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Report to the Chairman, Committee on Governmental Affairs, U.S. Senate

October 1991

REPRODUCTIVE AND DEVELOPMENTAL TOXICANTS

Regulatory Actions Provide Uncertain Protection

GAO/PEMD-92-3

GAO
United States
General Accounting Office
Washington, D.C. 20548

Program Evaluation and
Methodology Division

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The Honorable John Glenn
Chairman, Committee on Governmental Affairs
United States Senate

Dear Mr. Chairman:

In response to your request, we are submitting a report evaluating federal regulatory actions on environmental chemicals known to cause adverse reproductive and developmental outcomes. The report identifies 30 chemicals GAO found to be of high concern because of the widespread acknowledgment of their reproductive and developmental consequences; it then examines the extent and sufficiency of the regulatory actions of four federal agencies in regard to these chemicals. Our purpose was to assist your Committee in improving federal efforts to protect the public against these preventable adverse outcomes.

As we arranged with your office, we will be sending copies of this report to the Secretary of Health and Human Services, Chairman of the Consumer Product Safety Commission, Administrator of the Environmental Protection Agency, Commissioner of the Food and Drug Administration, and Assistant Secretary for Occupational Safety and Health. We will make copies available to others upon request.

If you have any questions or would like additional information, please call me at (202) 275-1854 or Mr. Kwai-Cheung Chan, Director of Program Evaluation in Physical Systems Areas, at (202) 275-3092. Other major contributors to this report are listed in appendix VII.

Sincerely yours,

Eleanor Chelimsky
Assistant Comptroller General

Executive Summary

Purpose

The health and educability of American children is a growing concern: our infant death rate is one of the highest in the developed world; a quarter of a million U.S. babies are born with birth defects each year; and a growing number of children have basic learning disabilities. Some of these seemingly diverse problems are caused by preventable exposures to environmental chemicals such as lead or mercury. Concerned about this issue, the Chairman of the Senate Committee on Governmental Affairs asked GAO to: (1) identify the environmental chemicals that are of high concern as reproductive and developmental toxicants, (2) determine the extent to which these chemicals are regulated by the federal government, (3) assess the degree to which these regulatory actions are based on reproductive and developmental toxicity, and (4) evaluate whether the regulatory protection currently provided to the public against reproductive and developmental disease is sufficient.

Background

Generally, reproductive diseases are those that impair the ability of men or women to conceive, while adverse developmental outcomes affect the growing child from conception on. In spite of severe limitations on data, the estimates that do exist suggest a significant problem. Birth defects are the single largest attributable cause of infant mortality in the United States—accounting directly for 20 percent. Many other outcomes, such as learning disabilities, become evident only at later ages. Still other adverse effects often go unrecorded and are far more common than generally realized: an estimated 8 percent of U.S. couples are infertile and 600,000 miscarriages are diagnosed and reported each year.

Federal responsibility for protecting the public against environmental agents that cause disease is spread over many federal offices, but the entities that play the largest regulatory role are the Consumer Product Safety Commission (CPSC), Environmental Protection Agency (EPA), Food and Drug Administration (FDA), and Occupational Safety and Health Administration (OSHA).

Results in Brief

In addressing the first question, GAO discovered that no federal agency has listed chemicals known or suspected to be human reproductive and developmental toxicants. Therefore, GAO independently identified 30 environmental chemicals that are of high concern for their adverse reproductive and developmental effects.

On the second question concerning extent of regulation, all but one of the 30 chemicals had at least one regulatory action. However, two of six

major regulatory domains relevant to chemical exposure—air and consumer products—are poorly covered by regulations.[1] One source of gaps in regulatory coverage was agencies' interpretation that they lacked authority to regulate certain products.

The third congressional question asked about the degree to which regulatory actions are based on reproductive and developmental toxicity. Here, GAO found that for the study chemicals, two-thirds of the decisions are not based on reproductive and developmental toxicities.

As for the last congressional question, GAO found that the protection against reproductive and developmental toxicity afforded the public by current regulation is uncertain at best. The lack of rigor in the risk assessment decisions for the 30 chemicals GAO examined suggest insufficient protection overall for reproductive and developmental hazards. GAO concludes that protective regulation for other environmental reproductive and developmental hazards may also be insufficient.

Principal Findings

Identifying Chemicals

The list of 30 chemicals developed by GAO represent some of the most widely recognized reproductive and developmental toxicants. It serves in this study as a tool to assess the regulatory agencies' performance in protecting the public from reproductive and developmental disease. Because there is no accepted federal list of reproductive and developmental toxins, such as that generated by law for carcinogens, federal agencies have had no index of whether they have regulated the most important hazards to reproduction and development.

Extent of Regulation

By surveying 10 offices in the four primary regulatory agencies, GAO identified a set of 138 major regulatory decisions covering the 30 chemicals. Three-quarters of the decisions were made since 1979 and all but one chemical are covered by at least one regulatory action. However, upon examining the six domains for the 117 bans and standards, separately, GAO found for some chemicals there existed neither bans nor standards. The food domain has regulatory actions for about half the

[1] Based on the missions of the four agencies included in our study, GAO identified six regulatory domains relevant to chemical exposure: water, toxics (including pesticides), air, consumer products, food, and workplace.

chemicals. The domains of workplace, water, and toxics (including pesticides) have regulatory coverage for two-thirds or more of the 30 chemicals. But in the areas of air and consumer products, GAO found two-thirds of the chemicals have none. This is troublesome, given that such a well-known hazard as tobacco smoke (air domain), for example, is thus not regulated.

Basis of Regulation

When chemicals are regulated, that regulation is seldom based on reproductive and developmental toxicity. Although GAO found that only 5 of the 12 relevant laws mention reproductive and developmental disease specifically, agency officials stated that they have interpreted responsibility for reproductive and developmental disease under the general health and safety provisions.

Regulatory Protection

A number of indicators suggest that the set of major regulations in place against the 30 chemicals are of uncertain protection against reproductive and developmental disease. Agency officials judged roughly half their own standards and guidelines to be of uncertain protection against reproductive and developmental disease. Also, GAO found that agency decisionmakers examined reproductive and developmental data in fewer than half of the regulatory decisions. Several deficient practices appear to have caused this pattern, including a low priority for reproductive and developmental disease, limited reproductive and developmental data in agency data bases, and the assumption that regulation for other diseases protects against reproductive and developmental disease.

Recommendations

In light of the finding that regulation of these 30 chemicals has not consistently included consideration of reproductive and developmental toxicity, GAO recommends that the Commissioners of CPSC, Administrator of EPA, Commissioner of FDA, and Assistant Secretary for Occupational Safety and Health (1) review existing regulatory actions for the 30 chemicals to determine if they should provide greater protection against reproductive and developmental diseases than is currently the case and revise them if necessary; (2) examine toxicity data for the unregulated chemicals among the 30; (3) henceforth, perform separate analyses for reproductive and developmental outcomes in risk assessment; and (4) ensure the availability of reproductive and developmental data to decisionmakers by reorganizing office data bases. More recommendations can be found at the ends of chapters 3 and 4.

Matters for Congressional Consideration

The Congress may want to give a higher priority to protection against reproductive and developmental disease and explore the feasibility of: (1) designating an entity to prepare a periodic report on reproductive and developmental hazards, which would list the substances thought to be reproductive and developmental toxicants, and monitor federal regulatory progress in this area over time; and (2) amending existing legislation to specify authority to protect developmental, female reproductive, and male reproductive health. See chapters 3 and 4 for additional matters for consideration.

Agency Comments

At the request of the Committee, GAO did not ask for written comments. Responsible agency officials who reviewed the draft report indicated that they are concerned about their limited ability to protect against reproductive hazards and agree with the need for more attention to the area. Their most significant observations were challenges to the considerations GAO offered the Congress to authorize the federal listing of significant reproductive and developmental hazards and to amend legislation to make it more specific in regard to the protection of these diseases. They believe lists are unduly alarming to the public and misrepresent the true hazard because lists cannot distinguish among degrees of exposure. Officials indicated that specific legislative mention of reproductive and developmental disease protection would not have a strong impact on what they do in regulatory decision-making and may overemphasize one disease at the expense of others. In addition, they had technical and editorial suggestions that GAO has adopted where appropriate.

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Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFSAN	Center for Food Safety and Applied Nutrition
CPSC	Consumer Product Safety Commission
CRS	Congressional Research Service
DBCP	Dibromochloropropane
DDT	1,1,1-Trichloro-2,2-bis(p-chlorophenyl)ethane
DES	Diethylstilbestrol
EGEE	Ethylene glycol monoethyl ether
EGME	Ethylene glycol monomethyl ether
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
GAO	General Accounting Office
IRIS	Integrated Risk Information System
OAR	Office of Air and Radiation
ODW	Office of Drinking Water
OERR	Office of Emergency and Remedial Response
OPP	Office of Pesticide Programs
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste
OTS	Office of Toxic Substances
OWRS	Office of Water Regulations and Standards
PBBs	Polybrominated biphenyls
PCBs	Polychlorinated biphenyls
REPROTOX	Reproductive toxicity data base
2,4,5-T	2,4,5-Trichlorophenoxyacetic acid
TCDD	2,3,7,8-Tetrachlorodibenzo-p-dioxin

Introduction

In the late 1970s, a researcher collected the baby teeth of first and second graders in Massachusetts and noted that the children with higher lead levels in their teeth had greater deficiencies in intelligence, speech, language, attention span, and classroom performance. Eleven years later, the group with the highest lead levels were seven times more likely to drop out of school and six times more likely to have a reading disability.[1]

There have been widespread developmental consequences to children in the United States from low-level lead exposure. Ten percent of U.S. children are born with lead poisoning. In addition, these and many other children are exposed to neurologically damaging levels of lead in their everyday activities through the household paint, air, food, water, soil, and dust in their environments. Lead's effects on other aspects of human reproduction and development include the damage it can cause before birth and reduced fertility. Maternal lead exposure is associated with higher rates of preterm births and stillbirths and both male and female lead exposures have been found to reduce the ability to conceive.

Reproductive and developmental diseases have a pervasive impact on our society. In 1988, about 250,000 U.S. children were born with birth defects, 600,000 women experienced a miscarriage or fetal death, and many young children were exposed in their homes and neighborhoods to chemicals that will reduce their ability to develop the intellectual skills necessary to function in the 21st century. There is growing scientific evidence that exposure to environmental chemicals causes a broad spectrum of adverse reproductive and developmental outcomes and that they are preventable if the exposures are better controlled.

Concerned about this issue, the Chairman of the Senate Committee on Governmental Affairs asked us to review the extent and sufficiency of federal regulation of chemicals that can cause adverse reproductive and developmental outcomes. In response to this request, we identified a list of 30 environmental chemicals that were of recognized high concern as causes of reproductive and developmental diseases. We reasoned that the federal regulatory action on these chemicals would show federal performance at its best and serve as an indicator, overall, of the caliber of regulatory protection against reproductive and developmental toxicants.

[1]H.L. Needleman, et al., "The Long-Term Effects of Exposure to Low Doses of Lead in Childhood: An 11-Year Follow-up Report," New England Journal of Medicine, 322 (1990), 83-88.

Adverse Reproductive and Developmental Outcomes

The events that concern us are commonly divided into two categories: (1) those that impair the ability of men or women to conceive a child are known as male and female reproductive toxicity and (2) those that adversely affect the growth or development of a child are known as developmental toxicity. (A glossary of terms appears at the end of this report.)

Prevalence of the Problem

Estimates of the rate of birth defects in the United States range widely. The National March of Dimes estimated in 1980 that 8 percent of newborns have birth defects, and the raw numbers presented in a recent National Research Council report indicate a rate between 6 and 8 percent for the decade of the 1980s. These figures fall in the middle of the estimate range. Very poor data are at the center of the uncertainty.

Limitations on the data about reproductive and developmental disease stem from the intrinsic difficulty of diagnosis and the lack of systematic national information. Diagnosis is difficult because some physical or neurological problems are impossible to identify at birth. For example, one study found that approximately 2 to 3 percent of a group of children were diagnosed with a detectable physical or functional disorder at birth, but follow-up examination of the same children found the actual rate of disorders reach 16 percent.[2] The dearth of nationwide information further limits our knowledge about reproductive and developmental disease. At present, no systems are in place for reporting on U.S. infertility or miscarriage rates. The only nationwide data source is the birth certificate program, which is state administered and suffers from incompatible data and inconsistent funding for analysis from state to state. In spite of these limitations, the estimates we do have of U.S. reproductive and developmental disease suggest a significant problem.

Even with the uncertainties, birth defects are better understood and better counted than other reproductive and developmental diseases. The study of these malformations—called teratology—is the oldest of the reproductive and developmental sciences. About 250,000 of the 3 to 4 million U.S. children born each year in the 1980s were diagnosed with birth defects. Classic birth defects account directly for 20 percent of the U.S. infant death rate. Although the U.S. rate has declined by half since 1968, from 21.8 per 1,000 to 9.7 per 1,000 in 1989, it is still higher than that of 22 other developed countries. Ten percent of recent U.S. infant

[2]C.S. Chung and N.C. Myrianthopoulos, "Factors Affecting Risks of Congenital Malformations," The National Foundation-March of Dimes, Original Articles Series, Vol. XI, No. 10., 1975.

mortality is attributable to low birthweight caused by the mothers' cigarette smoking. Further lowering of the infant death rate will require preventive measures, including the prevention of exposure to toxic substances.[3]

Other developmental diseases far outnumber birth defects. For example, the Agency for Toxic Substances and Disease Registry of the Department of Health and Human Services estimates that up to 17 percent of U.S. children are exposed to levels of lead that may damage the brain and central nervous system. This very large estimate is based on recent research indicating that levels of lead once thought safe are not.

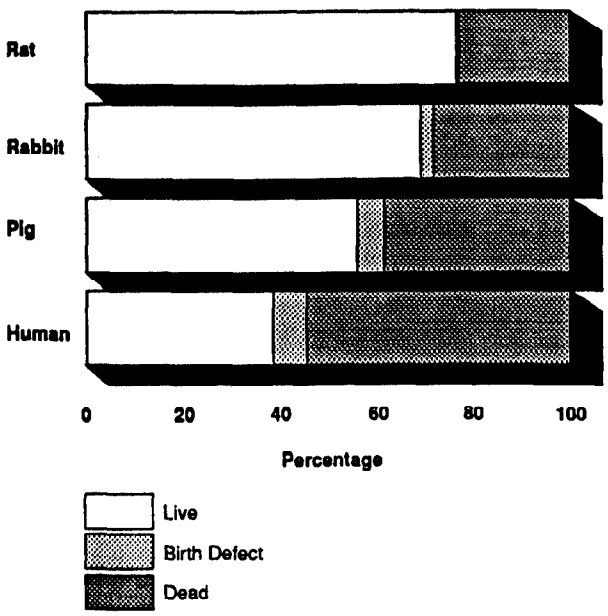
Some studies have estimated that 30 to 80 percent of human conceptions end in miscarriage. Accurate estimates are impeded by poor counts. Only a small portion of miscarriages are diagnosed, and a substantial proportion apparently go unrecognized by the mother. A recent review of studies of occupational exposures found 22 out of 41 studies positively associated reduced fertility with 26 separate environmental agents.[4]

Figure 1.1 indicates the relationships in occurrence of live births, birth defects, and estimated miscarriages for humans and for three commonly studied animals. This is necessarily a rough comparison since the animal rates are better known that the human estimated rates. However, human rates of prenatal death and of birth defects are notably higher than for the animals.

[3]Among the established human developmental toxicants are alcohol, mercury, and the drug thalidomide. Exposure to alcohol and mercury through the mother's diet during pregnancy has been shown to disturb the development of the infant's nervous system, producing lower intelligence and specific alterations in physical development. Thalidomide produced limb deformities worldwide in the offspring of the pregnant women who were prescribed it.

[4]D.D. Baird and A. Wilcox, "Effects of Occupational Exposures on the Fertility of Couples," Occupational Medicine, 1 (1986), 361-74.

Figure 1.1: Fate of Potential Offspring



Source: Adapted from A.K. Palmer, "Use of Mammalian Models in Teratology," Prevention of Physical and Mental Congenital Defects, Part A: The Scope of the Problem, M. Marois, ed. (New York: Alan R. Liss, 1985), pp. 97-106. Human data are derived from information presented in the chapter.

Some sources estimate that one in four women will experience a miscarriage. The National Research Council reported that 600,000 miscarriages are identified annually before the 20th week of gestation in addition to the 24,000 older fetuses who die before birth. These numbers, while certainly undercounts of the true prevalence, are nevertheless substantial in comparison to the roughly 3 million annual live births typical in the decade of the 1980s.

The Cause of Reproductive and Developmental Disease

The diverse nature of the proven toxicants and the serious outcomes they produce suggest that they and other suspected chemical reproductive and developmental hazards deserve serious regulatory consideration. Several hundred toxicants have been found to produce adverse reproductive effects in one or more experimental animals, but since no single animal species is a perfect predictor for effects in man, it has been

difficult to develop a protocol to identify which toxicants should be considered potential human hazards. In general, however, animal studies have good predictive value for man.

Human research linking environmental cause and disease is difficult, involving as it does, the complications of exposures to no less than the three relevant parties: the mother, the father, and the child. Not surprisingly, several of the best researched toxic agents are drugs. Two examples are thalidomide and diethylstilbestrol (DES), which caused limb deformities and cancer, respectively, in offspring. In cases of prescribed drugs, doses are often known precisely and the outcomes are dramatic and well defined. A nondrug example with a distinct outcome is DBCP, a pesticide that through occupational exposure produced absolute male infertility. By contrast, most exposures are not so easily measured as in drug research and most outcomes are not so dramatic or easily linked to an environmental agent. Thus, the well-established reproductive and developmental hazards may be only the tip of the iceberg.

The cause of most reproductive and developmental disease—more than 60 percent of it—is unknown. Only 3 percent can now be directly attributed to environmental chemicals. Better known causes are disease (such as rubella), radiation, or spontaneous mutations. However, the National Research Council believes that some of the disease with no attributable cause will be found to be environmentally induced. Thirty-seven percent of the experts we surveyed predicted between 10 and 25 percent will be found to have an environmental origin. Another 37 percent predicted that more than one-quarter of these diseases will be found to have such an origin. Since chemical exposure is probably the most preventable cause of reproductive disease, we focused on that in our evaluation.

The Federal Role

Some 15 federal agencies have mandates assigning environmental health responsibilities; however, four agencies are primarily responsible for regulating human exposure to chemicals: the Consumer Product Safety Commission (CPSC), the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA) in the Department of Health and Human Services, and the Occupational Safety and Health Administration (OSHA) in the Department of Labor.

The lack of scientific knowledge regarding reproductive and developmental toxicity presents a challenge to the development of a protective federal stance. This field has only a scant 40-year history. Data collection and understanding of the basic phenomena lag several decades

behind our specific knowledge of cancer, for example. Thus, one major obstacle to regulatory consideration of reproductive and developmental hazards is the lack of reproductive and developmental toxicity test information for most chemicals in commerce.

A second major obstacle to regulation of reproductive and developmental hazards is the continued lack of a quantitative risk assessment protocol, in spite of major efforts to develop one over the last decade.[5] For reproductive and developmental disease, as for all disease endpoints except cancer, agencies now use a less quantitative risk assessment protocol that does not make possible the estimation of numbers of cases at risk. In brief, cancer risk assessment assumes that even small amounts of a carcinogen contribute to the development of the disease. This is a non-threshold disease model. Risk assessment as currently practiced in the federal government for all other diseases, including reproductive and developmental risk assessment, makes a threshold presumption. That presumption is that theoretically there is a dose level (the threshold) below which exposure does not contribute to disease progression. Once a base dose has been established either by starting with a dose where no effects or no adverse effects were observed, the regulatory level is determined by modifying the base dose by using one or more safety factors (usually divisors of 10) to account for variation among people, the greater sensitivity presumed for humans, and so forth. Many scientists, and agency staff as well, are not comfortable with the assumptions of the protocol.[6] However, several draft risk

[5]EPA, "Proposed Amendments for the Health Assessment of Suspect Developmental Toxicants, Request for Comments, Notice," 54 Fed. Reg. 42, Mar. 6, 1989, 9385-403; "Proposed Guidelines for Assessing Female Reproductive Risk, Notice," and "Proposed Guidelines for Assessing Male Reproductive Risk and Request for Comments," 53 Fed. Reg. 126, June 30, 1988, 24833-847, and 24849-869. C.A. Kimmel, et al., "Overview of a Workshop on Quantitative Models for Developmental Toxicity Risk Assessment," Environmental Health Perspectives, 79 (1989), 209-15. B. Schwetz and R. Tyl, "Consensus Workshop on the Evaluation of Maternal and Developmental Toxicity Work Group III Report," Teratogenesis, Carcinogenesis, and Mutagenesis, 7 (1987), 221-327. D.M. Sheehan, et al., "Workshop on Risk Assessment in Reproductive and Developmental Toxicology: Addressing the Assumptions and Identifying the Research Needs," Regulatory Toxicology and Pharmacology, 10 (1989), 110-22.

