Information contained on MSDS should be complete, accurate, readable, and comprehensible.
- Elevate Environmental Staff — Staff people whose responsibilities include environmental compliance and policy development should be given high-ranking status within the decision-making apparatus of the corporation. Top-level management should be involved in the development of all major environmental polices.
- Promote Success — Businesses are encouraged to make the public aware of their successes in reducing their use of toxic substances. In addition to promoting non-toxic products and services at the retail level, manufacturers should also educate their industrial customers about the benefits of non-toxic products and materials.
- Trade Association Involvement — Industry trade associations have an important role in educating the business community. The trade associations should promote alternatives to the use of toxic chemicals among their membership.

Public

- Avoid Unnecessary Exposures to Toxicants Within the Home — While primary responsibility for reducing environmental exposures to toxic chemicals must rest with those who manufacture, use, and release those materials into the environment, individual decision-making is also important. As examples, individuals may:

  - Adjust buying habits to reduce exposure to reproductive toxicants and insist on labeling requirements that will enable them to make necessary changes.
  - Minimize use of chemical cleaners, pesticides, solvents, and solvent-based paints, strippers, and adhesives.
  - Purchase organically grown food whenever possible.
  - Have household water, paint, and garden soil tested for lead.
  - Insist on detailed chemical analysis of community water supplies and review results.

- Learn About Chemical Exposures at Work — Exposure to chemicals in the workplace may cause reproductive harm not only to workers, but also to their families who may be exposed to chemical residues on workers' skin or clothing. Employees should urge employers to investigate safer alternatives to chemicals that are known or suspected reproductive toxicants.
- Support Government Policies to Reduce Exposures and Increase Public Information — Political support for government regulations designed to reduce exposure to reproductive toxicants or increase the public's right-to-know about those chemicals will help to reduce the threat of environmentally induced reproductive disorders.
- Avoid Tobacco, Illegal or Unnecessary Drugs, and When Pregnant, Avoid Alcohol — Though this report is not intended to review the known reproductive hazards of exposure to alcohol, tobacco, or some drugs, individuals must bear in mind their own personal responsibility for behavioral choices made during reproductive years.

Non-Governmental Organizations

- Incorporate Knowledge About Reproductive Toxicants Into Existing Agenda — Information regarding the potential reproductive toxicity of chemical exposures may be incorporated into existing programs. Labor groups may use these data to advocate for safer working conditions; parent/teacher organizations may take steps to reduce toxic exposures in schools; and environmental and public health groups have a stronger basis for promoting a precautionary approach to chemical exposures.
- Support Policies to Reduce Exposures and Increase Access to Information — Non-governmental groups can be important advocates for governmental policies that may improve the lives of their membership or the public. Those organizations that get involved in the public policy arena should support policies that will minimize toxic exposures and increase the public's right-to-know about potential exposures.

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 toxic chemicals under the ToxFAQs program. Maintains on-line data base, HazDat, which contains information on hazardous waste sites and community health impacts.

Centers for Disease Control and Prevention (CDC) National Institute of Occupational Safety and Health (NIOSH) (800) 356-4674 www.cdc.gov/niosh/homepage.html NIOSH is responsible for investigating and assessing potential workplace hazards for OSHA. Call for information to obtain a health hazard evaluation of your office. NIOSH Pocket Guide to Chemical Hazards - information on 677 chemicals - one copy free, order By FAX: (513) 533-8573; E-mail: pubstaft@NIOSDT1.em.cdc.gov; or Mail: NIOSH Publications, Mailstop C-13, 4676 Columbia Parkway, Cincinnati, OH 45225.

National Library of Medicine Specialized Information Services 8600 Rockville Pike Bethesda, MD 20894 (301) 496-1131 www.nlm.nih.gov A gold mine of health, toxicological, chemical, and chemical release information accessible through MEDLARS (MEDical Literature Analysis and Retrieval System), comprised of two computer subsystems (ELHILL and TOXNET) on which reside over 40 online databases containing about 18 million references. Databases include: MEDLINE , NLM's premier bibliographic database with references from more than 3700 international biomedical journals; ChemID (Chemical Identification) and CHEMLINE (Chemical Dictionary Online); HSDB (Hazardous Substances Databank); RTECS (Registry of Toxic Effects of Chemical Substances); DART (Developmental and Reproductive Toxicology); IRIS (Integrated Risk Information System); TRI (Toxics Release Inventory); and TRIFACTS (Toxics Release Inventory Fact Sheets).

Occupational Safety and Health Administration (OSHA) U.S. Department of Labor 200 Constitution Avenue Washington, DC 20210 (202) 219-8148 www.osha.gov/ Entrusted with overseeing worker protection and is the enforcement agency for workplace environments. Works with state agencies. Web site offers information and links on programs and services, compliance assistance, standards, technical information.