[6]Several other aspects of the current risk assessment approach are in conflict with emerging knowledge about reproductive and developmental toxicity. There are well-known reproductive and developmental hazards which act like non-threshold agents. In the cases of lead and radiation, no dose has been found to be without deleterious effect. One of the differences between cancer causation and reproductive and developmental toxicity is that for the latter, single peak exposures at critical times could produce an adverse reproductive or developmental event but may appear to be of little consequence in cancer risk assessment where cumulative doses over a lifetime are calculated.

assessment guidelines proposed by EPA to improve it have yet to be finalized. The one EPA guideline for developmental risk that is final has not been implemented.[7]

Basically all four agencies offered these basic steps in the evaluation of a toxic chemical for regulatory action. First, they would look at available data for all disease endpoints. Secondly, they would pick the disease endpoint that occurs at the lowest exposure and proceed with risk assessment for it assuming regulation based on that disease would protect for all others. One result of the assumption that even small amounts of a carcinogen contributes to the disease is that cancer will usually be found to be the "most sensitive endpoint."

Understandably, agencies have regulated hazards predominantly on cancer risk, for which they have a quantitative and widely accepted protocol. As a consequence of the incomplete development of the emerging reproductive and developmental protocols, they are uncertain about how to evaluate the reproductive and developmental hazard of environmental agents.

Objectives and Scope of the Study

This report focuses on the extent and sufficiency of federal regulation of exposure to environmental chemicals that cause adverse reproductive and developmental outcomes. Specifically, we answered four questions posed to us by the Chairman of the Senate Committee on Governmental Affairs:

- What are the environmental chemicals of high concern for causing reproductive and developmental disease?
- To what extent are these chemicals regulated by the federal government?
- To what extent are the regulations based on reproductive and developmental toxicity?
- Does federal regulation for these chemicals provide sufficient protection from reproductive and developmental disease?

We conducted a broad assessment of the extent of federal efforts to prevent adverse reproductive and developmental outcomes, examining the regulatory actions of the four agencies noted above that are charged with primary responsibility for protecting people against environmental

[7]EPA published their "Guidelines for Developmental Toxicity" in 1986, but an EPA official admitted in September 1989 that not one chemical had been evaluated using them.

chemicals. In total, we studied the activities of the 10 offices in these four agencies.[8]

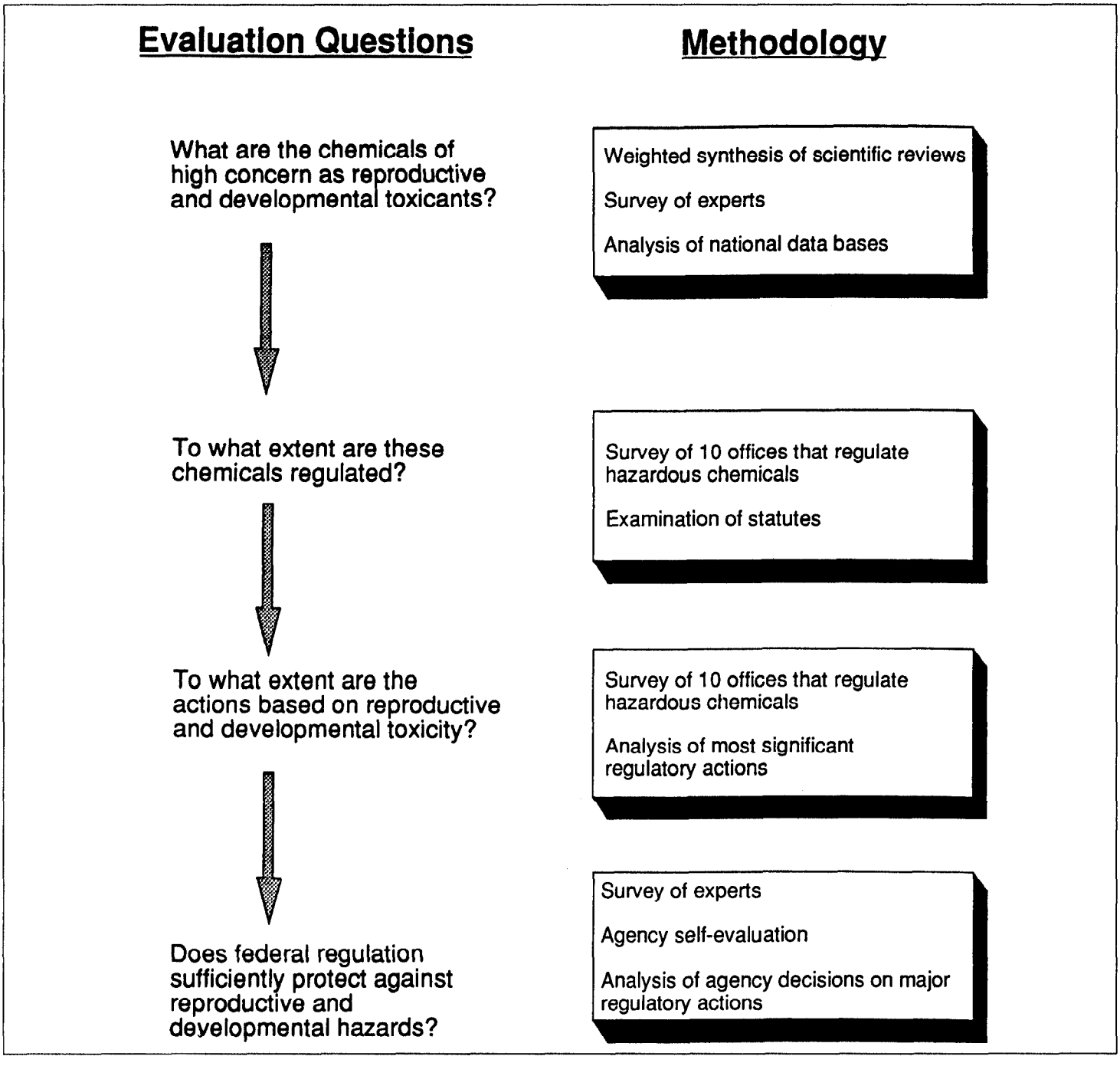
We limited our study to nondrug environmental chemicals of high concern as reproductive and developmental toxicants. While acknowledging the unknowns in the field, we derived a list of such chemicals by focusing on the consensus core of knowledge. We decided to include such compelling reproductive and developmental hazards as alcohol and tobacco smoke because they have a large impact and, yet, are often omitted from studies of both drugs and environmental exposures. We excluded from the study exposures gained through illegal personal activities such as taking cocaine.

Methodology

To answer our four evaluation questions, we used an integrated-stage design, in which the answer to the first question was used to answer the second and third, and the answers to these were used to answer the fourth. Figure 1.2 illustrates how the answers to each question set the stage for answering the next and shows the methods we used to answer each question.

[8]CPSC, FDA, and OSHA each have one office with primary responsibility for regulating environmental (nondrug) chemicals. EPA has seven offices with some regulatory responsibility for environmental chemicals. They are the Office of Air and Radiation (OAR), the Office of Drinking Water (ODW), the Office of Emergency and Remedial Response (OERR), the Office of Pesticide Programs (OPP), the Office of Solid Waste (OSW), the Office of Toxic Substances (OTS), and the Office of Water Regulations and Standards (OWRS). In a recent reorganization of the Office of Water at EPA, most of the functions of OWRS were transferred to the newly created Office of Science and Technology.

Figure 1.2: GAO Study of Federal Regulation of Reproductive and Developmental Hazards



Identifying Chemicals of High Concern

We needed to identify a list of environmental chemicals of high concern for their effects on reproduction and development that would serve as a tool in our study to demonstrate the extent and caliber of federal regulation of these hazards. To date, there is no single authoritative list of chemicals that adversely affect reproduction and development. Several organizations and individuals have proffered lists, but there is considerable disagreement among them, stemming from basic differences of professional opinion regarding the criteria for inclusion. Our needs concerned the core of information that is better known and more generally agreed upon. In acknowledgment of the disagreement, we strove for a convergence of scientific opinion, rigorously using systematic rules to extract and weigh information in each of three efforts.

As figure 1.2 shows, we derived the list of environmental chemicals of highest concern as reproductive and developmental hazards by combining the results of three separate efforts. Each of the three utilized a different approach to tapping the cumulative wisdom of the scientific field. First, we conducted a literature synthesis to determine the degree to which each of the chemicals was evaluated in recent reviews as a reproductive and developmental toxicant. Second, we conducted a survey of experts in the field. Third, we weighed the data on each chemical from two national data bases.

With the aid of methodologists, we developed a way to combine the results from our three evaluation methods. More detail on this methodology is contained in chapter 2. The list of toxicants of high concern identified by this task is provided in table 2.2.

To assess the extent of agency regulation of the chemicals of high concern, we surveyed officials at each of the 10 offices in our study. The survey asked respondents from each office to report on its general responsibility for reproductive and developmental toxicity and, specifically, on its regulatory actions vis-a-vis the 30 chemicals. This provided us with data on the 138 major regulatory actions taken on the chemicals of highest concern. Our data reflect regulatory actions in effect August 31, 1990.

To determine whether the agency regulations protect against the reproductive and developmental hazards posed by these chemicals, we examined the basis of these reported regulatory actions by using expert judgments, the agencies' own judgments, and our analysis of the decision-making process—including interviews with agency personnel and experts in the field.

Further discussion and detail of our methodology are in the appropriate chapters.

Strengths and Limitations of Our Study

Our report provides a broad view of the extent of federal regulation of environmental chemicals that are of high concern as reproductive and developmental toxicants. In addition to describing the federal regulatory structure for these chemicals, we evaluate the extent to which these regulations were based on considerations of reproductive and developmental disease.

A second strength of the study is the comprehensive way the scientific knowledge on reproductive and developmental toxicants could be cumulated to derive a list of toxicants of high concern. At the time we designed our study, we were not aware of any other that had integrated results from a literature synthesis, expert survey, and data base review to identify toxicants of high concern. More than a year into the study, we learned that the State Health Department of California also planned to employ a multi-method approach to identify and publish chemicals known to be reproductive or developmental toxicants.

We used conservative assumptions in our study design. By selecting chemicals of high concern, we have produced a list of those with the most evidence of adverse effects on reproduction and development and, therefore, the ones most likely to be regulated. Our selection process makes it unlikely that another selection of chemicals affecting reproduction and development would be more thoroughly regulated. In essence, we ensure that we do not exceed scientific knowledge in the area, but at the same time, we provide sound data upon which to base public policy decisions.

The major limitation in our study is that we do not directly assess the protection afforded by any particular federal regulation against reproductive and developmental disease. That is, we do not assess the degree of reproductive and developmental risk, if any, remaining under a standard. We do not think that would be feasible given the state of development of the risk assessment protocol. Instead, we rely on agencies' judgments regarding their own regulations, experts' judgments, and a critical examination of the agencies' regulatory decision-making process.

Another limitation is that we do not, for the most part, explore whether existing regulations are being effectively enforced. For example, a recent EPA Inspector General's study found many school water fountains

were out of compliance with EPA guidance designed to reduce the amount of lead in the water. This observation and others regarding the enforcement of the federal regulations in real-world situations falls outside our scope.

We discussed our findings with agency program officials and have included their comments where appropriate. Our evaluation was conducted between July 1989 and December 1990 in accordance with generally accepted government auditing standards.

Report Organization

In chapter 2, we introduce the 30 chemicals of high concern as reproductive and developmental toxicants that we identified. We discuss to what extent these toxicants are regulated and to what extent that regulation is based on reproductive and developmental toxicity in chapter 3. In chapter 4, we present our evaluation of the protective value of the existing regulations for these chemicals. Recommendations and matters for congressional consideration are discussed at the end of relevant chapters.

In appendix I, we reprint our survey of experts. Appendix II is a list of the experts in reproductive and developmental toxicity who responded to our sample survey. More detail about the adverse reproductive and developmental outcomes of the 30 chemicals we identified can be found in appendix III. Appendix IV is a table of all the regulatory actions reported by the four agencies in our survey on the chemicals we identified as of highest concern. Sections of the law relevant to the health protection actions covered by the 10 offices in those 4 agencies are presented in appendix V. Listed in appendix VI are the experts we consulted during the study. Major contributors to this report are listed in appendix VII.

Agents That Adversely Affect Reproduction and Development

For centuries, we have known that external agents can affect human reproduction and development. In ancient Rome, the adverse effects of lead were known. Studies linking lead to adverse reproductive and developmental outcomes were reported toward the end of the 19th century. The field of modern reproductive and developmental toxicology has taken shape in the last 40 years. A critical incident occurred in 1961 when thalidomide was found to cause serious limb defects in newborns whose mothers had taken the drug during pregnancy. This incident stimulated the study of not only the reproductive and developmental toxicity of drugs but of environmental chemicals as well. In the decades following the thalidomide incident, the number of papers published annually on reproductive and developmental toxicity have more than doubled.

In this chapter, we answer our first evaluation question, "What are the environmental chemicals of high concern for causing reproductive and developmental disease?" Our purpose was to identify a list of environmental (i.e., nondrug) chemicals to use in our evaluation of agency regulatory performance on reproductive and developmental toxicants. We begin with some definitions of terms.

Definitions

As noted above, we use the term "reproductive and developmental health" to cover not only the entire cycle of human reproduction but also later child development. The term "reproductive and developmental toxicant" means an agent that has an adverse effect on reproductive or developmental health. These broad definitions indicate that it is not only exposure during pregnancy that can be hazardous but also parental exposures before conception and children's exposures that can have adverse impacts. The field of reproductive and developmental toxicity is divided into three subfields: developmental toxicity, female reproductive toxicity, and male reproductive toxicity. Our evaluation reflects this division.

Developmental Toxicity

Developmental toxicity is defined as:

"the occurrence of adverse effects on the developing organism that may result from exposure during prenatal development or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism. The major manifestations of developmental toxicity include: (1) death

of the developing organism, (2) structural abnormality, (3) altered growth, and (4) functional deficiency."[1]

Overall, developmental toxicity is the most studied of the three subfields. Moreover, most of these efforts have concentrated on the investigation of birth defects (called teratology). These include such malformations as cleft palate, clubfoot, and spina bifida. (See the glossary.) Other examples of developmental toxicity, such as fetal death and mental retardation, are less well studied.

Female Reproductive Toxicity

Female reproductive toxicity is defined as:

"adverse effects observed in the female reproductive system that may result from exposure to chemical or physical agents. Female reproductive toxicity includes, but is not limited to, adverse effects observed in sexual behavior, onset of puberty, fertility, gestation, parturition, lactation, or premature reproductive senescence."[2]

In general, female reproductive toxicity deals with the ability of a female exposed to toxic substances to reproduce. Examples of adverse effects include alterations in the onset of puberty and menstrual irregularities.[3]

Male Reproductive Toxicity

Male reproductive toxicity is defined as:

"the occurrence of adverse effects on the male reproductive system that may result from exposure to environmental agents. The toxicity may be expressed as alterations to the male reproductive organs and/or the related endocrine system. The manifestation of such toxicity may include alteration in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of the male reproductive system."[4]

Indicators used to assess male reproductive toxicity include organ weights, histopathology of reproductive organs, and sperm count. The

[1]54 Fed. Reg. 42, Mar. 6, 1989, 9385-403. This definition depends heavily on the EPA definition cited here. However, the EPA definition also includes effects occurring because of exposure of either parent prior to conception. To keep our definitions mutually exclusive, we limited our definition of developmental toxicity to postconception exposures.

[2]53 Fed. Reg. 126, June 30, 1988, 24833-847.

[3]Accurately classifying an effect is difficult. A number of adverse reproductive outcomes can be caused by either a female reproductive effect or a developmental effect, or both.

[4]53 Fed. Reg. 126, June 30, 1988, 24849-869.

study of male reproductive toxicity is relatively recent. Traditionally, the study of reproductive and developmental toxicity has focused on associations between maternal exposure during pregnancy and birth defects in the offspring. It was only in the 1970s that it was first recognized that paternal exposure to toxicants can cause sterility, fetal loss, and birth defects.

Factors in Reproductive and Developmental Events

The definitions above suggest that there are three factors necessary for understanding an adverse reproductive or developmental outcome: the person or persons exposed, the time of the exposure, and the effect. The targeting and timing of exposures determines the classification of the effect as developmental or female or male reproductive toxicity. Developmental effects can be the result of postconception exposure of the pregnant female or postnatal exposure of the child. Female and male reproductive effects are the result of preconception exposures. The effects of toxicants can be: infertility, miscarriages, and abnormal development (including malformations and functional deficits). In table 2.1, we present this classification scheme along with examples of toxicants known to cause adverse reproductive or developmental effects in test animals or humans.

The richness of data supporting particular examples is highly variable. For instance, there are several occupational studies that support the finding that anesthetic gases can cause miscarriages. However, the evidence that exposure of males to the drug methadone can cause abnormal development of their offspring is supported only by animal data.

This range of data reflects the difficulties involved in conducting research in this field. One difficulty is that it is impossible to classify an effect as male reproductive, female reproductive, or developmental based solely on the effect caused. The results of exposures at different times can be the same. Other difficulties include the existence of high background rates of adverse reproductive and developmental events, which make it difficult to establish an excess of disease in an exposed population, and poor measures of exposure.

The best data for assessing human reproductive and developmental toxicity are human data. However, because of the difficulties involved in conducting human studies, the most common source of information about reproductive and developmental toxicities is from live animal

Table 2.1: Factors in Reproductive and Developmental Toxicity

	Exposure		Example		
Effect	**Target**	**Timing**	**Infertility**	**Miscarriage**	**Abnormal development**
Developmental	Female	Postconception	[a]	Anesthetic gases	Alcohol
				Lead	DES
					Mercury
					Thalidomide
	Child	Postnatal	[b]	[b]	Lead
					PBBs
					PCBs
Reproductive	Female	Preconception	Chlordecone	Carbon disulfide	Alcohol
			Mercury	Ethylene oxide	Ethylene oxide
			Smoking		
	Male	Preconception	Chlordecone	Chloroprene	Alcohol
			DBCP	Ethylene dibromide	Methadone
			Smoking	Lead	Vinyl chloride
				Vinyl Chloride	

[a]We did not locate any studies that addressed this possibility.

[b]By definition, these cells are empty.

tests. Overall, animal studies have good predictive value for humans. In general, the more species in which a reproductive or developmental effect is found, the more confidence we can have that a chemical will also have a reproductive or developmental effect in humans. However, no single animal species is a perfect predictor for effects found in humans. This further complicates the identification of human reproductive and developmental toxicants. In contrast to the situation for carcinogens, reproductive and developmental effects in animals are not necessarily seen as sufficient cause for concern in humans.

Identification of Reproductive and Developmental Toxicants

To carry out our evaluation, we needed a list of environmental chemicals that are compelling reproductive and developmental toxicants that we could use to evaluate agency activity. However, no federal agency is required to publish a list of known human reproductive and developmental toxicants like the one for carcinogens.[5] In this section, we describe the current federal situation and discuss efforts by organizations and individuals to identify reproductive and developmental toxicants.

[5]The 1978 amendments to the Community Mental Health Centers Act (P.L. 95-622) require that the Department of Health and Human Services prepare the Annual Report on Carcinogens, one part of which is to be a list of known or anticipated carcinogens to which a significant number of persons residing in the United States are exposed.

Federal Efforts

In 1987, the Congressional Research Service (CRS) asked eight agencies to "list all chemicals which your agency has identified as being reproductive toxicants."[6] Six of the agencies either did not respond or stated that the agency does not develop lists or identify reproductive and developmental toxicants. The Consumer Product Safety Commission reported that its staff had identified two chemicals as reproductive and developmental toxicants but then referred CRS to a 1981 document issued by the President's Council on Environmental Quality for a listing of more such toxicants. This document, which is dated and excludes postnatal exposures, cannot be viewed as a current authoritative source.

The National Institute of Environmental Health Sciences of the National Institutes of Health provided two lists to CRS, one for male and female reproductive toxicants and one for developmental toxicants. However, inclusion on these lists did not necessarily mean the chemicals were a human hazard, only that reproductively or developmentally toxic doses had been found in animal studies conducted at the Institute. The list said nothing about reproductive and developmental toxicants identified by other entities.[7]

In discussions with us, EPA officials stated that they do not develop lists of reproductive and developmental toxicants and were critical of lists developed by other entities. These statements support the views expressed by EPA respondents to the CRS survey.

State Efforts

Two states, California and Massachusetts, have undertaken efforts to identify reproductive and developmental toxicants. Both efforts have involved the examination of extant data.

In 1986, California voters passed Proposition 65, the Safe Drinking Water and Toxic Enforcement Act of 1986. One consequence of this law was the publication of two lists of chemicals, one identifying chemicals known to the state to cause reproductive or developmental toxicity and one identifying chemicals known to cause cancer. The lists must be updated at least annually. In discussions with officials in California, we

[6]In this study, the term reproductive toxicant was defined to encompass developmental, female reproductive, and male reproductive toxicants.

[7]Unpublished research, 1987.

found that nominations for the reproductive and developmental toxicant lists come primarily from their Scientific Advisory Panel. Currently, California officials are developing a more systematic method for identifying chemicals for consideration.

The law provides for the adoption of lists created by other authoritative bodies. Three institutions (the International Agency for Research on Cancer, the National Toxicology Program of the Department of Health and Human Services, and the Environmental Protection Agency) have been identified as authoritative bodies for designating carcinogens and reproductive and developmental toxicants. However, when we asked if they had identified any such lists for reproductive and developmental toxicants, California officials responded that they had not found any. The lists were for carcinogens, not reproductive and developmental toxicants.

State offices in Massachusetts have also been active in developing systematic methods to generate prioritized lists of chemicals for regulatory attention. In 1986, Brown, et al., published one of these efforts, which prioritizes air pollutants based on their reproductive and developmental hazard. As in California's exercise to develop a list, Massachusetts officials depended on a systematic assessment of existing information. In their case, the information was exclusively based on published research.[8]

Efforts by Individual Researchers

Various efforts by individual researchers have produced rather divergent lists depending on the interests of the author and their use of extant data. Many of the lists are limited to a particular subfield of reproductive and developmental toxicity. It is typical for an author to limit himself to either developmental, female reproductive, or male reproductive toxicants. It is not unusual for the limitations to be even greater, such as addressing only teratogenic agents. Although these lists are useful for understanding particular aspects of reproductive and developmental toxicity, they do not by themselves provide an examination of the entire field.

Authors also differ in how they treat evidence. Some authors only use animal evidence to buttress the human data. Others allow animal data

[8]Halina Szejnwald Brown, et al., "A Methodology for Assessing Developmental and Reproductive Hazards of Chemicals," Toxicology and Industrial Health, 2 (1986), 183-203.

alone to suggest the possibility of human reproductive and developmental toxicity. Since there are no universally accepted standards for determining human reproductive and developmental toxicity, authors set their own, often unstated, criteria.

Derivation of the List of Toxicants

Based on the evidence discussed in the previous section, we concluded that no authoritative list of reproductive and developmental toxicants currently exists in the United States. Therefore, to conduct our evaluation, we had to develop a list of environmental chemicals that affect reproduction and development. Our intent was not to be comprehensive, but rather to develop a list of toxicants for which consensus exists on their adverse reproductive and developmental effects. These could then be used to evaluate agency activity. We do not claim that these are the toxicants of greatest reproductive and developmental concern, only that there is some consensus that they are, in fact, reproductive and developmental toxicants.

The basis for our list was the work done by private researchers and state officials who reviewed and weighed the scientific evidence as they produced their own lists. To identify the environmental chemicals of high reproductive and developmental concern, we first developed a list of nominees from recent scientific review literature. We used only reviews published in the 1980s. Further, we selected only reviews that covered at least a subfield and that listed all of the substances within the subfield believed by the author to be toxicants. Over 300 environmental chemicals were mentioned as potential reproductive and developmental hazards. We reduced this list to the 72 chemicals that were mentioned in at least 25 percent of the reviews for one or more of the three disease categories (i.e., developmental, female reproductive, and male reproductive toxicity). Our 25-percent criterion ensured the existence of some agreement on the reproductive and developmental toxicity of these chemicals.

These 72 chemicals were used as the basis for the multi-method effort to develop our final list of toxicants of reproductive and developmental concern. To derive our final list, we (1) conducted a literature synthesis to determine the strength with which each of the 72 nominated chemicals was evaluated as a reproductive and developmental toxicant, (2) conducted a survey of experts in the field to determine their level of concern for the 72, and (3) analyzed data on each of the 72 chemicals from two national data bases.

We used a complex methodology, combining the results of the above three efforts, because we found that no two individual sources employed the same criteria for determining human reproductive and developmental toxicants and no two sources listed the same chemicals. Since we were, above all, interested in consensus regarding the reproductive and developmental toxicity of the chemicals in whatever list we developed, we employed a technique that combined the results of different methods. This produced a list most likely to reflect a consensus of opinion in the fields that contribute to reproductive and developmental toxicology.

We examined 24 review articles (listed in the bibliography) on reproductive and developmental toxicants published during the 1980s that met our criteria, including the California effort. We determined the level of concern expressed in each article for each of the 72 nominated chemicals as a reproductive and developmental toxicant.[9] For example, a chemical was rated as being of high concern if the author categorized it as a known human reproductive or developmental toxicant. In cases where the author did not specify the degree of support for a chemical as a reproductive and developmental toxicant, we calculated the level of concern based on the type of human data cited and the number of species in which there were indications of adverse reproductive and developmental outcomes. These results were then combined to form an overall assessment of concern. This yielded a rank-ordered list of chemicals for which the scientific literature indicated from high to little concern.[10]

To obtain the views of experts in the field, we developed a questionnaire and sent it to a random sample of 56 (of a universe of 173). Our sample was drawn from presenters and workshop leaders at major scientific conferences or workshops on hazards to reproduction and development in the last half of the decade (1985-89). We believe the respondents represent the most active scientists in the field. (See appendix II for a list of the respondents.)

[9]Level of concern was determined only for the health outcomes for which a chemical satisfied the 25-percent criterion. For example, if a chemical was nominated only as a male reproductive toxicant, a concern level was calculated only for it being a male reproductive toxicant. Concern levels were not determined for its developmental and female reproductive toxicity.

[10]Each of our methods yielded three lists of chemicals rank-ordered for degree of concern for the chemical as a developmental, female reproductive, or male reproductive toxicant.

In an initial telephone call, we verified that each of the participants was an expert in either the epidemiology, medicine, or toxicology of reproductive and developmental disease and secured their cooperation in the survey. Later, those who could not participate for a cause that fell within our definition of a "true mortality" were replaced by an oversampling technique. Respondents were asked to indicate on a three-point scale the degree of concern they had for each of the 72 chemicals nominated by the reviews as reproductive and developmental hazards. We averaged the concern expressed for a particular chemical and outcome category across respondents to determine experts' overall concern. For example, the chemical DBCP, a male sterilant, averaged a concern level of 2.8 out of a possible 3 for male reproductive toxicity. This exercise also resulted in three rank-ordered lists of chemicals, one each for developmental, female reproductive, and male reproductive toxicity. Based on the 89-percent response rate, we believe the answers represent the universe of all experts sampled, within ± 10 percent of the values we report.

We obtained reproductive and developmental toxicity information on the 72 nominated chemicals from two national data bases, the Hazardous Substances Data Bank and REPROTOX.[11] For each of the 72 chemicals, we recorded information about its reproductive and developmental toxicity, including the number of species in which adverse effects have been found, dose levels at which these effects were detected, and for human studies, the type of study (e.g., epidemiological or case study). We developed a formula to weigh the evidence for a chemical being a reproductive or developmental toxicant.[12] This process resulted in a list rank-ordered by the amount of evidence for the chemicals as reproductive or developmental toxicants.

We asked methodologists outside of GAO to help us develop a way to combine the results from the three methods. At this point, we had three lists of chemicals (developmental as well as female and male reproductive toxicants) from each of our three methods (literature synthesis, expert survey, and data base examination). The consultants, listed in appendix VI, recommended that we place more weight on the results of the expert survey as it was the most current and complete of the three

[11]The Hazardous Substances Data Bank is a peer-reviewed data base maintained by the National Library of Medicine. REPROTOX is maintained by the Columbia Hospital for Women, Washington, D.C. Both data bases are intended for a wide variety of users.

[12]The sources for our formula were Brown (1986); "Guidelines for Mutagenicity Risk Assessment," 51 Fed. Reg. 185, Sept. 24, 1986, 34005-012; and Frederick R. Jelovsek, et al., "Eliciting Principles of Hazard Identification From Experts," Teratology, 42 (1990), 521-33.

methods. Any chemical that received an average rating of moderate or greater concern from the experts was put on the final list. This rule generated a list of 30 chemicals of high concern. We found no other chemicals besides these 30 that were nominated by the other two methods. We are confident that the 30 chemicals developed by this means are a group with highly adverse effects on reproductive and developmental health. Our confidence is buttressed by the high degree of concurrence among the three methods.

The list of chemicals of concern for their reproductive and developmental effects includes agricultural chemicals, industrial chemicals, metals, natural food components, and potential food contaminants as well as several chemicals, such as alcohol, that are used in personal habits. All of the chemicals have other serious toxicities in addition to the adverse reproductive and developmental effects that secured their place on our list.

In table 2.2, we list alphabetically and briefly describe each of the 30 environmental chemicals used in this evaluation. The information provided for each chemical is: the adverse reproductive and developmental effects for which high concern was found in our study, other selected health effects, type of substance, selected uses, and selected manufacturing and trade information. Complete information was not available for all of the chemicals. Manufacturing and trade information are imperfect proxies for what is really of interest—the actual levels of exposure. Exposure levels can be higher than that indicated by production and trade data if, for instance, the substance remains in the environment after it is used or if it occurs naturally. In both cases, annual production or trade data represent only a portion of the true exposure potential. Nonetheless, production data frequently constitute the only information available and are often used when describing and ranking the potential risk of chemicals.

Table 2.2: Chemicals of Concern as Reproductive and Developmental Toxicants

Chemical	Reproductive and developmental effect[a]	Other selected health effect	Substance	Selected use	U.S. production[b]
Alcohol[c]	Developmental, male	Acute toxicity, heart, liver	Drink, fuel, industrial chemical	Drink, fuel, solvent	543 million gal in 1984
Arsenic	Developmental	Acute toxicity, cancer, kidney, neurotoxicity	Metal	Metallurgy, wood preservative	61.7 million lb imported in 1986
Cadmium	Developmental, male	Acute toxicity, cancer, kidney	Metal	Solder, electroplating	2.9 million lb in 1986
Carbon disulfide	Developmental, female, male	Eye, kidney, liver, neurotoxicity	Industrial chemical	Fumigant, insecticide, solvent	315.3 million lb in 1985
Carbon monoxide	Developmental	Acute toxicity, brain, heart	Combustion product	Metallurgy, in car exhaust, tobacco smoke	20,000 lb in 1982
Chlordecone	Developmental, female, male	Cancer, liver	Pesticide	Fungicide, insecticide	None
Chloroprene	Male	Acute toxicity, heart, respiratory	Industrial chemical	Rubber manufacturing	284.4 million lb in 1981
DDT	Developmental, female	Acute toxicity, cancer, liver, neurotoxicity	Pesticide	Insecticide	668,000 lb exported in 1985
DBCP	Female, male	Cancer, neurotoxicity	Pesticide	Soil fumigant, nematocide	None
DES	Developmental, female	Cancer	Human, animal drug	Animal growth promoter, food contaminant	343 lb imported in 1983
Ethylene dibromide	Female, male	Cancer, liver, lung, skin	Industrial chemical, pesticide	Fumigant, solvent	170 million lb in 1982
EGEE	Developmental, female, male	Kidney, neurotoxicity	Industrial chemical	Solvent, in varnish removers, cleaners	178.4 million lb in 1982
EGME	Female, male	Bone, kidney, liver, lung	Industrial chemical	Solvent, in cellophane, enamels	83.3 million lb in 1985
Ethylene oxide	Female, male	Acute toxicity, cancer, neurotoxicity	Industrial chemical, pesticide	Chemical manufacturing, fumigant, sterilant	5.32 billion lb in 1989
Gossypol	Male	Gastrointestinal, lung	Natural product	Stabilizer for vinyl polymers, food contaminant	
Hexachlorobenzene	Developmental, female	Cancer, liver, skin	Industrial chemical, pesticide	Fungicide, industrial waste	7,716 to 25,353 lb est. by-product of chlorinated solvents in 1984
Lead	Developmental, female, male	Acute toxicity, neurotoxicity	Metal	Batteries, construction material	2.8 billion lb in 1986
Lithium	Developmental	Acute toxicity, neurotoxicity	Metal	Drug, in fire extinguishers	600,000 lb imported in 1985

(continued)

Chemical	Reproductive and developmental effect[a]	Other selected health effect	Substance	Selected use	U.S. production[b]
Mercury	Developmental, female, male	Acute toxicity, kidney, immunotoxicity	Metal	Fungicide, in thermometers, pulp and paper manufacturing	7.7 million lb in 1986
Mirex	Female	Acute toxicity, cancer	Pesticide	Insecticide, fire retardant	717,871 lb exported March-May 1990
Nicotine	Developmental	Acute toxicity, eye	Natural product, pesticide	Fumigant, insecticide, in tobacco	485,000 lb imported in 1984
PBBs	Developmental, female	Cancer, neurotoxicity, skeletal, skin	Industrial chemical	Fire retardant, coating, lacquer	None
PCBs	Developmental, female	Cancer, liver, neurotoxicity, skin	Industrial chemical	In electrical transformers, plasticizers	None
2,4,5-T	Developmental	Gastrointestinal, skin	Pesticide	Herbicide	306,000 lb imported in 1982
TCDD	Developmental, female	Cancer, liver, neurotoxicity	Industrial chemical	Incineration by-product, pesticide contaminant	Undesirable by-product in some industrial processes
Tobacco smoke[d]	Developmental, male	Cancer, cardiovascular			
Toluene	Developmental, female	Acute toxicity, liver, renal	Industrial chemical	Gasoline additive, solvent	5.84 billion lb in 1989
Vinyl chloride	Developmental, female, male	Acute toxicity, cancer, liver, neurotoxicity	Industrial chemical	In plastics industry, glass, paper	9.62 billion lb in 1989
Vitamin A	Developmental	Acute toxicity, liver, neurotoxicity	Natural product, drug	Medication	2 million lb of synthetic retinol in 1985
Warfarin	Developmental	Hemorrhage, liver	Pesticide, drug	Rodenticide, drug	5,004 lb in 1982

[a]The reproductive and developmental effects listed are those for which high concern was found in our study. There may be other reproductive and developmental effects. A more detailed description of the reproductive and developmental effects of each chemical is given in appendix III.

[b]U.S. production and trade data may be incomplete.

[c]Alcohol refers only to ethyl alcohol.

[d]This does not include environmental tobacco smoke.

Summary

In this chapter, we answered the first evaluation question, "What are the environmental chemicals of high concern for causing reproductive and developmental disease?" Despite the lack of an authoritative federal source, we built on the efforts of state governments and individual researchers to develop a consensus list of 30 reproductive and developmental toxicants. This effort was based on a combination of three tasks: a literature synthesis, a survey of experts in the field, and an examination of two data bases. The reproductive and developmental health

effects vary among the chemicals. All of the chemicals have serious toxicities in addition to reproductive and developmental toxicity.

Matters for Congressional Consideration

This chapter has presented a finding that federal entities do not identify reproductive and developmental hazards for regulatory consideration. The Congress might consider designating an office with the responsibility for preparing a periodic report on reproductive and developmental hazards. This report would list, much as is done for carcinogens, the substances reasonably thought to be reproductive and developmental hazards to which a significant number of people in the United States are exposed. The same entity could, at regular intervals, describe regulatory actions on the substances and evaluate how much those actions have reduced the risks of exposure.

We believe that a listing effort at the federal level could stimulate regulatory attention to the problem and serve as an index of regulatory accomplishment. Such a list would allow the public, responsible agencies, and the Congress to focus on chemicals for which action may be necessary. Listing of reproductive and developmental toxicants has performed such a function in California. Listing would also provide a means for assessing federal regulatory agency protection against major agents with adverse reproductive and developmental potential.

Agency Comments and Our Response

Agency officials objected to the suggestion above that a federal listing process be considered. They assert that lists are not detailed enough to be useful for regulation, they may misinform, be misused, or even unduly alarm women into unnecessary abortions. In addition, at least one agency felt the 30 chemicals resulting from our investigation were not adequate to fully reveal their program.

While we appreciate their concern for the importance of quantification of exposures, and the role age, gender, and physiological state of the individual may play in reproductive and developmental disease, we continue to believe that a listing process would help to focus agency attention on the problem and, hence, stimulate regulatory protection.

Extent of Federal Regulation of Reproductive and Developmental Hazards

Recently, the administration announced a comprehensive $1 billion plan to cleanse the environment of toxic levels of lead, with the goal of preventing physical and mental retardation for millions of children. The effort, as planned, involves three major agencies in an effort to clean up the several pathways through which lead reaches children; that is, lead-based paint in older homes and contaminated soil and water sources. Clearly, for the reproductive and developmental risk of lead, the responsible agencies have decided to act decisively. We wondered if this level of commitment represented regulatory action generally on chemicals of high concern as reproductive and developmental toxicants.

In this chapter, we answer our second and third evaluation questions: (1) to what extent are these chemicals regulated by the federal government and (2) to what extent are the regulatory actions based on reproductive and developmental toxicity? After a brief discussion of the methods we used, we describe the extent of regulation of the chemicals we identified, highlighting the chemicals and the regulatory domains that appear to have received more or less regulatory attention. We then discuss the decision basis for the regulatory actions reported, distinguishing between those based on reproductive and developmental disease outcomes versus those that are not. Finally, as a partial explanation for the patterns we found, we present the legal context for the regulation of chemicals of reproductive and developmental concern.

Methodology

We surveyed the four agencies (including 10 offices) with primary responsibility for protecting the public against health-threatening exposures to environmental chemicals. Each of the 10 offices in our study completed a questionnaire for every one of the chemicals we identified as of high concern. The first part of the survey asked which legal mandates the office operates under and the office's position regarding its responsibility for protecting against reproductive and developmental toxicants. The second part of the survey asked each office to report on its regulatory actions on the 30 chemicals. In the cases where offices had taken several actions, we asked them to provide information on the most recent action with the greatest regulatory impact.

The information on the questionnaires and follow-up interviews provided us with a data base of the 138 most prominent federal regulatory actions taken on these 30 chemicals. In processing the completed questionnaires, we assessed the internal consistency of answers and reviewed documents such as the Federal Register and publications of federal and private entities to assess the validity of the answers. In over

half the cases where agency officials reported a major regulatory action, we followed up with them to clarify or revise the information.

Regulation of Reproductive and Developmental Chemicals

The agencies reported taking 138 major regulatory actions on our list of 30 chemicals. These actions consisted of (1) 20 cases of banning use of the chemical, such as cancellation of the uses of the pesticide DDT, (2) 97 cases of setting numerical standards or restrictions on the chemical, such as setting maximum levels of arsenic allowed in drinking water, and (3) 21 cases of establishing guidelines, such as the levels of mercury in fish that FDA guidance allows. We asked the agencies to report only on the most significant regulation they took on each chemical; thus, the set of actions represents the major federal structure of regulation for the chemicals we identified.[1]

The regulatory actions within this set represent a spectrum of actions, frequently designed to mitigate disease resulting from environmental exposures. They range from complete control of a chemical via banning, though moderate control via standards, to weak control via guidelines. While true within limits, this impression can be misleading.

Seventeen of the 30 chemicals we identified as of high reproductive and developmental concern have one or more federal bans imposed on them. Although it seems counterintuitive, a ban does not necessarily mean that a chemical is comprehensively regulated or eliminated from the environment. Arsenic, for example, has two bans. In 1984, the Consumer Product Safety Commission banned the contents of particular Easter baskets that had been preserved with arsenic. The ban is product specific—it does not protect the public from exposure to arsenic in the general environment. The EPA Office of Pesticide Programs issued a partial ban on arsenic for certain "non-wood" pesticidal uses in 1988, making exceptions for uses on ants and rodents, okra, cotton, and grapes. In addition, all "pressure-treated wood" uses of arsenical pesticides remain legal, although they must meet labeling restrictions.

[1]The set is not the entire structure. We asked offices for their major action; whereas, an office may have taken more than one. In 38 additional cases, offices reported actions other than standards, bans, or guidelines as their action with the greatest impact. In particular, CPSC reported a number of label requirements and FDA, several enforcement actions. We do not focus in this report on these actions. (See a complete presentation of regulatory actions by type of action and the office that proposed them in appendix IV.)

Clearly, even multiple bans by several federal offices, as reported here, cannot be taken to mean the chemical is comprehensively regulated. Several of the 20 bans reported to us should not necessarily be interpreted as indicative of comprehensive protection, even within the mission of the office. (Note our discussion later in this chapter of the missions of the offices.)

The most common type of major regulatory action reported, the standard, is an attempt to limit the amount of exposure to a chemical to the level below which the health consequences are understood as acceptable, while still allowing its use. The Occupational Safety and Health Act makes this clear:

" 'occupational safety and health standard' means a standard which requires conditions, or the adoption or use of one or more practices, means, methods, operations, or processes, reasonably necessary or appropriate to provide safe or healthful employment and places of employment."[2]

Guidelines are suggested numeric limits, without the force of law. The guidelines presented by the two federal water offices that use them most frequently have great influence on state-level decisions.

The Extent of Regulation of Chemicals

All but one of the 30 chemicals we identified are covered by one or more major regulatory actions. Two-thirds (20) of the chemicals are covered by at least four actions. Toluene, vinyl chloride, PCBs, and the heavy metals lead, arsenic, mercury, and cadmium were covered by seven or more actions. However, with regard to the enforceable actions (standards or bans), 11 of the 30 chemicals are covered by 3 actions or less.

In table 3.1, we show the type and number of major regulatory actions taken for each of our 30 chemicals. (See appendix IV for more detail on the type and number of actions reported by each office.)

[2]P.L. 91-596, section 3(8), Dec. 29, 1970.

Table 3.1: Major Federal Activities Reported for Chemicals of High Concern

Chemical	Type of regulation			Total
	Guideline	Standard	Ban	
Alcohol		2		2
Arsenic	1	6	2	9
Cadmium	2	4	1	7
Carbon disulfide		4	1	5
Carbon monoxide		4		4
Chlordecone		2	1	3
Chloroprene		2		2
DDT	1	3	1	5
DBCP	1	3	1	5
DES		3	1	4
Ethylene dibromide	1	3	1	5
EGEE		4	1	5
EGME		1	1	2
Ethylene oxide		5		5
Gossypol		1		1
Hexachlorobenzene	2	2	1	5
Lead	1	6	2	9
Lithium		3		3
Mercury	2	5	1	8
Mirex	1		1	2
Nicotine		4		4
PBBs		1		1
PCBs	2	5	1	8
2,4,5-T	2	3	1	6
TCDD	2	4		6
Tobacco smoke				0
Toluene	2	5		7
Vinyl chloride	1	5	2	8
Vitamin A		2		2
Warfarin		5		5
Total	**21**	**97**	**20**	**138**

Vintage of the Regulatory Actions

Seventy-one percent of the decisions were made since 1980, but some of the earlier ones are 15 to 50 years old. Generally, for regulations reported from CPSC, FDA, and OSHA, more than half were decided before 1980. For EPA the regulations are on average newer, with 80 percent decided in the last decade.