REPROTOX Reproductive Toxicology Center Washington DC. (202) 293-5946 Summaries of reproductive and developmental data for chemical and physical agents.

California State Agency Sources

California Department of Pesticide Regulation, 1020 N Street, Sacramento, CA 95814-5624, (916) 445-4300, www.cdpr.ca.gov. DPR regulates all aspects of pesticide use in California. The Department maintains an excellent web site which includes information about all pesticides registered in California and has links to many other state and federal websites. DPR also oversees a County Agricultural Commissioner in each County – a good source for local pesticide use and permit information.

California Air Resources Board, 2020 L Street, P.O. Box 2815, Sacramento, CA 95812, (916) 322 2990, www.arb.ca.gov. Oversees research, monitoring, policy

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 Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65).

California State Water Resources Control Board, 901 P Street, Sacramento, CA 95812-0100, (916) 657-1247, www.swrcb.ca.gov. Responsible for regulating water quality and managing water allocation in California. Maintains a variety of databases assessing surface and groundwater quality and regulatory compliance.

California Department of Health Services, Hazard Evaluation System and Information Service (HESIS), 2151 Berkeley Way, Annex 11, 3rd Fl, Berkeley, CA 94704, (510) 540-2115. Reviews information and responds to information on the health effects of toxic substances in the workplace. HESIS also provides information on safe work practices and methods of monitoring workers health.

Nongovernmental Medical and Health Sources

American Association of Occupational Health Nurses Atlanta GA (800) 241-8014 Professional organization of occupational health nurses; educational activities; standards of care and practice.

American College of Obstetricians and Gynecologists Washington, DC. (800) 673-8444 or (202) 863-2518 Professional organization of obstetricians and gynecologists; CME; referrals.

American College of Occupational and Environmental Medicine Arlington Heights, IL (708) 228-6850 A professional organization of occupational medicine physicians.

American Lung Association National Office: 1740 Broadway New York, NY 10019-4374 (212) 315-8700 www.lungusa.org Variety of printed resources on air pollution, chemical hazards in the air.

Association of Occupational and Environmental Health Clinics (AOEC) 1010 Vermont Avenue NW #513 Washington, DC 20005 (202) 347-4976, (202) 347-4950 FAX An association of 55 clinics and 255 individual members in the U.S. and Canada specializing in occupational and environmental health issues. Provides referrals to clinics for medical advice and care; conducts educational activities, and maintains a lending library including slide shows and videotapes. occ-env-med.mc.duke.edu/oem/aoec.htm.

March of Dimes/California Birth Defects Monitoring Program, 3031 F Street, Suite 200, Sacramento, CA 95816-3844, (916) 443-0816, (916) 443-6657. A public health program devoted to finding causes of birth defects. It is funded through the California Department of Health Services and jointly operated with the March of Dimes Birth Defects Foundation.

MedWeb - Emory University Health Sciences Center Library Numerous on-line links to public and private environment and health resources. www.gen.emory.edu/MEDWEB/medweb.html.

National Institute of Child Health and Human Development 31 Center Dr., Rm. 2A32, Bethesda, MD 20892-2425 301-496-5133 www.nih.gov.nichd Supports and conducts basic clinical and epidemiological research on the reproductive, neurobiological developmental and behavioral processes.

Center for Bioenvironmental Research -Tulane 1430 Tulane Avenue, SL-3; New Orleans, Louisiana 70112; (504) 585-6910. Check out their Environmental Concepts Made Easy Home Page on Environmental Estrogens and Other Hormones. This page presents overviews, details and discussions of the scientific, public

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.

Books and Publications

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 Guide for Clinicians. Ed.: Maureen Paul. Williams & Wilkins, Baltimore, MD, 1993.

Our Stolen Future. Theo Colburn, Dianne Dumanoski, John Peterson Myers. Penguin Books, New York, NY, 1996. www.osf-facts.org Maintains a web site on endrocrine disruption linked to related sites.

Reproductive Hazards of the Workplace. Linda M. Frazier, Marvin L. Hage. Van Nostrand Reinhold, New York, NY, 1998.

(See others listed in references by chapter)

Patient Referrals – Occupational and Environmental Medicine Clinics

Occupational and Environmental Medicine Clinic, San Francisco General Hospital, 1001 Potrero Ave., Bldg 30, 5th Floor, San Francisco, CA 94110, (415) 206-4320.

Occupational and Environmental Medicine Clinic, UC Davis Medical Center, 2221 Stockton St., Primary Care Center Building, Sacramento, CA 95817 (916) 734-2715.