The Extent of Regulation Over Regulatory Domains

The regulatory domains the 10 offices are assigned by law to regulate are: water, toxics (including pesticides), air, consumer products, food, and workplace. To understand whether there were regulatory actions to protect the public against the 30 chemicals in these domains, we examined only bans and standards reported to us; that is, only the 117 regulatory actions enforceable by law. We focused on gross patterns of regulation, or lack thereof, in the six domains covered.

Of the six regulatory domains, five are media or product specific. Four offices within EPA are responsible for preserving clean water: the Office of Water Regulations and Standards (OWRS), the Office of Drinking Water (ODW), the Office of Emergency and Remedial Response (OERR), and the Office of Solid Waste (OSW). Water contamination is a concern for the latter two in the control of hazardous waste and spills. EPA's Office of Toxic Substances (OTS) and Office of Pesticide Programs (OPP) share responsibility for toxics (and pesticides).[3] The remaining four domains are primarily the responsibility of one office each; that is, EPA's Office of Air and Radiation (OAR) for air, the Consumer Product Safety Commission (CPSC) for consumer products, the Center for Food Safety and Applied Nutrition (CFSAN) at FDA for food, and the Occupational Safety and Health Administration (OSHA) for the workplace. (See table 3.2.)

The actual hazard posed by the 30 chemicals depends on factors outside the scope of this study, such as the extent and magnitude of exposures. However, by using surrogate indices frequently used by the agencies themselves, we have established that the presence of most of the 30 chemicals in our environment is likely. We used the indices of production volumes and public concern as evidenced in the press. Public concern is regularly and recently to be found for many of these toxicants in the national press.[4] In chapter 2, we presented U.S. production data for all but 2 of the 30 chemicals. (See table 2.2.)

[3]The regulatory domain of EPA's Office of Pesticide Programs (OPP) partially crosscuts other media or products. OPP is responsible for pesticides in the home and for pesticide applicators, and it has a role in food safety. Put simply, OPP registers pesticides for use and sets the levels of a pesticide allowed in food. FDA has the complementary role of monitoring and enforcing to ensure those levels are not exceeded. Here, we have recorded OPP activities (bans and standards) in the "toxics" column and have not repeated it in the others. For more detail on the roles of FDA and EPA in food safety, please see two recent GAO reports, Food Safety and Quality: Who Does What in the Federal Government, Vols. A and B (GAO/RCED-91-19A and GAO/RCED-91-19B, Dec. 21, 1990).

[4]Recent headlines report concern over the effects of exposures to lead, mercury, TCDD, PCBs, DDT, cadmium, tobacco smoke, and alcohol. The extent of exposure to toxic environmental chemicals, including those that have adverse reproductive outcomes, is a matter about which agencies may know little. For example, the Office of Drinking Water reported that 11 of our chemicals "have not been found" in drinking water, but that the Office is "not collecting data at the present time." Yet, they anticipate the possibility of contamination of drinking water by searching for case reports of drinking or surface water contamination here and abroad and postulate that most items in commerce could be spilled into water.

Table 3.2: The Extent of Regulation of Regulatory Domains by Chemicals of High Concern for Reproductive and Developmental Health[a]

	Domain					
Chemical	Water[b]	Toxics[c]	Air[d]	Consumer products[e]	Food[f]	Work[g]
Alcohol					X	X
Arsenic	XXX	X	X	X	X	X
Cadmium	XXX	X				X
Carbon disulfide	XX	X			X	X
Carbon monoxide			X	X	X	X
Chlordecone	XX	X				
Chloroprene	X					X
DDT	XX	X				X
DBCP	XX	X				X
DES	XX			X	X	
Ethylene dibromide	XX	X				X
EGEE	XX	X			X	X
EGME		X				X
Ethylene oxide	XX	X			X	X
Gossypol					X	
Hexachlorobenzene	XX	X				
Lead	XXX	X	X	X	X	X
Lithium				X	X	X
Mercury	XXX	X	X			X
Mirex		X				
Nicotine	XX	X				X
PBBs		X				
PCBs	XX	XX			X	X
2,4,5-T	XX	X				X
TCDD	XX	X			X	
Tobacco smoke						
Toluene	XX			X	X	X
Vinyl chloride	XXX	X	X	X		X
Vitamin A				X	X	
Warfarin	XX	X		X		X

[a]The total number of bans and standards is 117. Multiple Xs indicate a major regulation from more than one office.

[b]The water pathway regulations include those reported to us by ODW, OWRS, OSW, and OERR.

[c]The toxics pathway regulations include those reported to us by OTS and OPP, which may have set limits on the amount of pesticides that can occur in food or specified labels for pesticides used as consumer products, although not necessarily for this list of 30 chemicals.

[d]The air pathway regulations include only those reported to us by OAR.

[e]The consumer products regulations include only those reported to us by CPSC.

[f]The food regulations include only those reported to us by CFSAN.

[g]The workplace regulations include only those reported to us by OSHA.

Spills and contamination of water are possible for any chemical produced, stored, or used in the United States. Once released into the environment, chemicals are transported by natural geological cycles and food chains. Pesticides, for example, have been found to migrate by air and rainfall to locations distant from the point of application. In a very few cases, the possibility of exposure seems remote; for example, DES and vitamin A in air.

Several of the 30 chemicals break down very slowly, and as a consequence, are "persistent" in the environment. Exposures to DDT, PCBs, and hexachlorobenzene, for example, begin transplacentally before birth and continue through breast-feeding, and indeed throughout life. Even the 16 pesticides with one or more canceled uses in this country may be manufactured or formulated here, or imported or exported. This suggests exposures are possible to Americans in their workplaces and through accidental releases or normal transport, through water and air, or through imported products from countries where they are legal for use. (See table 2.2.)

The Air and Consumer Product Domains

Table 3.2 shows that, overall, the Office of Air and Radiation and the Consumer Product Safety Commission reported regulations for less than two-thirds of the 30 chemicals. These pathways have the potential of exposing large numbers of the public as they live and work breathing indoor and outdoor air and using consumer products in the home, office, and school.

The OAR reported only 5 regulations for the 30 chemicals of high reproductive and developmental concern and acknowledged they have not considered reproductive and developmental disease a priority. They considered six of our chemicals to fall outside their mandate; however, that still leaves 19 chemicals within their mandate that they have not regulated. In the 1990 revisions to the Clean Air Act, the Congress specified 190 chemicals and chemical compounds as air pollutants. Fifteen of these were on the list of chemicals used in our study.

Conversely, the Consumer Product Safety Commission reported no lower priority for reproductive and developmental disease. Although they have taken only 9 major actions on our list of 30 chemicals, CPSC's authority is exercised on a case-by-case postmarket basis. They appear to have taken some action on the majority of the 30 chemicals which are under their authority. They indicated 12 of the chemicals are not under

their authority.[5] In the remaining nine cases, they have three instances of labeling and single instances of enforcement and education. They have not regulated the other four either because they have not found the chemical in consumer products or they believe consumer exposure presents no health risk.

The Food Domain

Like consumer products, food has a major potential impact because of the numbers of people involved. The FDA's Center for Food Safety and Applied Nutrition has set standards or bans for toxicants in food for less than half of the 30 chemicals. They reported 13 standards and 1 ban. Their standard-setting is primarily exercised in premarket approval of deliberate food additives or contamination resulting from the manufacturing process, such as the inclusion of minute quantities of sanitizing solution. Since our list contains many well-known toxicants, it is not surprising to find that food manufacturers have not applied to include many of them in their products. FDA told us that for well-known toxicants such as these, their enforcement actions would play a large role.

The Center is responsible for enforcing the food adulteration provisions of the Federal Food, Drug, and Cosmetic Act. Under it, FDA can take action without having to promulgate a standard or a ban if they find a substance that renders food injurious to health.[6] One important example of this role is enforcing the limits that EPA sets for pesticides on food. If there is no allowed limit, as in the case of warfarin, any amount found in food is an adulterant. But pesticide levels found on food within the tolerance levels EPA sets are treated as food additives by FDA. They reported past enforcement activities on seven pesticides in foods (monitoring or seizure), but also informed us that they will no longer routinely monitor for several of these.[7] They report never having monitored for other chemicals on our list. Since much U.S. food is imported, and foreign farmers are under no obligation to obey EPA bans, this constitutes a potential gap in regulatory protection.

[5]Nine of these are pesticides that they are expressly excluded from dealing with under law. The responsibility for pesticides is reserved for EPA's Office of Pesticide Programs, which relies heavily upon labeling. See our discussion in chapter 4 regarding the regulatory protection afforded pesticides in the home.

[6]We found it difficult to reconstruct or evaluate these decisions made without a standard or benchmark for FDA to follow. Not only are they done on a case-by-case basis, but the systemic lack of protocols or documentation meant we could not even examine, much less assess, the decision process.

[7]Specifically in the case of ethylene dibromide, FDA has ceased routine monitoring despite having found levels that violate the action level on many shipments of honey they sampled in 1989, the last year of monitoring. DBCP and 2,4,5-T are two other pesticides FDA no longer routinely monitors.

The Workplace, Water, and Toxics Domains

OSHA is responsible for protection of workers against substances or situations that can have a "material impairment of health" in their workplaces.[8] One estimate posits that 20 million workers may be exposed to toxic substances in their workplaces. We have no estimates of the numbers of workers exposed to the 30 chemicals we identified. However, many or most of these chemicals do occur in American workplaces. OSHA indicated their potential regulatory authority for all 30. This is true in spite of the high number of pesticides (16) among the 30 with uses restricted or canceled in the United States. Canceled pesticides can still be manufactured or formulated in this country, raising the potential need to control workplace exposure in plants that produce or formulate them for export. OSHA had 13 standards for the 16 canceled pesticides on our list, leaving workers unprotected by a chemical-specific regulation for the remaining three. Nine other chemicals in the 30 have no major OSHA regulatory action.[9]

The two domains of water and toxics (including pesticides), where several offices share the responsibility, appear better covered by formal regulation. In part, this is attributable to multiple offices covering for one another. For example, in the water pathway, the Office of Solid Waste and Office of Emergency and Remedial Response set most of the regulations. The Office of Water Regulations and Standards set no standards or bans, but created 12 guidelines, not shown here. The Office of Drinking Water set five standards and seven guidelines.

The Office of Pesticide Programs has been active in regulating these 30 chemicals, canceling or limiting use on 16 and setting standards for 4 more. They found seven of our chemicals do not fall under their mandate because they are not pesticides. Thus between legal exclusions and actions, they covered all but three. The Office of Toxic Substances has regulated only two of our list and claims their mandate excludes them from another five. Regardless of little regulatory activity by some offices in the water and toxics domains, numerous regulations control them.

[8]OSHA is not responsible for the pesticide exposure of farm applicators, deferring under law to EPA. However, an agency official told us the regulatory authority for pesticide exposure in the "general industry realm" is entirely OSHA's.

[9]OSHA indicated that eight chemicals fell under their Hazard Communication Standard. This is a generic information standard that falls outside the scope of chemical-specific regulatory actions included in our study. It consists of a general obligation of employers to warn employees of the ill-health effects of chemicals for which there is "one well-conducted study." OSHA could not establish that they had any documentable activity for these eight, including the identification of the one study. We report their activities under the Hazard Communication Standard in appendix IV.

Summary

Overall, we found a considerable amount of regulatory activity for the 30 chemicals. This degree of activity was not unexpected as most of these chemicals have serious toxicities in addition to their reproductive and developmental toxicity. Three-fourths of the decisions were taken in 1980 or since. For the domains of air and consumer products, less than 10 of the 30 chemicals had received any major regulatory action. Although it is difficult to draw conclusions regarding how much regulation is enough in a broad overview such as ours, we find the small amount of regulatory activity in these two domains problematic for 30 widely acknowledged reproductive and developmental hazards.

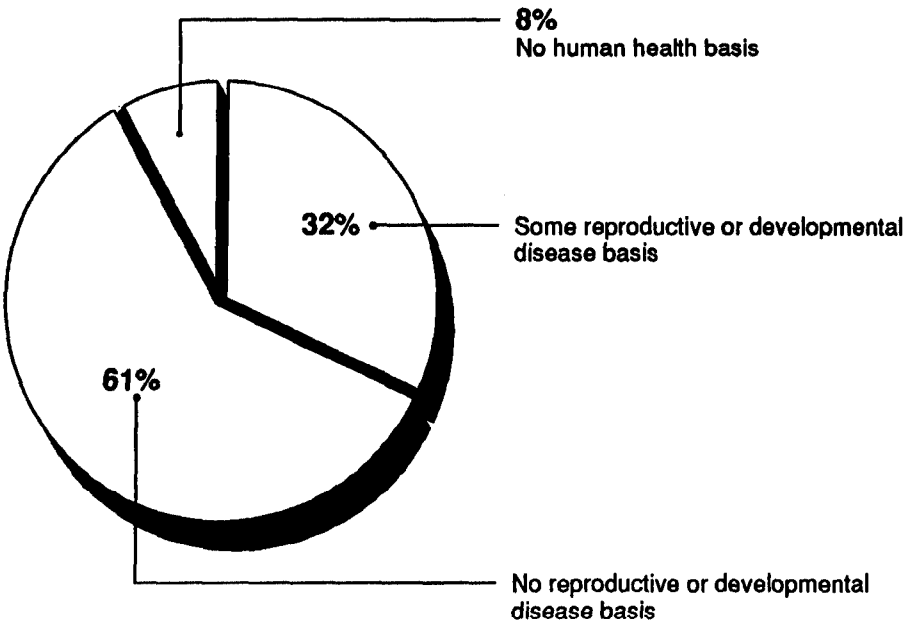
The Health Basis of Regulatory Actions

For the set of 117 regulatory actions where the decision could be reconstructed, that regulation is most frequently based on diseases other than reproductive and developmental toxicity. Aside from bans, almost three-quarters (73 percent) were based on considerations exclusive of reproductive and developmental toxicity.[10] Cancer and acute toxicity play a large role. Cancer is the sole basis or shared basis of 42 percent of the decisions. Just less than one-third of the decisions for the 30 chemicals were based, to any extent, on consideration of reproductive and developmental outcomes, although data for these toxicities may have been examined. (See figure 3.1). This pattern derives from the nature of the 30 chemicals with their multiple toxicities and the history of regulation the United States, which has been predominantly focused on cancer and acute toxicity.

The pattern raises the issue of whether a set of regulations primarily based on other concerns can protect against reproductive or developmental toxicity. The agencies assure us that is the case. However, a randomly selected group of nationally recognized experts in reproductive and developmental toxicity we surveyed have expressed serious and substantial reservations about the ability of cancer-based regulation, in particular, to protect against reproductive and developmental disease.

[10]The cases where reproductive disease was claimed as a basis for the regulation may have been exaggerated. One agency official told us they presented their decisions "in the best light." Further, the official feared the "predominant impression" from our study would be that much federal attention is paid to reproductive toxicity. Privately, that was not his assessment. He gave an example in his agency's responses to our survey where reproductive disease was falsely represented as a basis for a regulation, when instead, the entire decision focused on cancer.

Figure 3.1: The Basis of Major Regulatory Actions



Note: Based on 117 regulatory actions that could be reconstructed. Most bases are health related. Two examples of a non-human health basis for regulation are the definitions of a food, such as the percentage of alcohol in vanilla, and aquatic toxicity. (Percentages do not equal 100 due to rounding.)

We cannot conclude based on this issue alone that set of regulations described fails to protect against reproductive and developmental toxicities. In some cases, regulation targeting one disease may protect against other toxicities. Yet, there are significant questions about the assumption that regulation for another disease will protect against reproductive and developmental disease. We deal further with the sufficiency of protection of the regulations in chapter 4.

Specific Legislative Authority as Context for Regulation

Agency Responsibility

All 10 offices accepted responsibility, in principle, for preventing reproductive and developmental disease, in some cases under very general health protection mandates. Agency officials indicated their acceptance of responsibility in essays on the survey they completed for us and in

various interviews and discussions with us. For example, an OSHA official indicated that under their general health protection mandate, which does not specifically mention reproductive and developmental disease, they are responsible not only for protecting workers' children from birth defects due to the workers' chemical exposures, but also for male and female reproductive and developmental hazards.

Authority to Regulate Causes of Reproductive and Developmental Disease

The 10 offices have authority to protect public health under 12 laws. However, only five of these laws specifically mention reproductive and developmental health outcomes, which, in turn, affect the jurisdiction of half of the offices. The other five agencies operate under laws that do not suggest any priority for reproductive and developmental disease protection. Table 3.3 lists the offices, their missions, their relevant laws, and whether the laws specifically mention adverse reproductive and developmental outcomes. Table 3.3 also shows that the 10 offices have distinctive, sometimes overlapping, missions. However, in other cases, far from constituting an overlapping of missions, mandates appear to leave some responsibilities unassigned or still to be negotiated.

The references to reproductive and developmental disease protection are frequently specific to only a few of the possible disease outcomes. Most frequently, the laws refer to birth defects or mutations. (Appendix V contains relevant language from the 12 laws.) This pattern is understandable, particularly in the past, when physical deformities were the only well-studied adverse reproductive and developmental outcome. However, it may be an overly narrow restriction in a field where miscarriages and functional and neurological disabilities considerably outnumber birth defects and may have substantially greater costs both to the family and society.

In at least one of the five laws that mention reproductive and developmental disease, the responsibility the office is charged with is narrower than a comprehensive charge to protect or prevent the disease. For example, "teratogenic" and "mutagenic" are mentioned in the Clean Air Act only in relationship to authority to do clinical and laboratory studies.[11]

[11]The Clean Air Act was revised in November 1990. It provides for the authority to revise the list of chemicals for OAR attention based upon threats to health including mutagenic, teratogenic, and reproductive dysfunction. In the text, we refer to the act which was in effect and most relevant to the activities OAR reported to us in August 1990.

Table 3.3: Office Mission and Mandate to Protect Reproductive and Developmental Health

Office	Mission	Legislation[a]	Mandate[b]
CPSC	Protect consumers from unreasonable risks of injury or illness from all household products	Consumer Product Safety Act	Yes
		Federal Hazardous Substances Act	No
		Poison Prevention Packaging Act	No
FDA/CFSAN	Protect human health by regulating exposure to harmful chemicals in food, not chemicals per se	Federal Food, Drug, and Cosmetic Act	No
OSHA	Ensure safe and healthful working conditions	Occupational Safety and Health Act	No
EPA/OAR	Protect and enhance the quality of the nation's air in order to promote the public health	Clean Air Act	Yes
EPA/ODW	Ensure safe drinking water supplies against contamination	Safe Drinking Water Act	No
EPA/OERR	Protect human health and the environment from threats by uncontrolled releases of hazardous substances	Comprehensive Environmental Response, Compensation, and Liability Act	Yes
EPA/OPP	Register pesticides ensuring no unreasonable risks to people or the environment and set legal limits for pesticides on food and feed crops	Federal Insecticide, Fungicide, and Rodenticide Act	No
EPA/OSW	Ensure that hazardous waste management protects human health and the environment	Solid Waste Disposal Act	No
EPA/OTS	Protect public health and the environment from unreasonable risks posed by chemicals in commerce	Toxic Substances Control Act	Yes
EPA/OWRS	Restore and maintain the integrity of the nation's waters	Federal Water Pollution Control Act (Clean Water Act)	Yes

[a]Other federal laws provide for the regulation of toxic substances; however, they deal either with agencies or with types of hazards outside the scope of this study. In addition, these 10 offices have laws that are not relevant to our study.

[b]Indicates whether reproductive and developmental toxicity is specifically mentioned in the law.

Other laws are more comprehensive. The Clean Water Act and the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) go beyond a mention of birth defects to include "behavioral abnormalities," "malfunctions in reproduction and development," and

"serious or irreversible reproductive and developmental dysfunctions." Although these laws provide express authority regarding the prevention of reproductive and developmental disease, the actions reported to us do not necessarily reflect the offices' additional authority. The Office of Water Regulations and Standards reported that, under law, they have to look for reproductive and developmental toxicity during regulatory decision-making, but that, in fact, the office regulates for cancer.

We did not find that specific statutory authority produced a more active record of regulations of our 30 chemicals. Five of the offices operate under general public health protection mandates. Even though their statutory authority lacks specific mention of reproductive and developmental disease, each of them indicated that they are responsible for protecting against those diseases. Yet, two of the regulatory domains with the fewest regulations (air and consumer products) are the primary responsibility of entities with reproductive and developmental disease mentioned in their laws. Conversely, the law governing the food domain, with regulations for only half the chemicals, has no mention of reproductive and developmental disease. Thus, regulatory performance is not consistently related to the mention of reproductive and developmental disease in the law. Likewise, there is little association between regulation based on reproductive and developmental toxicity considerations and the presence or absence of a specific mention in the legislative authority for the office.

Limits on Authority for Specific Chemicals

In several instances, restrictions in the law or offices' interpretation of the law prevent them from dealing with particular products or pathways, narrowing their range of activity on our list of chemicals of high reproductive and developmental concern. For example, the Office of Toxic Substances at EPA is responsible for protecting the public health and the environment from unreasonable risks posed by chemicals in commerce. However, their legislation excludes them from regulating pesticides, tobacco, food, or any chemical that falls under the mandate of another office. Similarly, OSHA's legal mandate contains exclusions based on other federal standards.

The perceived or real legal restrictions on the regulation of alcoholic beverages and tobacco produced a pattern of little or no regulation of these substances by the 10 offices we surveyed—that is, those federal offices primarily responsible for the health effects of environmental chemical exposures. Yet, we were told by agency officials that the adverse reproductive and developmental effects of these two chemicals

are some of the most widespread and preventable of reproductive and developmental damage.

We will first examine tobacco authority for the 10 offices as reported to us and then alcohol authority. Eight of 10 offices told us they do not have the authority to act on tobacco smoke. Roughly their rationale for this position fit one of three types: specific exclusion in the law (CPSC and OTS); by definition,the substance falls outside the target of their authority (CFSAN, OWRS, OPP, and OAR); or tobacco is not on the discrete list that constitutes the office's legitimate target (OSW, OERR). Of the two offices that stated they did have authority to act on tobacco (OSHA and ODW), neither has acted; however, OSHA is considering the regulation of tobacco smoke in the workplace.

The pattern of authority to regulate alcohol is the reverse of that for tobacco. Here only 2 of the 10 offices told us they are excluded from dealing with alcohol (OSW and OERR). But for various reasons, none of the remaining eight has issued any regulations or restrictions on beverage alcohol. In short, none of the 10 major federal regulatory offices has regulated the alcohol in beverage alcohol for its known adverse effects on reproductive and developmental health.

The eight offices that declared themselves responsible for the reproductive and developmental health effects of alcohol expressed significant caveats and exceptions to that responsibility. FDA is the primary agency charged with regulating the safety and health of food and beverages. FDA officials include alcoholic beverages as foods. Although responsibility for the health effects of beverage alcohol was a "grey area" (that is, in potential conflict with Bureau of Alcohol, Tobacco, and Firearms' authority), because of FDA concern with adverse reproductive and developmental effects, they proposed some labeling and packaging restrictions in 1975. They were not successful in promulgating these restrictions because the U.S. District Court of the Western District of Kentucky decided that alcohol beverage labeling authority rested exclusively with the Bureau.[12] FDA officials told us they have since interpreted that decision broadly in the context of the 21st amendment to the U.S. Constitution to preclude their action on the health effects of beverage alcohol. However, they continue an active review of the contaminants in these beverages.

[12]Brown-Forman Distillers Corp., et al., v. F. David Mathews, No. 76-0042-0, Aug. 31, 1976.

Of the eight offices that acknowledge some responsibility for alcohol, FDA is the only one with possible authority to act on beverage alcohol. In the remaining seven, two are explicitly excluded from dealing with food and, therefore, from alcoholic beverages (CPSC and OTS) and two others find that alcoholic beverages fall outside their assigned authority (OPP and OAR). Of the remaining three, ODW and OWRS have not acted on alcohol of any kind, but reason that most items in commerce could get into water and would therefore be under their authority. OSHA has a regulation on industrial exposures to alcohol.

Between 1965 and 1989, the Congress passed legislation requiring warning labels that include reference to the reproductive and developmental health consequences of alcohol and tobacco.[13] These represent cases where the Congress recognized that health responsibility was not assigned and took action. The offices we studied were not optimistic they could have any regulatory impact on the reproductive or developmental effects of tobacco or alcohol. In addition to limited authority, they point out the unique character of these personal habit substances. Yet, given the adverse events associated with smoking and alcohol consumption, creative options could be explored. In particular, taxation, state regulated age-restricted sales and pricing, or closer regulation of the concentration of alcohol are options that states or federal agencies might evaluate for their potential to reduce reproductive and developmental damage.

In another case, the division of responsibility between federal agencies appears to leave a domain only lightly regulated. The Consumer Product Safety Commission is specifically excluded from regulating pesticides, including their use in homes, offices, and schools. We will look again in more detail at the intersection of CPSC with household pesticides in chapter 4.

Summary and Conclusions

We opened this chapter with a brief mention of the new comprehensive federal plan to prevent children's exposure to lead. Then, we pursued the Committee's second and third evaluation questions regarding the extent of regulation for reproductive and developmental hazards and the extent to which they are regulated on the basis of reproductive and developmental toxicity. In contrast to the commitment represented by

[13]One of the current rotating messages on cigarettes and cigarette advertising reads: SURGEON GENERAL'S WARNING: Smoking By Pregnant Women May Result in Fetal Injury, Premature Birth, And Low Birth Weight.

the new effort directed at lead, we found that for the set of chemicals we identified, the effort may be incomplete and is not focused on reproductive and developmental disease.

We asked each of 10 offices in the 4 regulatory agencies most responsible to report their most important regulatory action. They reported at least one major regulation for all but one of the chemicals on our list of 30. The resulting set of 138 actions constitutes the major federal regulatory effort for the reproductive and developmental chemicals of highest concern. However, we found two regulatory domains are regulated for only about one-third or fewer of the chemicals.

The existing regulatory actions tend not to be based on reproductive and developmental disease. Despite considerable scientific evidence on the reproductive and developmental toxicity of these 30 chemicals (see appendix III), offices have not, for the most part, based their regulatory decisions on these toxicities. Instead, two-thirds of the major decisions for the chemicals of highest reproductive and developmental concern are coincidental to decisions that focused on safeguarding the public against cancer, acute toxicity, and other concerns. In the next chapter, we will examine the decisions in more detail and try to understand if regulations not based on reproductive and developmental toxicity can sufficiently protect against those diseases.

The laws the 10 offices operate under are sometimes vague or incomplete regarding protections against reproductive and developmental disease. We found that only 5 of the 12 relevant laws specifically mention reproductive and developmental disease, but there was no greater likelihood of offices with the more specific laws basing their regulations on these diseases than those with less specific laws. Nonetheless, a specific assignment to protect the public against reproductive and developmental disease in all of its manifestations would certainly assist in focusing agency attention. Some reassessment and clarification of the real and perceived restrictions from dealing with certain products or pathways in the laws would facilitate more complete regulatory coverage and ensure that agencies are not prevented from regulating the most dangerous and convincing reproductive and developmental hazards.

Recommendations

We recommend that the Commissioners of CPSC, Administrator of EPA, Commissioner of FDA, and Assistant Secretary of OSHA:

- develop information on the occurrence of each chemical in the media, products, or situations of their responsibility; and
- conduct a search for and examination of the reproductive and developmental toxicity data for the unregulated chemicals proceeding to a thorough hazard assessment.

Matters for Congressional Consideration

In light of our finding that reproductive and developmental toxicity information is not being utilized in regulatory decision-making for even the 30 chemicals of high concern, the Congress should consider amending those laws that do not currently specify the protection of the broad range of reproductive and developmental health and use of reproductive and developmental data. The Congress could specify that all environmentally caused developmental, female reproductive, and male reproductive disease is part of the public health protection responsibility under the 12 laws.

Agency Comments and GAO Response

Officials from several agencies observed that (1) a specific mention of reproductive and developmental disease in their mandate would not change the way they handle these toxicants without congressional attention to other parts of their laws (including the judicial decisions that limit their authority), their limited resources, and the consequent need to prioritize; (2) laws with general health protective mandates are more useful; and (3) specific mention of these diseases would deemphasize others.

We appreciate the legal and resource constraints the agencies operate under and urge them to petition the Congress for changes that would facilitate their increasing use of a broader spectrum of toxicity as a basis for decisions where it is appropriate. Reproductive and developmental outcomes have been largely neglected in regulation, and they need to be included as one of many important health outcomes for consideration by regulators. Since several other diseases already have priority, by virtue of history, our suggestion to the Congress aims at righting an imbalance.

Federal Regulatory Protection

The Supreme Court recently ruled that a car battery manufacturer's "fetal protection policy" constituted an illegal gender-based employment policy.[1] The policy had excluded women from jobs that were higher paying but where exposure to lead would exceed safe levels for fetal health. Several commentators noted that, as a result, employers will have to provide a less toxic, more healthful workplace for both men and women. Estimates of U.S. workers exposed to toxic materials range up to 20 million. The task of providing a healthful environment at work and away from work brings us to the fourth question: Does federal regulation for these chemicals provide sufficient protection from adverse reproductive and developmental effects?

To answer this question, we first report on the overall judgment of the scientific community on the protection afforded reproductive and developmental health by federal regulation. We then examine the agencies' own judgments of the protective value of their major regulatory actions. Third, we present an analysis of some aspects of the decision-making process by which agencies arrive at their regulations.

Methodology

The primary basis for the findings in this chapter is our analysis of two surveys: (1) a survey of experts in the field of reproductive and developmental toxicity, and (2) a survey of the four agencies primarily responsible for regulating environmental hazards to health.

In addition to requesting the scientists' judgment of levels of concern over the reproductive and developmental effects of 72 chemicals implicated in reproductive and developmental failure, we asked their judgment of the protective value of federal regulation against environmental chemical hazards to reproductive and developmental health. We also asked them a series of questions about the utility of various kinds of research data as a basis for assessing the reproductive and developmental hazards of environmental chemicals.

Each of 10 offices in the 4 agencies answered a survey reporting their major protective decisions on the 30 chemicals of high reproductive and developmental concern. As a second indicator, we asked for a self-assessment; that is, whether in their judgment their regulatory actions

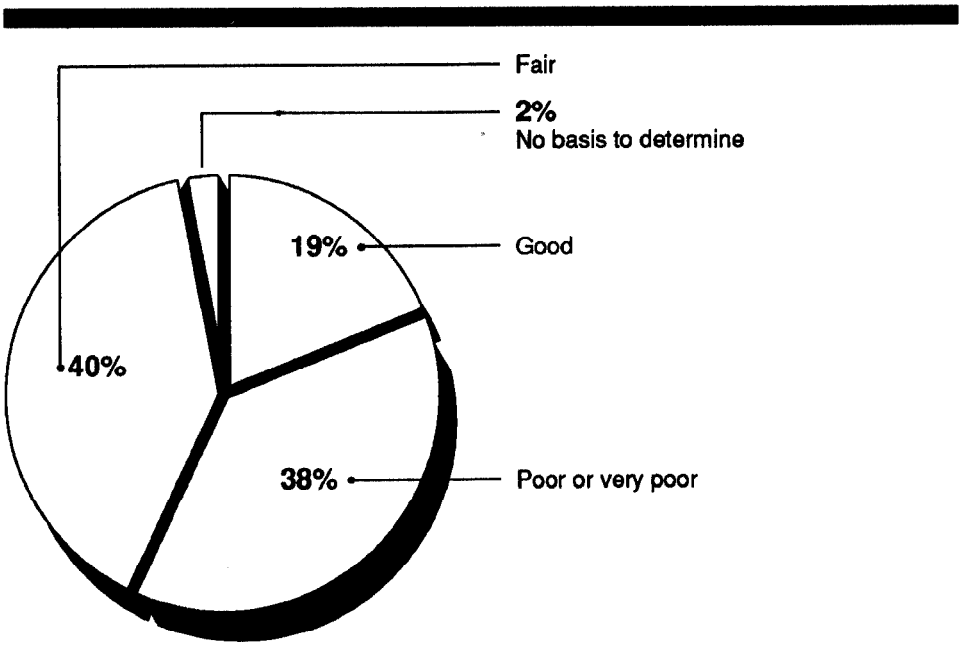
[1] International Union, United Automobile, Aerospace and Agricultural Implement Workers of America, UAW, et al., v. Johnson Controls, Inc., No. 89-1215.

would protect against adverse reproductive and developmental outcomes. As a third indicator, we examined the substance of the 138 regulatory decisions, including the data examination activities, and whether or not regulations were under review. We buttressed these steps by conducting interviews with agency personnel and experts in the field and examining selected recently published literature.

Expert Judgments

Experts we surveyed in the spring of 1990 held a generally negative view of the protection offered by the current federal regulation of reproductive and developmental toxicants. We asked a random sample of experts to rate federal regulatory protection overall against the reproductive and developmental effects of environmental chemicals. On a five-point scale from "very good" to "very poor", 40 percent of the respondents judged the protection to be "fair," while another 38 percent judged it "poor to very poor." (See figure 4.1)

Figure 4.1: Experts' Judgments of Federal Protection for Reproductive and Developmental Toxicity



Note: Based on judgments of 47 experts (3 did not respond to this question). Percentages do not equal 100 because of rounding.

In the last chapter, we found that two-thirds of the regulations for the most compelling reproductive and developmental chemicals are not

based on reproductive and developmental toxicity. We wondered if regulations based on other diseases could be expected to effectively protect against reproductive and developmental diseases. The single most common basis for this set of major federal regulations is cancer. We asked the experts to judge if regulation of a chemical on the basis of cancer would protect against its reproductive and developmental effects. Fifty-five percent of them responded that this kind of regulation would not necessarily protect in all cases against adverse reproductive and developmental events, and a further 37 percent said "probably not" or "definitely not." Thus, the experts we surveyed were generally negative, overall, on the federal performance to prevent environmentally caused reproductive and developmental disease.

Agency Judgments

For each of the regulations reported for our list of chemicals, we asked the offices to judge the protective value against reproductive and developmental toxicity. They judged all bans protective, while standards and guidelines were found wanting. In the following section, we explore the variation in the protective value claimed for regulations across different types of actions (bans, standards, and guidelines) and across the offices.

Seventeen chemicals are affected by the 20 bans. The offices of origin report in each of the 20 cases that their action protects against reproductive and developmental disease. We note that some of these banning incidents are of limited scope, such as product-specific bans or when only certain uses of a product are canceled. The Office of Pesticide Programs (OPP) canceled only certain uses of pesticides that contain arsenic, but not all. As we noted in the last chapter, our list of 30 chemicals contains many pesticides for which OPP has canceled uses in the United States, although they may still be manufactured or formulated here. (DDT and Mirex are examples.) OPP is probably justifiably certain of the protection their complete cancellation affords over their area of responsibility. But exposures continue outside that legal domain, such as occupational settings, exposures through food, water, storage, leaks, dumping, and persistence in the environment.

Offices judged their guidelines and standards less protective overall than bans. Only 49 percent of standards, which have the force of law, and 33 percent of guidelines, which do not, were judged to be protective against reproductive and developmental disease by the originating office. On average, for the 118 standards and guidelines, the offices judged only 46 percent to be protective against reproductive and developmental diseases and were uncertain about roughly an equally large

number of actions. In the absence of a quantitative risk assessment protocol for reproductive and developmental toxicity, agency officials may have found it difficult to establish what, if any, risk is left under a regulation aimed primarily against other diseases.

We have reservations about the protection offered in certain of these cases. Altogether, in 54 percent of cases, officials indicated either the regulation did not protect or they were uncertain. Below, we give an example of one regulation judged protective and one judged uncertain—categories representing 90 percent of the responses.

Regulation Judged Protective

The Office of Pesticide Programs claimed their 1981 registration standard for warfarin protects against reproductive and developmental disease. Warfarin is a pesticide the office registered for use on rodents. Labeling to direct use is a major way OPP regulates pesticide exposure. The active chemical in warfarin is the same as a well-researched anticoagulant, which in 1981 was known to cause birth defects and stillbirths. No food uses or food tolerance levels are set on rodenticides. Under the 1981 standard, use of some products is restricted to licensed personnel and general warning labels are required. However, a draft OPP document submitted to us reported numerous human exposures to warfarin annually reported to poison control centers and anticipated new warnings about reproductive and developmental toxicity. We find some incongruity between OPP's judgment of the protective value of their 1981 registration standard and their information about poisonings.

Regulation Judged Uncertain

The Occupational Safety and Health Administration rated their 1989 carbon monoxide standard of uncertain protection against reproductive and developmental effects. When they made the decision, they examined summary reproductive and developmental toxicity data presented by the National Institute for Occupational Safety and Health. The Institute found reproductive and developmental effects and recommended regulation on that basis, but OSHA based the regulatory decision exclusively on cardiovascular disease and pulmonary impairment. OSHA indicated that the numerical standard based on the latter was more protective than the standard would have been if based on reproductive or developmental toxicity.

Positive judgments by individual offices regarding their guidelines and standards as protection against reproductive and developmental disease range from 8 percent at the Office of Water Regulations and Standards

to 100 percent at the Office of Toxic Substances, with an average of 46 percent. Six of the offices reported confidence in their own guidelines and standards between 30 and 70 percent of the time. In table 4.1, we show the percentage of regulations for each office judged by their originating office to be protective for reproductive and developmental toxicity.

Table 4.1: Offices' Judgments of the Protective Value of Their Guidelines and Standards for Reproductive and Developmental Toxicity

	Judged to be Protective[a]		
Office	**Percentage**	**Number**	**Number of actions**
CPSC[b]	33	2	6
FDA	53	8	15
OSHA	33	7	21
EPA			
OAR	40	2	5
ODW	83	10	12
OERR	70	14	20
OPP[b]	25	1	4
OSW	33	7	21
OTS	100	2	2
OWRS	8	1	12
Total	**46**	**54**	**118**

[a]Offices were asked to report whether, in their current assessment, the standard or guideline reported was protective against reproductive and developmental toxicity. They chose among "yes," "no," or "uncertain" in a multiple-choice format. The information in this table reflects only those answers that were affirmative.

[b]CPSC and OPP reported bans for several chemicals. Bans are not shown on this table; thus, numbers here do not equal all of the CPSC and OPP activity reported. (See text for discussion of the agencies' evaluation of bans.)

Overstated Protective Value

Some agencies may have overstated the protective value of their regulations. We examined the decision-making process for regulations in which the agencies expressed confidence. In several cases, we found reason for concern. Many of those who expressed confidence could not, in fact, reconstruct their decision-making process. In 31 percent of the cases where agencies were convinced of the protective nature of their standards or guidelines, they reported they did not know if they had examined reproductive and developmental data because they could not document or reconstruct the decision that led to the regulation.

The Office of Emergency and Remedial Response at EPA is an extreme example of this problem. This office adopts environmental standards

and uses them as goals for the cleanup of hazardous waste. They cannot document examining reproductive and developmental toxicity data in 90 percent of their regulations, but reported confidence in the protective value for those outcomes for 70 percent of them. The confidence they expressed may not be warranted. Despite having made all of their regulatory decisions since 1985—which might have given them access to recent research—they are unable to reconstruct whether or not they examined reproductive and developmental data in 90 percent of their decisions. They explained their own confidence in their regulations by indicating that they based the regulation on a formal risk assessment or on the most sensitive disease for which they had data. However, this is one of the offices that regularly depends on the Integrated Risk Information System (IRIS) data base, which does not consistently contain reproductive and developmental data. They also indicated that they often presumed that protection against other health outcomes, such as cancer, would protect against reproductive and developmental toxicity.

Review of Regulations

One-quarter of the major regulatory decisions were made before 1980. Many of these need revision either because they did not consider reproductive and developmental toxicity data that were available at the time or because new data have become available since then. For example, the Center for Food Safety and Applied Nutrition reported to us that they weakened the guideline for mercury in fish from 0.5 to 1 part per million in 1979 without examining data on mercury's reproductive and developmental toxicity. The original standard considered evidence from the Minamata Bay, Japan, experience showing the dangers to offspring of eating fish contaminated with industrial mercury. However according to the Federal Register notice of the revision, studies of acute symptoms in adults were the basis. Today, the Center is uncertain if that guideline protects against reproductive and developmental toxicity, and they report that they are actively seeking information and assessing the need to revise it.

A sizable portion of regulations judged not to be protective or to be of uncertain protection against reproductive and developmental toxicity are neither under revision nor under consideration for revision. For major regulatory actions, excluding bans, 42 percent of those judged not to be protective for reproduction and development are neither being revised nor being assessed for the need to revise. Similarly, 67 percent judged to be of uncertain value are neither being revised nor being assessed for the need to revise.

Federal Use of Reproductive and Developmental Toxicity Data

We analyzed the use of reproductive and developmental data in regulatory decision-making and found that offices often did not examine reproductive and developmental data when they made the decision leading to their most important regulation for a chemical. We expected a higher rate of examination of data based on several pieces of information. First, data are available on the list of 30 chemicals of concern; we found them being utilized (1) by our published reviewers, (2) as entries in the national data bases, and (3) by our experts when they judged these chemicals to be of high concern. Secondly, the several efforts to develop risk assessment protocols for reproductive and developmental toxicity assume that available data will be examined, although they differ on the exact interpretation of the data.[2] Finally, of the experts we surveyed, 98 percent indicated that reproductive and developmental data should "definitely" or "probably" be examined during risk assessment for chemicals that have multiple toxicities that include reproductive and developmental toxicity.

Data Examination

Offices reported examining reproductive and developmental data only 44 percent of the time when they made the 138 major regulatory decisions. This falls short of our expectations and the agencies own policies, which call for looking at all relevant disease endpoints. The pattern of infrequent data examination throws doubt on the protective value of regulations against reproductive and developmental disease outcomes.

In the remaining 56 percent of actions where respondents did not examine data, they split their answers between stating that they did not examine reproductive and developmental data (28 percent) and indicating that they could not document the regulatory decision in enough detail to know if reproductive and developmental data were examined (25 percent).[3] Inaccessible or lost files on past regulatory decisions were a problem in several of the offices.

As table 4.2 shows, seven offices examined reproductive and developmental data in only 40 to 60 percent of their principal decisions for the

[2]EPA, 54 Fed. Reg. 42 and 53 Fed. Reg. 126; Kimmel, et al., 1989; Schwetz and Tyl, 1987; and Sheehan, et al., 1989.