Center for Occupational and Environmental Health, 19722 MacArthur Blvd, Irvince, CA 92612, (714) 824-8641.

Right-to-Know, Community Action, Environmental Advocates, Workers' Rights Organizations

Bio-Integral Resource Center (BIRC) P.O. Box 7414 Berkeley, CA 94707 (510) 524-2567, (510) 524-1758 FAX www.igc.apc.org/birc/ Provides information on all aspects of environmentally-sound pest management practices.

California Public Interest Research Group, 450 Geary Street, Suite 500, San Francisco, CA 94102, (415) 292-1487, www.pirg.org CALPIRG is a non-profit, non-partisan public interest organization with over 70,000 mem-

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 cleanups, publishes Everyone's Backyard and Environmental Health Monthly.

Center for Labor Research and Education, University of California at Los Angeles, 1001 Gayley Ave, 2nd Fl, Los Angeles, CA 90024, (310) 825-9603. Offers worker training, publications, films, newsletters on health and safety issues and technical assistance in Spanish.

Children's Environmental Health Network 5900 Hollis Street, Suite E Emeryville, CA 94608 (510) 450-3818, (510) 450-3773 FAX www.cehn.org A national project dedicated to pediatric environmental health. It is the only national multi- disciplinary project whose sole purpose is to protect the health of children as it relates to environmental hazards. Three areas of concentration are education, research and policy.

Environmental and Occupational Health Sciences Institute 681 Frelinghuysen Rd/ PO Box 1179 Piscataway, NJ 08855-1179 908-445-0200 www.eohsi.rutgers.edu.

Environmental Defense Fund 257 Park Ave., South New York, NY 10010 510-658-8008 www.edf.org Maintains the “Chemical Score Card” enabling on-line users to find information quickly about facility emissions anywhere in the country. This unprecedented resource enables users to locate emissions by zip code, identify health effects of emitted chemicals and view maps of emitting facilities.
Environmental Research Foundation P.O. Box 5036 Annapolis, MD 21403 (410) 263-1584, (410) 263-8944 FAX erf@igc.org www.monitor.net/rachel/ Publishes one of the most respected environmental publications, Rachel's Environment & Health Weekly, on-line subscription available by sending e-mail to: rachel-weekly-request@world.std.com. Publication: How to Research Chemicals: A Resource Guide. 1995, an excellent guide on strategies for researching toxic chemicals and their effects.

IGC Network Institute for Global Communications Progressive Internet network includes EcoNet, WomensNet, LaborNet, ConflictNet, PeaceNet. Includes links to hundreds of progressive member organizations. www.igc.apc.org.

INFORM, Inc. 120 Wall St., 16TH Floor New York, NY 10005-4001 (212) 361-2400, (212) 361-2412 FAX www.informinc.org A nonprofit environmental research organization which has published numerous excellent publications including Preventing Industrial Toxic Hazards: A Guide for Communities and Toxics Watch 1995.

Labor Occupational Health Program (LOHP); University of California at Berkeley, School of Public Health, 2525 Channing Way, Berkeley, CA 94720, (510) 642-5507. Offers worker training, publications, films, newsletters on health and safety issues and technical assistance in Spanish.

National Coalition Against the Misuse of Pesticides (NCAMP) 701 E Street SE #200 Washington, DC 20003 (202) 543-5450, (202) 543-4791 FAX www.ncamp.org Coalition of groups working for pesticide reform. Information on alternative pest management. Pesticide Action Network of North America 116 New Montgomery, #810 San Francisco, CA 94105 (415) 541-9140, (415) 541-9253 FAX www.panna.org/panna/ Information and activism for pesticide reform.
Mothers and Others 40 W. 20th St NY, NY 10011-4211 (202) 543-5450 www.igc.org/mothers Their Green Guide gives regular information on reproductive toxicants and suggests ways to avoid them.

Pesticide Education Center San Francisco, CA (415) 391-8511 NGO that educates the public about the use and health effects of pesticides.

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).

Specific Information from Companies

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 (510) 540-3138 Fact sheets and other information on the health effects of chemicals in the workplace.

Chemtrec -(Chemical Transportation Emergency Center) (800) 262-8200. Obtain Material Safety Data Sheets (MSDS) for chemicals from companies that have registered with them and that have agreed to allow release of the MSDSs. All chemicals that have registered with Chemtrec have MSDSs available at 50 cents per page, with a $5.00 minimum.

New Jersey Department of Health and Senior Services Right-To-Know Program Cn 368 Trenton, NJ 08625-0368 (609) 984-2202 www.state.nj-us/health/eoh/rtk-web/rtkhome.htm Hazardous Substance Fact Sheets.

Part VII

Index of Chemicals