[3]In four cases: DES, lithium, vitamin A, and warfarin—3 percent of the total—CPSC selected the fourth option to the data examination question; i.e., "data examination not a part of the activity." CPSC shares responsibility with FDA for oral prescription drugs. For these four cases, risk assessment is the responsibility of FDA. Once the drugs are approved for use, CPSC categorically demands childproof caps through its administration of the Poison Prevention Packaging Act.

30 chemicals. Only the Office of Water Regulations and Standards' performance approaches the ideal. Two others, the Office of Emergency and Remedial Response and the Office of Solid Waste, have low rates of examining reproductive and developmental data when they decide regulations for the chemicals of highest reproductive and developmental concern.

Table 4.2: Rates of Examining Reproductive and Developmental Data in Regulatory Decision-Making[a]

	Responses							
	Yes		No		Not part of activity		Cannot document	
Office	Percent	Number	Percent	Number	Percent	Number	Percent	Number
CPSC	44	4	11	1	44	4		
FDA/CFSAN	44	7	50	8			6	1
OSHA	43	9	57	12				
EPA								
OAR	40	2	60	3				
ODW	58	7	8	1			33	4
OERR	10	2					90	18
OPP	60	12	25	5			15	3
OSW	29	6	29	6			43	9
OTS	50	1	50	1				
OWRS	92	11	8	1				
Total	**44**	**61**	**28**	**38**	**2.9**	**4**	**25**	**35**

[a]The decisions shown here represent only those leading to standards, guidelines, and bans.

Explanations

We identified three possible causes of the common pattern of failure to examine reproductive and developmental data in regulatory decision-making for the reproductive and developmental chemicals of highest concern. First, some offices indicated a neglect of the data that stems, in some cases, from a low priority for reproductive and developmental diseases. Secondly, several offices assume that regulation for other diseases will protect against reproductive and developmental disease. Lastly, some offices have deficient information processing for risk assessment.

Neglect of the Data

We analyzed agency survey answers to understand the high rate of nonexamination of reproductive and developmental data. This effort yielded patterns of answers that suggest neglect of reproductive and developmental data and diseases. Those respondents who answered "no" to the question of examining reproductive and developmental data (28 percent of the regulatory cases), answered a second question on the

reasons for their nonexamination of the data. The most common answers were that the "office mandate did not require it" and that the data were "unavailable." A third option, "agency focus was not on reproduction and development" was also frequently checked. We will examine each of these in turn.

Three offices (the Occupational Safety and Health Administration, the Office of Drinking Water, and the Center for Food Safety and Applied Nutrition) did not examine the reproductive and developmental data in a total of 12 cases where they had adopted standards from an authority. They declared their mandates did not require data examination when adopting a "national consensus standard" as allowed under their law. These regulations are unlikely to protect against reproductive and developmental disease because they were borrowed from decisions made more than two decades ago, before much reproductive and developmental data were available. Several environmental laws provided for the adoption of existing standards from other authorities and for the revision of these regulations if necessary.

Two examples of these adopted standards cast doubt on the protection they might provide. In 1971, the Occupational Safety and Health Administration adopted—from 1968 recommendations by the American Conference of Governmental Industrial Hygienists (ACGIH)—limits for worker exposure for seven of the chemicals on our list: cadmium, EGEE, EGME, lithium, PCBs, 2,4,5-T, and warfarin.[4] Similarly, the Office of Drinking Water adopted standards for heavy metals (arsenic, cadmium, lead, and mercury) in drinking water from Public Health Service levels published in 1962. Although ODW is in the process of revising these standards, the legally permitted levels in U.S. drinking water in August 1990 (the time of our survey) were based on 1962 decisions that antedated most of the study of reproductive and developmental toxicity.[5]

[4]OSHA published final rule-making involving hundreds of revised air standards in 1989. Again they adopted ACGIH revised standards as their own. However, they excluded substances for which the ACGIH has not revised their 1968 levels. Thus the seven chemicals noted in the text maintain the 1968 ACGIH standards. According to an ACGIH official, the ACGIH is only now considering the development of a code to indicate in their volumes that a chemical has been shown to be a reproductive or developmental toxicant.

[5]Since we collected these data, ODW has published final rule-making on revised standards for several of the chemicals on our list. These include lead, asbestos, cadmium, mercury, ethelyne dibromide, DBCP, and PCBs. See 56 Fed. Reg. 110, 26,460, June 7, 1991, and 56 Fed. Reg. 20 Jan. 30, 1991, 3,526.

Answers indicating that reproductive and developmental data were not available may represent a true absence of data or may represent a reluctance to seek and examine reproductive and developmental data. It was certainly true in the past that data on reproductive and developmental toxicity were scarce for many chemicals. However, this is less likely to be the case for our list of toxicants because it was largely drawn from review literature of the early and middle 1980s, which is dependent on earlier research. Furthermore, our selection process operated in favor of chemicals for which there is more abundant information. This leaves us with the second explanation—a reluctance to seek and use reproductive and developmental information. Our analysis of the rates of data examination in major agency decisions reveals that, overall, the agencies increased their rate of examining reproductive data for decisions over time, as we would expect with data becoming more available. For this set of regulatory actions, they examined data in only 10 percent of the cases before 1980 but in 66 percent of the cases between 1980 and 1984. The trend did not continue, but experienced some degree of retrenchment for decisions made since 1985 to only 55 percent of the cases.

In one case, the circumstances of a particular "data unavailable" answer reveal that the answer could not be taken literally. In the course of a 1990 decision to ban mercury from indoor house paint, the Office of Pesticide Programs reported no examination of reproductive and developmental evidence and explained that it was "unavailable." We asked them to explain their answer as we knew of well-researched evidence of neurological damage in children resulting from exposure to mercury through their mother's diet in Minamata Bay, Japan. An agency official then suggested that the Minamata data might not be relevant, because the mercury in the Minamata example is organic, whereas the mercury in housepaint was elemental. The same official said that OPP based their ban on a case of acute toxicity (acrodynia) in a toddler in Michigan. Although the ban will be effective against both acute toxicity and reproductive and developmental effects, we think that they should have examined data on possible long-term consequences of exposure; that is, the developmental consequences.

In 13 cases, respondents explained not examining reproductive and developmental data because of the fact that their office's "focus was not on reproduction and development." Instead—whatever the reason—in at least these 13 cases, offices chose to focus on other regulatory agendas than reproductive and developmental diseases when they made important regulatory decisions on our list of 30 chemicals of high concern for reproductive and developmental outcomes. More than two-

thirds of these cases were in offices that do not have a mention of reproductive and developmental disease in their mandates.

Assumptions About Protection

Several offices told us that regulatory protection for other diseases would protect against reproductive and developmental disease, as well. This belief is linked to a predisposition to regulate based on what is known about cancer. Several authorities have observed that cancer is the driving force behind U.S. protective regulation. Cancer regulation is also facilitated by a widely accepted risk assessment process for cancer. However, the experts we surveyed indicated that regulation based on cancer or other diseases will not necessarily protect against reproductive and developmental disease.

The Center for Food Safety and Applied Nutrition at FDA has a policy that has led them to ignore reproductive and developmental disease outcomes in favor of regulating for cancer.[6] In several cases, CFSAN explained positive judgments on the protective nature of their regulations by insisting they regulated on "the most sensitive disease endpoint." However, one official explained it more as an assumption than a matter for investigation that their regulations based on cancer considerations will protect against all other toxicities.[7]

We believe it is unlikely that regulation based on other diseases will protect against reproductive and developmental outcomes in all cases. We base this judgment on the response of the experts we surveyed, on several recent studies, and on interviews with EPA officials and experts in the field. One study found that for well-studied chemicals with both reproductive or developmental and other toxicities, reproductive and developmental outcomes were equally sensitive or more sensitive than other noncancer outcomes in 65 percent of the chemicals studied. Another study found chemicals equally potent for reproductive and developmental and cancer outcomes in roughly half the cases examined and at least one reproductive and developmental outcome occurred at

[6]FDA officials linked this pattern to the Delaney Clause of the Federal Food, Drug, and Cosmetic Act. They told us they have invoked its strict demands on carcinogens only in regard to the potential concentration of pesticides in processed food beyond the levels allowed on raw produce. These considerations apply only to premarket approval decisions and are not necessarily relevant for hazardous contaminants.

[7]In the late 1970s, CFSAN conducted a comparison of the levels of protection afforded by their cancer regulation for the reproductive and developmental outcomes of one chemical, acrylonitrile. They ascertained that cancer-based regulation would protect against the reproductive and developmental outcomes and generalized the result to a policy of assuming reproductive and developmental outcomes will always be protected if they regulate based on cancer.

far lower levels than cancer.[8] EPA officials noted that reproductive and developmental toxicity can result from a single peak exposure during a sensitive phase of pregnancy or rapid cell division (as in sperm production), whereas the same dose would be averaged over a life span for cancer risk assessment.

Information Processing

The use of a centralized data base at EPA may exacerbate the pattern of neglect of reproductive and developmental data by regulatory decisionmakers there. The Integrated Risk Information System (IRIS) is a relatively new, centrally generated data base of toxicity information at EPA. It represents, according to one agency official, the consensus "reference dose" decisions for the agency. Reproductive and developmental toxicity data are represented inconsistently in the data base. If widely adopted, as planned, its purposeful emphasis on cancer may limit the information the offices have to make decisions on other disease outcomes. The data base reports cancer information in detail, but noncancer toxicities are reported only for the outcome with the greatest sensitivity, according to an EPA description of the rules for generating the data base. We found that several of our 30 index chemicals are not included in IRIS at all, including some chemicals like TCDD, which has multiple toxicities. For those chemicals on our list that IRIS does contain, mention of the reproductive and developmental toxicity is not consistent. Finally, the data base is not organized so that one can search for reproductive and developmental toxicities.

We found that for the existing 138 major regulations on our 30 chemicals, data on their reproductive and developmental toxicities were examined less than half the time during the decision to regulate.[9] One-quarter of the decisions could not be reconstructed, and reproductive and developmental data were definitely not examined for the other one-quarter (28 percent). Further analysis identified a pattern of neglect of reproductive and developmental data, including allegations of data unavailability that were not entirely credible, the absence of an office "focus" on reproductive and developmental toxicity for regulatory protection, and 12 cases where agencies maintained 25-year-old adopted standards they have not revised. The assumption that regulation based

[8]David W. Gaylor, "Comparison of Teratogenic and Carcinogenic Risks," Regulatory Toxicology and Pharmacology, 10 (1989), 138-43, and Herman B.W.M. Koeter, "Relevance of Parameters Related to Fertility and Reproduction in Toxicity Testing," American Journal of Industrial Medicine, 4 (1983), 81-86.

[9]In spite of our supposition that regulatory actions would be, on average, more protective against reproductive disease if reproductive data were examined during the process, we realize that various other constraints could vitiate the protection.

on other diseases will protect against reproductive and developmental disease plays a major role in explaining the neglect of reproductive and developmental data at the Center for Food Safety and Applied Nutrition and may be considerably more widespread. Finally, at EPA, centralized data for risk assessment emphasizes cancer and only inconsistently presents reproductive and developmental toxicity data.

Statutory Limits to Protection

Thus far, we have considered the value of existing major regulation to protect against the chemicals of highest reproductive and developmental concern. Now we will consider the effect of the missing regulatory actions on overall protection. In the last chapter, we found two of six domains had few bans, standards, or guidelines for our 30 chemicals. And we also found some of these gaps were the result of several instances of agencies' being expressly excluded by law from regulating the chemicals on our list. These exclusions explain 12 missing actions for one regulatory domain, that of consumer products. With two examples, we will try to suggest the reduced protective impact of two of the mandatory exclusions: (1) those for alcohol and tobacco, and (2) those for pesticides in the consumer product domain. We think public health protection would be better served if the 10 offices had more clearly defined authority for regulating alcohol and tobacco. If OPP does not exercise its authority to require childproof packaging for household pesticides, the Consumer Product Safety Commission should be allowed to regulate these household products.

Alcohol and tobacco are well-studied, highly toxic reproductive and developmental hazards with wide exposure in the population. Fetal alcohol syndrome is now epidemic in some American Indian communities, causing a burden of mental retardation in these small groups. Similarly, smoking of tobacco is known to cause low birthweight. The Secretary of Health and Human Services recently estimated that one-tenth of U.S. infant mortality is caused by mothers' smoking. Yet most of the 10 offices in our study find uncertain authority or are excluded by law from actively regulating the health effects of personal uses of alcohol and tobacco.[10] After 25 years of warning labels on tobacco packages, it may be time to consider other approaches to limiting exposures to these hazardous substances.

[10]They may regulate uses of alcohol and tobacco that are not personal. For example, OSHA has recently announced that they will consider regulating passive smoke exposure in work areas, a domain that is currently unregulated. OSHA noted that for smoke in certain public areas, such as shopping malls, EPA would be responsible.

One of the Consumer Product Safety Commission's major activities is enforcing the protective packaging of household products to prevent accidental poisoning. They reported requiring childproof caps for four of our chemicals, including warfarin. Actually, they enforce the special caps only on the cognate chemical when it is prescribed as the prescription drug, coumarin, because they are excluded from requiring protective packaging for pesticides. Thus, on a household shelf with a bottle of coumarin and a package of warfarin next to it, only the drug would be in childproof packaging. In spite of their comparable childproof packaging authority, EPA has not specified special packaging for this common rodenticide.

The package for popular pellet forms of warfarin is a simple envelope in a readily opened cardboard box. The Office of Pesticide Programs noted the "numerous" reports of poisoning from warfarin reported each year. If the Consumer Product Safety Commission were allowed to specify the childproof packaging on such pesticides, poisonings could be reduced. The Office of Pesticide Programs takes another approach to the control of these poisonings, expecting that more explicit labels will encourage careful storage and use. The persistence of the poisoning rates suggests that for household pesticides, labels may not be an effective control strategy. Although many of the specific pesticides on our list of 30 chemicals have canceled or restricted uses, the principle holds true for the larger set of reproductive and developmental hazards, many of which may be active household pesticides like warfarin. Childproof packaging, as administered by either EPA or CPSC, would be a more effective way of regulating these reproductive and developmental hazards.

Summary

Roughly half of the existing set of major regulations for the chemicals of high concern for their reproductive and developmental toxicities are of doubtful protection against those toxicities. We found three indications of the dubious protection.

Experts' Judgments

- Experts we surveyed judged the federal regulation of environmental threats to reproductive and developmental health as providing only fair-to-poor protection.
- Experts overwhelmingly agreed reproductive and developmental toxicity data should be examined in regulatory decision-making in the case of multiple toxicities, a pattern contrary to what we found.

Offices' Judgments

- Offices judge their own standards and guidelines to be protective of reproductive and developmental health less than half of the time.
- Regulations are not reviewed or revised regularly, even if the agencies believe the regulation may not protect against reproductive and developmental toxicity.

Data Examination

- Offices do not consistently examine reproductive and developmental data in the regulatory decision process.
- Their reasons for not examining the data strongly suggest an active pattern of neglect of the data and the diseases.
- Some office policies and data bases make it easy to overlook reproductive and developmental data in decision-making.

In addition to the lack of rigor in examining and using reproductive and developmental data and the lack of regulation for certain of these chemicals, offices and agencies do not believe they have the authority to regulate in some areas that are critical for reproductive and developmental health (e.g., the effects of alcohol and tobacco and consumer-use pesticides in the case of the Consumer Product Safety Commission).

Recommendations

In light of our finding that existing regulation of chemicals of high concern for reproductive and developmental diseases often does not include consideration of reproductive and developmental toxicity, we recommend that the Commissioners of CPSC, Administrator of EPA, Commissioner of FDA, and Assistant Secretary of OSHA: (1) review the existing regulations on the 30 chemicals to ensure that they provide sufficient protection against reproductive and developmental diseases and revise them if necessary, (2) perform separate analysis for reproductive and developmental outcomes in risk assessments for these 30 chemicals and for future regulatory decision-making, and (3) ensure the ready availability of reproductive and developmental data to decisionmakers by asking the Congress for the power to demand reproductive and developmental toxicity test data from entities manufacturing, importing, selling, emitting, or discarding reproductive and developmental hazards, and by organizing office data bases so that reproductive and developmental data is available.

Matters for Congressional Consideration

We found that most of the 10 offices believe they do not have authority over various chemicals, and thus, alcohol, tobacco, and pesticides are less well regulated than they might otherwise be. In light of this, the Congress should consider making authority for alcohol and tobacco regulation explicit for the appropriate offices. In addition, the Congress could either encourage EPA to exercise its childproof packaging authority or include household pesticides in CPSC's authority for childproof packaging.

Second, the Congress should consider how to increase the availability of these data. This could include revising the laws to allow agencies to demand reproductive and developmental toxicity testing at the expense of the entities manufacturing, importing, selling, emitting, or discarding products containing chemicals.

In light of our finding that one-quarter of the major regulatory decisions on the reproductive and developmental chemicals of high concern antedate 1980 and that a dozen standards adopted from nonfederal authorities are still the effective regulation or standard, the Congress should establish a periodic review of regulations using recent information on reproductive and developmental toxicity. Specifically, the Congress should consider limiting the length of time regulations adopted from outside authorities can be maintained in lieu of federal decisions.

Agency Comments and Our Response

Agency officials felt that the pattern of neglect and nonexamination of reproductive and developmental data we found is a dated picture, since the regulations were decided upon long ago, before there was much data in this field. However, as we have indicated, the fact is that fully 75 percent of the regulations reported to us were made in 1980 or more recently. Related to that, officials felt we had not displayed fully their recent policy and protocol statements as evidence of their increasing attention to reproductive and developmental toxicity. Although we regret that the full spectrum of any office's activities cannot be displayed in a review such as this, we don't view that as a significant problem in this case. Instead, we believe that our study of agency regulatory actions against 30 well-known toxicants is not only a telling indicator of public protection with regard to these 30, but also raises troubling questions about the extent of that protection against the chemicals we did not examine.

Survey of Reproductive and Developmental Health Experts

United States General Accounting Office

Survey of Reproductive and Developmental Health Experts

The U.S. Congress has asked the General Accounting Office (GAO) to evaluate the extent of Federal regulation of chemicals that have adverse reproductive or developmental effects. Our first task is to identify which chemicals, if any, the scientific community is concerned about. We are surveying experts in the fields of reproductive and developmental health as part of this task.

Specifically, we are asking experts about their level of concern for chemicals reported consistently in the scientific review literature since 1980 as producing adverse reproductive or developmental outcomes in man or animals. Acknowledging that the information base is better for drugs, we focus on environmental chemicals encountered in normal life activities and occupational settings. Consequently, legal and illegal drugs, disease states, physical agents, and nutrient deficiencies are not considered here. The exclusion of drugs extends to occupational exposure to drugs.

The results of the survey will be combined with the findings from a literature synthesis and a review of existing data bases. These sources will then be analyzed, in consultation with experts, to identify which chemicals, if any, most concern the scientific community as possible human reproductive or developmental toxicants. Federal agency actions will be reviewed for the chemicals of greatest concern.

In addition to the survey of concern over these chemicals, we are asking a few questions about respondents' experience and their philosophy of hazard identification for possible reproductive and developmental toxicants.

Your response to the questionnaire is vital. We are trying to obtain a representative view from the scientific community, and your judgment is necessary for us to obtain a balanced perspective. Even if you believe there is insufficient information on most listed chemicals to venture an opinion or there should be little or no concern about the chemicals, this is important information for us to share with Congress.

If you have any questions about the survey, please do not hesitate to call Barbara Chapman at (202) 275-1413. If you misplace the return envelope, please return your completed questionnaire to:

Barbara Chapman
Senior Evaluator
U.S. General Accounting Office
Room 5844
441 G Street, N.W.
Washington, D.C. 20548

Your identity will be kept confidential and the results of this survey will be reported only in the aggregate. To minimize the burden on you, the questionnaire is designed to be completed without consulting references. Done this way, the questionnaire will require approximately twenty-five minutes of your time.

Thank you for your assistance.

DEFINITIONS

We have adopted the EPA definitions, quoted here, for the major subfields of male reproductive toxicity, female reproductive toxicity and developmental toxicity.

Developmental Toxicity. The....adverse effects on the developing organism that may result from exposure during prenatal development or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism. The major manifestations of developmental toxicity include: (1) Death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) functional deficiency.

Female reproductive toxicity. Adverse effects observed in the female reproductive system that may result from exposure to chemical or physical agents. Female reproductive toxicity includes, but is not limited to, adverse effects observed in sexual behavior, onset of puberty, fertility, gestation, parturition, lactation, or premature reproductive senescence.

Male reproductive toxicity. The occurrence of adverse effects on the male reproductive system that may result from exposure to environmental agents. The toxicity may be expressed as alterations to the male reproductive organs and/or the related endocrine system. The manifestation of such toxicity may include alteration in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of the male reproductive system.

For definitions of the different phases of the risk assessment process, we depend on the National Academy of Sciences, 1983, *Risk Assessment in the Federal Government: Managing the Process.*

Risk Assessment. Risk assessment is the qualitative or quantitative characterization of the potential health effects of particular substances on individuals or populations. Risk assessment is further divided into 4 sequential steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization and is separated logically from risk management, the deliberative step which decides how the regulatory body will deal operationally with the agent.

Hazard Identification[is] the process of determining whether exposure to an agent can cause an increase in the incidence of a health condition...

Occupational Groups concern [focuses upon] the ill health effects of factors to which people are exposed in the workplace environment. (from Peter Gann, p.302 in Mausner, J. and S. Kramer, *Epidemiology, an Introductory Text*)

General Population concern is based on the ill health effects of factors to which people are exposed in non-workplace environments. Activities include eating and drinking, breathing indoor and outdoor air, using soaps and cosmetics, pursuing habits, etc. Exposures from uncompensated work settings such as childcare and housework are usually placed here.

BACKGROUND INFORMATION

1. Which of the following categories best describes the occupation in which you currently work? *(Check one.)*

(4)

1. ☐ Toxicologist---Reproductive
2. ☐ Toxicologist---Developmental
3. ☐ Toxicologist---other than reproductive or developmental
4. ☐ MD---Clinician
5. ☐ MD---Non-Clinician (e.g., administrator)
6. ☐ Pathologist
7. ☐ Epidemiologist
8. ☐ Regulatory Scientist/Administrator
9. ☐ Other (Specify)_____

2. How would you describe the extent to which your career has involved research or regulation of **reproductive toxicity**? *(Check one.)*

(5)

1. ☐ Very great
2. ☐ Great
3. ☐ Moderate
4. ☐ Some
5. ☐ Little or none

3. How would you describe the extent to which your career has involved research or regulation of **developmental toxicity**? *(Check one.)*

(6)

1. ☐ Very great
2. ☐ Great
3. ☐ Moderate
4. ☐ Some
5. ☐ Little or none

4. Which of the following best describes the economic sector you are currently working in? *(Check one.)*

(7)

1. ☐ Hospital/Medical care environment
2. ☐ Federal government---regulatory agency
3. ☐ Federal government---non-regulatory agency
4. ☐ State or local government
5. ☐ Industry
6. ☐ Academic Research/Consulting
7. ☐ Private Research/Consulting
8. ☐ Non-/not-for-profit research/consulting
9. ☐ Other (Specify)_____

5. Roughly, what percentage of your current support including salary, grants or contracts comes from state or local government?_____

(8-9)

6. Roughly, what percentage of your current support including salary, grants or contracts comes from chemical or drug firms?_____

(10-11)

Questions # 7 through 9 ask about your level of concern for chemicals nominated in the review literature since 1980. The chemicals are presented in three matrices by the endpoints they were reported to affect, i.e. as male reproductive, female reproductive, or developmental toxicants. Using the definitions given on page 2, complete the matrix quickly from current knowledge. Current restrictions or regulations should not affect your level of concern for a chemical. The central factor in your response should be any relevant information you have that the substance has an adverse effect on the system in question. *(Place one check under general population concern and one under occupational group concern for each chemical. If you believe there is insufficient scientific data or if you are not sufficiently familiar with the chemical to form a judgment, check the appropriate option.)* You may list chemicals other than those mentioned.

7. We would like to know how concerned, if at all, you are about these chemicals as **human male reproductive toxicants.** (12-43)

MALE REPRODUCTIVE TOXICANTS

Chemical	Extent of Concern for Adverse Male Reproductive Effects — GENERAL POPULATION (Check one)					OCCUPATIONAL GROUPS (Check one)				
	Little or No Concern (1)	Moderate Concern (2)	Great Concern (3)	Insufficient scientific data (4)	Not sufficiently familiar (5)	Little or No Concern (1)	Moderate Concern (2)	Great Concern (3)	Insufficient scientific data (4)	Not sufficiently familiar (5)
Pesticides/Rodenticides										
1. Carbaryl (Sevin)										
2. Chlordechone (Kepone)										
3. DDT										
4. Dichlorvos										
5. Dieldrin										
6. Fluoroacetate (Fluoroacetamide)										
7. Methyoxychlor										
Fungicides/ Fumigants/ Sterilants										
8. Dibromochloropropane (DBCP)										
9. Ethylene dibromide (EDB)										
10. Ethylene oxide (EtO)										
11. Maneb										
Metals/Metal Compounds										
12. Arsenic										
13. Boron /Boric acid										
14. Cadmium										
15. Lead										
16. Mercury										

Male reproductive toxicants, continued.

Check one ▼ *Check one* ▼ 2(4-41)

Chemical	Extent of Concern for Adverse Male Reproductive Effects: GENERAL POPULATION — Little or No Concern (1)	Moderate Concern (2)	Great Concern (3)	Insufficient scientific data (4)	Not sufficiently familiar (5)	OCCUPATIONAL GROUPS — Little or No Concern (1)	Moderate Concern (2)	Great Concern (3)	Insufficient scientific data (4)	Not sufficiently familiar (5)
Industrial Chemicals--Solvents										
17. Benzene										
18. Carbon disulfide										
19. Ethylene glycol monoethyl ether										
20. Ethylene glycol monomethyl ether										
Other Industrial Chemicals										
21. Chloroprene										
22. Epichlorohydrin										
23. Dibutyl phthalate (DBP)										
24. Di(2-ethylhexyl) phthalate (DEHP)										
25. Polybromated biphenyls (PBBs)										
26. Polychlorinated biphenyls (PCBs)										
27. Vinyl chloride										
Miscellaneous										
28. Alcohol (ethanol)										
29. Caffeine										
30. Cyclamate										
31. Gossypol										
32. Metanil yellow										
33. Tobacco smoke (not passive)										
Specify Other Male Reproductive Chemicals										
34.										
35.										

8. We would like to know how concerned, if at all, you are about these chemicals as human **female reproductive toxicants.** (42-75)

FEMALE REPRODUCTIVE TOXICANTS

Check one ▼ *Check one* ▼

Chemical	Extent of Concern for Adverse Female Reproductive Effects: GENERAL POPULATION — Little or No Concern (1)	Moderate Concern (2)	Great Concern (3)	Insufficient scientific data (4)	Not sufficiently familiar (5)	OCCUPATIONAL GROUPS — Little or No Concern (1)	Moderate Concern (2)	Great Concern (3)	Insufficient scientific data (4)	Not sufficiently familiar (5)
Pesticides /Rodenticides /Herbicides										
1. Aldrin										
2. Carbaryl (Sevin)										
3. Chlordecone (Kepone)										
4. 2,4- Dichlorophenoxyacetic acid (2,4,D)										
5. DDT										
6. Dieldrin										
7. Lindane										
8. Mirex										
9. Parathion										
Fungicides /Fumigants /Sterilants										
10. Dibromochloropropane (DBCP)										
11. Ethylene dibromide (EDB)										
12. Ethylene oxide (EtO)										
13. Formaldehyde										
Metals/Metal Compounds										
14. Chromium										
15. Lead										
16. Manganese										
17. Mercury										

matrix continued...

Female reproductive toxicants, continued.

Check one ▼ *Check one* ▼ 3(4-46)

Chemical	Extent of Concern for Adverse Female Reproductive Effects: GENERAL POPULATION — Little or No Concern (1)	Moderate Concern (2)	Great Concern (3)	Insufficient scientific data (4)	Not sufficiently familiar (5)	OCCUPATIONAL GROUPS — Little or No Concern (1)	Moderate Concern (2)	Great Concern (3)	Insufficient scientific data (4)	Not sufficiently familiar (5)
Industrial Chemicals--Solvents										
18. Benzene										
19. Carbon disulfide										
20. Ethylene glycol monoethyl ether										
21. Ethylene glycol monomethyl ether										
22. Toluene										
23. Xylene										
Other Industrial Chemicals										
24. Caprolactam										
25. Chloroprene										
26. Hexachlorobenzene										
27. Phthalate acid esthers										
28. Polybromated biphenyls (PBBs)										
29. Polychlorinated biphenyls (PCBs)										
30. Styrene										
31. Vinyl chloride										
32. 2,3,7,8- Tetrachlorodibenzo-P-dioxin (TCDD)										
Miscellaneous										
33. Cyclamate										
34. Diethylstilbestrol (DES)										
35. Monosodium glutamate (MSG)										
36. Tobacco smoke (not passive)										
Specify Other Female Reproductive Chemicals										
37.										
38.										

9. We would like to know how concerned, if at all, you are about these chemicals as **human developmental toxicants.** (48-73)

DEVELOPMENTAL TOXICANTS

Check one ▼ *Check one* ▼

Chemical	Extent of Concern for Adverse Developmental Effects: GENERAL POPULATION — Little or No Concern (1)	Moderate Concern (2)	Great Concern (3)	Insufficient scientific data (4)	Not sufficiently familiar (5)	OCCUPATIONAL GROUPS — Little or No Concern (1)	Moderate Concern (2)	Great Concern (3)	Insufficient scientific data (4)	Not sufficiently familiar (5)
Pesticides /Rodenticides /Herbicides										
1. Chlordecone (Kepone)										
2. DDT										
3. 2,4,5- Trichlorophenoxyacetic acid (2,4,5-T)										
4. Warfarin										
Metals/Metal Compounds										
5. Arsenic										
6. Cadmium										
7. Lead										
8. Lithium										
9. Mercury										
Industrial Chemicals--Solvents										
10. Benzene										
11. Carbon disulfide										
12. Chloroform										
13. Ethylene glycol monoethyl ether										
14. Toluene										

matrix continued...

Developmental toxicants, continued.

Check one ▼ *Check one* ▼ 4(4-37)

Chemical	Extent of Concern for Adverse Developmental Effects: GENERAL POPULATION — Little or No Concern (1)	Moderate Concern (2)	Great Concern (3)	Insufficient scientific data (4)	Not sufficiently familiar (5)	OCCUPATIONAL GROUPS — Little or No Concern (1)	Moderate Concern (2)	Great Concern (3)	Insufficient scientific data (4)	Not sufficiently familiar (5)
Other Industrial Chemicals										
15. Dimethyl sulfoxide										
16. Di (2-ethylhexyl) phthalate (DEHP)										
17. Hexachlorobenzene										
18. Polybrominated biphenyls (PBBs)										
19. Polychlorinated biphenyls (PCBs)										
20. 2,3,7,8- Tetrachlorodibenzo-P-dioxin (TCDD)										
21. Vinyl chloride										
Miscellaneous										
22. Alcohol (ethanol)										
23. Caffeine										
24. Carbon monoxide										
25. Diethylstilbestrol (DES)										
26. Methyl salicylate										
27. Nicotine										
28. Tobacco smoke (not passive)										
29. Vitamin A										
Specify Other Developmental Chemicals										
30.										
31.										

GENERAL INFORMATION

10. In your judgment, what are the **overall** rates for adverse human developmental outcomes (post-implantation) including "background rates"? *(Check one.)*

(38)

1. ☐ 75% or more of conceptions
2. ☐ 50-74% of conceptions
3. ☐ 25-49% of conceptions
4. ☐ 10-24% of conceptions
5. ☐ Under 10% of conceptions
6. ☐ No basis to judge

11. In your opinion, what percentage of adverse developmental events in humans will ultimately be found to be **caused by environmental agents** (including ambient and occupational exposures from all causes: diet, drugs, etc.)? *(Check one.)*

(39)

1. ☐ 75% or more of events
2. ☐ 50-74% of events
3. ☐ 25-49% of events
4. ☐ 10-24% of events
5. ☐ Under 10% of events
6. ☐ No basis to judge

12. In general, should agents that produce cancer and also have a reproductive or developmental effect be considered during risk assessment for **both** reproductive or developmental effects and cancer? *(Check one.)*

(40)

1. ☐ Definitely yes
2. ☐ Probably yes
3. ☐ Undecided
4. ☐ Probably no
5. ☐ Definitely no
6. ☐ No basis to judge

13. In your opinion, should regulations be based on the most sensitive health outcome, choosing among cancer, reproductive or developmental effects and other health outcomes? *(Check one.)*

(41)

1. ☐ Definitely yes
2. ☐ Probably yes
3. ☐ Undecided
4. ☐ Probably no
5. ☐ Definitely no
6. ☐ No basis to judge

14. In your opinion, does the regulation of a chemical on the basis of carcinogenic properties provide protection against its reproductive and developmental toxicity? *(Check one.)*

(42)

1. ☐ Definitely yes
2. ☐ Probably yes
3. ☐ Not necessarily (sometimes yes, sometimes no)
4. ☐ Probably no
5. ☐ Definitely no
6. ☐ No basis to judge

15. How optimistic are you that epidemiologic studies can reduce uncertainty about environmental chemicals suspected of reproductive or developmental toxicity? *(Check one.)*

(43)

1. ☐ Very optimistic
2. ☐ Moderately optimistic
3. ☐ Slightly optimistic
4. ☐ Neither optimistic nor pessimistic
5. ☐ Slightly pessimistic
6. ☐ Moderately pessimistic
7. ☐ Very pessimistic
8. ☐ No basis to judge

16. How optimistic are you that in-vitro tests can reduce uncertainty about environmental chemicals suspected of reproductive or developmental toxicity? *(Check one.)* (44)

1. ☐ Very optimistic
2. ☐ Moderately optimistic
3. ☐ Slightly optimistic
4. ☐ Neither optimistic nor pessimistic
5. ☐ Slightly pessimistic
6. ☐ Moderately pessimistic
7. ☐ Very pessimistic
8. ☐ No basis to judge

17. In your opinion, how large or small a role should the following data play in indicating human reproductive or developmental risk in hazard identification? (45-53)

	THE ROLE DATA SHOULD PLAY					
Data Type	Very large (1)	Large (2)	Some (3)	Little (4)	No role (5)	No basis to judge (6)
"Minor alterations"						
"Reversible endpoints"						
Animal data in the absence of human data						
Animal data (+) with negative human data						
Epidemiologic results when available						
In vitro mutagenicity test results						
In vivo mutagenicity test results						
In vitro developmental test results						
In vitro reproductive test results						

18. Overall, how would you rate federal regulatory agencies on how well or poorly they are protecting the U.S. public from the environmental chemical risks to reproduction and development? *(Check one.)*

(54)

1. ☐ Excellent
2. ☐ Good
3. ☐ Fair
4. ☐ Poor
5. ☐ Very poor
6. ☐ No basis to judge

19. Please use this space to give us any comments on the questionnaire or more generally on the subject of reproductive and developmental toxicants and the protection of public health.

THANK YOU FOR YOUR ASSISTANCE!

Experts Participating in GAO Survey

We wish to thank the 50 scientists and administrators who responded to our survey in April 1990. We have listed their names in alphabetical order, along with their affiliation. We regret that several questionnaires were returned too late to be included in the analysis.

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Dr. Joe Leigh Simpson
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Selected Adverse Reproductive and Developmental Outcomes of the 30 Chemicals

	In this appendix, we describe some of the reproductive and developmental effects of the 30 chemicals used in this study. The descriptions are not comprehensive, but are instead intended to give the reader a clearer understanding of the type of effects considered in this report.
Alcohol	Alcohol consumption in pregnancy has been associated with a variety of abnormalities in the newborn. Fetal alcohol syndrome is characterized by a spectrum of features including prenatal and postnatal growth deficiency, central nervous system dysfunction, a distinctive pattern of facial features, and major organ system malformations. Chronic alcoholism in men has been associated with impotence and sperm abnormalities.
Arsenic	Arsenic exposure during pregnancy in humans has been tentatively associated with decreased birthweight of newborns and increased spontaneous abortions. Arsenic is teratogenic in hamsters, mice, and rats.
Cadmium	Fetal death and malformations are among the effects associated with cadmium exposure of pregnant animals. Male exposure to cadmium is associated with testicular toxicity, altered libido, and infertility.
Carbon Disulfide	Women exposed to carbon disulfide have been found to have alterations in their menstrual cycles. Men exposed to carbon disulfide have experienced altered libido and an increased proportion of abnormal sperm forms.
Carbon Monoxide	Carbon monoxide poisoning has been associated with intrauterine fetal death and with neurological deficits in surviving infants.
Chlordecone	Among the developmental effects associated with chlordecone exposure in animals are malformations, stillbirths, and abortions. Female rats fed chlordecone exhibited constant estrus with some damage to the ovaries. Male workplace exposure to chlordecone has been associated with reduced sperm count and motility.
Chloroprene	Male exposure to chloroprene has been associated with sexual impotency and loss of libido.

DDT	Human prenatal exposure to DDT has been associated with premature birth and altered development of the reproductive system. Female reproductive effects include menstrual irregularities.
DBCP	Female animal exposure to DBCP has been shown to alter ovarian function and decrease fertility. In men, occupational exposure has been associated with decreased sperm counts and infertility.
DES	Human exposure in utero is associated with numerous developmental outcomes including an increase in vaginal and cervical clear-cell adenocarcinoma in female offspring and an increased frequency of abnormalities in reproductive tracts in male offspring. Hyperestrogenism has been associated with women's occupational exposure to DES. Female reproductive effects in animals include ovarian cystadenomas in mice and ovarian lesions in dogs.
Ethylene Dibromide	Female chickens are sensitive to ethylene dibromide exposure as evidenced by impaired follicle growth and egg size. Female rat estrous cycles were impeded but only at doses lethal to 20 percent of the animals. Male agricultural workers have exhibited decreased sperm density and percent normal forms after ethylene dibromide exposure.
Ethylene Glycol Monoethyl Ether	Birth defects were found in the children of women exposed at work. EGEE is teratogenic in mice, rats, and rabbits. Exposure to EGEE has caused infertility in female animals. Exposure of male rats, rabbits, dogs, and mice has been shown to induce testicular damage.
Ethylene Glycol Monomethyl Ether	EGME exposure has been shown to cause infertility in female animals and testicular damage in male mice, rats, and rabbits.
Ethylene Oxide	A study of hospital workers who used sterilization equipment revealed an increase in the spontaneous abortion rate that was associated with exposure to ethylene oxide. Exposure of female rats to ethylene oxide prior to mating results in increased fetal abnormalities and mortality. Reduced testicular weight has been observed in male rats after ethylene

	oxide exposure. Monkeys exhibit decreased sperm concentration following exposure to ethylene oxide.
Gossypol	Gossypol has been shown to cause sterility in male humans, dogs, monkeys, rats, and hamsters.
Hexachlorobenzene	In humans, exposure of pregnant women has been associated with stillbirths, pink sores on the skin of infants, muscle atrophy, and death in exposed children within 1 year of birth. Female rat exposure to hexachlorobenzene before mating and throughout gestation resulted in decreased litter size and reduced birth weight. Female monkeys exposed to hexachlorobenzene exhibited histopathological changes in their ovaries.
Lead	Pregnant women exposed to lead have shown increased rates of spontaneous abortion. Female exposure to lead has been associated with menstrual disorders and infertility. Occupational studies of male workplace exposure to lead show dose-related disturbances in sperm-related factors.
Lithium	Lithium exposure of pregnant women has been associated with cardiac defects in their offspring.
Mercury	Mercury exposure has been shown to cause severe brain damage in children born to women exposed during pregnancy and has also been associated with spontaneous abortions. Menstrual disorders have been shown to follow female occupational exposure. Male occupational exposure has been associated with altered libido, while animal studies show altered sperm production and decreased fertility.
Mirex	Mirex has been shown to cause low fertility in female mice and to inhibit ovulation in female rats.
Nicotine	Nicotine has been shown to impair fetal growth in rabbits and rats. Skeletal defects and cleft palate were produced in offspring of pregnant mice exposed during pregnancy.

Polybrominated Biphenyls	An inverse relation has been shown between children's body-fat PBB level and performance on a test measuring children's abilities. Developmental effects found in animals include liver carcinomas in rat offspring and abnormalities in the thyroid and liver in pig offspring. Female monkeys exhibited disrupted menstrual cycles after being fed PBBs.
Polychlorinated Biphenyls	PCB exposure of pregnant women can cause dark brown pigmentation in offspring, shorter gestation length, and lower birthweight. Altered menstrual cycles have also been associated with female exposure.
2,4,5-Trichlorophenoxyacetic Acid	An epidemiological study showed a significant increase in neural tube defects in infants conceived during summer months, corresponding to seasonal high use of 2,4,5-T. An EPA epidemiological study concluded that 2,4,5-T exposure was likely linked to human miscarriages.
TCDD	TCDD exposure in mice has resulted in kidney damage and cleft palate in offspring, while rat exposure has resulted in hemorrhage of internal organs. Female animals exposed to TCDD exhibit changes in estrous cyclicity.
Tobacco Smoke	Cigarette smoking has been associated with retarded fetal growth, increased incidence of spontaneous abortion, bleeding during pregnancy, increased incidence of sudden infant death syndrome, and long-term lag in physical growth. Cigarette smoking by males has been implicated as a cause of decreased sperm counts and normal forms.
Toluene	Among the developmental effects associated with toluene exposure in human offspring are central nervous system dysfunction, craniofacial and limb anomalies, and developmental delay. Uterine pain was experienced by female shoemakers exposed to toluene.
Vinyl Chloride	Ovarian dysfunction, benign uterine growths, and prolapsed genital organs have been reported in women exposed to vinyl chloride. A decline in sexual function has been observed in both men and women exposed to vinyl chloride. Occupational exposure of males has been associated with increased rates of spontaneous abortions in their wives.

Vitamin A	Urinary tract anomalies and central nervous system defects in offspring are among the effects associated with maternal ingestion of excess vitamin A.
Warfarin	Among the human effects of warfarin exposure during pregnancy are stillbirths and malformations of the central nervous system, eye, and jaw in the newborn.

Principal Federal Regulatory Activities as Reported in Agency Questionnaire[a]

Chemical	CPSC	FDA	OSHA	OAR	ODW	OERR	OPP	OSW	OTS	OWRS
Alcohol		S	S				O			
Arsenic	B	S	S	S	S	S	B	S		G
Cadmium	O	G	S	O	S	S	B	S	O	G
Carbon disulfide		S	S			S	B	S		
Carbon monoxide	S	S	S	S						
Chlordecone		O	O			S	B	S		
Chloroprene		O	S					S	O	
DDT		O	S			S	B	S		G
DBCP		O	S		G	S	B	S	O	
DES	S	B	O			S		S		
Ethylene dibromide		O	S		G	S	B	S		
EGEE	O	S	S			S	B	S	O	
EGME	O		S				B		O	
Ethylene oxide		S	S	O		S	S	S	O	
Gossypol		S	O				O			
Hexachlorobenzene		O	O		G	S	B	S		G
Lead	B	S	S	S	S	S	B	S		G
Lithium	S	S	S							
Mercury		G	S	S	S	S	B	S	O	G
Mirex		O	O				B			G
Nicotine			S			S	S	S		
PBBs		O	O						S	
PCBs	O	S	S		G	S	B	S	S	G
2,4,5-T		O	S		G	S	B	S		G
TCDD	O	S	O		G	S	S	S	O	G
Tobacco smoke										
Toluene	S	S	S		G	S	O	S	O	G
Vinyl chloride	B	O	S	S	S	S	B	S		G
Vitamin A	S	S	O							
Warfarin	S	O	S			S	S	S		
Total	**14**	**27**	**29**	**7**	**12**	**20**	**23**	**21**	**11**	**12**
Bans	3	1					16			
Guidelines		2			7					12
Standards	6	13	21	5	5	20	4	21	2	
Other Activities	5	11	8	2			3		9	

[a]B = ban; G = guideline; S = standard or restriction; and O = other activity (e.g., educating or labeling).

Legislative Authority

In this appendix, we present the legislation for the 10 offices in our study. There are other laws that govern their actions; however, these 12 provisions are the only ones the offices reported as governing their principal activities—those with the greatest impact—for our 30 toxicants. For each law, we present the office that administers it, its purpose, key definitions, and the citations, if any, of reproductive and developmental toxicity.

Clean Air Act

The Clean Air Act is administered by the EPA Office of Air and Radiation. Major revisions to the Clean Air Act were enacted after our research was conducted. The citations below come from the law prior to these revisions. Reproductive health is mentioned.

"The purposes of this Act are—

"(1) to protect and enhance the quality of the Nation's resources so as to promote the public health and welfare. . . ."

"(1) In carrying out research pursuant to this Act, the Administrator shall give special emphasis to research on the short-and long-term effects of air pollutants on public health and welfare. . . .

"(2) In carrying out the provisions of this subsection the Administrator may—

"(A) conduct epidemiological studies of the effects of air pollutants on mortality and morbidity;

"(B) conduct clinical and laboratory studies on the immunologic, biochemical, physiological, and the toxicological effects including carcinogenic, teratogenic, and mutagenic effects of air pollutants. . . ."

Comprehensive Environmental Response, Compensation, and Liability Act

This act (generally referred to as CERCLA or Superfund) is administered by the Office of Emergency and Remedial Response at EPA. Reproductive health is mentioned. The purposes of the law are "to provide for liability, compensation, clean-up, and emergency response of hazardous substances released into the environment, and the clean-up of inactive hazardous waste disposal sites."

"The term 'pollutant or contaminant' shall include, but not be limited to, any element, substance, compound, or mixture, including disease-

causing agents, which after release into the environment and upon exposure, ingestion, inhalation, or assimilation into any organism, either directly from the environment or indirectly by ingestion through food chains, will or may reasonably be anticipated to cause death, disease, behavioral abnormalities, cancer, genetic mutation, physiological malfunctions (including malfunctions in reproduction) or physical deformations in such organisms or their offspring. . . ."

"A chemical may be added [to the list of those covered by the Act] if . . . there is sufficient evidence to establish any one of the following:

"(A) The chemical is known to cause or can reasonably be anticipated to cause significant adverse acute human health effects at concentration levels that are reasonably likely to exist beyond facility site boundaries. . . .

"(B) The chemical is known to cause or can reasonably be anticipated to cause in humans—

"(i) cancer or teratogenic effects, or

"(ii) serious or irreversible—

"(I) reproductive dysfunctions,

"(II) neurological disorders,

"(III) heritable genetic mutations, or

"(IV) other chronic health effects. . . ."

Consumer Product Safety Act

The act is administered by the Consumer Product Safety Commission. Reproductive health is mentioned.

"The purposes of this Act are—

"(1) to protect the public against unreasonable risks of injury associated with consumer products. . . ."

"The term 'consumer product' means any article, or component part thereof, produced or distributed (i) for sale to a consumer for use in or around a permanent or temporary household or residence, a school, in

recreation, or otherwise, or (ii) for the personal use, consumption or enjoyment of a consumer in or around a permanent or temporary household or residence, a school, in recreation, or otherwise; but such term does not include —

"(A) any article which is not customarily produced or distributed for sale to, or use or consumption by, or enjoyment of a consumer,

"(B) tobacco and tobacco products, . . .

"(D) pesticides (as defined by the Federal Insecticide, Fungicide, and Rodenticide Act), . . .

"(I) food. The term "food" . . . means all "food" as defined in . . . the Federal Food, Drug, and Cosmetic Act. . . ."

"The term 'risk of injury' means a risk of death, personal injury, or serious or frequent illness."

"The Commission shall appoint Chronic Hazard Advisory Panels . . . to advise the Commission . . . respecting the chronic hazards of cancer, birth defects, and gene mutations associated with consumer products."

"The Commission may not issue an advance notice of proposed rulemaking . . . relating to a risk of cancer, birth defects, or gene mutations from a consumer product unless a Chronic Hazard Advisory Panel . . . has . . . submitted a report to the Commission with respect to whether a substance contained in such product is a carcinogen, mutagen, or teratogen."

"Before the Commission issues an advance notice of proposed rulemaking . . . relating to a risk of cancer, birth defects, or gene mutations from a consumer product, the Commission shall request the [Chronic Hazard Advisory] Panel to review the scientific data and other relevant information relating to such risk to determine if any substance in the product is a carcinogen, mutagen, or a teratogen. . . ."

Federal Food, Drug, and Cosmetic Act

This act is the primary law which provides the Food and Drug Administration at the Department of Health and Human Services with the authority to protect foods from toxicants. It is also the law under which the Office of Pesticide Programs at EPA sets pesticide residue limits on foods. Reproductive health is not mentioned.

[Sec. 201 (s)] "The term 'food additive' means any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food . . . except that such term does not include—

"(1) a pesticide chemical in or on a raw agricultural commodity; or

"(2) a pesticide chemical to the extent that it is intended for use or is used in the production, storage, or transportation of any raw agricultural commodity; or

"(3) a color additive; or

"(4) any substance used in accordance with a sanction or approval granted prior to the enactment of this paragraph pursuant to this Act, the Poultry Products Inspection Act or the Meat Inspections Act . . .; or

"(5) a new animal drug."

[Sec. 402] "A food shall be deemed to be adulterated—

"(a)(1) if it bears or contains any poisonous or deleterious substance which may render it injurious to health; but in case the substance is not an added substance such food shall not be considered adulterated under this clause if the quantity of such substance in such food does not ordinarily render it injurious to health; or

"(2)(A) if it bears or contains any added poisonous or added deleterious substance (other than one which is (i) a pesticide chemical in or on a raw agricultural commodity, (ii) a food additive, (iii) a color additive, or (iv) a new animal drug) which is unsafe within the meaning of section 406; or (B) if it is a raw agricultural commodity and it bears or contains a pesticide chemical which is unsafe within the meaning of section 408 (a); or (C) if it is, or it bears or contains, any food additive which is unsafe within the meaning of section 409 . . .; or (D) if it is, or it bears or contains, a new animal drug (or conversion product thereof) which is unsafe within the meaning of section 512. . . ."

[Sec. 402 (c)] "If it is, or it bears or contains, a color additive which is unsafe within the meaning of section 706(a)."

[Sec. 406] "Any poisonous or deleterious substance added to any food, except where such substance is required in the production thereof or cannot be avoided by good manufacturing practice shall be deemed to be unsafe . . . but when such substance is so required or cannot be so avoided, the Secretary shall promulgate regulations limiting the quantity therein or thereon to such extent as he finds necessary for the protection of public health. . . . In determining the quantity of such added substance to be tolerated in or on different articles of food the Secretary shall take into account the extent to which the use of such substance is required or cannot be avoided in the production of each such article, and the other ways in which the consumer may be affected by the same or other poisonous or deleterious substances."

[Sec. 408(a)] "Any poisonous or deleterious pesticide chemical, or any pesticide chemical which is not generally recognized . . . as safe for use, added to a raw agricultural commodity, shall be deemed to be unsafe . . . unless

"(1) a tolerance for such pesticide chemical in or on the raw agricultural commodity has been prescribed by the Administrator of the Environmental Protection Agency . . . and the quantity of such pesticide chemical . . . is within the limits of the tolerance so prescribed; or

"(2) . . . the pesticide chemical has been exempted from the requirements of a tolerance. . . ."

[Sec. 408(b)] "The Administrator [of EPA] shall promulgate regulations establishing tolerances with respect to the use in or on raw agricultural commodities of poisonous or deleterious pesticide chemicals which are not generally recognized . . . as safe for use, to the extent necessary to protect the public health."

[Sec. 409(c)(3)(A)] "No such regulation shall be issued if a fair evaluation of the data before the Secretary—

"(A) fails to establish that the proposed use of the food additive. . . will be safe. . . ."

[Sec. 412 (a)(1)] "An infant formula shall be deemed to be adulterated if —

"(A) such infant formula does not provide nutrients as required . . .;

"(B) such infant formula does not meet the quality factor requirements prescribed by the Secretary . . .; or

"(C) the processing of such infant formula is not in compliance with the quality control requirements. . . ."

[Sec. 512(a)(1)] "A new drug shall, with respect to any particular use or intended use of such drug, be deemed unsafe for the purposes of . . . section 402(a)(2)(D) unless—

"(A) there is in effect an approval of an application . . . with respect to such use or intended use of such drug,

"(B) such drug, its labeling, and such use conform to such approved application, and

"(C) in the case of a new animal drug . . . from a batch with respect to which a certificate or release issued . . . is in effect with respect to such drug."

[Sec. 512(d)(1)] "If the Secretary finds . . . that

"(A) the investigations . . . do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof;

"(B) the results of such test show that such a drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions . . . he shall issue an order refusing to approve the application."

[Sec. 706(a)] "A color additive shall, with respect to any particular use (for which it is being used or intended to be used or is represented as suitable) in or on food or drugs or devices or cosmetics be deemed unsafe for the purposes of the application of section 402(c) . . . unless—

"(1)(A) there is in effect, and such additive and such use are in conformity with, a regulation . . . listing such additive for such use . . . and (B) such additive either (i) is from a batch certified . . . for such use, or (ii) has, with respect to such use, been exempted . . . from the requirement of certification; or

"(2) such additive and such use thereof conform to the terms of an exemption. . . ."

[Sec. 706(b)(4)] "The Secretary shall not list a color additive under this section [as suitable and safe] for a proposed use unless the data before him establish that such use, under the conditions of use specified in the regulations, will be safe. . . ."

Federal Hazardous Substances Act

This act is administered by the Consumer Product Safety Commission. Reproductive health is not mentioned. The purpose of this law is "to regulate the interstate distribution and sale of packages of hazardous substances intended or suitable for household use."

"The term 'hazardous substance' means:

"1(A) Any substance or mixture of substances which (i) is toxic, (ii) is corrosive, (iii) is an irritant, (iv) is a strong sensitizer, (v) is flammable, or (vi) generates pressure through decomposition, heat, or other means, if such substance or mixture or substances may cause substantial personal injury or substantial illness during or as a proximate result of any customary or reasonably foreseeable handling or use, including reasonably foreseeable ingestion by children. . . .

"2 The term 'hazardous substance' shall not apply to pesticides subject to the Federal Insecticide, Fungicide, and Rodenticide Act, nor to foods, drugs, and cosmetics subject to the Federal Food, Drug, and Cosmetic Act, nor to substances intended for use as fuels when stored in containers and used in the heating, cooking, or refrigeration system of a house, nor to tobacco and tobacco products, but such term shall apply to any article which is not itself a pesticide within the meaning of the Federal Insecticide, Fungicide, and Rodenticide Act but which is a hazardous substance . . . by reason of bearing or containing such an economic poison."

"The term 'toxic' shall apply to any substance (other than a radioactive substance) which has the capacity to produce personal injury or illness to man through ingestion, inhalation, or absorption through any body surface."

Federal Insecticide, Fungicide, and Rodenticide Act

This act is administered by the Office of Pesticide Programs at EPA. Reproductive health is not mentioned. The purpose of the law is to regulate production, storage, distribution, sale, use, and disposal of pesticides.

"The term 'pesticide' means (1) any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest, and (2) any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant."

"The terms 'protect health and the environment' and 'protection of health and the environment' mean protection against any unreasonable adverse effects on the environment."

"The term 'unreasonable adverse effects on the environment' means any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide."

Federal Water Pollution Control Act

The Federal Water Pollution Control Act (Clean Water Act) is administered by the Office of Water Regulations and Standards at EPA. Reproductive health is mentioned.

"The objective of this Act is to restore and maintain the chemical, physical, and biological integrity of the Nation's waters."

"The term 'toxic pollutant' means those pollutants or combinations of pollutants, including disease-causing agents, which after discharge and upon exposure, ingestion, inhalation, or assimilation into any organism, either directly from the environment or indirectly by ingestion through food chains, will, on the basis of information available to the Administrator, cause death, disease, behavioral abnormalities, cancer, genetic mutations, physiological malfunctions (including malfunctions in reproduction) or physical deformations, in such organisms or their offspring."

". . . such modification [in requirements] will not result in the discharge of pollutants in quantities which may reasonably be anticipated to pose an unacceptable risk to human health or the environment because of bioaccumulation, persistency in the environment, acute toxicity, chronic toxicity (including carcinogenicity, mutagenicity or teratogenicity), or synergistic propensities."

Occupational Safety and Health Act

This act is administered by the Occupational Safety and Health Administration in the Department of Labor.[1] Reproductive health is not mentioned.

"The Congress declares it to be its purpose and policy . . .to assure so far as possible every working man and woman in the Nation safe and healthful working conditions . . .

"(3) by authorizing the Secretary of Labor to set mandatory occupational safety and health standards applicable to businesses affecting interstate commerce. . . ."

"The term 'occupational safety and health standard' means a standard which requires conditions, or the adoption or use of one or more practices, means, methods, operations, or processes, reasonably necessary or appropriate to provide safe or healthful employment and places of employment."

Poison Prevention Packaging Act

This act is administered by the Consumer Product Safety Commission. Reproductive health is not mentioned. The objective of this act is "to provide for special packaging to protect children from serious personal injury or serious illness resulting from handling, using, or ingesting household substances. . . ."

"The Commission, may establish in accordance with provisions of the Act, by regulation, standards for the special packaging of any household substance. . . ."

Safe Drinking Water Act

The Safe Drinking Water Act is administered by the Office of Drinking Water at EPA. Reproductive health is not mentioned. The purpose of the law is to assure safe drinking water.

"The Administrator shall publish maximum contaminant level goals and promulgate national primary drinking water regulations for each contaminant . . . which . . . may have any adverse effect on the health of persons and which is known or anticipated to occur in public water systems."

[1]Jurisdiction may be limited to the extent that other agencies exercise statutory authority to regulate occupational safety and health.

Solid Waste Disposal Act

This act is administered by the Office of Solid Waste at EPA. It is sometimes referred to as the Resource Conservation and Recovery Act, a major set of amendments enacted in 1976. Reproductive health is not mentioned.

"The objectives of this Act are to promote the protection of health and the environment and to conserve valuable material and energy resources by . . .

"(4) regulating the treatment, storage, transportation, and disposal of hazardous wastes which have adverse effects on health and the environment. . . ."

"The term 'hazardous waste' means a solid waste, or combination of solid wastes, which . . . may—

"(A) cause, or significantly contribute to an increase in mortality or an increase in serious irreversible, or incapacitating reversible, illness; or

"(B) pose a substantial present or potential hazard to human health or the environment when improperly treated, stored, transported, or disposed of, or otherwise managed."

Toxic Substances Control Act

This act is administered by the Office of Toxic Substances at EPA. Reproductive health is mentioned. The objective of the law is "to regulate commerce and protect human health and the environment by requiring testing and necessary use restrictions on certain chemical substances. . . ."

"The health and environmental effects for which standards for the development of test data may be prescribed include carcinogenesis, mutagenesis, teratogenesis, behavioral disorders, cumulative or synergistic effects, and any other effect which may present an unreasonable risk of injury to health or the environment."

"There is established a committee to make recommendations to the Administrator respecting the chemical substances and mixtures to which the Administrator should give priority consideration for the promulgation of a rule. . . . In establishing such list, the committee shall give priority attention to those chemical substances and mixtures which are known to cause or contribute to or which are suspected of causing or contributing to cancer, gene mutations, or birth defects."

"Upon the receipt of —

"(1) any test data required to be submitted under this Act, or

"(2) any other information available to the Administrator, which indicates . . . that . . . a chemical substance or mixture presents a significant risk of serious or widespread harm to human beings from cancer, gene mutations, or birth defects, the Administrator shall . . . initiate appropriate action . . . to prevent or reduce to a sufficient extent such risk or publish in the Federal Register a finding that such risk is not unreasonable."

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Glossary

Acrodynia	A syndrome seen in infancy and occasionally in older childhood, of extreme irritability alternating with periods of apathy, anorexia, pink itching hands and feet, scarlet tip of the nose and cheeks, sensitivity to light, profuse sweating, excessive rapidity of action of the heart, hypertension, and decrease of normal tonicity (especially muscle) or pressure (especially intraocular), and frequently peeling of the skin of the hands and feet. This condition is associated with ingestion of or contact with mercury, but also with inflammatory changes of obscure origin in the central nervous system.
Acute Toxicity	The ability of a substance to cause poisonous effects resulting in severe biological harm or death soon after a single exposure or dose. Also any severe poisonous effect resulting from a single short-term exposure to a toxic substance.
Background Level	Level (of a parameter of occurrence) determined by characteristics other than that under study.
Cleft Palate	A cleft from front to back along the middle of the palate or roof of the mouth, caused by the failure of the two parts of the palate to join in prenatal development.
Clubfoot	A congenital deformity of the foot, characterized by a misshapen or twisted, often clublike, appearance.
Desiccant	A chemical agent that absorbs moisture; some desiccants are capable of drying out plants or insects, causing death.
Developmental Toxicity	The occurrence of adverse effects on the developing organism that may result from exposure during prenatal development or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the lifespan of the organism. The major manifestations of developmental toxicity include: (1) death of the developing organism, (2) structural abnormality, (3) altered growth, and (4) functional deficiency.

Endocrine	Designating or of any gland producing one or more internal secretions that are introduced directly into the bloodstream and carried to other parts of the body whose function they regulate or control.
Female Reproductive Toxicity	Adverse effects observed in the female reproductive system that may result from exposure to chemical or physical agents. Female reproductive toxicity includes, but is not limited to, adverse effects observed in sexual behavior, onset of puberty, fertility, gestation, parturition, lactation, or premature reproductive senescence.
Fumigant	A pesticide that is vaporized to kill pests; used in buildings and greenhouses.
Fungicide	Pesticides which are used to control, prevent, or destroy fungi.
Herbicide	A chemical pesticide designed to control or destroy plants, weeds, or grasses.
Hydrocephalus	A condition characterized by an abnormal increase in the amount of fluid in the cranium, especially in young children, causing enlargement of the head and destruction of the brain.
Insecticide	A pesticide compound specifically used to kill or control the growth of insects.
Male Reproductive Toxicity	The occurrence of adverse effects on the male reproductive system that may result from exposure to environmental agents. The toxicity may be expressed as alterations to male reproductive organs or the related endocrine system. The manifestation of such toxicity may include alteration in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of the male reproductive system.

Malformations	Permanent structural changes that may adversely affect survival, development, or function.
Morphology	The branch of biology which deals with the form and structure of animals and plants.
Mutagen	Any substance that can cause a change in genetic material.
Nematocide	A chemical agent which is destructive to nematodes (round worms or threadworms).
Persistence	Refers to the length of time a compound, once introduced into the environment, stays there. A compound may persist for less than a second or indefinitely.
Pest	An insect, rodent, nematode, fungus, weed, or other form of terrestrial or aquatic plant or animal life or virus, bacterial, or microganism that is injurious to health or the environment.
Pesticide	Substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest. Also, any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant.
Risk Assessment	The qualitative or quantitative characterization of the potentially adverse effects of exposure to environmental hazards based on an evaluation of the results of epidemiological, clinical, toxicological, and environmental research; judgments as to the number and characteristics of persons exposed at various concentrations; and the extrapolation from these results to project the type and extent of adverse effects under different conditions of exposure.
Rodenticide	A chemical or agent used to destroy rats or other rodent pests, or to prevent them from damaging food, crops, and so forth.

Spina Bifida	A congenital defect characterized by imperfect closure of part of the spinal column, exposing some of the nervous system and often resulting in hydrocephalus, paralysis, and so forth.
Teratogen	A chemical that causes structural defects that affect the development of an organism.
Teratology	The science of malformations and monstrosities.
Tolerances	The permissible residue levels for pesticides in raw agricultural produce and processed foods. Whenever a pesticide is registered for use on a food or feed crop, a tolerance (or exemption from the tolerance requirement) must be established. EPA establishes the tolerance levels, which are enforced by FDA and the Department of Agriculture.

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